alcohol

SCIENCE, POLICY, AND PUBLIC HEALTH

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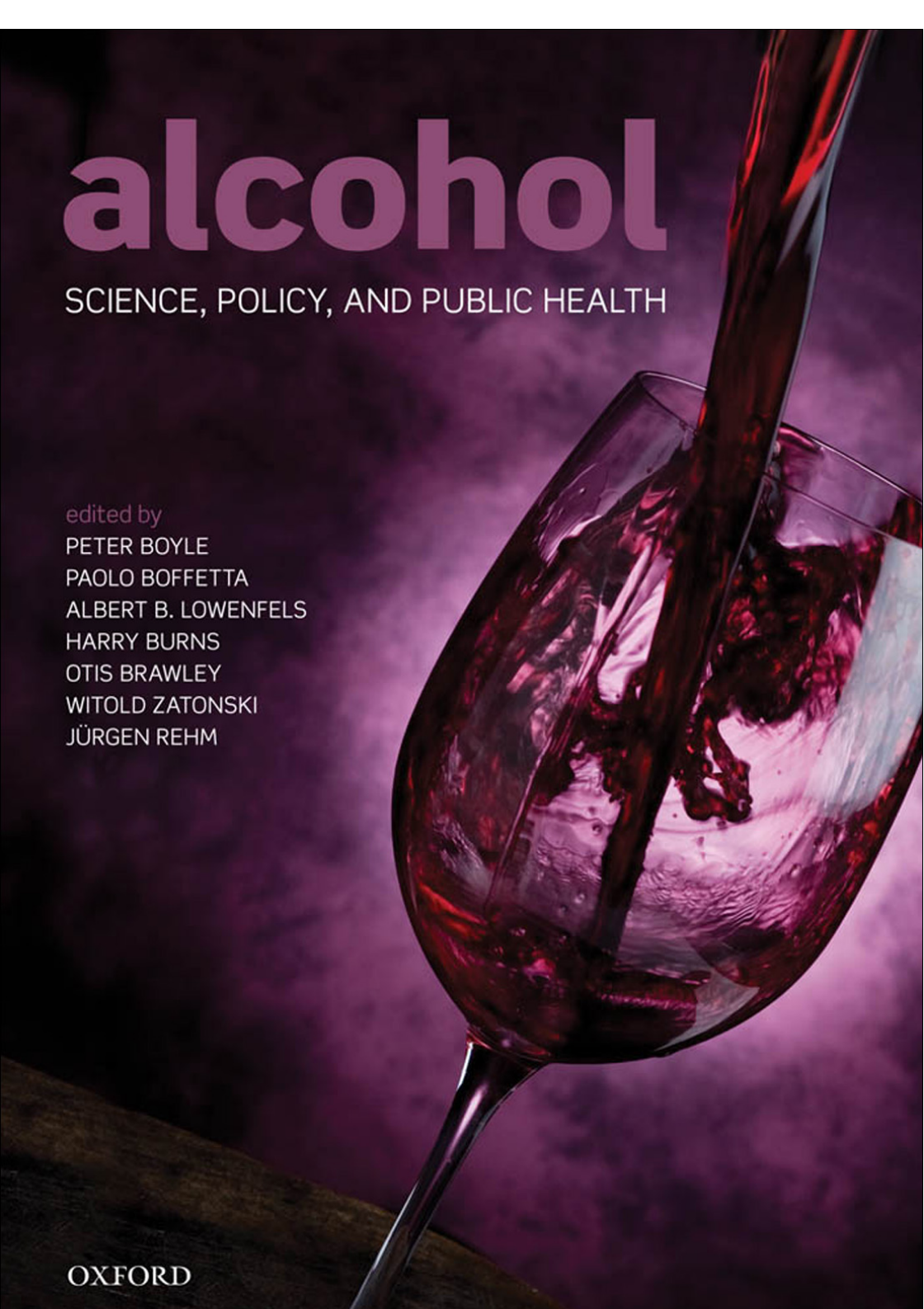

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Of the nearly seven billion persons currently inhabiting the earth, about half have consumed alcohol. Although most alcohol consumers drink moderately, the World Health Organization estimates that there are approximately 2.5 million alcohol-related deaths annually—a number that greatly exceeds any possible health benefits from consuming alcohol. For males in the age group 15–59 years, alcohol is the major risk factor for death.

Even though most people consume alcohol without any measurable health consequences, these stark numbers reflect the global magnitude of alcohol-related disease and injury. Alcohol is an established risk factor for a wide list of benign and malignant diseases, as well as one of the commonest causes for preventable diseases. Unlike many other health-related factors, problems associated with alcohol are not restricted to a single gender, socio-economic group, or particular country, but are truly global. Furthermore, alcohol affects not only the individual, but also the family, and eventually the entire community.

The idea for this book came about following the enthusiastic reception of the previously published volume titled *Tobacco: Science, Policy, and Public Health*. The editors and Oxford University Press believed that another text with the same general format, but with a new focus on alcohol, would be useful to a wide range of readers.

The purpose of the book is to provide an interdisciplinary source of information that links together science, policy, and public health—three areas that are often considered separately. It is the viewpoint of the editors that science

should be the source for alcohol policy, which in turn, should be the driving force for public health decisions. Just as scientific information about smoking, often based on epidemiological studies, led to public health awareness and eventually to dramatic legislative decisions, we believe that a science-based approach should be equally important in strengthening alcohol-related public policy.

The book is divided into nine sections with the first being an introductory set of chapters covering the historical evolution of alcohol, key early studies on alcohol, and cultural and social aspects of alcohol. Additional sections then follow covering the biology and chemistry of alcohol; consumption patterns; gender and age-related issues; injury and violence; alcohol-associated benign and malignant disease; and therapeutic aspects. The book concludes with a final section on alcohol policy.

In a field as large as alcohol, there are many topics that had to be excluded simply because of space limitations. However the Editors believe that the chapters selected for inclusion in the current volume represent key areas of interest to a wide audience.

The authors for each chapter are international leaders in the field of alcoholism and are recognized for their research that has helped to advance this domain. One of the strengths of the book is that each author has a unique approach that leads to a broad view of the overall subject. The information presented is current and represents the highest standards of research within the field of alcoholism.

We anticipate that the book will appeal to a broad audience. Scientists will be interested in developments outside of their own field. Public health officials will find valuable current information on alcohol-related diseases and on what can be done to minimize the impact of alcohol
on the social fabric. Legislators will find the facts they need to bring about effective alcohol policy.

As expected in any multiauthored comprehensive text there are likely to be some differences in viewpoints expressed by different authors. When present, these differences reflect current debates within the discipline and are areas that need additional public debate before they can be resolved.

Preface

The editors would like to thank their colleagues, who devoted their time and effort to writing these concise chapters which comprehensively cover and elaborate on the science and policy issues relevant to alcohol today.

The editors deeply appreciate the editorial and administrative support of Laura-Louise Fairley and Faustine Valentini at the International Prevention Research Institute for their great efforts. Albert Lowenfels would like to personally thank the Smithers Foundation (Mill Neck, New York), a private philanthropic organization with an interest in alcohol, for providing their valuable support.

Thanks also go to Oxford University Press for their guidance and timely publication.

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AAD	alcohol-attributable death
ABV	alcohol by volume
ACE	angiotensin-converting enzyme
ACM	alcoholic cardiomyopathy
ADH	alcohol dehydrogenase
AFR	African Region
AH	alcoholic hepatitis
AIDS	acquired immune deficiency syndrome
AIIs	alcohol ignition interlocks
ALD	alcohol-related liver disease
ALDH	aldehyde dehydrogenase

ALS	administrative licence suspension
AMR	Region of the Americas
APC	adult per capita consumption
ARBD	alcohol-related birth defects
ARDI	Alcohol-Related Disease Impact
ARND	alcohol-related neurodevelopmental disorders
ART	antiretroviral therapy
AUD	alcohol use disorder
AUDIT	Alcohol Use Disorders Identification Test
BAC	blood alcohol concentration
BAL	blood alcohol level

BMI	body mass index
BOP	bottom of the pyramid
CAD	coronary artery disease
CAM	continuous alcohol monitoring
CDT	carbohydrate-deficient transferase
CHD	coronary heart disease
CI	confidence interval
CM	cardiomyopathy
CNS	central nervous system
CPK	creatine phosphokinase
CPM	central pontine myelinolysis
CRA	Comparative Risk Assessment

CRH	corticotrophin releasing hormone
CSR	corporate social responsibility
DA	dopamine
DALY	disability-adjusted life year
DASS	Depression, Anxiety, and Stress Scales
DCM	dilated cardiomyopathy
DEP	diethyl phthalate
DNA	deoxyribonucleic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DT	delirium tremens
DUI	driving under the influence

DWI	driving while intoxicated
DWS	driving while suspended
EAAP	European Alcohol Action Plan
ED	emergency department
EF	ejection fraction
EMR	Eastern Mediterranean Region
EPHA	European Public Health Alliance
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	(o)estrogen receptor
EU	European Union
EUR	European Region

FAE	fetal alcohol effects
FAEE	fatty acid ethyl ester
FAO	Food and Agriculture Organization
FARS	Fatality Analysis Reporting System
FAS	fetal alcohol syndrome
FASD	fetal alcohol spectrum disorders
FAST	Fast Alcohol Screening Test
FFQ	food frequency questionnaire
FMPV	female-to-male partner violence
fMRI	functional magnetic resonance imaging
g/dL	grams per decilitre

GABA	gamma-aminobutyric acid
G × E	gene × environment
GAPA	Global Alcohol Policy Alliance
GBD	Global Burden of Disease
GDL	graduated driver licensing
GF	graduated frequency
GI	gastrointestinal
GISAH	Global Information System on Alcohol and Health
GORD	gastro-oesophageal reflux disease
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus

HD	heavy drinking
HDL-C	high-density lipoprotein cholesterol
HE	hepatic encephalopathy
HED	heavy episodic drinking
HIC	high-income country
HIV	human immunodeficiency virus
HOPE	Hawaii's Opportunity Probation with Enforcement
HPV	human papillomavirus
IARC	International Agency for Research on Cancer
ICAP	International Center for Alcohol Policies
ICD-10	International Classification of Diseases, tenth revision

IHD	ischaemic heart disease
INHANCE	International Head and Neck Cancer Epidemiology (consortium)
IOM	Institute of Medicine (United States)
IPV	intimate partner violence
kg	kilograms
LIC	low-income country
LMIC	low- and middle-income countries
LV	left ventricular
MAST	Michigan Alcohol Screening Test
mDF	Maddrey discriminant function

MEOS	microsomal ethanol oxidizing system
MFPV	male-to-female partner violence
MI	myocardial infarction
MIC	middle-income country
ml	millilitre
MLDA	minimum legal drinking age
MVC	motor vehicle collision
NAD	nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide, reduced
NADP	nicotinamide adenine dinucleotide phosphate
NADS	National Advanced Driving Simulator

NCD	non-communicable disease
NESARC	National Epidemiologic Survey of Alcohol and Related Conditions
NHTSA	National Highway Traffic Safety Administration
NIDA	National Institute on Drug Abuse
NLAES	National Longitudinal Alcohol Epidemiologic Survey
NMDA	N-methyl-D-aspartate
NRS	National Roadside Survey
NSAID	non-steroidal anti-inflammatory drug
NSDUH	National Survey on Drug Use and Health
OR	odds ratio

PAD	peripheral arterial disease
pFAS	partial fetal alcohol syndrome
PFC	prefrontal cortex
PHMG	polyhexamethyleneguanidine hydrochloride
PPI	proton pump inhibitor
PR	progesterone receptor
QF	quantity–frequency
RBT	random breath testing
ROS	reactive oxygen species
RR	relative risk
SASQ	Single Alcohol Screening Questionnaire
SCC	squamous cell carcinoma

SCRAM	Secure Continuous Remote Alcohol Monitor
SBI	screening and brief interventions
SEAR	South East Asian Region
SF-36	short-form-36 health survey
SFST	standard field sobriety test
SNP	single nucleotide polymorphism
STI	sexually transmitted infection
SVN	single-vehicle night-time
SVNC	single-vehicle night-time collision
TAA	tobacco–alcohol amblyopia
UADT	upper aerodigestive tract

UGI	upper gastrointestinal
VTE	venous thromboembolism
WHO	World Health Organization
WPR	West Pacific Region
YPLL	years of potential life lost

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Part I
Framing the issues

Chapter 1
Historical evolution of alcohol consumption in society

David J. Hanson

Introduction

Consuming alcoholic drinks has long been a part of human life. This chapter traces major developments in the production, consumption, and function of drinking around the world over time.

Prehistory

There is no certainty as to when humans first produced alcoholic drinks. The earliest alcoholic drink may have been made from berries or honey. However, the discovery of late Stone Age beer containers dating back to 8000 BCE demonstrates that humans have been fermenting alcoholic drinks for at least 10,000 years (1). The establishment of grain farming and permanent communities in the Near East 10,000–12,000 years ago may have been prompted by the desire to brew beer—a drink which may have preceded bread as a dietary staple (2–4).

The fermentation of wine in the region seemingly occurred later. Residue in a jar found in what is now Iran, dating back to 5400–5000 BCE, indicates that it once held wine (5). A similar pattern of agriculture and sedentary settlements preceding alcohol production has been found in northern

China where residue found in jars, dating from 7000–6600 BCE, indicates that they contained a fermented drink made from rice, honey, grapes, and hawthorn berries (6).

Ancient world

Wine first appeared in Egyptian pictographs around 4000 BCE (7) and labourers building the pyramids of Giza received a daily ration of one and one-third gallons of beer. The beer provided nourishment and the estimated 5% alcohol content provided much-needed calories (5). The drink was believed to be a necessity of life invented by the god Osiris and was brewed daily in the typical home (8). At least 17 types of beer and 24 varieties of wine were produced (9) and used for pleasure, nutrition, medicine, religious ritual, remuneration, and funeral purposes (10). Drinking was both widespread and generally moderate (11).

According to oral tradition, the Hebrews began drinking wine during their captivity in Egypt. When Moses led them to Canaan (Palestine) around 1200 BCE they are reported to have regretted leaving behind the wines of Egypt (Numbers 20:5) but found that vineyards grew well in their new land (12).

By 1000 BCE, on the other side of the globe, the Mayan civilization of present-day Mexico was a mead-drinking society. Mayans also fermented a drink from corn or maize (5) and were typical in drinking alcohol. By the millennium, alcohol was being consumed around the world wherever people had settled in permanent communities (5). However, there were exceptions, as will be discussed.

In ancient China, alcohol played an important role in religion and other parts of life; ‘In ancient times people always drank when holding a memorial ceremony, offering sacrifices to gods or their ancestors, pledging resolution before going into battle, celebrating victory, before feuding and official executions, for taking an oath of allegiance, while attending the ceremonies of birth, marriage, reunions, departures, death, and festival banquets’ (13, p. 13).

A Chinese imperial edict from around 1116 BCE asserted that the moderate consumption of alcohol was a religious obligation and by the time of Marco Polo (1254–1324 CE) it was typically consumed on a daily basis by all segments of society and was a major source of revenue for the treasury (14).

Among ancient Babylonians the primary drink was beer, but wine was also important, and by 2700 BCE they worshiped a wine goddess and other wine deities (15). Babylonians regularly used both beer and wine as offerings to their gods (13). Around 1750 BCE, the Code of Hammurabi attempted to establish fair commerce in alcohol (16).

Winemaking reached the Hellenic peninsula by 2000 BCE (17) and by 1700 BCE it was commonplace in what is now Greece. Wine was offered to deities, used as a medium of exchange, as part of rituals, as a medication, to quench thirst, and to promote conviviality (18). By 700 BCE wine was central to Greek culture and identity; alcohol abstainers were considered to be lethargic and to emit an unpleasant odour (5). In some Greek states such as Athens, the consumption of wine was a civic duty. At public feasts officials ensured that everyone received an equal share of wine; from this grew the

concept of demokratia, and then democracy (5). In the fifth century BCE, Plato argued in his *Republic* that young people must learn to drink in order to promote moderation, (5) a view now supported by cross-cultural (19) and empirical research (20).

Greeks generally promoted drinking in moderation and frowned on drunkenness. Xenophon (431–351 BCE), Plato (429–347 BCE), and Cato the Elder (234–149 BCE) all promoted drinking in moderation. Exceptions to this ideal of moderation were the cult of Dionysus, for whom intoxication was believed to bring people closer to their deity (21, 22), and the symposium, a gathering of men for an evening of conversation, entertainment, and drinking, which typically ended in intoxication (18).

Following the Exile of the Hebrews in 539 BCE, wine became a common drink for everyone, including the very young. It provided a major source of nourishment, an important element in festivities, a widely used medication, an essential provision for any fortress, and an important commodity. It thus came to be an essential element in the life of the Hebrews, who had developed Judaism (22).

At about the same time in Persia (around 523 BCE), King Cyrus promoted the moderate consumption of alcohol. Nevertheless, ritual intoxication appears to have been used as an adjunct to decision-making and, at least after his death, drunkenness was not uncommon (23).

From the founding of Rome in 753 BCE until the third century bce, the Romans consumed alcohol in moderation (23). They considered wine to be of such importance to their

society that in 160 BCE the Roman Senate ordered the translation of a Carthaginian book on viticulture in order to promote its production (5).

After the Roman Empire spread throughout the Mediterranean region (509–133 BCE), the traditional Roman values of temperance, frugality, and simplicity were gradually replaced by heavy drinking, ambition, degeneracy, and corruption (18, 24). Excessive drinking in the Roman Empire was exacerbated by such practices as drinking before meals on an empty stomach, inducing vomiting to permit the consumption of more food and wine, and playing drinking games. The latter promoted the rapid consumption of large amounts of alcohol (18).

By the second and first centuries BCE, intoxication was no longer a rarity, and most prominent men of affairs were praised for their moderation in drinking. This would appear to be in response to
growing misuse of alcohol in society, as before that time temperance was not singled out for praise as exemplary behaviour. As the empire continued to decline, excessive drinking spread and some individuals, such as Marc Antony (d. 30 BCE), even took pride in their destructive drinking behaviour (23).

1–500 CE

The abuse of alcohol in the Roman Empire appears to have peaked around 50 CE (25). With the decay of the empire many displaced persons from the hinterlands descended upon Rome. To placate this deluge of immigrants, large quantities

of wine were distributed free or at cost (18). This led to occasional excesses at festivals and other celebrations and the four emperors who ruled from 37 to 69 CE were well known for their abusive drinking.

With the rise and spread of Christianity, the beliefs of Christians and the Church became increasingly important. Jesus is reported to have used wine (Matthew 15:11; Luke 7:33–35) and approved of its moderate consumption (Matthew 15:11). However, he was very critical of drunkenness (Luke 21:34, 12:42; Matthew 24:45–51). Paul the Apostle (d. 67 CE) considered wine to be a creation of God and therefore inherently good (1 Timothy 4:4) and recommended its use for medicinal purposes (1 Timothy 5:23), but condemned intoxication (1 Corinthians 3:16–17, 5:11, 6:10; Galatians 5:19–21; Romans 13:3) and recommended abstinence for those who could not control their drinking.

The doctrines and beliefs of Christianity were favourable to the production and consumption of alcohol, especially wine (21, 26). The Church taught that wine was an inherently good gift of God to be used and enjoyed. Individuals could choose not to drink, but to despise it was prohibited as heresy. The Church favoured drinking in moderation but rejected its abuse as a sin. Those who could not drink in moderation were urged to abstain in order to avoid sinning (23).

Among the Anglo-Saxons alcohol was usually consumed in a mead hall. Every settlement and village had one or more of these buildings, which were the centre of Anglo-Saxon culture. They were the houses of the rich and powerful, who

used them to maintain their wealth, fame, and power through the generous distribution of food, mead, and gifts (5).

Around 400 CE the Huns invaded much of Europe and seriously disrupted the production and consumption of alcoholic drinks for a period of time. They destroyed vineyards, killed vineyard workers, and 'drank the cellars dry' (5, p. 52). However, this did not have a long-term adverse effect.

501–1000 CE

Wine was the favourite alcoholic drink in what are now Italy, Spain, and France. However, mead, beer, and wild fruit wines became increasingly popular, especially among Celts, Anglo-Saxons, Germans, and Scandinavians (18).

Following the collapse of the Roman Empire in 476 CE and the disintegration of its society (18), monasteries became the major institution in which to maintain and advance knowledge of brewing and winemaking techniques. The art of brewing essentially became the province of monks, who carefully guarded their knowledge (10). Monks brewed virtually all beer of good quality until the twelfth century.

It is unknown when and where brewing with hops began (27). However, hopped beer was actually 'a new drink altogether, a product of the technique of precise fermentation using only barley, and in which addition of hops ensured an agreeable taste and the possibility of better conservation' (27, p. 10).

During the period 850 to 1100 CE alcohol was central to Viking culture and their heaven was conceived as a place

where they would drink endless quantities of mead. Although they preferred mead, they usually drank ale, which was also a sweet drink (5).

1001–1500 CE

In the eleventh century, an observant physician practising in Constantinople reported that drinking wine in excess caused inflammation of the liver (21).

In England the dietary staple for commoners was ale, which they considered to be a food rather than a drink. Men, women, and children all had ale for breakfast, with their dinner, and before they went to bed. A gallon a day was the typical consumption level for adults (5).

Ale was considered so vital to the existence of commoners that in 1267 King Henry III regulated its quality and price by law (5). The most popular festivities in the country were known as ‘ales’, and both ale and beer were commodities that could be given to lords in payment of rent (10).

Wine was imported and expensive in England and few commoners ever tasted it. However, it became very popular among the gentry. The resulting demand led to a dramatic viticultural expansion in the Bordeaux region of France (5).

During the twelfth century in Germany, towns were granted the privilege of brewing and selling beer locally. This led to a flourishing brewing industry in many towns, about which there was strong civic pride (10).

A major development in alcohol during the Middle Ages (about 500–1500 CE) was the discovery of distillation and the subsequent production of distilled spirits. However, there is no agreement as to exactly when or where distillation was first perfected. Authorities disagree as to whether it was in China, Greece, Italy, Arabia, or elsewhere (1). However, strong evidence suggests that it was in Arabia (28–30). What is clear is that Albertus Magnus (1193–1280) was the first person to clearly describe the process whereby distilled spirits could be produced (1).

Physicians, monks, and others slowly became interested in distilling alcohol as a medication rather than as a drink produced for enjoyment or other purposes. It was a professor of medicine, Amaldus of Villanova (d. 1315), who apparently named distilled spirits *aqua vitae* (water of life). He wrote, 'We call it [distilled liquor] aqua vitae, and this name is remarkably suitable, since it is really a water of immortality. It prolongs life, clears away ill-humors, revives the heart, and maintains youth' (31, p. 172). During the fifteenth century a German physician identified over two dozen conditions that he claimed distilled spirits benefitted or cured (31).

The consumption of spirits as a drink rather than as an assumed elixir began to occur by the end of the Middle Ages (30). Being a distilled spirit, brandy was first known as *aqua vitae*. The more specific name of brandy was derived from the Dutch term *brandewijn*, meaning cooked or burnt (distilled) wine (32). The Dutch were also the first to flavour distilled spirits with juniper berries. The first distilled spirit to be made from beer was produced in Sweden, where mention of it dates back to 1469 (21).

The consumption of alcohol appears to have been high. For example, beer consumption in Bavaria was probably about 300 litres per capita a year (compared to about 150 litres today) and in Florence wine consumption was about ten barrels per capita a year (23). Over time, the use of alcohol became ubiquitous. It was brewed in the home, consumed with meals, and served to children. It was used in religious services and intoxication was considered natural and blameless (5).

During this period of time the popularity of beer spread to England, France, and Scotland (23). By 1493, the brewers of London established their own guild (5) and the adulteration of beer or wine became a crime punishable by death in Scotland (10).

Beginning in 1492, the Spanish found diverse drinking cultures in the Americas. Mesoamerican civilizations were very ingenious in identifying potential sources of alcohol; ‘They fermented cacti and their fruits, maize and its stalks, the sap of a good two-dozen species of agave, honey, sasparilla,
the seed pods of the mesquite tree, hog plums, and the fruit and bark of various other trees’. The Spanish noted that ‘no tribe has been found which is content to drink only water’ (5, pp. 95–6).

However, ‘The introduction of large quantities of alcohol into a volatile environment of colonial domination disrupted traditional indigenous social structures, even in areas with long-standing traditions of alcohol use’ (2, p. 51). Although many forms of native alcoholic drinks became less popular

after the Spanish conquest, pulque, the fermented juice of the maguey plant, grew in popularity (5).

1501 CE–present

The first official census of England, conducted in 1577, reported the existence of 14,202 alehouses, 1,631 inns, and 329 taverns. This equalled a pub for every 187 persons, and excluded other outlets such as tippling houses and street vendors (5).

In 1620, the Puritans brought more beer than water on the *Mayflower* and they landed at Plymouth rather than continuing their journey because their provision of beer was running low (33). Subsequently, brewing beer became one of the earliest industries in colonial North America (2).

Except for several tribes in the Southwest, Native Americans did not have alcoholic drinks before their introduction by Europeans in the 1600s. The Apache and Zuni consumed alcoholic drinks which they produced for secular consumption, while the Pima and Papago produced alcohol for religious ceremonial consumption. Although Papago consumption was heavy, it was limited to a single peaceable annual ceremony and the drinking among other groups was also infrequent and not associated with any drinking problems (34). Similarly, 'Alcohol was virtually unknown in Australia until Europeans began arriving in the late eighteenth century' (35, p. 212).

During the first century and a half (1620–1775) of the North American Colonies that became the United States, alcohol

was widely and heavily used. Alcohol was viewed positively, while its abuse was condemned. The Catholic Church taught that alcohol was a gift of God and created to be used in moderation for pleasure, enjoyment, and health; drunkenness was viewed as a sin (23). In 1673, the leading Puritan minister, Increase Mather, asserted that 'Drink is in itself a creature of God, and to be received with thankfulness' (36, p. 10). This was consistent with the teachings of earlier protestant religious leaders such as Martin Luther (1483–1564) and John Calvin (1509–1564). On the other hand, Islam taught that the consumption of alcohol, in any amount, was unacceptable; 'And besides, wine would be available in heaven' (5, p. 67).

To reduce the death rate, the governor of Virginia advertised in 1609 for two brewers (5) and colonial Connecticut required each town to ensure that a place could be made available for the purchase of beer and ale (37).

Taverns were central to colonial life and were often legally required to be located near schools and churches. Religious services and court sessions were often held in taverns and they also served as venues for plays, political debates, lodge meetings, and socializing (38).

Sparkling wine or generic champagne first occurred in England when wine from the Champagne region was stored in cellars over the winter and underwent a secondary fermentation. It was called 'brisk champagne' and appeared in the English language in 1664. However, the French considered bubbles in wine to be sacrilege (5). Contrary to common myth, Dom Pérignon, the wine master in a French abbey, did not invent champagne. He did, however, improve

the process by using appropriately strong bottles, invented a more efficient corking system, and began the practice of blending the contents (39).

Whiskey, the first grain spirit, is believed to have first been distilled in Ireland. While its specific origins are unknown (40) there is evidence that by the sixteenth century it was widely consumed in
some parts of Scotland (31). It was also during the same century that Franciscus Sylvius (or Franz de la Boe), a professor of medicine at the University of Leyden, distilled spirits from grain (31).

The production and distribution of spirits spread slowly. Spirit drinking was still largely for medicinal purposes throughout most of the sixteenth century. It has been said of distilled alcohol that 'the sixteenth century created it; the seventeenth century consolidated it; the eighteenth popularized it' (30, p. 170).

The increase in distilling was promoted in part by the expansion of sugar production in the Caribbean, which provided molasses for the production of rum (2). The first mention of this drink was made in a 1651 description of Barbados (5).

The cost of rum dropped after the North American colonists began importing molasses and cane sugar directly and distilled their own. By 1657, a rum distillery was operating in Boston and within a generation the production of rum became colonial New England's largest and most prosperous industry (31). In addition, almost every important town from Massachusetts to the Carolinas had a rum distillery to meet

the local demand, which had increased dramatically (36). In the 'Triangle Trade', rum was traded for African slaves, who were then traded to the West Indians for more molasses to be made into more rum (41).

In 1690, England passed legislation to promote distilling, and within four years the annual production of distilled spirits, most of which was gin, reached nearly one million gallons (31). This resulted in the so-called 'Gin Epidemic'. 'While the negative effects of that phenomenon may have been exaggerated' (21, p. 21, 27), Parliament passed legislation in 1736 to discourage consumption by prohibiting the sale of gin in quantities of less than two gallons and raising the tax on it dramatically (39). However, consumption continued to rise and the peak was reached seven years later, when the nation of 6.5 million people drank over 18 million gallons of gin. Most of this was consumed by the small minority of the population then living in London and other cities; people in the countryside largely remained loyal to beer, ale, and cider (39, 42).

There was a general recognition in most of the world of the positive nature of moderate consumption of alcohol combined with a concern about the negative effects of drunkenness. Nevertheless, the consumption of alcohol was sometimes high. During the 1500s, alcohol consumption reached 100 litres per person per year in Valladolid, Spain, and Polish peasants consumed up to three litres of beer per day (30). In Denmark, the usual consumption of beer appears to have been a gallon per day for adult labourers (23). The average amount of beer and ale consumed in Coventry, England, was about 17 pints per person per week, compared to about three pints

today (43); Swedish beer consumption may have been 40 times higher than in modern Sweden (23).

Before the early 1700s the supply of alcoholic drinks in Europe was generally lower than the demand. However, the agricultural revolution produced so much grain and fruit that the supply of alcohol met the high demand. Workers and peasants were then able to drink at the same levels as the affluent, a situation later described by the French government as the democratization of alcohol (44).

In 1830, the inhabitants of Great Britain consumed daily nearly four ounces of pure alcohol per capita. Consumption peaked in the 1870s and then began a downward trend. The comparable figure for Sweden was just below two ounces. By the end of the 1800s, consumption in Britain, Ireland, and Denmark had fallen to about one ounce per day per capita (44).

Some historians attribute this decline in alcohol consumption to the increasing caloric content provided by other foods such as bacon, sugar, and butter (44). However, there were clearly many other factors operating, a major one being the spreading temperance movement.

Vineyards were established in Australia by the first fleet of convicts to arrive in New South Wales in 1788. By 1795, alcohol had become a medium of exchange there (5).

Absinthe was invented in Switzerland and introduced into France in 1805. In subsequent decades it became especially popular there and in the French colonies (21).

As industrialization progressed, drunkenness became seen as inconsistent with the need for a reliable and punctual workforce and labour efficiency. Problems commonly associated with industrialization and rapid urbanization were also attributed to alcohol. Thus, issues such as urban crime, poverty, and high infant mortality rates were blamed on alcohol, although 'it is likely that gross overcrowding and unemployment had much to do with these problems' (21, p. 21).

During the second half of the 1800s, many Protestant Churches began to reject traditional Christian beliefs about alcohol and started to teach that the substance of alcohol was evil and that drinking it was a sin. However, this new doctrine created a dilemma because the Bible reports that Jesus both made and drank wine. To address this predicament, theologians developed the 'two-wine' theory. According to the new doctrine, whenever 'wine' was used by Jesus or praised as a gift of God, it was really grape juice; only when it caused drunkenness or other problems was it wine. Thus, they came to interpret the Bible as asserting that grape juice is good but that alcohol is bad and that drinking it, even in moderation, is a sin (45, 46). Thus, the 'good gift of God' became 'Demon Rum'.

Over time, more and more personal, economic, criminal, family, social, moral, and religious problems were attributed to alcohol. This led to the rise of temperance groups, which were first established in the United States in 1808, in England in 1817, in Sweden in 1818, in Ireland in the 1820s, in New Zealand in 1836, in Sri Lanka in 1898, and in dozens of other countries around the globe (19, 37).

Groups typically began by promoting voluntary temperance or the moderate use of alcohol. They then sometimes called for mandatory temperance. But virtually all would soon come to demand mandatory and legally enforced prohibition. They insisted that the total prohibition of the production, distribution, sale, and consumption of all alcoholic drinks would eliminate most, if not all, poverty, crime, violence, immorality, marital conflict, and other personal and societal problems (19, 45).

Strong temperance movements resulted in the establishment of prohibition of alcohol in Russia (1916–1917), Hungary (21 March–1 August 1919), Norway (1919–1927), Finland (1919–1932), Iceland (1919–1932), the United States (1920–1933), Canada (provinces implemented and abolished prohibition independently over time), and many other countries around the world. Unfortunately, countries discovered that implementing alcohol prohibition did not eliminate social problems but would compound the situation by creating additional, unanticipated, but very serious problems (19, 37).

In 1935, Alcohol Anonymous was organized to address alcoholism and has since spread to about 190 countries around the world (46). The year 1973 saw the identification of what is now known as fetal alcohol syndrome or FAS (47). In 1980, Mothers Against Drunk Driving (MADD) was established to reduce alcohol-impaired driving and quickly raised consciousness about the severity and unacceptability of the crime.

In addition to concerns about the negative effects of inappropriate alcohol consumption, there was increasing

evidence, beginning in the 1970s, that, unless contraindicated, the moderate consumption of alcohol (beer and other malt drinks, wine, and distilled spirits) is associated with better health and greater longevity than is either abstaining or abusing alcohol (48–50).

Over the last three decades there have been increasing calls for further restrictions on the availability and consumption of alcohol. These include tax increases; higher minimum legal drinking ages; lower legal blood alcohol concentration levels for operating motor vehicles and other equipment; promotion of abstinence from drinking; more vigorous enforcement of alcohol laws; more
severe punishment for alcohol law violators; stronger server (commercial and social) liability laws; stronger warning labels on alcoholic drink containers; increased restrictions on alcohol advertising and promotion; and the stigmatization of alcohol and marginalization of those who consume alcohol, even when doing so in moderation (19, 45).

What additional measures this most recent movement will propose in its effort to reduce alcohol abuse cannot be known at this time.

Summary

Alcoholic drinks have been produced and consumed by humans for thousands of years and have played an important role in religion; supplying nutrition and energy; providing medicinal, antiseptic, and analgesic benefits; quenching thirst; facilitating relaxation; promoting conviviality and social cohesion; increasing the pleasure of eating; providing

pharmacological pleasure; and generally enhancing the quality and pleasures of life.

The function(s) in society that alcoholic drinks should have, if any, have often been highly controversial and the subject of great debate. Illustrative of this was the establishment and later retraction of nationwide prohibitions of alcohol in many countries over the past century. Still today, there exists a conflict of views as to whether alcohol is an attractive elixir or a dangerous poison.

The current debate about alcohol can often be found in the spheres of politics, public policy, religion, morality, popular culture, law, medicine, and public health.

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Chapter 2
Key studies of alcohol and disease

Jürgen Rehm and Kevin D. Shield

Introduction

Alcohol has been consumed by humans for at least several thousand years, and possibly for over 10,000 years (see Chapter 1, 'Historical evolution of alcohol consumption in society') (1). For many centuries, alcohol's relationship to disease, both as a risk factor and as a remedy, has been recognized. For example, medicinal tinctures based on alcohol have been used in China since the Han dynasty (2). This chapter attempts to summarize the highlights of alcohol epidemiology, starting with classic overview studies and then proceeding to a description of key studies on the relationship between alcohol consumption and specific disease categories. Finally, the most impactful studies of the last 15 years on the relationship between alcohol consumption and different disease outcomes will be outlined.

Classic studies on the impact of alcohol consumption on morbidity and/or mortality

In 1785 (originally published in a newspaper in 1784), in his overview of the health consequences of the chronic use of 'ardent spirits' (3), Benjamin Rush listed the following disease categories as being caused by long-term heavy alcohol use: gastrointestinal problems; liver disease, including jaundice; infectious diseases such as tuberculosis

('consumption' was the term used at the time) and pneumonia; diabetes; epilepsy; gout; and mental health problems.

Based on current evidence of the causal impact of alcohol consumption on disease (4), Rush's conclusions show great insight. Most of his hypotheses on the causal impact of heavy drinking or alcohol dependence on disease still hold true today, with some of these links having been only recently re-established (e.g. the link between heavy drinking and infectious diseases such as tuberculosis (5, 6) and pneumonia (7); see Chapter 37, 'Infectious disease'). What is also very advanced is Rush's emphasis on the relative positive impact of moderate drinking of low-alcohol content drinks compared to chronic heavy drinking or drinking to intoxication (2).

Another milestone with respect to alcohol epidemiology was Sir William Osler's *Principles and Practice of Medicine* (8). Once more, Osler's textbook is replete with causal relations between drinking and different diseases, including the reiterated link between heavy drinking and tuberculosis. These causal relations consist of alcohol as a risk factor for disease as well as the use of alcohol in treatment, for example, the light consumption of wine after acute myocardial infarctions. Osler's textbook also constitutes a breakthrough in characterizing alcoholism (or in modern terms, alcohol use disorders) as a disease, differentiating between acute intoxication and chronic alcoholism. After describing the disease of alcoholism he notes that 'Chronic alcoholism is a condition very difficult to treat, and once fully established the habit is rarely abandoned. The most obstinate cases are those with marked hereditary tendency' (8, p. 1004).

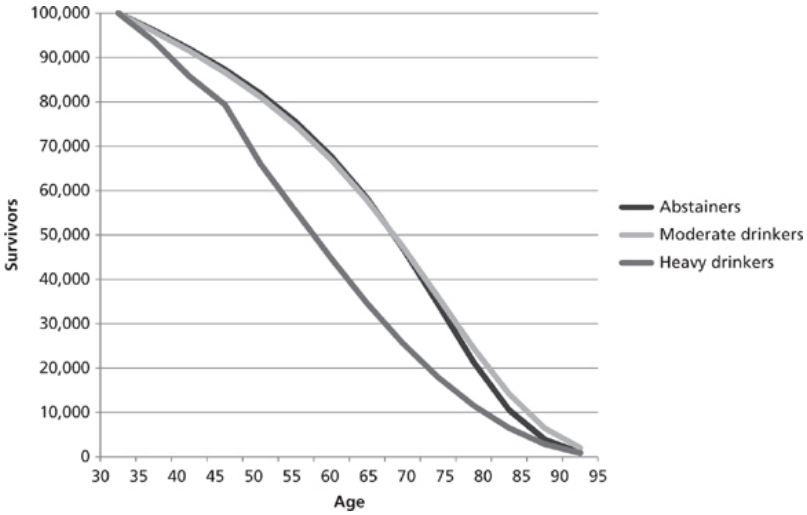

Figure 2.1 Survival curves for men based on drinking status.

Data from Pearl R, *Alcohol and longevity*, Knopf, New York, NY, Copyright © 1926.

Another highly influential text in alcohol epidemiology is *Alcohol and longevity* by Pearl (9). Not only did he discover the J-shaped curve relationship between the average volume of alcohol consumption and all-cause mortality (Figure 2.1), but he also highlighted the importance of drinking patterns within the same average volume of drinking, e.g. the detrimental impact of heavy drinking occasions in overall moderate level drinkers (see (10), for a contemporary overview on the effects of irregular heavy drinking sessions in overall moderate level drinkers).

Pearl observed that men aged 60 years or older who were moderate drinkers had a decreased risk of mortality when

compared to abstainers. Men aged 30 years or older who were heavy drinkers had an increased risk of mortality when compared to both abstainers and moderate drinkers.

Alcohol consumption and cardiovascular diseases

While the studies reported so far have focused on the overall relationship between alcohol and morbidity/mortality, the following is an overview of the various relationships between alcohol consumption and specific disease categories, starting with the relationship between alcohol consumption and the cardiovascular system (see the summary in (11)). A number of studies in the nineteenth and early twentieth-century pointed out both the detrimental effects of heavy drinking on various cardiovascular disease categories and the cardioprotective benefits:

♦ Alcoholic cardiomyopathy was one of the first diseases clearly associated with heavy drinking in various studies (11). Bollinger, a pathologist working in Munich, described the *Münchner Bierherz* (Munich beer-heart), characterized by cardiac dilatation and hypertrophy, and caused by high levels of beer consumption in Bavaria (12).

♦ The relationship between high levels of alcohol consumption and hypertension was first described in French soldiers during World War I (13).

♦ Black's (14) observation, in 1819, that angina pectoris is more prevalent in Ireland than in France, together with the explanation from a French colleague that this could be attributed to the French lifestyle factor of wine consumption,

has been cited as the first mention of the 'French paradox'. More than one and a half centuries later, St. Leger and colleagues (15) examined potential influencing factors for ischaemic heart disease mortality in an ecological study and concluded that neither wealth nor health systems' variables, such as the relative number of medical doctors or nurses, but rather consumption of alcohol, especially wine, had the largest association with the rate of ischaemic heart disease, indicating a potential cardioprotective effect of alcohol consumption.

These examples should suffice as indicators that the impact of different styles of drinking on various organs of the cardiovascular system has been discussed for a long time. Of course, not all hypotheses of the nineteenth and twentieth centuries have been as accurate in their predictions as the earlier-noted references; in fact there was quite a lot of speculation on the role of alcohol at that time which turned out to be unsubstantiated. For example, one of the first publications on the relationship between alcohol consumption and arteriosclerosis (16) was written to disprove a large association between alcoholism and the arteriosclerotic process in middle-aged adults. The author showed that there were a large number of abstainers among patients, and those who died prematurely under the age of 50, who had arteriosclerosis. These results correspond to the current knowledge that regular consumption of alcohol prevents coronary heart disease up to high levels of alcohol consumption (17, 18).

As shown by the studies presented in this chapter, it has long been recognized that alcohol consumption is causally linked to various cardiovascular disease categories. Moreover, it has

been clear for some time that the impact of alcohol on cardiovascular health outcomes could be protective or detrimental, depending on consumption patterns (see (19, 20) for overviews and Chapter 30, 'Cardiac disease' and Chapter 31, 'Vascular disease'). Of course, we have a better understanding now of the specific conditions and the biochemical processes underlying these relationships (18, 20) than several decades ago. However, the broad picture has been known for some time.

Alcohol consumption and cancer

As early as 1910, Lamy observed that approximately eight out of ten patients with cancer of the oesophagus and the cardiac region of the stomach were alcoholics (21); for many of these patients absinthe was the alcoholic drink of choice. This observation was followed by ecological studies which found higher risks of head and neck cancers in people whose professions were associated with the production and distribution of alcohol, while groups of people who abstained for religious reasons had markedly lower risks of these forms of cancer (22).

These observations were later confirmed in standard epidemiological studies using either case–control or cohort designs. The International Agency for Research on Cancer (IARC) conducted a thorough review, not only of epidemiological studies but also of relevant basic research on mechanisms, and concluded that there was sufficient evidence of the carcinogenicity of alcoholic drinks in humans. The occurrence of malignant tumours of the oral cavity, pharynx,

larynx, oesophagus, and liver was found to be causally related to the consumption of alcoholic drinks (22).

In a more recent evaluation conducted by IARC (23), female breast and colorectal cancers were added to the list of cancers causally impacted by the consumption of alcoholic drinks. Moreover,
ethanol was identified as a carcinogenic ingredient of alcoholic drinks, and the creation of acetaldehyde from the oxidation of ethanol was identified as one of the major pathways which increased the risk of cancer (see also the various chapters on bases and epidemiological research for different categories of cancer in the IARC volume).

The epidemiological study with the most impact on the inclusion of colorectal cancer was most likely the European Prospective Investigation into Cancer and Nutrition (EPIC) (24, 25), with the basic studies supporting the results of human epidemiological studies also being of importance. Since for breast cancer the risk per drink is rather small, the meta-analyses and the collaborative epidemiological study by Hamajima et al. (26), which combined results from more than 50 studies, were influential and provided evidence for a stable link between level of alcohol consumption and risk of breast cancer.

Alcohol consumption and injury

Injury is often overlooked as a consequence of alcohol consumption, presumably as the adverse effects of drinking alcohol on decision-making and psychomotor abilities is self-evident (27). Moreover, for many injury outcomes the

causality has long been questioned. For example, in the 1950s, the causal role of alcohol consumption in traffic injury was not as evident as it is now. First, it was argued that after moderate levels of consumption people could still drive, and possibly even better, as they paid more attention to traffic conditions since they were aware of their consumption and the potential adverse effects. Second, while many traffic accidents involved alcohol consumption, it was argued that this was not a causal effect, at least not at lower levels of blood alcohol concentration, but merely reflected the fact that many people were driving cars with alcohol in their blood. Finally, it was argued that only people with a disposition for riskiness would cause alcohol-related injury, as such a disposition would cause both the alcohol consumption and the situation which led to the injury.

A seminal study of Borkenstein (28, 29), conducted between 1962 and 1964, provided crucial evidence to rebut most of these arguments. Borkenstein and his team collected accident data from locations in Grand Rapids, Michigan—areas with high frequencies of road traffic accidents, including information concerning the exact place, time of the day, whether it was a weekday, and in which month. At the time of the highest probability for injury, more than 7,000 random controls were assessed for their blood alcohol concentration. From almost every accident in the study areas (N = 5,786), data on drinking and blood alcohol concentration were collected. As a result, relative risks could be determined for involvement in traffic accidents based on blood alcohol concentration. The results showed an exponential increase (see also the analysis of Hurst et al. (30)) and thus, the higher the blood alcohol concentration, the higher the risk for traffic accident involvement. The authors concluded that any blood

alcohol concentration above 0.04% created too high a risk for traffic accidents and recommended that people with blood alcohol concentrations above this limit should not be allowed to drive.

This study impacted alcohol policy in the United States and abroad, and its results were the explicit basis for many laws regarding acceptable levels of blood alcohol concentration while operating a motor vehicle. These laws acted as interventions which led to the possibility for their evaluation using natural experiments. These natural experiments demonstrated the effectiveness of the laws in reducing traffic fatalities and also showed the reversibility of the effects of drinking which is one of the criteria for causality (31). Later evaluations have shown that alcohol fulfils all of the standard criteria for causality in traffic accidents (32).

Recent studies of special impact in alcohol epidemiology

Russia during the Gorbachev anti-alcohol campaign

Alcohol epidemiology is mainly an observational science using either case-control or cohort studies, with limitations in establishing causality (31). Designs with more control, such as the Grand Rapids Study described above, are rare. However, sometimes more control is possible by using so-called natural experiments. The Gorbachev anti-alcohol campaign was such a case. In 1985 the campaign introduced restrictions to the supply and sale of alcohol and was supplemented by a large-scale educational campaign. While unrecorded consumption increased (see Chapter 15, 'Unrecorded alcohol consumption'), this increase did not

replace the decrease in state supplies (33, 34). Annual per capita consumption of pure alcohol fell from 14.2 litres in 1984 to 10.7 litres in 1987, and then increased to 14.5 litres in 1993.

As a consequence, Leon et al. (34) observed that all-cause mortality rates in Russia of 40–44-year-olds decreased by 39% for men and by 29% for women between 1984 and 1987. Subsequently, between 1987 and 1994 all-cause mortality rates for this same age group more than doubled for men and almost doubled for women. Disease-specific rate ratios can be found in Figure 2.2.

Life expectancy increased in the three years of restricted alcohol supply by more than three years for men and by 1.3 years for women, albeit from a low life expectancy level in 1984 of 61.7 and 73.0 years, respectively. Between 1987 and 1994, life expectancy decreased by 7.3 years for men and by 3.3 years for women and by the mid 1990s was at 57.6 and 71.0 years, respectively.

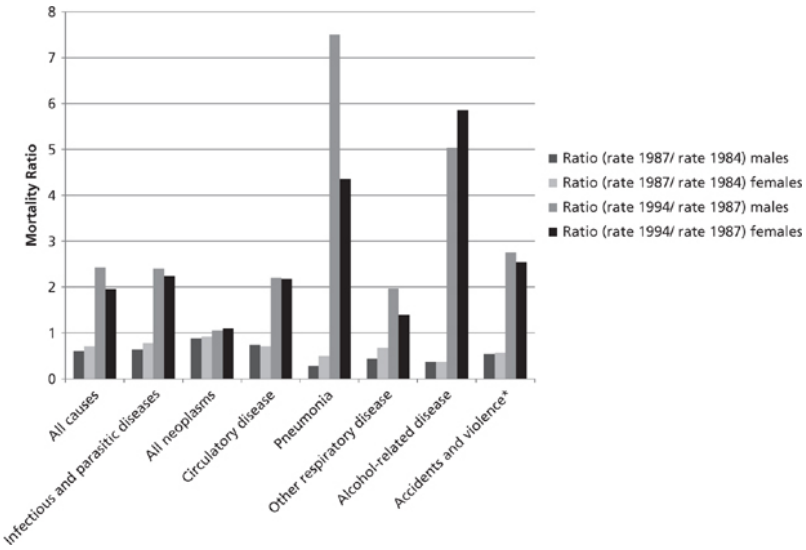

Figure 2.2 Relative changes in mortality in Russia, 1984–1994, by cause and sex for people aged 40–44 years. * Excludes accidental poisoning by alcohol.

Data from *The Lancet*, Volume **350**, Issue 9075, Leon et al., Huge variation in Russian mortality rates 1984–94: artefact, alcohol, or what?, pp. 383–388, Copyright © 1997, Elsevier. DOI: <http://dx.doi.org/10.1016/S0140–6736(97)03360–6>.

Interpretation of these figures strongly suggests a marked impact of alcohol on mortality rates and life expectancies, especially for the period 1984–1987. During this time, most other social determinants of health, most notably economic indicators, worsened, so it was not easy to find alternative explanations for the rapid improvement of mortality rates (34). On the other hand, for the upturn in mortality rates after 1987 other reasons could be found, most importantly

economic reasons, as these years of transition and dissolution of the Soviet Union into several sovereign states were characterized by various economic problems for the general population.

Why did the publication of Leon et al. have such an impact? First, it was an impressive demonstration of the impact of alcohol consumption on population health indicators, mainly mortality. Clearly, Russian drinking patterns have been markedly more detrimental to the population than was observed on a worldwide basis, both in terms of volume and frequency of heavy drinking sessions (35, 36), but the empirical demonstration of such a high impact on mortality was still surprising.

Second, the unique situation of a rapid change in alcohol consumption at the population level without other changes for the years 1984–1987 created an opportunity to study the effects of drinking at the population level with relatively more control as compared to the usual ecological studies. Also, several additional indicators (e.g. highest relative change in the mortality of alcohol-related diseases and almost no change in cancer mortality, which is compatible with the biology for cancer where changes in exposure lead to changes in incidence or the mortality rate only decades later (37)) support the interpretation of alcohol as an underlying main cause of the changes in Russian mortality data.

Third, the observed changes in Russia served as a powerful demonstration of the complex relationship between alcohol consumption and cardiovascular mortality. Clearly, in a country like Russia, the overall effect of alcohol consumption on cardiovascular death is negative as the prevailing drinking

patterns of frequent but irregular heavy drinking sessions are not associated with cardio-protection or with a beneficial impact on ischaemic stroke (for a newer, individual-level study see (38) and also see Chapter 14, 'Impact of extreme drinking on mortality').

Finally, the Russian example underlined the importance of alcohol policy. It showed that the alcohol-attributable burden of disease could be reversed and that a large proportion of this burden could be reversed quickly (39, 40).

The Comparative Risk Assessments within the Global Burden of Disease Studies

The Comparative Risk Assessments (CRAs) within the Global Burden of Disease (GBD) studies of 2000 and 2005 were established to quantitatively compare the contribution to global mortality and burden of disease of a set of selective risk factors (41). Risk factors were selected based on the following criteria:

♦ Likelihood to be among the leading causes of the disease burden globally or regionally.

♦ Specificity; i.e. not too specific such as, for example, every one of the hundreds of air pollutants or specific foods, nor too broad, such as the environment or diet taken as a single exposure.

♦ The likelihood of causality between the risk factor and the outcome had to be high based on collective scientific knowledge.

♦ Available data on the relationship and risk had to be calculated from continuous data or from numerous levels of exposure.

♦ The risk factors had to be potentially modifiable.

Alcohol consumption was selected as one of more than 20 risk factors for the CRAs of the GBD 2000 study (32, 42), and the ongoing GBD 2005 study. In addition, alcohol consumption was one of the factors considered in the GBD 2004 interim analyses on global health risks (43).

The CRA results showed that alcohol was one of the major risk factors for the global burden of disease. As shown in Figure 2.3, alcohol consumption proved to be one of the most important risk factors for the global burden of disease overall, and the most important one for middle-income countries. Even though it was known that alcohol was a major risk factor, its associated level of burden of disease and its rank among all risk factors as more detrimental to global burden of disease than high blood pressure, high glucose, high cholesterol, or tobacco smoking were surprising.

Alcohol consumption has been causally linked to many disease categories. More than 30 ICD-10 (International Classification of Diseases, tenth revision) three-digit or four-digit disease codes include alcohol or alcoholic in their name or definition, indicating that alcohol consumption is a necessary cause of these diseases (e.g. alcohol dependence, alcoholic liver cirrhosis, alcohol-induced chronic pancreatitis). Furthermore, more than 200 ICD-10 three-digit disease codes exist in which alcohol is a component cause (4). This resulted in alcohol consumption being a cause for more

than 25 GBD disease and injury categories; GBD categories are wider than ICD codes (see (4, 44) for a discussion of causality and an overview of meta-analyses to quantify the risk relations to the GBD disease and injury categories).

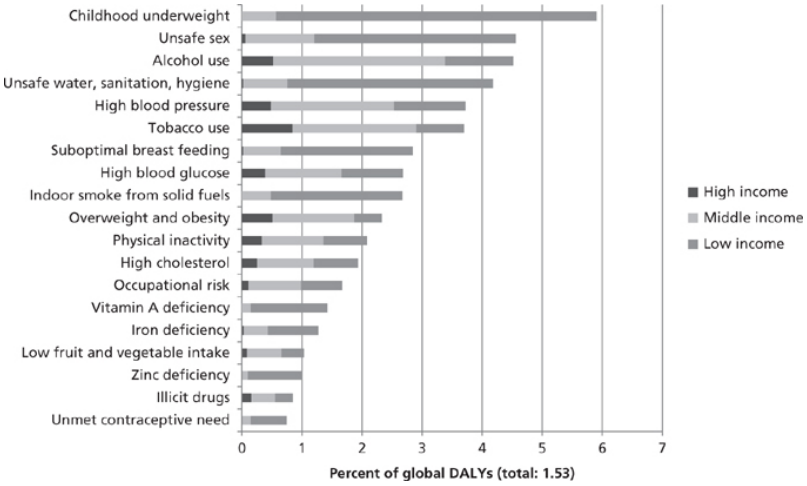

Figure 2.3 Global burden of disease attributable to selected risk factors in 2004.

Reproduced with permission from *Global Health Risks: Mortality and burden of disease attributable to selected major risks*, pp. 10, Copyright © 2009, World Health Organization, available from <http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf>.

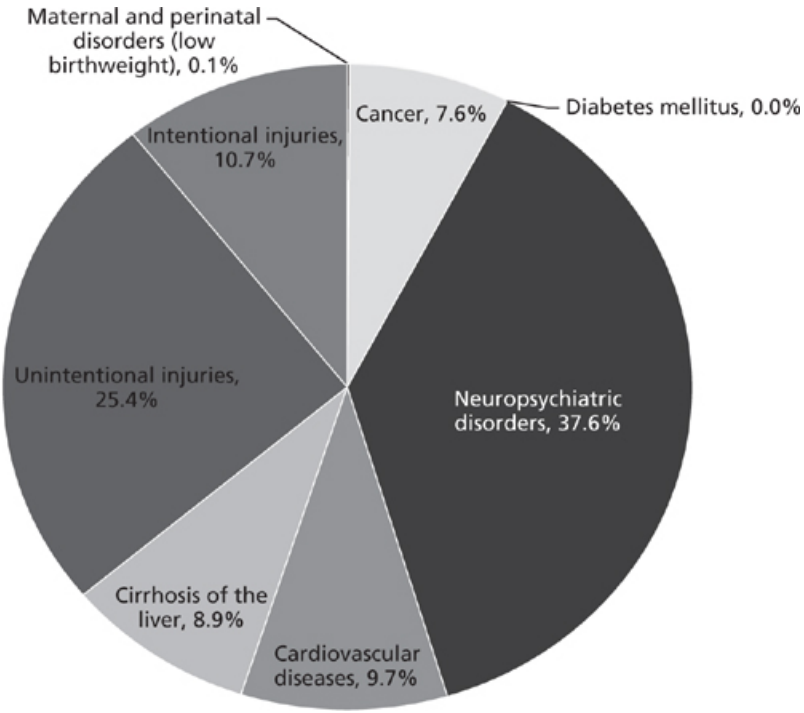

Figure 2.4 Disability adjusted life years (DALYs) attributable to alcohol consumption for men, globally, in 2004 by cause.

Data from *The Lancet*, Volume **373**, Issue 9682, Jürgen Rehm et al., Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders, pp. 2223–2233, Copyright © 2009, Elsevier. DOI: <http://dx.doi.org/10.1016/S0140–6736 (09)60746–7>.

See Rehm et al. (45) and Figures 2.4 and 2.5 for an outline of the magnitude and components of the alcohol-attributable burden of disease.

The CRA was important as for the first time the impact of alcohol consumption of the full spectrum of diseases was made clear (although infectious diseases were excluded as the causal impact and quantification of alcohol consumption could not be established at the time). As indicated, the result was surprising to many: as alcohol consumption impacts on so many different disease categories with comparable small population-attributable fractions, the overall effect had been underestimated. The CRA study also showed that middle-income countries comparatively experience the largest amount of alcohol-attributable harms.

Thus, the CRA was an influential factor in the World Health Organization initiating policy activities since the year 2000, culminating in the Global Strategy (46) adopted by the World Health Assembly in 2010. Unsurprisingly, given the epidemiological results of the CRA, a lot of support came from middle-income countries such as Thailand.

Alcohol consumption also played a major role in the recent activities to lower the burden of non-communicable diseases (NCDs) by the World Health Organization and the United Nations, as alcohol has been identified as one of the four major risk factors for NCDs (along with tobacco smoking, lack of physical activity, and diet; see (47) and (48) and for background see (49)).

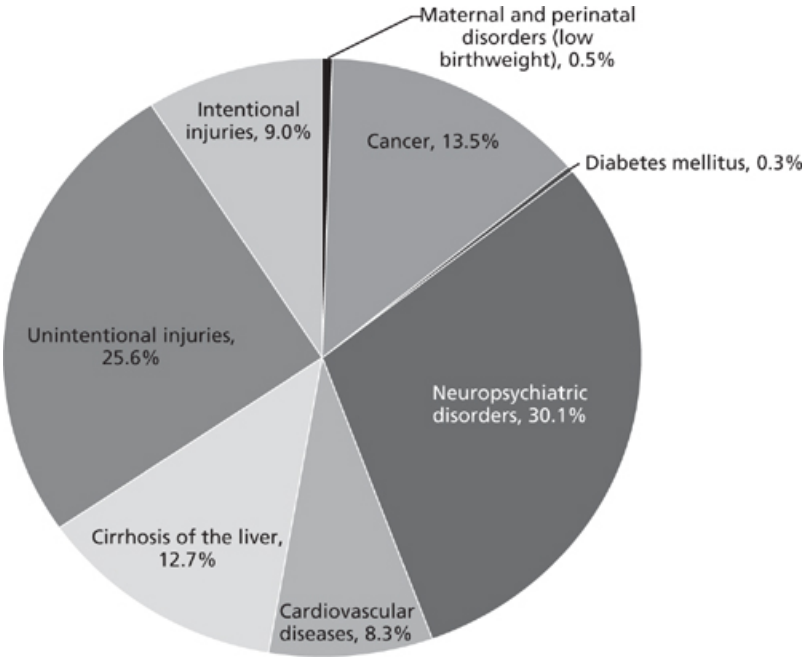

Figure 2.5 DALYs attributable to alcohol consumption for women, globally, in 2004 by cause.

Data from *The Lancet*, Volume **373**, Issue 9682, Jürgen Rehm et al., Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders, pp. 2223–2233, Copyright © 2009, Elsevier. DOI: <http://dx.doi.org/10.1016/S0140–6736(09)60746–7>.

The effects of alcohol consumption are much better recognized now than 30 years ago and if the alcohol policy interventions started by the World Health Organization are successful, alcoholic drinks will continue to be consumed well into the future, albeit in a more healthy way with less associated disease and injury.

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Chapter 3
Cultural aspects: representations of alcohol use in visual art

James Harris

[Bacchus] discovered the juice of the grape and introduced it to mankind, stilling thereby each grief that mortals suffer from … and sleep that brings forgetfulness of daily ills, … 'twas he that gave the vine to man, sorrow's antidote.

Euripides, 407 BCE, *The Bacchae* (1, pp. 7–8).

Gin cursed Fiend, with Fury fraught/Makes human race a Prey.
It enters by a deadly Draught/And steals our Life away.

The Reverend James Townley, Hogarth's *Gin Lane*, 1751 (2, p. 147).

Alcohol in art, literature, and film

Over the centuries, artists, writers, and film-makers have illustrated the effects of alcohol on humanity. They show us that the mythological Bacchus' gift of wine to humankind has proved to be a mixed blessing. When used in moderation, artists and writers have celebrated its use since antiquity as a means to elicit cheerfulness, a way to relieve weariness and grief, and as a comfort for our sorrows. Conversely, excessive use and abuse of alcohol has been reviled and its destructive effects on the individual and society illustrated in the arts.

Because of the severity of its detrimental effects, historically, alcohol use has been legally regulated with varying degrees of success. The most comprehensive way to regulate it was through Prohibition, the Eighteenth Amendment to the United States Constitution, 'The Noble Experiment'. During the 13 years Prohibition was in effect it proved to be unenforceable; its most unfortunate consequence was an increase in crime. The impact of Prohibition on society has been dramatically shown in award-winning films.

Chapters 3–5 highlight the effects of alcohol and show how the viewer, the reader, and the audience observe the impact of alcohol use and abuse collectively and on individual lives. These chapters provide visual representations of alcohol use by painters and print makers, in literary descriptions, reflections on alcohol use in poems, plays, and narratives, and dramatizations of alcohol's effects in the movies. Although it is sometimes claimed that creativity is enhanced by alcohol use, this claim is rarely supported; far more commonly alcohol use has destructive effects on the creative impulse and creative process.

Representations of alcohol use in visual art

Representations of alcohol use have long been the subject of works of art that range from Diego Velázquez's painting of Bacchus offering the gift of wine to mankind as a deliverance from sorrow (epigraph, Euripides) (3) through to Franz Hals' depiction of the merry drinker and Peder Kroyer's artists' party toast. All of these paintings present positive effects of alcohol use. Conversely, Vincent van Gogh depicts the solitary and lonely absinthe drinker and, more tragically,

William Hogarth illustrates the ravages that alcohol abuse brought to London in *Gin Lane* (epigraph, Townley). Other artists, like Maurice Utrillo (4) and Jackson Pollack, were alcoholics themselves; Utrillo traded his drawings and paintings for drink.

Accounts of the lives of artists have raised questions about the relationship between alcohol use and creativity; does alcohol use facilitate or hinder artistic creativity or is it linked to creativity at all (5)? Indeed, does the act of creative expression result in increased use of alcohol by artists? Alcohol abuse contributed to Franz Hals' death. Yet despite his excessive drinking, many would say he never lost his skill, cunning, or an eye for his subject. For Jackson Pollack his most creative time was when he was abstinent; ultimately Pollack could not control his drinking and died in an alcohol-related car crash. Utrillo, after several hospitalizations for alcohol abuse, was threatened with lifelong inpatient psychiatric commitment but opted instead for what amounted to outpatient commitment under the supervision of his mother and then his wife. Vincent van Gogh abused alcohol, particularly along with absinthe. When his brother complained of his substance use Vincent replied in writing, 'to attain the high yellow note that I attained last summer, I had to be pretty well keyed up' (6). He remained creative until his suicide, despite his abuse of alcohol.

One study (5) retrospectively examined the issue of creativity and alcohol use in the biographies of 34 famous, heavy-drinking, twentieth-century writers, artists, and composers/performers. Alcohol use was found to be detrimental to productivity in over 75% of the sample, especially in their later years. Few claimed direct and/or

indirect benefits. Some reported drinking to relieve tension before starting their work but stopped drinking as they became fully engaged in their creative endeavour. Several, with diagnoses of bipolar disorder, specifically reported self-medication with alcohol to regulate their emotional state. Over half viewed their drinking as not being related to their creativity. Some reported that their level of alcohol use was reduced after prolonged periods of creative activity. The pattern of alcohol use varied with each individual but, overall, excessive use was clearly detrimental. Thus the association of alcohol use with creativity is largely a myth.

Artists have long illustrated various aspects of alcohol use and abuse in their paintings. Hals' *Merry Drinker* (1628–1630) is a positive portrayal. His drinker is well dressed with his hat elegantly tilted, raising his glass to salute the viewer. This painting demonstrates the jaunty style that made Hals famous. Kroyer's *Hip Hip Hurrah!* (1888) artist party shows men and women celebrating one another with a toast of alcohol. Conversely, Vincent van Gogh's self-portrait, entitled *Glass of Absinthe* (1887), focuses on the solitary drinker, sitting alone in the corner of a café. The chair opposite him is empty; passing pedestrians turn their backs to him. The viewer feels his sense of abandonment. His isolation is accentuated by window bars that separate him from passers-by.

Velázquez's painting, *The Triumph of Bacchus* (1629) (7), and Hogarth's print, *Gin Lane* (1751) (2), respectfully illustrate the comradery and relief from distress that alcohol can provide on the one hand, and its detrimental effects on the individual and on social order on the other. Velázquez

illustrates the comradery that comes with Bacchus' gift of wine to humankind.

Bacchus (Dionysus in Greek mythology) was the love child of Jupiter and the mortal Semele, daughter of the king of Thebes. He was raised in Velázquez's native land of Spain away from Juno's vengeance for her husband's infidelity. Raised by women and attractive to them, Bacchus was seduced by a king's wife who offered her favours on the condition that Bacchus give her the gift of wine as a special gift for her husband. Cunningly, she believed that drinking wine would ease her husband's anger and make him forget her betrayal. Thus wine, in this tale, was bestowed on humanity to satisfy a queen's lust (8). Later, Bacchus is said to have offered grape plants to a poor but noble farmer whom he befriended. The farmer thrived until his neighbours got drunk on his wine. Thinking themselves poisoned they killed him (8), illustrating that the bestowal of wine to humanity was a mixed blessing. Bacchus' (Dionysus') revels with wine are a basis for both the Greek comedies and tragedies. Two annual theatrical festivals, the Lenaia and the Dionysia, were held in Athens in Ancient Greece each year in his honour.

Velázquez was a royal portrait painter and completed *The Triumph of Bacchus* (Figure 3.1) for his patron King Philip IV of Spain (7); it is his most popular work on a mythological theme.

Velázquez shows Bacchus cavorting with ordinary people and brightening their lives. Bacchus, wearing a tunic and crowned with vine leaves, has a pale complexion distinct from that of the ruddy peasants who surround him. His companion resting behind him holds up a crystal glass of white wine. The jolly,

clever rogues who surround Bacchus are of various ages and occupations. A beggar looks on and, apparently seeking a drink, doffs his hat to draw attention to himself. Bacchus, seemingly absentmindedly, crowns a soldier, who kneels before him with a garland. In *The Triumph of Bacchus* Velázquez presents the viewer with a charming drinking scene.

Unlike Velázquez, English artist William Hogarth's (1697–1764) aim in illustrating alcohol use is not to entertain but to instruct. *Gin Lane* (Figure 3.2) and Beer Street are prints from engravings issued in 1751. In these images Hogarth moves away from illustrating laughable human foibles, instead focusing on the serious contemporary issues of poverty and crime. Viewed alongside one another the prints contrast the despair of gin drinkers with the seeming prosperity of beer drinkers. Unlike the hopelessness depicted in *Gin Lane*, people living on *Beer Street* have robust health, are industrious, and jolly. In the verse that accompanied the print Hogarth's friend the Reverend James Townley wrote 'Beer … Can sinewy Strength impart/And wearied with Fatigue and Toil/Can chear each manly heart' (2, p. 146). Hogarth is very much aware that the prosperous beer-drinking governing-class's oppression of the poor is a contributing factor to the use of gin in the working-class poor.

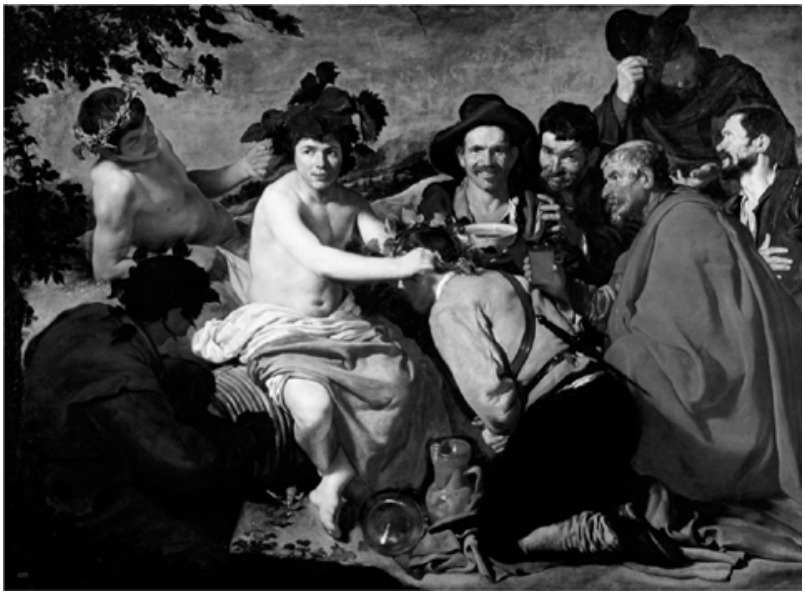

Figure 3.1 *The Triumph of Bacchus*.

Credit: Triumph of Bacchus, 1628 (oil on canvas) by Diego Rodriguez de Silva y Velazquez (1599–1660), Prado, Madrid, Spain/ Giraudon/The Bridgeman Art Library. Nationality / copyright status: Spanish / out of copyright.

Figure 3.2 *Gin Lane.*

Credit: Gin Lane, 1751 (engraving) (b/w photo) by William Hogarth (1697–1764). British Museum, London, UK/ The Bridgeman Art Library. Nationality / copyright status: English / out of copyright.

Hogarth and others recognized that by the 1720s, a new form of nihilistic and reckless drinking had appeared which was linked to the consumption of inexpensive gin, a distilled alcohol flavoured with juniper which was far more potent than wine. The so-called 'gin craze' (9, 10) resulted from the wide availability of gin; anyone could distil spirits from British grain. The populace spoke of 'Mother Geneva' or 'Mother Gin' (9) because women often were gin drinkers and merchants. Beer was sold primarily in alehouses and taverns frequented by men but not visited regularly by women. Gin was cheap and easily available to women and thus took on a female identify that Hogarth decided to illustrate. At one time there were 7,000 retailers of gin in the London suburbs, excluding those in London itself (2). The impact of gin abuse on women was accompanied by a fall in the birth rate and an increase in birth defects.

For his setting for *Gin Lane* Hogarth chose the parish of St. Giles, Westminster. It was a well-known slum district where gin sellers and distillers (one is labelled 'Kilman Distiller'), pawnbrokers, and undertakers grew rich while the populace lived in despair. Hogarth focuses the viewer's attention on an intoxicated woman in the foreground; her breasts are exposed and secondary syphilitic sores are apparent on her legs. Preoccupied with her snuff tray she remains oblivious as her child plunges to his death into a gin cellar stairwell. The emblem over
the stairwell is a drinking vessel, 'Gin Royal'. Above the stairwell door is the legend 'Drunk for a penny/Dead drunk for two pence'. In depicting such horror Hogarth may be reflecting on the story of Judith Defour who strangled her child, sold its clothing to buy gin, and left the child's body in a ditch. Below the blighted woman we find a starving man; he

has a gin bottle in his basket along with unsold pamphlets that moralized against the evils of drinking; one is titled 'The downfall of Mdm Gin'. Beside him there is a black dog, a symbol of despair. Above and to the left stands 'S. Gripe', a pawnbroker, negotiating with a carpenter to sell his coat and saw, the possessions central to his livelihood, to purchase gin. Gripe also negotiates with a woman for her kitchen pots, apparently for money to buy drink. Further back in the picture a man beats his head with a bellows whilst holding a baby aloft on a skewer. A woman pours gin down the throat of her child. Some people brawl; others offer one another a gin toast. Behind them all is a brick building that is collapsing from neglect. A barber nearby has hanged himself for lack of business. Further back there is a funeral procession; a woman, whose child despairs, is placed in a coffin. Seemingly a coda to all this chaos, the sign of the pawnbroker's shop forms a cross above the parish church of St George's Bloomsbury, which can be seen in the far background.

Hogarth's engravings and the writings of his friend, Henry Fielding, contributed to public knowledge of, and drew public attention to, the consequences of gin use. The first Gin Act of 1736 had been soon repealed due to public protest; its severe measures proved unenforceable and citizens turned into criminals. Hogarth and Fielding were rewarded by the passage of the new Gin Act of 1751 that ultimately led to a dramatic reduction in the number of London gin shops. The Gin Act doubled the tax, improved police surveillance, and rewarded informers. Unlike twentieth-century Prohibition in the United States, the Gin Act of 1751, whose passage was facilitated by the efforts of Hogarth and others, was successful in dramatically reducing the use of gin though regulation. Taxation proved more effective politically than

Prohibition. Thus, the gift of Bacchus remains legal today. Modern approaches focus on controlling alcohol use and seeking to prevent early use in adolescence. Such early use has been linked to other forms of substance abuse (11). There is a need for ongoing development of new approaches (12) to deal with the complications that excessive alcohol use and abuse have created for individuals and society. Artists and photographers continue to have a role in the twenty-first century in documenting the effects of alcohol use and reminding the public that the gift of Bacchus continues to be a mixed blessing.

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Chapter 4
Cultural aspects: illustrations of alcohol use in literature

Anya Taylor

Literature recreates the experience of drinking alcohol in a multivalent language that is rhythmical, sensuous, and layered in its meanings. Alcohol in itself and the act of drinking it pertain to literature as frequent subjects and spurs to creativity. From ancient Greece to twenty-first century Europe and America, poems, plays, and narratives describe group festivity or isolated individual breakdown and evoke emotions from jubilation to despair.

From the earliest times, songs of drinkers have praised the fermentations of grain and grape; narratives have invented deities who hypostasize the emotions unleashed by wine or beer; dramas in Greece have been performed to honour Dionysus, the spirit of creativity that sparked the plays themselves. In Renaissance plays and narratives, rotund characters like Shakespeare's Falstaff and Rabelais's Pantagruel were icons of energy, liberty, and excessive consumption. In the Restoration period in England, numerous songs by Herrick, Marvell, Rochester, and Gay urged lovers and friends to eat, drink, and be merry, thanking the grape for quickening the soul. Harvest, satiety, and pleasure are toasted. Even in early literature, however, there are warnings of the danger in excessive drinking. In Euripides' *The Bacchae* the intoxicated followers rip Pentheus apart. Milton warns in *Comus* of the dangers of drunken stupefaction to rational

virtue. Despite the occasional appearance of reckless drunkards like Barnardine in Shakespeare's *Measure for Measure*, drinking is usually seen as a gift, a natural miracle where corruption sweetens. It provides an escape from tedium and anguish; it releases inhibitions; it momentarily transforms the personality. But pleasure can turn to pain, freedom to bondage.

Such a turning was initiated by the intensification and distribution of distilled spirits in the late seventeenth century. The literature of the eighteenth century reflects this change. James Boswell confessed his weakness for whiskey in his journals. Samuel Johnson admitted to drinking to throw himself away; he analysed the self-destructive mendacity of his drunken friend Richard Savage. Men's drinking was euphemized in the words 'irregularities' 'dissipations', and 'weaknesses'. Writings by doctors such as Thomas Trotter, John Dunlop, Thomas Beddoes, Anthony Fothergill, and Robert MacNish registered this negative shift, describing the gin drinking of the poor as a disease. The poet George Crabbe noticed the ubiquity of sots on all levels of society in his first published poem *Inebriety* (1775). In *The Borough* (1810), he classified groups of drinkers. The Scottish poet Robert Burns wrote drinking songs praising 'John Barleycorn'; his popular poem *Tam o' Shanter* sported a drunken wanderer. Tam was widely imitated until Dr James Currie revealed in 1800 that drunkenness led to Burns' early death. Seeking to exonerate the poet's frailties and to understand the connection between drunkenness and creativity, William Wordsworth in 1803 composed a sequence of three meditative poems at the grave of Burns; he mourned his early death; imagined Burns wreathed in holly; and worried that Burns' sons would follow in his

footsteps. While Wordsworth in *Letter to a Friend of Burns* defended Burns' Dionysian spirit, he himself chose to be a water-drinker like Milton. He continued to meditate on what kinds of pleasure, natural or artificially induced, should be celebrated in poetry, to the derision of hard-drinking contemporaries like Lord Byron and William Hazlitt.

During this epoch of increased use of spirits, many individual drinkers recorded experiences of personal fragmentation and psychic dissolution. Three Romantic writers—Samuel Taylor Coleridge, John Keats, and Charles Lamb—revealed the interior experience of drunkenness either in personal confessions or in fictional or hypothetical forms. They described the experience of inebriation from the inside. Coleridge, whose huge output in poems and in political, philosophical, and religious speculations continued heroically despite his well-known opium addiction, was also an alcoholic, cross-addicted to brandy as well as laudanum (tincture of opium dissolved in wine). Although he sought pleasure in composing drinking songs and drank goblet after goblet, he worried more about his drinking than about his laudanum consumption, believing, as did contemporaries such as William Wilberforce, that laudanum was medicinal. In notebooks he confessed that spirituous drinks summoned the brutal aspects of his nature and undermined his will and free agency. When Coleridge applied metaphors of intoxication to literature, however, as in *Biographia Literaria* (chapter 18), they were positive. Intoxication was an aspect of pleasure for Coleridge; it became a metaphor for the writing of metrical verse, speeding up verse and rousing imagination, artificially heightening and intensifying the experience in the rhythm of poetry. He describes the pleasure of creativity as physically tipsy (1). Keats' interest in wine, while real, also serves to

explain an aesthetic experience of oblivion and ecstasy, particularly in his *Ode to a Nightingale* (stanza 2) where vintage from the south wafts the suffering human being away from his cares and in *Lamia* where wine creates pleasing illusions. Percy Bysshe Shelley in *Queen Mab* forbids alcohol as well as meat.

Charles Lamb, Coleridge's close friend since childhood, called himself a sot, addicted to the juniper berry. Alcohol allowed him to endure his ailments, the disasters of his life (his sister Mary killed their mother and he had to protect her), his stuttering, and his solitude. It allowed him to keep the puns flowing. Two extended works give ironic hints of his pain, but do so through masks and displacement. *Confessions of a Drunkard* (1813), the forerunner of twentieth-century confessions by F. Scott Fitzgerald in his late Pat Hobby stories and John Berryman in his optimistically titled memoir *Recovery*, claims to be fictional, but nevertheless analyses the condition as it leads to dishonesty and the betrayal of friends; the double consciousness of the author watches himself drown in unconsciousness. He blames heavy-drinking companions for leading an insecure person to drink; he warns young men to avoid his slide into oblivion. In his little-known play about the English Civil War, *John Woodvil: A Tragedy* (1801), drink deprives the hero of courage at a crucial moment when he betrays his father and brother. These Romantic writers recognize the joys of drinking but also the desolation (2, pp. 157–222).

In nineteenth-century fiction, often influenced by the temperance movement, alcohol is analysed from the outside as a scourge to families. Already in *The Old Manor House* (1793), Charlotte Smith blames the dissipation of the older

son Philip for the family's ruin; wives must live with alcoholic men without legal recourse. The Bronte sisters know such violence well from the example of their drunken brother Branwell; Anne Bronte in *The Tenant of Wildfell Hall* examines the disintegration of Arthur Huntingdon, the drunken husband, and the effects on the son. Dickens, a tippler himself, features benignly jovial drinkers in *The Pickwick Papers* and a self-destructive hero in *Tale of Two Cities*. Trollope in *Doctor Thorne* shows doctors crowding around the sequential deathbeds of the Scatcherd father and son, noting the stages of their *delirium tremens*. George Eliot scrutinizes the loosening grips of Dr Tertius Lydgate in *Middlemarch* and of Janet,
a rare woman drunkard in the short story *Janet's Repentance*. Thomas Hardy's drunken Henchard in *Mayor of Casterbridge* brings on his own downfall by selling his wife at a fair. In France, Émile Zola in *L'Assommoir* (1877) catalogues an impoverished Paris, an environment that by the precepts of scientific naturalism inevitably causes the disintegration of an innocent working-class couple, Gervaise and Coupeau, who sink from drinking wine to drinking spirits, his graphically described death a tour de force. In *Good Morning, Midnight*, Jean Rhys torments her solitary female drunkard in the same city. Rare is the nineteenth-century fiction that sees a joyful aspect to drinking.

Late nineteenth- and early twentieth-century Irish literature is heavily populated with alcoholics due to the availability of whiskey, the oppressiveness of British rule, the lack of meaningful work, and other causes. James Joyce mimics in oblique voices the intonations of his own father's drunkenness. In the story 'Counterparts' from *Dubliners*, Farrington drinks at work, insults his boss, is fired, and then

turns his rage on his son. In 'The Dead' the feeble voice of Freddy Malins gets increasingly drunk until he is humiliated by a condescending drunken Englishman. Looming behind the eventual liberation of Stephen Dedalus in *Portrait of the Artist as a Young Man* is the spectre of his father's dogged decline, as, sipping from his pocket flask, he loses his property in Cork and leaves his family in squalor (chapter 2). Polyphemus in *Ulysses*, chapter 12, is a bullying amalgam of drunkards (3, pp. 85–158). Other Irish writers preoccupied with alcoholic violence of fathers include Synge and O'Casey.

Attention to alcohol and literature moves west from the British Isles in the late nineteenth century, so powerfully that W.J. Rorabaugh dubbed the United States 'the alcoholic Republic' (4). Mark Twain's *Huck Finn* initiates the furious drunken father, willing to kill his son to control him. Pap is the precursor of James Tyrone in Eugene O'Neill's *Long Day's Journey into Night*. Jack London's *John Barleycorn*, influenced by Burns, brags about his capacity to drink and denies his alcoholism. Sherwood Anderson in the short story *I'm a Fool* introduces the alcoholic liar, influencing Ernest Hemingway's self-deceiving Jake in *The Sun Also Rises*, led astray by the lying drunkards who pretend to love each other in a Spanish revel (5, pp. 43–64). Hemingway's intricate stories such as *Snows of Kilimanjaro* explore drunken loss in italicized memories and drunken putrefaction in the present. Richard Yates in *Disturbing the Peace* traces layers of drunkenness leading to the insane asylum; William Kennedy in *Ironweed* glorifies the homelessness of his Celtic hero. In a bleak Northwestern America, Raymond Carver brings his characters to alcoholic paralysis, a willed deafness in *Careful*, a rejection of life in *Chef's House*. The medically observed

last stages of alcoholism are rigorously detailed by Charles Jackson in *The Lost Weekend*.

American literature also explores neglected populations in relation to alcohol. As in Irish writing, alcohol is a mournful refrain for Native Americans, especially in Louise Erdrich's *Love Medicine* and Leslie Mormon's *Ceremony*. African American writers such as Richard Wright and James Baldwin see drink in relation to brutality and sexual experimentation. Women have been rare in the literature of drinking but there are exceptions. Elizabeth Bishop's unfinished poem *A Drunkard* confronts the void adumbrated in her famous poem *One Art*. Some young women writers set out in college to equal men in all ways including drinking, as in Koren Zailckas' *Smashed: Story of a Drunken Girlhood*. Contemporary writers on alcohol record their suffering to create order out of chaos and connection out of isolation.

Literature observes and expresses these alcoholically altering states. In *Lucky Jim* and *The Ginger Man*, British Kingsley Amis and Irish J.P. Donleavy respectively return full circle to the Renaissance pleasures of living raucously and disrupting the status quo.

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Chapter 5
Cultural aspects: alcohol use in film

Judy Cornes

Prohibition and gangsters: 'The Noble Experiment' according to Hollywood

The Eighteenth Amendment to the United States Constitution (ratified by the states exactly one year earlier and enforced at midnight on 17 January 1920), which banned the manufacture, sale, and transportation of intoxicating liquors in the United States, was exceedingly controversial. For several months before the amendment became law, alcohol consumers throughout the United States were bracing themselves, and in anticipation of its enforcement, concerned individuals began to stockpile alcohol, hiding it in cellars, attics, warehouses, and safe-deposit boxes. Liquor store owners advertised special going-out-of-business sales. One such enterprising proprietor placed a sign over his shop entrance, beckoning customers 'BONE DRY FOREVER/ BUY NOW/For the rest of your life' (1, p. 30).

Prohibition did seem a long dry spell for many. Yet, from the start, it should have been clear that The Noble Experiment would not succeed. At 0.01 am on 17 January 1920, six gunmen broke into a Chicago railroad yard and seized two freight cars filled with barrels of alcohol worth $100,000 (1, p. 32). The gangster wars had begun. Always alert to trends in society, the film studios of Hollywood jumped on the now dry

bandwagon and developed stories taken from the headlines, namely, alcohol use during Prohibition.

Many silent films portrayed people enjoying Prohibition alcohol, but with the arrival of sound in film in 1927 came new dimensions to the on-screen portrayal of illicit alcohol: in particular, gang wars for control of the illegal alcohol market. Audiences could now, for the first time, hear gangsters speaking as well as enjoy the sound of the accompanying violence, notably, the machine gun blasts and the firebombs that eliminated large buildings harbouring rival gangsters. With sound, came the unique voices of the actors portraying these outlaws. Among the most well known of these were James Cagney, Edward G. Robinson, and Humphrey Bogart; all were charismatic figures with distinctive speech cadences; all became popular with film audiences, thrilled by the rebellious intensity behind their screen personalities. As criminals facing the inevitability of violent death, they depicted characters who nonetheless seemed surprised by their own mortality.

Three of the most renowned Prohibition gangster films are *Little Caesar* (1931), *The Public Enemy* (1931), and *The Roaring Twenties* (1939). Although the last film was made after the repeal of the Eighteenth Amendment, it is set in the 1920s and, with newsreel-style narration, conveys an indelible impression of the period. These three memorable films have similar plots; all show the rise and fall of a criminal who joins the rackets (illicit businesses) at the start of Prohibition and becomes prosperous by selling 'bootleg booze'. Further, all of these Prohibition gangsters live by a strict code of revenge—one killing is avenged by another (this plot element is carried to calculated senselessness in *The*

Public Enemy when Cagney and his partner, on hearing that one of their gang
members has died in a horse riding accident, shoot the horse). Finally, all represent the American Dream gone sour, for in each of the three films, these enterprising lawbreakers suffer a rapid decline in fortune and die none too gracefully.

The cherubic-faced actor

Little Caesar is one of the earliest of the Prohibition-era gangster films with audible dialogue. Edward G. Robinson plays Caesar Enrico Bandello, a social climber, mob boss, and efficient killer. Robinson was a versatile actor, adept in many genres, but here his physical presence and his voice are perfectly suited to the gangster film. Short and chubby, with a cherubic face, Robinson, with a low-pitched voice more menacing than soothing, asserted his position. And Robinson's 'Little Caesar' quickly positions himself at the top.

Caesar first appears as a small-town criminal, robbing a gas station and murdering the attendant. But he soon tires of killing for petty cash and heads to the city, where he swiftly ingratiates himself with the powerful Prohibition gang boss, Sam Vettori. To prove himself, Caesar leads the Vettori gang in a New Year's Eve hold-up at an upmarket nightclub run by Little Arnie Lorch, a Vettori rival, for control of the alcohol trade. Present at this party, where alcohol flows freely, is crime commissioner Alvin McClure. Though McClure is obviously enjoying his choice of drink, Caesar kills him during the robbery, thus securing his position as the leader of the Vettori mob. Next, hearing that the getaway driver Tony

is on his way to confess his recent sins to a priest, Caesar pursues him and guns him down. However, with no hint of irony, Caesar attends Tony's funeral and contributes a large commemorative wreath.

Caesar cements his leadership at a testimonial dinner in his honour where, as a token of the gang's esteem, he is given a diamond and platinum watch, which the mob bosses have recently snatched in a jewellery store heist. Caesar's reign is short-lived, however. After his ex-partner's girlfriend informs the authorities of him, he is forever pursued by the police. Caesar finally lands in a 15-cents-a-night hotel, still dressed in his now frayed suit and tie, the only remaining trappings of his brief success. Robinson's face in these squalid surroundings is a study in drunken, futile defiance. Intoxicated, unshaven, eyes puzzled and glazed, nostrils oozing water, he stumbles out of his shelter and phones the police, daring them to come after him. And they oblige. Still puzzled but defiant, Caesar dies by gunfire.

Never at rest

James Cagney was one of the most kinetic actors ever to appear on screen; a Broadway dancer in the 1920s, he carried his balletic grace into films. He is forever in motion; from his constantly roving eyes to his fast-moving feet, he never just walks into a scene. So too, his speech is fast and disjointed. In *The Public Enemy*, as Tom Powers, he displays this tremendous energy; first, as a young man involved in petty crime with childhood friend Matt Doyle; then, with the advent of Prohibition, as a distributer of illegally produced beer, beating up owners who refuse to buy his brand. Like Caesar,

he quickly acquires symbols of accomplishment: an expensive car, a custommade suit, and a beautiful mistress.

Another emblem of success appears in one darkly humorous scene in which Tom's family plan a celebration to honour his brother, home from the Great War. The dinner table centrepiece is a huge keg of beer, which Tom and Matt lovingly heave onto the table. It sits there, acting as a grotesque reminder of Tom's source of wealth, while the uncomfortable guests peer awkwardly around it during the meal. The dinner ends abruptly when Tom's shell-shocked, frenzied brother
hurls the massive keg into a corner, wildly yelling 'It's not beer in that keg! It's *beer* and *blood! Blood of men!*' (2, p. 125).

Cagney's character sneers at such moral subtleties, however, and he continues his fast-track career until he is eventually wounded by rival gangsters. Taken to the hospital, he appears to be recovering, but a short time later we learn that he has been kidnapped from the hospital by the same rival gang. In the film's chilling final scene inside the Powers' house the doorbell rings, Tom's brother opens the door and sees Tom precariously wobbling, head bandaged, wrapped in sackcloth with a rope holding the wrapping in place. Finally, the body falls inside, head first. We now realize that Tom's body has been delivered to his house 'as though it were the day's supply of meat' (3, p. 271).

The Roaring Twenties no longer roar

Eight years after he appeared in *The Public Enemy*, James Cagney made *The Roaring Twenties*. In this film, Cagney plays the far more sympathetic character of Eddie Bartlett, who is trapped in circumstances beyond his control. A veteran of the Great War, he returns from France and discovers that the world he left behind has no place for him. Unable to get his old job back as a mechanic, he finds work driving a taxi. One night, a passenger gives him a carefully wrapped package to take into a nightclub. Obeying orders, he naively announces his presence—and the package with the bottle inside—to the woman who runs the club. Arrested but quickly out of jail, he discovers that manufacturing illegal alcohol is more profitable than driving a taxi. He soon has his own fleet of taxis and a herd of employees; these entrepreneurs take orders, manufacture wood alcohol (obtained through a process of fermenting sawdust—cheap to make, it quickly caused brain damage but was popular during Prohibition) under various brand names, and hijack alcohol-laden boats belonging to rival gangs. Yet for all his brash bravado, Cagney's character is also wistful and lonely: a misfit in a post-war world.

The antagonist in the film is George Hally, played by Humphrey Bogart. He is Bartlett's old army friend: a crafty character, his voice nasal and whiny, the perfect counterpart to Bartlett's bouncy fervour. Although the Bartlett and Hally characters don't trust each other, they collaborate on the hijacking and manufacture of alcohol. When Prohibition ends, Bartlett's money runs out, along with his alcohol and his partnership with Hally. Learning that Hally plans to kill a

mutual friend who has become a district attorney and knows too much about their past, Bartlett shoots and kills the astonished Hally. However, unlike Caesar and Tom Powers, Bartlett knows that his own death is now inescapable. Running from Hally's apartment, he is shot by Hally's gunmen. Stumbling to the steps of a nearby church, he finally dies.

Censors

The Roaring Twenties was released in 1939, five years after the strict enforcement of the Hollywood Production Code of 1930. This code contained self-censorship rules established by Hollywood in order to avoid government interference with film content. However, *Little Caesar* and *The Public Enemy* were made before 1934, the year in which the rigid implementation of the code began (4, p. 6). More risqué than *The Roaring Twenties*, these two earlier films imply casual sex, show wanton violence, and make alcohol abuse look exhilarating. When Warner Bros. wanted to reissue *The Public Enemy* in 1935–1936, it was unable to get a Code seal of approval. The studio did not try again until 1953, and succeeded only when it agreed to delete two suggestive lines from the original (2). Both *Little Caesar* and *The Public Enemy* were finally reissued in 1954, but with
an added prologue warning viewers of society's criminals. Although Prohibition had perished approximately 20 years earlier, filmgoers of the 1950s evidently still needed to be reminded that violation of the Eighteenth Amendment had been a horrible sin against society.

Acknowledgment

Extract from Cohen, Henry, ed. THE PUBLIC ENEMY © 1981 by the Regents of the University of Wisconsin System (reference 2, p. 125). Reprinted by permission of The University of Wisconsin Press.

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Chapter 6
Sociocultural aspects of alcohol consumption

Robin Room

The historical rise and spread of drinking

Alcoholic drinks have been used by humans since prehistoric times. As European explorers and empires expanded across the world from 1500 to 1900, they found indigenous alcoholic drinks in all parts except Australasia, Oceania, and North America roughly north of the United States–Mexico border (1). In traditional and village societies, alcoholic drinks were produced by home or craft fermentation, in small batches; most was consumed close to where it was produced and soon after production as brewed drinks spoiled quickly. Production of the drinks depended, to a considerable extent, on the existence of an agricultural surplus. While men were the primary drinkers in many cultures, the producers were often women, which meant that women often had some control of their men's drinking.

There were three main factors which transformed this situation. Firstly, the introduction of distillation meant that alcoholic drinks could be made and transported more cheaply and (as spirits or fortified wine) did not spoil. Distillation made its way from Arabia to Europe by the Middle Ages, but it had been used primarily to produce medicines and it was not until about 1600 that spirits departed from the medicine cabinet and became used socially in daily life. Secondly, the industrial production of alcoholic drinks was an early step in

the Industrial Revolution, meaning a wider and more consistent availability of cheaper alcoholic drinks. Thirdly, the European expansion brought industrially-produced alcoholic drinks, notably spirits, to all parts of the world, with alcohol often a major trade item and inducement to labour.

In society after society, both in Europe and elsewhere, the availability of cheap spirits produced a slow-burning social crisis. In many places the results were substantial movements of social response and revitalization, reaching a crescendo in English-speaking and some other societies in the temperance movements of the late nineteenth and early twentieth centuries. These temperance movements had substantial and lasting effects on the cultural position of drinking, but much of their legacy was gradually shed in these countries from 1945 on, in an era of deregulation and free-market fervour.

Use-values and the cultural position of alcoholic drinks: both physically and culturally determined

We can distinguish several different primary use-values for alcoholic drinks, based on their physical properties (2). In some societies, an alcoholic drink is defined as a foodstuff, and indeed opaque beer in Africa is a substantial source of nutrition in village societies. Another use-value is as a thirst-quenching drink. Alcoholic drinks are, of course, also psychoactive. They can be used in
moderate quantities to alter mood. They can also be used in larger quantities when the drinker is seeking intoxication. Apart from alcohol's physical properties, alcoholic drinks have also often been assigned strong cultural meanings and values—to give diverse examples, as a sacrament, as a source

and occasion of stigma, and as a signal of commensality and fellowship. Many of these different aspects of alcohol's meaning and value will be present in any particular culture, and drinking for any one purpose will tend to hold implications for the others. Reverently drinking up the left-over sacramental wine, or quenching thirst with beer, may have the side effect of resulting in intoxication.

Societies and cultures differ greatly in the cultural position of alcohol and its consumption. In some, such as Islamic societies, it is forbidden outright. In others, it is primarily associated with intoxication and drinking is often heavily limited in terms of time, place, and who is permitted to drink. Quite commonly, children are forbidden access to alcohol and in many traditional societies drinking by women is also disapproved and quite rare. Contrary to the ubiquity of drinking in many rich societies and in media and advertising, the majority of adults in the world today are abstainers (3).

There is a substantial literature on differences in the cultural position of alcohol (4). Discussions have often revolved around an idealized picture of what is known as 'Mediterranean drinking'. Where alcohol use becomes a banal accompaniment of everyday life, its psychoactive nature may be muted; in southern European wine cultures, wine tends to be differentiated from intoxicating 'alcohol' and wine drinkers are expected to maintain the same comportment after drinking as before.

Such a pattern is contrasted with various cultural patterns of intermittent use, for instance, at festivals or only on weekends, which incidentally minimize the build-up of tolerance to alcohol. It is in the context of such patterns that

the greatest attention is likely to be paid to alcohol's psychoactive properties. The drug may be understood by both the user and others as having taken over control of the user's behaviour, thus explaining otherwise unexpected behaviour, whether bad or good (5). Given the power attributed to the substance, access to it may be limited: in traditional societies, by sumptuary rules keyed to social differentiations; in industrial societies, by other forms of market restriction.

In industrial societies, a third pattern of use has become recognized: addicted or dependent use or alcoholism, marked by regular use, often of large doses (6). In this framing, addiction is defined as an individual failing rather than as a social pattern. While attention is paid to physical factors sustaining regular use, such as use to relieve withdrawal symptoms, most formulations of addiction focus on psychological aspects, including an apparent commitment to drug use to the exclusion of other activities and despite default of major social roles. An addiction concept thus also focuses on loss of normal self-control, but the emphasis is not so much on the immediate effects of the drug as on a repeated or continuing pattern of an apparent inability to control or refrain from use, despite adverse consequences.

Dimensions of diversity in drinking cultures

Cultural and economic factors influence the relative dominance of different patterns of drinking in a society. The level and patterns of drinking is also influenced by the societal reactions to the problems associated with drinking. There are substantial adverse effects of drinking on those around the drinker (7), as well as on the drinker him/herself,

and there is a substantial history of political and social efforts to diminish the harms from drinking, both by influencing the circumstances of drinking and through limiting the amount and permissible times and places of drinking (8).

In considering the diversity of drinking cultures, the range of potential dimensions is quite large. One obvious dimension is the degree of regularity of drinking. Along with regularity of drinking, there is a need for a differentiation on how widespread at least occasional intoxication is in the culture (4).

Several more dimensions should probably be taken into account. One is the degree to which drinking and drunkenness are associated with violence. Parallel to this, and unexplored in the typological literature, is the degree to which drinking and drunkenness are culturally associated with sexuality. Another dimension has to do with the social definition of intoxication. There are cultural differences in 'how drunk is drunk' which relate to how intoxication fits with core cultural values. We may hypothesize that where trances and altered-consciousness experiences are valued, drinking to extreme intoxication, with radical changes from sober behaviour, will often be a goal for the drinker rather than an accidental misjudgement. Where drinking is a more common lubricant of everyday sociability, intoxication may be quite frequent, but it will be less extreme and less marked by a change in behaviour.

A further dimension for consideration is the relationship between heavy drinking groups and contexts and the larger culture. To what extent are drinking and heavy drinking reserved for particular social categories and circumstances,

and how do they relate to the culture: as carriers of high prestige or of low? Along with who does the heavy drinking, there is the question of its context and relationship to other cultural elements: is heavy drinking hidden from daily and family life, entrenched within it, or not clearly differentiated from it?

As already noted, the two key dimensions for classifying the cultural position of drinking in societies are regularity of drinking and extent of intoxication. In recent international epidemiological studies, a 'hazardous drinking score' has been developed, differentiating societies essentially on a dimension of what proportion of the alcohol consumed in the society is on occasions of intoxication (9). The dimension of regularity of drinking is related to the overall volume of drinking in the society, the other dimension used in current estimates of the contribution of alcohol to the burden of disease and disability in a society (3).

Between the culture and individual patterns: drinking customs

Drinking customs present an intermediate level of analysis between cultures and individual patterns of drinking. A culture can be described as being composed of an assortment of customs, some of them centred on drinking, some potentially including it, and others specifically excluding it. Over time, the mixture of customs in a culture may change and some customs or types of occasions may become more frequent. Customs exist above the individual level and their historical development can be traced, but drinking customs are not necessarily direct emanations of a culture as a whole.

Some drinking customs are intangible, part of everyday sociability; for instance, the custom in many cultures of informal 'toasting'—making a gesture or speaking some verbal formula as an invitation to drink together. Others take on, or are associated with, institutional forms: in many cultures, there are places where people gather to drink, which we will refer to as pubs (public houses), with recognizable spatial and architectural arrangements that are typical in the cultural setting.

There are three kinds of drinking custom which are very widespread, but which take on diverse typical forms in different cultures: (i) the drinking group and reciprocity customs within it; (ii) communal celebrations; and (iii) the pub or on-premises drinking shop. These by no means exhaust the inventory of drinking customs but they are exemplary of the range of widely diffused aspects of drinking culture.

The drinking group and reciprocity customs

In all societies, drinking is mainly a social activity. Even most of those who sometimes drink alone usually drink more often in groups. While drinking and intoxication affect the individual's consciousness and body, they are thus intrinsically social activities, carried on in front of those with whom the drinker is drinking, and often also before an audience of those who are not part of the drinking group. In the context of the drinking group, drinking is a medium of solidarity and in a great many societies drinking together is a sign of mutual trust and status levelling. But the drinking group is also potentially a source of social division where

others are excluded, whether explicitly or customarily, and by assumption.

The drinking group can function in almost any location—in someone's home, on the street, out in the bush or countryside, or in a restaurant or pub. Typical locations of social drinking vary with the culture and physical circumstances. Half of the males in a Mexican sample, for instance, reported that their last drinking occasion was in someone's home, while this was true for only 20% of the male respondents in Zambia. Conversely, for 18% of males in Mexico, but 33% in Zambia, the last drinking occasion was in a pub (10).

Anthropological accounts from many cultures have emphasized the congruence of drinking with cultural values such as hospitality, kinship, and reciprocity (11–13). Even where alcohol was not present in the traditional culture, it has come to serve as a vehicle for the reciprocal relationships that the culture prescribes (14). An account of the drinking patterns of a group of regular customers at a village beer shop in Togo (15) typifies drinking group patterns in many societies, although the specifics of the reciprocity expectations and rituals will differ.

The solidarity of the drinking group is often to some extent in opposition to and at the expense of others in the society. Where drinking is primarily limited to men, the solidarity is among men, and the women may be and feel excluded from it (16, p. 199). In Fiji, Walter (17) reports that drinking groups are primarily composed of young men who do not generally have a high status in the village; women who discover homebrew routinely put salt in it to ruin it; overnight drinking parties are carried on in the bush outside the village as

initially, at least, there is ‘an exaggerated concern to keep quiet lest the party be exposed’. In other societies, those outside the drinking group may have less social power to act, but nevertheless harbour considerable resentment.

The customs of the drinking group often function to encourage or enforce drinking, even against the individual’s immediate desires. In many societies, games played in the context of the drinking group require further drinking as a reward or penalty. Customs of buying rounds, with their expectations of reciprocity, tend to favour the pattern of the heaviest drinker in a group; other members of the group may fear being considered unsociable and ungenerous if they do not stay in the successions of drinking rounds to the end. An example from fieldwork in a Mongolian community in China (18) describes vividly the pressures to drink within the drinking group.

The choice of drinking or not is thus not solely an individual decision. In many contexts, rejecting a drink will be interpreted as indicating disrespect of the other participants or of important and even sacred communal rituals. Some forms of sociability around drinking actually enforce drinking in ways that may be dangerous.

Communal celebrations

From a sociological perspective, it is useful to distinguish between two types of communal celebrations as ‘time out’ from normal activities, and often from normal rules of behaviour. In carnivaltype celebrations, roles and power relationships blur, vanish, or are even reversed (19), whereas

fiesta-type celebrations express fraternization and affirmation of roles. In the following, our focus is on fiesta drinking.

A fiesta lasts at least a day and more usually several days. Fiestas are normally scheduled in terms of particular seasons or dates: at harvest time, when a local market meets, on a special occasion in a religious calendar, around a national anniversary date. They may mark significant life transitions for individuals in the locality, notably a local marriage.

In most societies, drinking, often heavy drinking, has been at least an accompaniment of fiesta-type celebrations and often at the heart of them. The alternative state of consciousness of intoxication is both a symbol for, and a means of casting aside, everyday concerns and rules. Eber's account (20) of the fiesta in a town in the Highlands of Chiapas in Mexico underlines the involvement of alcohol not just in the general celebrations but also in the communal ritual of the occasion.

In village societies with fiesta traditions, it has been quite common for drinking to be primarily associated with the fiestas. Fiesta drunkenness in the past may have been the only occasions of drinking, at least for poorer members of the community. Now the fiesta drunkenness may commonly be just a part of a drinking repertoire including other, more regular, patterns of drinking.

In many developed societies, part of the process of industrialization was a long fight against popular traditions of the fiesta, which were seen as threatening not only public order but also productivity. The jocular expression among British labourers, 'Saint Monday', expressed the pre-industrial reality that Monday was often taken as an

unofficial holiday to rest up from the drinking of the weekend. Slowly, in many parts of Europe, the old traditions of markets and fairs as local fiestas were repressed in the interests of a 'rationalization of leisure' (21). In Chiapas too, Eber reports (20, p. 99), the tradition of drinking at fiestas has been challenged, although not the holding of the fiesta itself. The candidate for president of a neighbouring town had 'led a vigorous prohibition campaign, arguing that [the people] could move out of poverty if they would stop drinking rum. He won the people over and enacted a "dry" law when he took office'. At the fiesta there, 'the town centre was full of people drinking sodas and fruit-flavoured drinks; however, not everyone was sober'. Drinking, though probably less than before, still went on at stands on the outskirts of town.

The pub

Csikszentmihalyi (22) describes in detail three different types of traditional drinking-places in European cultures: the open and airy wine shop in Mediterranean cultures, with drinkers sitting in small groups around tables; the huge, darkened beer halls of Germany and Austria, with long parallel tables flanked by benches; and the stand-up bar of the English pub, with drinkers standing in a line. The range of variation in drinking-places in a wider global perspective is even greater (23). Our primary focus here is on places it is possible to buy and consume alcoholic drinks in a glass, mug, bottle, or other open container without having a meal. This excludes places which are primarily for eating, even if drinks can be consumed along with the meal, and places which sell alcoholic drinks only for consumption elsewhere. In practice, in many societies, these categories are often not so clearly

differentiated, despite any precision in the regulatory definitions. And places that are primarily pubs often sell a variety of other goods as well.

As places of 'public accommodation', pubs are natural meeting-places, and frequently have a variety of functions besides serving drinks. With their wide range of connections with drinkers in the community, pub landlords are often politically well-connected and may become involved in politics themselves.

In most developing societies, pubs are primarily male-dominated spaces, in part simply reflecting the clientele. But as places of public accommodation, they are also commonly meeting places for those with romantic and sexual relationships in mind. Given that many cultures make a strong association between drinking and sexuality, particularly with regard to women (24), drinking in pubs sometimes casts questions on a woman's social standing. In quite a few societies it would
traditionally put her outside the pale of respectability. On the other hand, particularly in eastern and southern Africa, where making the traditional drinks has been women's work, keeping a pub, official or unofficial (a 'shebeen'), has been a major source of employment and support for widowed women and mothers (25). Increasing competition from commercially produced drinks, often sold by politically-connected male pub landlords, has threatened this traditional source of support for female-headed households (26).

Besides any pressure the drinker may feel from members of the drinking group, there is a built-in extra source of pressure

for more drinking in the pub—the drinks he or she buys essentially pay the rent for the public accommodation that the drinker is occupying and using. Normally, there is no charge for occupying the space per se; instead, the pub landlord expects to earn the overhead costs and a profit from the drinks the drinker buys. The pub drinker who does not keep up the expected drinking pace may come under various subtle or open pressures to 'drink up'.

Over the years, governments in many places have sought to control or eliminate the pressures on the pub drinker to drink more. Governments often took over operation of pubs themselves, to remove the private profit interest in greater sales. With a mixture of this motive and a concern for social control of the black population, European-controlled governments all over southern Africa set up municipal beer halls in the early 1900s as the main legal venue for drinking by the black working class (27, 28). While it can be argued that the halls did alleviate some problems from drinking, it is clear from the subsequent experience that governments themselves are not immune to the desire to profit by increasing sales (29).

Conclusion

Consuming alcoholic drinks is inescapably a personal behaviour, but the behaviour is influenced at multiple levels by social context, culture, and society. The decision to drink is not necessarily personal; customs such as round-buying or toasting may dictate drinking regardless of personal preference. Social and cultural factors at many levels influence when and how much a person drinks: examples of

such factors include differential expectations about drinking by gender, age, and social position; the position of the drinker's ethnic identification in the larger society; the habits and expectations of the drinking group; and the intertwining of drinking and courtship customs. Social, cultural, and societal reactions to the drinker are also important both in shaping drinking practices and in determining what happens next—whether and how much trouble results from the drinking event, whether the drinker is praised or stigmatized. To focus only on the physical effects of alcohol in the body, on genetic factors, or on attributes of the individual drinker, is to miss the inescapably social nature of most drinking behaviour, and the interpersonal and cultural mechanisms which strongly influence both the behaviour and its consequences.

Acknowledgements

This chapter includes data from references (1, 4, 30).

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Part II

Alcohol: chemistry and biology

Chapter 7
Chemistry of alcoholic beverages

Laurence I. Peterson

Introduction and scope

In view of the overarching purpose of this book and constraints imposed by length, the goal of this chapter is to provide the reader with an overview of the chemistry of alcoholic drinks and leave highly technical details or the nuances of these drinks to more comprehensive books on the subject (1–7). An alcoholic drink is one containing ethanol, a substance known to the general public by many names, including ethyl alcohol, grain alcohol, and drinking alcohol, but most often simply as ‘alcohol’.

Since production and consumption of alcoholic drinks dates back at least 10,000 years, a vast number of alcoholic drinks have evolved. In essentially all cases, these drinks can be placed in three categories, namely beer, wine, and distilled spirits, based upon the ingredients and methods of manufacture. These alcoholic drinks are generally yeast fermentation products of staple foods such as grains, grapes, or potatoes. The process of manufacturing an alcoholic drink involves crushing (mashing) carbohydrate-rich grains, fruits, or vegetables, and subsequently fermenting the resulting mash in a vat for a controlled period of time.

During fermentation, yeast converts the relatively high level of sugars present in all grain, fruit, and vegetables into

alcohol (ethanol) and carbon dioxide gas that subsequently bubbles out of the brew into the air. The initial level of sugar (typically 10–26%) determines the amount of alcohol (5–12%) produced in the final drink. Since wine grapes possess higher sugar levels (up to 26%) than grains (maximum of 12%), the alcohol content of wines is typically at least twice that of beers. Special types of yeast are used in wine production that tolerate higher alcohol levels and thereby produce higher levels of alcohol (in some cases up to 14%, or even higher) in the final product.

The common link in all three types of alcoholic drink is the production of alcohol, by yeast-promoted fermentation of the carbohydrates, more commonly referred to as sugars. The more precise name for the alcohol, since 'alcohol' is a generic term, is ethanol. When the term alcohol is used hereafter in this chapter, we are referring only to this two-carbon primary alcohol (C_2H_5OH) that chemists refer to as ethanol or ethyl alcohol (8). During the fermentation of complex carbohydrates found in the many different grains and fruits used in the production of alcoholic drinks, many other alcohols such as methanol, propanols, butanols, C-5 alcohols, and 2,3-butanediol, as well as glycerine (a three-carbon triol) are produced, albeit in relatively low levels compared to ethanol.

Alcohol (ethanol) is a colourless, highly flammable liquid at room temperature, more volatile than water with a boiling point of 78°C at atmospheric pressure and which freezes at ∇114°C, much lower than water. Alcohol mixes in all proportions with water meaning the two substances are mutually soluble. Alcohol will burn in air when there is between 3% and 19% ethanol in the vapour and can be

ignited at 9°C. Alcohol is an excellent solvent and consequently many industrial
and consumer products, particularly in the cosmetic and health care area, are based on substances dissolved in alcohol. An overview of the chemistry of alcohols, and ethanol in particular, along with the synthesis, manufacture, accumulation of alcohol in the body, as well as its metabolism, can be found online at ChemCases.com (8).

The two principal chemical components in all fermented alcoholic drinks are water (85–95%) and alcohol (ethanol) typically in the 5–15% range, respectively. The alcohol percentage is typically expressed as volume percentage rather than weight percentage. Distilled alcoholic drinks contain significantly higher amounts of alcohol, at levels up to and even exceeding 50% in some cases. Owing to additional processing and higher alcohol content, distilled alcoholic drinks typically cost more and are more potent in terms of the physiological effect when consumed.

The serving size or ‘standard drink’ is a term used to quantify the amount of an alcoholic drink consumed by individuals and varies from country to country. For example, in the United States, a ‘standard drink’ is an alcoholic drink that contains 18 ml (14.1 g) of alcohol, whereas in Japan the standard drink contains 25 ml (19.75 g), in the United Kingdom 10 ml (7.85 g), and in Austria 7.62 ml (6 g). In the United States, the ‘standard drink’ is approximately the amount of alcohol in a 12-ounce (350 ml) glass of beer, a 5-ounce (150 ml) glass of wine, or a 1.5-ounce (44 ml) 40% alcohol by volume (80 proof) distilled spirit (9).

Chemical composition of alcoholic drinks

An alcoholic drink, in addition to the alcohol and water that comprise at least 98% of the contents, contains naturally occurring or naturally produced chemical substances that are termed either macronutrients or micronutrients, depending on their nature and quantities. A macronutrient is a substance required in significant quantities for human growth and health, whereas a micronutrient is a substance or even element required in only minute quantities by the human body (2).

Methanol

Methanol, certainly the most toxic common alcohol, invariably occurs in beers, wines, and distilled drinks. In beers, the methanol level is usually very low (below five parts per million, hereafter, ppm) although hard data is difficult to find. However, in wines, particularly red wines, the methanol level is sometimes as high as 100–200 ppm and levels greater than 600 ppm have been reported (6). The level of methanol in white wines is typically lower and generally under 100 ppm. Methanol is not a fermentation product (4) but originates from pectins found in the juice and the use of commercial enzymes produces the highest level of methanol.

Due to concentration during the distillation process, the quantities of methanol in distilled spirits is considerably higher, particularly in fortified wines such as brandies and cognacs where the level of methanol can be in the 100–750 ppm range and levels of 0.2–0.5% (2,000–5,000 ppm) have been reported for some apricot and plum brandies (7).

Because of methanol's inherent toxicity, consumption of large quantities of some distilled spirits, especially illicit sprits, might prove fatal (7).

Higher alcohols

The generic term alcohol includes a large number of related substances with similar chemical and structural properties, many of which are much more toxic than ethanol. Generically, an alcohol is best described as a hydroxyl group attached to a carbon atom in an alkyl group or carbon backbone. During the fermentation process, the carbohydrates present in grain, fruit, and vegetables
used to produce the alcoholic drink are converted to many other alcohols depending upon the yeast, carbohydrate, and reaction conditions, particularly at higher temperatures.

These other higher, more complex alcohols are generally known as fusel oils and, in fact, are important to certain alcoholic drinks because of desirable characteristics imparted to the final product. The major aliphatic higher alcohols occurring in beers, wines, and subsequently found in distilled spirits are 1-propanol (n-propanol), 2-methyl-1-propanol (isobutyl alcohol), n-amyl alcohol, 2-methyl-1-butanol (amyl alcohol), and 3-methyl-1-butanol (isoamyl alcohol), resulting from fermentation of the carbohydrates and/or amino acids (6). In contrast to the ethanol produced, the other alcohols total at the most 500 ppm and represent less than 0.5% of the total alcohol content.

However, more often these fusel oils (higher-molecular-weight alcohols) are considered undesirable and impair the character of the alcoholic drink.

For example, levels of n-propanol, isopropanol, n-butanol, and amyl alcohols may be inadvertently increased during fermentation if temperature, pH, or yeast conditions are not properly maintained or effectively monitored (2). These fusel oils can carry over into distilled spirits depending upon the distillation conditions that vary greatly within different distilleries and with different products. Some believe high levels of fusel oils are responsible for beers and wines that produce prodigious headaches and hangovers (2, p. 966).

The higher alcohols, and derivative esters (*in situ* reaction products of the alcohols with carboxylic acids such as acetic acid present in the fermentation brew), are significant and important contributors to the aroma and flavour of many distilled spirits and are present in larger quantities in distilled spirits than other volatile compounds because of their initial levels and physical properties relative to the higher-molecular-weight esters, ketones, aldehydes, such as furfural, and carboxylic acids.

Carboxylic acids, esters, aldehydes, and ketones in alcoholic drinks

In addition to the large quantities of alcohol (ethanol) and relatively low levels of higher alcohols in beers and wines, there are also very significant quantities of organic acids (carboxylic acids) present in significant levels in the juice of fruits, particularly grapes, that are subsequently fermented to produce wines. The organic acids present in the largest quantity are tartaric acid (prevalent in unripe grapes), malic acid (present in green grapes and apple juice), and citric acid, along with lesser quantities of succinic, benzoic, cinnamic,

and gluconic acids (2). Most of these acids are found along with their corresponding ethyl esters.

Chemical analysis of wines reveals a myriad of other organic acids and corresponding esters, albeit in only miniscule amounts, since tartaric, malic, and citric acid accounts for over 90% of the organic acids in wines.

Tartaric acid is the key acid in wines and is unique in occurring solely in vine fruits, such as grapes. Tartaric acid is present in grapes at 1–7 g/L (1,000–7,000 ppm) and generally represents at least 50% of the total acid content of wines. Malic acid, another four-carbon diacid, found in large quantities in apples, is also present in grapes in significant levels (1–4 g/L), whereas citric acid is generally in the 0.150–0.300 g/L range (3).

Along with the organic acids found in the original fermentation juices, other organic acids are produced in the fermentation process such as acetic, lactic, glucaronic, galacturonic, and pyruvic acid. Most of these are undesirable by-products of the yeast fermentation or result from poor quality control, inadvertent contaminants, and/or microorganisms such as lactic bacteria that thrive at low pH conditions during fermentation. In addition to organic acids, a large number of
aliphatic aldehydes (acetaldehyde being the major component) and some ketones, particularly acetone and 2,3-butanedione (diacetyl), are found in beer, wines, and distilled spirits, albeit at very low levels (5, pp. 50–72). Terpenes such as geraniol, linalool, and alpha-terpineol have also been detected at the 100–400 ppm level, particularly in some wines (4, pp. 128–31). All of these substances

contribute to the taste and particularly the bouquet of the final product.

Macronutrients

The macronutrients of an alcoholic drink are generally considered to be water, alcohol (ethanol), carbohydrates, nitrogenous matter (proteins and amino acids), and lipids (fats). Carbohydrates are present in significant levels in fermented alcoholic drinks such as wines and beers and the latter two macronutrients are present in relatively low levels, whereas all three of these macronutrients are absent in distilled spirits. Alcohol is considered to have some nutritional value since it provides energy from breakdown within the body to the metabolic end products—carbon dioxide and water. However, the nutritional value of alcohol resulting from ingestion of several glasses of beer, wine, or distilled spirit is generally only 5–10% of the recommended daily requirement.

Micronutrients

The micronutrients found in alcoholic drinks are many and highly variable depending upon the source of the grain, fruit, or vegetable from which the drink is made and may be substantially different from that expected based upon the original ingredients, depending upon the processing conditions. Chemical analysis of the final product is required to know the actual micronutrient content. The micronutrients of beers and wines include essential elements such as calcium, potassium, copper, iron, magnesium, and phosphorus, as well as selenium and zinc along with

commonly recognized vitamins such as thiamine, riboflavin, niacin, pantothenate, pyridoxine, biotin, vitamin C, choline, and betaine, among others. All of these substances are found in almost undetectable amounts, up to a few hundred ppm level at the high end. For more detail and concentration ranges in various fermented drinks see reference (2).

The quantities of essential elements, electrolytes, vitamins, and other substances are present in beers and wines at a level such that they can make significant contributions to the daily diet of regular consumers of these alcoholic drinks, but the contributions are quite variable depending upon the nature and source of the particular beer or wine consumed. These micronutrients are not present in even measurable quantities in distilled spirits because of separation during the distillation process, unless added afterward.

As with all fruits, the level of potassium in wine is typically a factor of ten greater than that of sodium, another essential electrolyte in our bodies, and is found in the range of 600–1,200 mg per litre. At this level, a single glass of wine can provide almost 5% of the minimum daily requirement in our diet, whereas a glass of beer only provides less than half that amount since potassium levels in grains are significantly lower. It should be noted that with wine and beer, sodium and chloride levels are such that consumption has little effect on our body's electrolyte balance since the levels are almost negligible compared with potassium (2).

Phytochemicals and antioxidants

Phytochemicals are the compounds within grains, fruits, and vegetables derived from secondary plant metabolism, in particular bioactive phytoestrogens and antioxidants. These substances have been of great interest over the last two decades owing to the nutritional potential and purported health benefits. These health benefits, including antibiotic and anti-inflammatory claims, are beginning to gain credibility through carefully controlled clinical studies (2). Vitamins and other naturally-occurring antioxidants, typically phenolic compounds such as resveratrol, are found in relatively high levels in a majority of beers and wines, particularly red wines. These substances impart significant levels of antioxidants to consumers of the alcoholic drinks.

The main components of both white and red wines that impart bitterness appear to be relatively low levels of monomeric flavan-3-ols, catechins, and leucocyanidins (3,4-diols) (4). Levels of flavan-3-ols exceeding 35 ppm are considered undesirable but are not usually found in white wines. In red wines, amounts of the flavan-3-ols are much higher than in white wines and are typically above the threshold level of 35 ppm. Also, anthocyanins in combination with tannins have a marked bitterness and are found especially in young wines before ageing modifies their structures. Bitterness is frequently the result of too much extraction of tannins and other flavour components from the skins during fermentation (4).

In red wines, astringency is an essential sensory characteristic which adds ‘bite’ to the drink. This astringency is primarily attributed to flavanoid phenolic compounds that are natural

constituents of the grapes from which the wines are derived. If a high concentration of these substances is extracted from the grape skins during lengthy fermentation, the wine may be considered too harsh and too astringent and therefore will need considerable ageing time to mellow (3, 4).

Additives in alcoholic drinks

Sulphur dioxide (SO_2) has been used in wines since the time of the Romans and is still one of the most useful additives employed in winemaking. Sulphur dioxide has strong antimicrobial activity and when added prior to fermentation of fruit juices inhibits the growth of indigenous yeasts and undesirable contaminating bacteria, particularly acetic acid and lactic acid bacteria that cause spoilage of beers and wines. The yeast strains used in winemaking are not as sensitive to the presence of sulphur dioxide and can tolerate levels approaching 64 ppm. Also, sulphur dioxide or potassium bisulfite ($KHSO_3$) is used during wine storage and just before bottling to both inhibit spoilage of the wines and reduce browning of phenolic compounds that can impart undesirable colour (4, p. 101).

One reason for allowing wines, especially red wines, to 'breathe' for a period of time before serving, is to allow time for small amounts of residual sulphur dioxide or a reduction product hydrogen sulphide to escape. Both of these gases impart an unpleasant sulphur or gunpowder odour to a wine. Decanting the wine is an ideal way of allowing the wines to 'breathe' and also provides aeration that helps enhance the bouquet and taste of most red wines.

In addition to naturally occurring macronutrients and micronutrients, phytochemicals and antioxidants are found in fermented beers and wines, and inorganic ions and heavy metals along with additives, such as preservatives and clarifying agents, as well as pesticide residues. An additive in the context of this chapter is a substance that is intentionally added in small amounts to an alcoholic drink during manufacture. Generally, these additives play important roles in the manufacturing process and are processing aids essential for product characteristics and quality control. Plant materials such as hops, herbs, or spices used to flavour an alcoholic drink are not considered additives.

Because of negative health consequences, there has been considerable interest in the last several decades in the presence and source of heavy-metal contaminants such as Cd^{2+}, Cu^{2+}, Pb^{2+}, Mn^{3+}, and Zn^{2+} in alcoholic drinks. In most instances, the source of these heavy metals is the soil from which the grapes or grain has been harvested and fortuitously the parts-per-million (ppm) or,
more likely, parts-per-billion (ppb) quantities found in most drinks are below levels producing adverse health effects. However, metal and non-metal resides can also result from environmental pollution, adulteration, and contamination by the process equipment employed in the production of the drinks.

For example, when cobalt salts were used in Canada in the late 1960s to stabilize the formation of beer froth, the mortality rate among those who drank large volumes of beer rose to about 50% due to the cobalt ion causing a weakness in the heart muscles that was termed ‘Canadian beer-drinker heart’ (10). The cobalt was used in quantities well below the

legal limit. However, the victims were drinking prodigious quantities of their favourite drink, on average 12 quarts a day of the particular beer. Shortly thereafter, a similar epidemic was noted in Omaha, Nebraska where there were 64 cases and 30 deaths even though the Omaha beer drinkers consumed on average only a six-pack per day (10). Today, cobalt is no longer used as an additive in beer.

During the fermentation process, the concentration of many metallic and heavy metal ions is reduced significantly, at least in part, due to precipitation and/or chemical reactions and subsequent precipitation (e.g. Cu^{2+} as insoluble CuS) from interaction with hydrogen sulphide present in the fermentation liquors. In the case of distilled spirits, most of the minerals and heavy metals are left behind during distillation; however some are still carried over in the distillate. Copper (II) ions (Cu^{2+}) found in some whiskies and distilled spirits are derived largely from the materials-of-construction of the copper stills. In contrast, higher levels of Ni^{2+} and Cu^{2+} are found in beers and wines than in distilled spirits owing to the distillation process.

Distinctive chemical characteristics of beers

The major chemical differences between beers and wines are dictated by the inherent differences between grains and grapes. The grains which are the starting raw materials for beers typically contain half as much sugar as wine grapes. However, beers contain higher levels of complex carbohydrates that frequently survive the fermentation process and are retained in the resulting product. The carbohydrate content of beers ranges from 2.9–3.4% for a

lager beer to 4.6–6.6% for a porter or stout beer. In contrast, low-carbohydrate or light beers contain almost half (0.7–1.8%) the carbohydrate level.

The alcohol content of most beers ranges from 4.0% to 5.7% except for the low-alcohol beers where the typical alcohol content is around 0.4% (2). Alcohol contributes more than the carbohydrate content to the energy or nutritional value of most beers. Proteins may be broken down into smaller peptides and amino acids by activated proteinases that help make the beer clearer. However, some proteins are allowed to remain to hold the head of the beer. Production of low carbohydrate beers is achieved with enzymes that convert the carbohydrates to simple sugars such as glucose and fructose that subsequently are converted into alcohol.

Distinctive chemical characteristics of wines

Sommeliers and those wine drinkers who identify themselves as connoisseurs use the chemical sensors in their nose and mouth to taste or identify the various aromatic chemicals present in their wines with the ostensible purpose of screening the wines for quality or identifying those that have soured by turning to vinegar (acetic acid) generally through air oxidation of the alcohol. The chemical compositions of wines vary widely and with sophisticated analytical instruments hundreds of compounds can be detected at, or below, the ppm level. Someone seeking more specific information and details can consult texts referenced at the end of this chapter (1–7).

Chemistry of spirits (distilled alcoholic drinks)

Distillation of alcoholic fermentation brews from either fruits or grains concentrates the alcohol in the distillate and leaves behind many chemicals such as the proteins, carbohydrates, and some of the higher alcohols or acids that are not volatile under the distillation conditions. Spirits, such as whiskies, brandies, and flavoured liqueurs are concentrations of alcohol (ethanol) typically in the 35–60% range containing other volatile aromatic chemicals. The chemistry of the spirits or whiskies is changed somewhat by ageing in containers such as charred oak caskets that add colour and flavour. In some instances, other chemicals or flavours are added to the resulting distillate. Simplistically, whiskey is beer without the hops that has been distilled and rum is the distilled alcoholic drink made from sugar cane. In contrast, brandies and cognacs are wines that have been distilled. Distilled alcoholic drinks were known in China as early as 800 BCE when rice wine was distilled (4).

The concentration of alcohol as mentioned previously is generally specified as the percentage of alcohol by volume and the term 'proof' is approximately a 2:1 ratio to the alcohol content by volume (e.g. 80 proof = 40% alcohol by volume) and the alcohol content cannot exceed 191 proof since at that level alcohol (ethanol) co-distils with water. Alcoholic drinks with this alcohol content are referred to as grain alcohol. As an aside, alcohol is also used in fuel in the United States principally to improve the combustion of the gasoline to reduce the level of environmental pollution. For this use, the remaining 5% of water contained in the

distillation is removed to improve storage and reduce fuel line freezing or separation of the water in cold weather.

The complexity of alcoholic drinks is exemplified by chemical analysis of whiskey, rum, and brandy that reveals these drinks' complexity by the use of gas chromatography. Using similar methods and sensitivity, 269 aroma compounds were detected in whiskey, 497 in rum, and over 546 in brandy (4, pp. 436–44). Understandably, these figures will vary for each brand and type of distilled spirit as well as with the type and sensitivity of the analytical method. However, these relative number of aroma components do indicate the complexity of the various alcoholic drinks.

Higher alcohols (more than two carbon atoms) are believed to have a major impact on the flavour and aroma of distilled drinks. In one study, the largest amounts of the higher alcohols (primarily propanol, isobutanol, 2-methylbutanol, and isopentanol) were found in a heavily flavoured bourbon whiskey containing more than 2 g/L (2,000 ppm). While the same study found some Irish and Scotch whiskies had somewhat less than 2 g/L of the higher alcohols and other whiskies with a light aroma and lighter flavour had only 0.5 g/L of these higher alcohols. Other studies have found the higher alcohol levels to range from 1.6 to 5.0 g/L in bourbon whiskies. These and related studies seem to suggest a correlation of higher alcohol levels with perceived aroma and flavour (5, pp. 27–9).

Chemistry of spoiled alcoholic drinks

The spoilage of fermented alcoholic drinks, both beers and wines, is generally attributed to either acetic acid bacteria (*Acetobacter pasteurianus*) or lactic acid bacteria (*Lactobacillus*). The former converts ethanol to acetic acid and imparts a vinegary or 'mousy' sweet-sour taste and turbidity (3, p. 394) to the beer or wine. Acetic acid bacteria can also esterify the acetic acid producing ethyl acetate that imparts unpleasant organoleptic characteristics reminiscent of nail polish remover and vinegar. If left exposed to the air, the bacteria can convert all of the alcohol in wine to acetic acid and hence produce wine vinegar.

Lactic acid bacteria are the more likely and more important bacteria involved in the spoilage of wine producing souring, off-tastes, turbidity, and even slime production. Sweet (high-sugar) wines are most affected. The lactic acid bacteria convert malic acid in what is called malolactic fermentation to lactic acid and carbon dioxide. This often occurs even in bottled wines in the presence of no or little oxygen.

In most cases of beer or wine spoilage, however, yeasts are the most likely organism causing taste defects, cloudiness, and sediment formation along with gas (carbon dioxide) production. Yeasts can produce undesirable flavours, including estery, acidic, phenolic, or medicinal tastes along with hydrogen sulphide (odour of rotten eggs). These wild yeasts remain in the beer or wine after fermentation due to ineffective filtration procedures and produce their effects during storage or even after bottling.

Chemical substances in alcoholic drinks leading to hangovers

The root cause of all alcoholic drink-induced hangovers is the consumption of more alcohol than your body can metabolize efficiently. The source of most hangovers is chemicals present in such drinks that, either directly or indirectly through metabolism within the body, supply toxins that make a person feel sick and hence cause a hangover. The primary toxin in an alcoholic drink is alcohol (ethanol) itself that is subsequently metabolized to an even more toxic substance, acetaldehyde through oxidation in the liver by the enzyme alcohol dehydrogenase. Acetaldehyde is the alcohol by-product that most research indicates as the cause of the worst hangover symptoms. Fortunately, over time, the acetaldehyde is further oxidized within the body to the relatively non-toxic acetic acid.

Congeners, impurities produced in the drinks during the fermentation process that give them a pleasing colour, flavour, and smell, are another cause of hangovers. Examples of typical congeners are amines, amides, ketones, polyphenols, methanol, and histamine. Low-quality wines and particularly many dark-coloured alcoholic drinks tend to have high levels of congeners. One rule of thumb is the darker the drink, the worse the hangover potential.

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Chapter 8
Alcohol metabolism and genetic control

Philip J. Brooks and Samir Zakhari

Introduction

Alcohol metabolism plays a key role in the biological and toxic effects of alcohol consumption on the human body. In this chapter we discuss the main pathways of alcohol metabolism, as well as the role of genetics in modulating alcohol metabolism. The three main enzymes that carry out alcohol oxidation are alcohol dehydrogenase, cytochrome P450 2E1, and, to a lesser extent, catalase, all of which generate acetaldehyde. In addition to these three enzymes, we also discuss the importance of microbial alcohol metabolism, as the production of acetaldehyde by microbes in human gastrointestinal (GI) tract plays an important role in alcohol-related carcinogenesis. While we also mention the implications of genetic variation in alcohol metabolism for the development of alcoholism and alcohol-related carcinogenesis, these topics are the main focus in other chapters of this book and the reader is directed to those chapters for a detailed discussion.

Overview

The concentration of ethanol in alcoholic drinks ranges from approximately 800 mM in beer to over 8 M in hard liquor (50% ethanol). When consumed orally, alcoholic drinks pass through the oral cavity and oesophagus to the stomach.

Ethanol is slowly absorbed from the stomach, but rapidly absorbed from the small intestine. Only about 2–10% of the absorbed alcohol is eliminated via the lungs and kidneys; the remaining 90% is metabolized by enzymatic oxidation, mainly in the liver.

Enzymes involved in alcohol oxidation

Alcohol dehydrogenases

The major pathway of ethanol metabolism in the human body is oxidation to acetaldehyde by the enzyme alcohol dehydrogenase (ADH). As illustrated in Figure 8.1, ADHs require nicotinamide adenine dinucleotide (NAD) in its oxidized form, NAD+, for catalysis. As ethanol is oxidized to acetaldehyde, NAD+ is reduced to NADH. Changes in the reduction/oxidation (redox) state of NAD during ethanol metabolism can have significant effects on liver function, as discussed in more detail in the section entitled 'Redox changes from alcohol metabolism'.

The human genome contains seven *ADH* genes (Table 8.1). The products of the *ADH1* genes, which in humans includes *ADH1A*, *ADH1B*, and *ADH1C* (1) are collectively referred to as class I ADHs. Each *ADH1* gene encodes a polypeptide of roughly 40 kD in mass. These different polypeptides form functional homo- or hetero-dimers, which are the active forms of the enzymes. These genes are expressed at highest levels in the liver, but are also expressed in other tissues including the GI tract and reproductive tissues (4). Notably, class 1 ADHs are not expressed in brain or placenta. In the liver, the class I ADHs are estimated to be responsible for roughly 70% of the

hepatic ethanol metabolism, with the remainder being carried out by the product of the *ADH4* gene, and, under conditions of high blood alcohol level, by CYP2E1, as will be discussed.

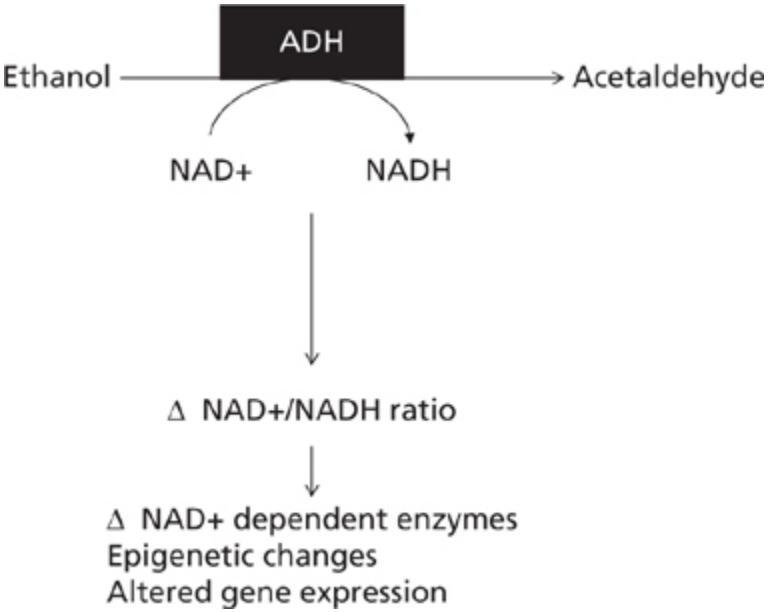

Figure 8.1 Alcohol dehydrogenase (ADH) oxidizes ethanol to acetaldehyde. ADH requires NAD+ as a co-factor, which is reduced to NADH during catalysis. Changes in the redox state of NAD (the NAD+/NADH ratio) resulting from alcohol metabolism can impact other cellular processes.

Table 8.1 Human ADH genes and proteins

Gene nomenclature		Protein subunit	Km (mM)	Vmax (min^{-1})	Populations with high allele frequencies
New	**Former**				
ADH1A	*ADH1*	α	4.2	27	Europe, Africa
*ADH1B*1*	*ADH2*1*	β1	0.05	9	Europe, Africa
*ADH1B*2*	*ADH2*2*	β2	0.9	400	Asia
*ADH1B*3*	*ADH2*3*	β3	34	300	Africa, Native American
*ADH1C*1*	*ADH3*1*	γ1	1.0	87	All
*ADH1C*2*	*ADH3*2*	γ2	0.6	35	Europe
*ADH1C*2*	*ADH3*2*	γ3	NR	NR	Native American
*ADH4*1*	*ADH4*1*	π1	34	40	All
*ADH4*2*	*ADH4*2*	π2	10.6	10.5	Sweden
ADH5	*ADH5*	χ	>1000	100	All
ADH6	*ADH6*	NP	30	NR	All
ADH7	*ADH7*	σ	30	1800	All

Note: the nomenclature for the *ADH* genes was changed in 1999 (1); the former nomenclature is included here as it used in some of the older literature. The population distribution indicates those populations which have high allele frequencies, but alleles are found in other populations as well. The Km for ethanol is given in mM. Vmax (maximum velocity) values are given as turnover number (/min) for comparison between enzymes. NP = not purified, NR = not reported.

The importance of the class I ADHs for hepatic alcohol metabolism in humans is not only due to high levels of expression in the liver, but also to their affinity for ethanol as well. The Km for ethanol, listed in Table 8.1, is the concentration at which the rate of enzyme activity is half the maximal rate. As shown in the table, the Km of many of the class I ADHs for ethanol are generally less than 1 mM—well below the blood ethanol for legal intoxication (in the United States), which is roughly 20 mM. Therefore, at blood alcohol levels that can be readily achieved during social drinking, class 1 ADHs oxidize ethanol at near maximal capacity.

ADH7 is the only *ADH* gene that is not expressed in the liver. *ADH7* expression is highest in cornea, as well as in epithelial cells in the oesophagus, oral cavity, and stomach. The Km of human ADH7 for ethanol is 30 mM (5), which is relatively high compared to the class I enzymes. This enzyme also has a higher turnover rate (Vmax) than other ADHs. However, by virtue of its expression in the oral cavity, oesophagus, and stomach, cells expressing *ADH7* are transiently exposed to ethanol at concentrations present in alcoholic drinks, which can be very high (in the molar range). Therefore, ADH7 likely plays an important role in local alcohol metabolism in certain tissues, especially in the stomach.

ADH7 has a high affinity for retinol, suggesting that its primary function in the body is as a retinol dehydrogenase (5). As such, metabolism of ethanol by ADH7 not only generates acetaldehyde, but may also competitively inhibit retinol metabolism, which can have powerful effects on cellular differentiation and development, and possibly carcinogenesis (6, 7).

The *ADH1B* and *ADH1C* genes are polymorphic in humans. Table 8.1 shows the different variants of these genes as well as their functional consequences. The *ADH1B*2* allele, encoding a protein containing His at position 47 rather than Arg, is particularly notable for its nearly 100-fold higher activity compared to *ADH1B*1*. This allele is found at highest frequencies in Asian populations, but is also present at a lower frequency in the Ashkenazi Jewish population, and in both populations, individuals with the *ADH1B*2* variant have a reduced risk of alcoholism (8, 9). This protective effect may be attributed to aversive properties of elevated acetaldehyde levels in the GI tract and liver (10).

In European populations, the *ADH1B*2* allele was reported to be protective against alcohol-related cancer of the upper aerodigestive tract (11). This same study provided evidence for a protective effect of a variant in *ADH7*, although the functional significance of the *ADH7* marker was not determined. In Asians, the effect of the *ADH1B*2* on alcohol-related cancer is complex, and affected by the *ALDH2*2* allele, which is common in this population (12). The *ALDH2*2* results in the inability to metabolize acetaldehyde, which in turn dramatically effects the risk of oesophageal cancer (13), as will be discussed. The relationship between *ADH* gene polymorphisms and cancer are addressed in Chapter 24, 'Alcohol and carcinogenesis: mechanisms and biomarkers', Chapter 25, 'Upper aerodigestive tumours: mouth, pharynx, larynx, and oesophagus', and references (2, 14).

Cytochrome P4502E1

The second major clinically relevant pathway of ethanol oxidation involves the enzyme cytochrome P450 2E1, referred to as CYP2E1 (Figure 8.2). CYP2E1 is a major enzymatic component of the so-called microsomal ethanol oxidation system (MEOS) discovered by Charles Lieber in the 1970s (15). The term MEOS is primarily found in the older literature but is sometimes still encountered today. In this context, it should be noted that while the majority of CYP2E1 is found in the endoplasmic reticulum ('microsomes') more recent studies have demonstrated that some CYP2E1 protein is also present in the mitochondria (16).

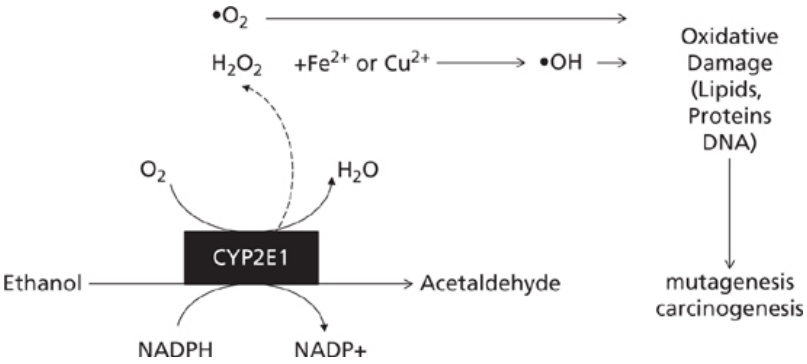

Figure 8.2 CYP2E1 oxidizes ethanol to acetaldehyde, in a reaction requiring molecular oxygen, which is converted to water, and NADPH, which is converted to NADP+. During catalysis, CYP2E1 can release reactive oxygen species (ROS), including superoxide and hydrogen peroxide, and can result in oxidative damage to cellular components, including DNA.

From a mechanistic standpoint, CYP2E1 is a fundamentally different enzyme than alcohol dehydrogenase. CYP2E1 utilizes the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor, and also requires molecular oxygen, which is reduced to water during catalysis. The Km of CYP2E1 for ethanol is 10 mM, which is roughly one order of magnitude higher than that of ADH1. Therefore, at low blood alcohol levels, the contribution of CYP2E1 to ethanol oxidation is limited. In addition to kinetic considerations, another reason for the increased importance of CYP2E1 for ethanol metabolism of high blood alcohol levels is that the enzyme is inducible by ethanol. Ethanol is both a substrate for CYP2E1 and decreases its degradation (17), resulting in an elevated steady-state level of CYP2E1. This

property is the reason that CYP2E1 is referred to as the ethanol-inducible cytochrome P450 (18, 19). At high blood alcohol levels, up to 30% of hepatic ethanol metabolism may be due to CYP2E1 (2).

The *CYP2E1* gene is expressed at highest levels in the liver, and an elevated level of CYP2E1 protein under conditions of alcohol exposure are readily demonstrated in this tissue. Importantly however, *CYP2E1* is also expressed in a variety of other tissues, albeit at lower levels than in the liver, and is alcohol-inducible in both liver and extrahepatic tissues, including the brain (20, 21).

As already noted, the contribution of CYP2E1 to acetaldehyde production is relatively small compared to that of ADH. From the human health standpoint however, the major significance of CYP2E1 is not so much acetaldehyde production but the production of reactive oxygen species (ROS). CYP2E1 is a loosely coupled cytochrome P450 (22), which essentially means that it has a high capacity to generate the ROS superoxide and hydrogen peroxide during catalysis (Figure 8.2). Superoxide is an oxygen radical which can rapidly react with other cellular constituents, resulting in oxidative damage. Hydrogen peroxide, while not a radical, can react with iron or copper via the Fenton reaction to generate the hydroxyl radical. The hydroxyl radical is extremely reactive, and can cause damage to DNA or lipids, resulting in lipid peroxidation products which can cause additional damage to cellular constituents (23). Based on these considerations, as well as multiple experimental studies, there is substantial evidence for a role for oxidative stress resulting from CYP2E1 in alcohol-induced liver injury (24).

In addition, of relevance to alcohol-related cancer, lipid peroxidation products resulting from alcohol metabolism by CYP2E1 have been shown to react with DNA to produce mutagenic ethenobase DNA adducts (25). As such, lipid peroxidation resulting from ethanol metabolism by CYP2E1 may play a mechanistically important role in several alcohol-induced cancers, particularly those arising in highly proliferative epithelial tissues such as those in the upper GI tract, colon, and breast.

Some work has been done on genetic polymorphisms in the *CYP2E1* gene. A continually updated list of these can be found online (26). Perhaps the most well-studied *CYP2E1* genetic variants are the c1 and c2 alleles present in the 5′ flanking region of the *CYP2E1* gene that have been reported to affect gene expression (27, 28). The relationship between these and other different *CYP2E1* alleles and alcohol-related pathologies has been reviewed by Neafsey et al. (29) A conclusion from this analysis is that although some studies have reported relationships between certain *CYP2E1* genetic variants and alcohol-related pathologies, most of the studies have been underpowered to detect moderate effects, and many of the effects that have been reported in the literature have not been consistently replicated. One reason for this is likely to be the fact that, as noted earlier, a major mechanism of CYP2E1 regulation is protein stabilization by ethanol and other substrates (18, 19). In view of this, and the multiple substrates of CYP2E1 that can both stabilize the enzyme and are metabolized by it, the detection of strong relationships between genetic polymorphisms in *CYP2E1* and alcohol-related pathologies may be difficult to demonstrate.

Finally, it is important to stress that in addition to ethanol, CYP2E1 can also metabolize a wide variety of low-molecular-weight organic compounds, including commonly utilized drugs such as acetaminophen, as well as pro-carcinogens such as dimethyl nitrosamine (30, 31). For this reason, induction of CYP2E1 is of potential medical relevance not only in relation to the effects of alcohol per se, but also in the context of drug interactions. As one example, ingestion of acetaminophen by individuals following alcohol consumption can lead to serious and in some cases fatal liver damage as a result of metabolism by ethanol-induced CYP2E1 (32).

Catalase

A third enzymatic pathway for alcohol oxidation involves the enzyme catalase, which is more commonly known for its ability to degrade hydrogen peroxide (33). Catalase can oxidize ethanol in the presence of hydrogen peroxide which is a necessary substrate for the reaction (Figure 8.3).

The majority of recent research in this area has focused on the role of catalase in the metabolism of ethanol into acetaldehyde in the brain. Based upon several lines of evidence, it seems that catalase does represent one enzymatic pathway by which ethanol can be metabolized to acetaldehyde in the brain (34, 35). A separate, yet related question is the extent to which alcohol metabolism into acetaldehyde by catalase is involved in the rewarding effects of alcohol. Previous studies have provided evidence for this possibility (reviewed in (34, 35)) but are difficult to interpret unambiguously because of questions regarding the specificity

of the enzyme inhibitors utilized. However, a recent study by Israel et al. (36), using lentiviral vectors to modulate catalase and ALDH2 levels in the brain, has provided additional evidence of acetaldehyde production as a result of ethanol metabolism by catalase. In addition, they also provided evidence that acetaldehyde production in the ventral tegmental area of the brain is involved in mediating the rewarding effects of ethanol in a rat model.

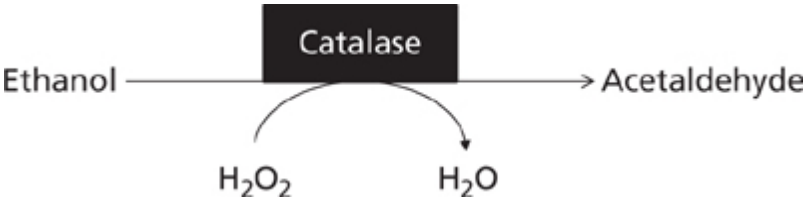

Figure 8.3 Catalase oxidizes ethanol to acetaldehyde, in a reaction requiring H_2O_2.

Several common polymorphisms in the catalase (*CAT*) gene polymorphisms have been described in the literature, but these do not alter catalase enzyme activity (37). Notably, rare inactivating mutations in the human *CAT* gene have been reported in the Japanese, Hungarian, and Swiss populations (38). Interestingly, the diseases associated with these mutations are variable, including increased risk of oral gangrene, metabolic abnormalities, and diabetes mellitus (37). Given the different populations, this heterogeneity in the clinical presentation of catalase deficiency is likely to reflect either genetic variation in other genes that regulate hydrogen peroxide production or degradation, and/or exposure to environmental sources of hydrogen peroxide production. In view of the evidence for an important role for acetaldehyde

derived from ethanol metabolism by brain catalase in the rewarding effects of ethanol, investigation of alcohol drinking by catalase-deficient humans would seem to be of great interest.

Having considered the three classes of enzymes responsible for ethanol oxidation, we now turn to the next step in the ethanol oxidation pathway, which is the oxidation of acetaldehyde to acetate.

Acetaldehyde metabolism

The metabolism of acetaldehyde into acetate is carried out by the enzyme aldehyde dehydrogenase (ALDH) (Figure 8.4). The human ALDH gene superfamily contains at least 19 known genes, with varying aldehyde substrates (39). With regard to the metabolism of acetaldehyde resulting from alcohol degradation, the three most relevant are *ALDH2*, *ALDH1B1*, and *ALDH1A*. These will now be discussed in order of affinity for acetaldehyde (40).

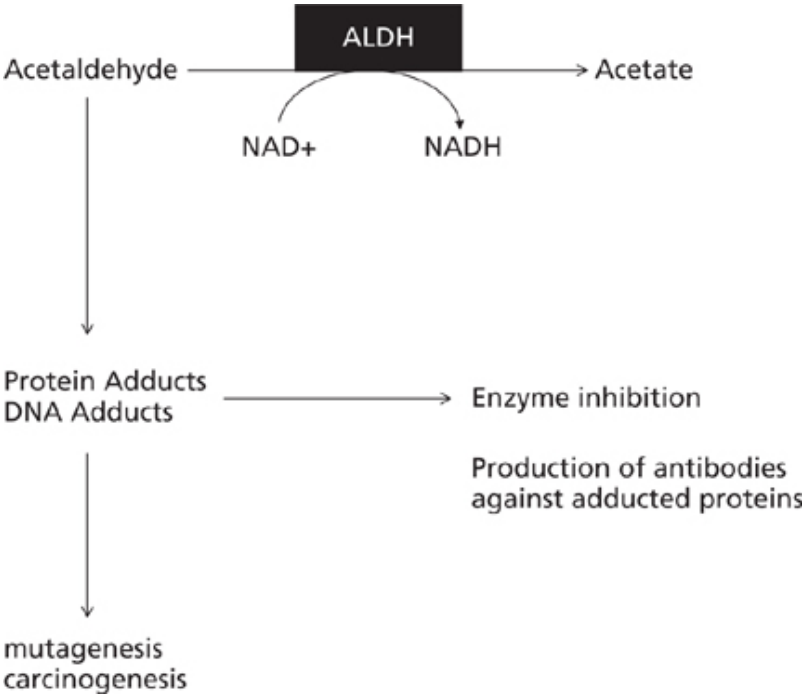

Figure 8.4 Aldehyde dehydrogenase (ALDH) converts acetaldehyde to acetate, thereby protecting cells and tissues against the toxic effects of acetaldehyde. Like ADH, ALDH requires NAD+ as a co-factor, which is reduced to NADH during catalysis. Changes in the redox state of NAD (the NAD+/NADH ratio) resulting from alcohol and acetaldehyde metabolism can impact other cellular processes.

ALDH2

The ALDH2 protein, which is localized in the mitochondrion, is the most well-studied and most relevant enzyme from the standpoint of alcohol metabolism in humans. It has the

highest affinity for acetaldehyde (Km <5 uM), and its co-factor requirements ensure activity under conditions of alcohol metabolism *in vivo*. The active form of the enzyme is a tetramer, the structure of which has been determined (41). *ALDH2* is expressed at highest levels in the liver, although lower levels are expressed in multiple other tissues, including kidney, skeletal and cardiac muscle, and mammary tissue (42). There is also biochemical evidence for ALDH2 activity in the human parotid gland, which influences acetaldehyde levels in the saliva during alcohol drinking (43).

The crucial importance of ALDH2 in the metabolism of acetaldehyde derived from ethanol oxidation is demonstrated by the effects of a functional polymorphism in *ALDH2* which is common in East Asian populations. Specifically, roughly 40% of individuals of East Asian descent have a genetic variant, the *ALDH2*2* allele, which changes the amino acid at position 487 from glutamate to lysine. This amino acid substitution acts in a semi-dominant manner, resulting in dramatic reductions in ALDH2 enzyme activity in both heterozygous (*ALDH2*1/*2*) and homozygous (*ALDH2*2/*2*) individuals (44).

When ALDH2-decificent individuals consume alcohol, they experience the so-called alcohol flushing reaction, characterized by facial flushing, tachycardia, and nausea (45). The facial flushing itself is the result of acetaldehyde stimulation of histamine release (46). The intensity of the flushing reaction is greater in homozygotes compared to heterozygotes, as expected given that heterozygotes retain a small amount of functional enzyme. Because of the aversive effects of acetaldehyde resulting from drinking alcohol, the *ALDH2*2* allele is protective against the development of

alcoholism. This protection is particularly strong for *ALDH2*2* homozygotes, as alcoholism is extremely rare in this population. *ALDH2*2* heterozygotes are roughly five times less likely to become alcoholic than those with fully active ALDH2 (for review see (10)).

The relationship between the *ALDH2*2* allele, alcohol drinking, and oesophageal cancer is a particularly interesting example of genotype–phenotype interactions, involving both behavioural and biochemical processes. Essentially, because of the aversive effects of acetaldehyde generated from ethanol metabolism, *ALDH2*2* homozygotes consume very little alcohol. As such, they are not only better protected against alcoholism, but because alcohol drinking is a risk factor for oesophageal cancer, *ALDH2*2* homozygotes are at statistically lower risk of oesophageal cancer than those with fully active ALDH2 (47). However, subsets of *ALDH2*2* heterozygous individuals do become heavy drinkers, perhaps due in part to environmental factors (13). In these individuals, alcohol drinking results in a dramatically elevated risk of oesophageal cancer compared to those with fully active ALDH2, with odds ratios of over 100 for very heavy alcohol consumption in this population (for review see (13)). It was largely on the basis of studies of oesophageal cancer in ALDH2-deficient Japanese alcoholics, initiated by Yokayama et al. (12, 48), that led to the IARC designation of acetaldehyde as carcinogenic to humans in the oesophagus (49). This topic is addressed in more detail in Chapter 24, ‘Alcohol and carcinogenesis: mechanisms and biomarkers’.

ALDH1B1

Like ALDH2, ALDH1B1 is localized to the mitochondria, though the Km of ALDH1B1 for acetaldehyde is roughly an order of magnitude higher than ALDH2 (40). However, this enzyme could still be of physiological relevance under conditions of ethanol metabolism, especially in ALDH2-deficient individuals, and also in the GI tract, where high levels of acetaldehyde can be
generated as a result of alcohol metabolism by microbes. Also, there is evidence that expression of *ALDH1B1* is a potential biomarker of colon cancer (50).

ALDH1A1

The major cytoplasmic aldehyde dehydrogenase of relevance to alcohol metabolism is ALDH1A1. The Km of ALDH1A1 for acetaldehyde is higher than that for ALDH1B1 (40), but as discussed for that enzyme, it may still be relevant for alcohol metabolism in ALDH2-deficient individuals and in the oral cavity and GI tract. Also, similar to ADH7 the primary physiological role for ALDH1A1 appears to be in retinoid metabolism, and here again, high levels of acetaldehyde could impact cellular differentiation by acting as a competitive inhibitor of retinal metabolism (6).

Toxicity of acetaldehyde

Acetaldehyde is responsible for many of the aversive effects of drinking ethanol, as well as many of the health consequences, including alcohol-related oesophageal cancer. Like other aldehydes, acetaldehyde is highly reactive, and can

form covalent adducts with cellular components that contain free amino groups, which include biogenic amines, proteins, and nucleic acids (Figure 8.4). Acetaldehyde-protein adducts can interfere with cellular functions (51) as well as inhibit the activity of enzymes (52), notably that of DNA methyltransferase (53). In addition, the reaction of acetaldehyde with proteins can generate immunogenic compounds that may play a role in some toxic effects of alcohol (54).

In addition to effects on proteins, acetaldehyde can also react directly with the exocyclic amino group of deoxyguanosine, resulting in a variety of acetaldehyde-DNA adducts (55). Elevated levels of acetaldehyde DNA adducts have been detected in the DNA of white blood cells from ALDH2-deficient alcoholics, in whom the risk of oesophageal cancer from alcohol drinking is highest, providing circumstantial evidence for mutagenic DNA damage in alcohol-related carcinogenesis. Direct evidence of acetaldehyde adduct formation in the human oral cavity following alcohol drinking has recently been published (56). Acetaldehyde also causes hyperregeneration in the GI tract (57), which may facilitate the generation of some forms of acetaldehyde-DNA adducts (58). Other evidence supports a role for ethenobase DNA adducts resulting from CYP2E1 in alcohol-related oesophageal carcinogenesis (25).

In terms of genetic control, recent work has highlighted the importance of the Fanconi anaemia (FA)-BRCA DNA damage response network (59) in protecting against acetaldehyde-related toxicity. Following the demonstration that acetaldehyde can activate the FA-BRCA network in human cells *in vitro* (60), Langevin et al. (61) showed that

mice lacking the *FancD2* gene are highly sensitive to the genotoxic effects of endogenous aldehydes that are normally metabolized by Aldh2, and also to the effects of ethanol. Although FA is a rare disease, the extreme sensitivity of FancD2-deficient mice to acetaldehyde raises the possibility that humans with hypomorphic variants in the *FANC* or *BRCA* genes, which do not in themselves result in overt clinical effects, might be differentially susceptible to the carcinogenic or other toxic effects of acetaldehyde resulting from ethanol metabolism (62). The possible role of genetic variation in *FANC* and *BRCA* genes could be tested in human genetic epidemiology studies.

Other pathological effects of alcohol metabolism

In terms of the mechanistic basis of the toxic effects of alcohol metabolism, acetaldehyde and reactive oxygen species resulting from CYP2E1 have understandably received the most attention.

Here we consider two other effects of alcohol metabolism, acetate production and redox changes in NAD, which are also of potential clinical relevance and likely to be the subject of additional research in the future.

Acetate production

The final product of alcohol metabolism by the canonical pathway of ADH and ALDH is acetate. Most of the acetate resulting from ethanol metabolism leaves the liver, because liver mitochondria generally lack acetyl CoA synthase 2, a mitochondrial enzyme involved in the oxidation of acetate (63). As a result, acetate resulting from ethanol metabolism in

the liver is eventually metabolized to CO_2 via the tricarboxylic acid cycle in tissues that can convert acetate to acetyl CoA, such as the heart, skeletal muscle, and brain.

While acetate is generally not considered a toxic substance, acetate can itself have important effects in the body, including increased portal blood flow in the liver, central nervous system depression, and other metabolic effects (64). A recent study suggests that acetate may play a role in hangovers (65).

At least some of the effects of alcohol on the brain may be the result of the brain using acetate as a substrate rather than glucose (66), analogous to the use of fatty acids in severe starvation when glucose levels are low. Under conditions of moderate alcohol consumption, it is not clear whether levels of serum acetate would be high enough to explain the effects of alcohol on brain metabolism. However, under *in vivo* conditions of heavy alcohol consumption, perhaps in combination with hormonal or other pathological states (66), it seems possible that acetate resulting from hepatic alcoholism metabolism could impact brain function, and play a role in alcohol-related brain pathology. Aside from *ALDH2*, the possible role of genetic variation in mediating the effects of acetate produced from ethanol metabolism is largely unstudied.

Redox changes from alcohol metabolism

Another important and underappreciated aspect of alcohol metabolism is the change in the ratio of NAD+ and NADH that occurs as a result of alcohol metabolism, especially in the liver. As ethanol and acetaldehyde are oxidized by ADH and ALDH, respectively, NAD+ is reduced to NADH, resulting in

substantial changes in cellular levels of these co-factors (67). Since NAD+ is involved in many other biochemical processes, these changes in NAD+ levels resulting from alcohol and acetaldehyde metabolism have the potential to impact many other biochemical reactions in hepatocytes, causing a marked alteration in multiple reversible metabolic pathways (68). A full discussion of all of these pathways is beyond the scope of this chapter, but several comprehensive recent reviews are available (69). To give just one relevant example, alcoholic steatosis (fatty liver) is due, at least in part, to redox changes in the liver resulting from alcohol metabolism, leading to inhibition of fatty acid oxidation, (70) although other biochemical mechanisms are involved as well (71).

One well-studied class of enzymes whose activities are regulated by changes in NAD+ levels are the sirtuins, encoded by the *SIRT* genes. Sirtuins are NAD+ deacetylases that control the activity of many downstream factors by regulating protein acetylation, including histone proteins (72). Since histone acetylation is an epigenetic regulator of gene expression, (73) changes in NAD+ levels during alcohol metabolism can be dynamically translated into epigenetic changes controlling gene expression via modulation of sirtuin activity. As such, the impact of genetic variation in *SIRT* genes, as well as genes involved in other NAD+ regulated biochemical pathways, will be an important aspect of research on the health effects of alcohol metabolism in the future.

Non-oxidative pathways of ethanol metabolism

In addition to enzymatic oxidation, ethanol can be non-oxidatively metabolized by at least two pathways: one leads to the formation of fatty acid ethyl esters (FAEEs) and the other to phosphatidylethanol. FAEEs are esterification products of ethanol and endogenous fatty acids or fatty acyl coenzyme A (74). There is some evidence that FAEE could mediate ethanol-induced tissue damage after chronic high ethanol consumption (75). However, the role of FAEE in ethanol-induced tissue damage remains to be further evaluated. Because FAEEs are detectable in serum and other tissues after ethanol ingestion and persist long after alcohol is eliminated, the primary interest in these compounds is as biomarkers of ethanol consumption (76).

The second non-oxidative pathway requires phospholipase D (PLD) and inserts ethanol in place of choline on phosphatidylcholine to form phosphatidylethanol (77). Phospholipase D has a high Km for ethanol, and therefore the reaction would be most important predominantly at high circulating ethanol concentrations. However, phosphatidylethanol is poorly metabolized and may accumulate to detectable levels following chronic consumption of large amounts of ethanol. The effect of phosphatidylethanol on biomembranes and phospholipid-dependent processes remains to be established.

Alcohol metabolism by microbes in the human body

A complete understanding of alcohol metabolism in the human body must include not only human genes and proteins,

but also the genes and proteins encoded by resident microorganisms. Microbes exist at multiple sites in the human body (78), but from the standpoint of alcohol metabolism, the most relevant are those in the intestines and oral cavity. Regarding the intestines, pioneering studies by Salaspuro and colleagues demonstrated the importance of microbes in colonic alcohol metabolism (79). After a bolus of ethanol, acetaldehyde concentrations in the colonic contents reached the 0.1–1 mM range, and in some cases even higher. Importantly, acetaldehyde production is much lower in animals treated with antibiotics to deplete the bacterial population of the colon, thereby proving that much of this colonic alcohol metabolism was carried out by bacteria (80). Similarly, altering the characteristics of the gut microbiota influences acetaldehyde production from dietary ethanol (81). Given this capacity for microbial acetaldehyde production from alcohol, it would be expected that alcohol consumption would result in adaptive changes in the composition of the gut microbiota, and in fact this is the case (82).

Salaspuro and colleagues have also shown that microbes in the human oral cavity can convert alcohol into acetaldehyde (83). Cigarette smoking also impacts the composition of the oral microbiota, which in turn affects acetaldehyde production in the oral cavity (84). There is also evidence for functional interactions between microbial alcohol metabolism in the oral cavity and human genetic variation in the *ADH* and *ALDH* genes (85–87). The situation is complex, in that alcohol consumption and acetaldehyde production, which are under genetic control, can impact the composition of the oral microbiota, while on the other hand, the levels of salivary acetaldehyde generated by microbial ethanol metabolism will be regulated by human genetic variation in *ALDH2*. It is

likely that a similarly complicated set of interactions between host genetic variation and microbial ethanol metabolism occurs in the colon, and may regulate alcohol-related colorectal cancer as well.

From a broader perspective, in view of the increasing focus on the microbiome in relation to human health (78), it is likely that more such studies will be carried out in the future, involving not only the *ADH* and *ALDH* genes, but other genes as well.

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Chapter 9
Implications of the genetics of alcoholism and addictions for public policy

David Goldman

Introduction

Knowledge of the neuroscience and epidemiology of addictions is one factor in striking the right balance for the regulation of addictive agents (1). In the two decades since Kalant and Goldstein discussed this problem, neuroscience has greatly advanced and the progress includes unprecedented genetic discoveries, including the identification of genetic loci modulating vulnerability to addiction. However, their conclusions, reflecting a conservative approach to easing access to addictive agents, are perhaps unchanged. On the other hand, in a conversation largely uninformed by neuroscience, it has been questioned whether alcoholism and other addictions are indeed diseases. At the root of this question is the role that volition plays in addictions. Although there seems no realistic possibility that addictions will be discarded as medical diagnoses, in part because other complex diseases also involve choice, the perception that addiction is a choice or sin has a chilling influence on the everyday likelihood that addicts are diagnosed and treated, and also curbs enthusiasm for the establishment and funding of medical care. Paradoxically, experts in the genetics of psychiatric diseases have advanced the idea that genetic research on alcoholism should be a lower priority than for other diseases because of the fact that one cannot be an

alcoholic if one chooses not to drink. By one way of thinking, the problem of alcoholism, and by extension other addictions, can be solved by more effective prevention, rather than investments in research (2).

This chapter offers a perspective on implications of the genetics of alcoholism for public policy, rather than a comprehensive review. It draws from reviews (3, 4) as well as original sources, with a focus on alcoholism. The genetics of alcoholism is a highly active research domain with numerous discoveries that are potentially far-reaching but futuristic in their implications, such as genes that alter alcohol-associated behaviours of *Drosophila melanogaster* (5, 6). These studies are representative of an ongoing and intensifying pursuit of the origins of alcoholism, but generally do not critically inform present-day policy discussion.

Questions to consider

What is the heritability of alcoholism, the role of genes in addiction processes, and uses and limitations of genetic research? To what extent do genetic findings validate the medical disease model of alcoholism? How are the medical and self-help models informed by genetic research, and how is either evolving in response to genetic findings?

Genetic epidemiology of alcoholism

According to the World Health Organization (WHO), two billion people consume alcoholic drinks and 76.3 million have alcohol use disorders (7). The 2009 National Survey on Drug Use and Health (NSDUH) reported that 130.6 million

Americans are current drinkers. Alcohol accounts for 69.4 million disability-adjusted life years (DALYs)—years of life lost due to premature mortality or disability—4.5% of all DALYs (7). Tobacco and illicit drugs, agents for which addictions inheritance is, in part, shared with alcoholism, account for more. Tobacco subtracts 59.1 million DALYs (4.1%) and illicit drugs lead to loss of 12.2 million (0.8%) DALYs (8). Worldwide, alcohol use and alcoholism are more common in males than in women; however, the male/female ratio for use of alcohol and other psychoactive substances has narrowed over time, consistent with changing social roles. Women generally have lower first-pass metabolism of alcohol and therefore may be more vulnerable to adverse effects.

The consumption of alcohol follows the distribution of people; more alcohol is consumed in China than in any other country on the planet (9). However, there is substantial transnational variation, with severalfold variation between countries and a strong correlation between alcohol consumption and alcoholism (10). This relationship does not diminish the importance of other exposures, such as stress, and as will be discussed there are specific gene × environment (G × E) interactions involving stress. Furthermore, alcoholism and other addictions thrive among the poor and deprived, who have higher rates of mental disorders (11). Overall determinants of health and resiliency include education, social support, income, social status, nutrition, clean water, environmental quality, employment, and access to health services. Alcoholism in turn leads to deterioration in several of these socially-based determinants. The relationship between alcoholism, other addictions, and mental illness to poverty is complex, reciprocal, and self-maintaining (12).

Although genotype determines the reaction range of individuals exposed to alcohol, reaction range is multidimensional both in terms of types of exposures, and, as will be discussed, types of vulnerabilities. Leading to different types of exposures, alcohol is regulated differently in various societies and local jurisdictions. In North Korea, alcohol is served only on Saturdays. In Saudi Arabia, alcohol consumption is punished by lashing. In the United States, variable parameters include forms of alcohol that can be sold, labelling, and standards for assessing driving while intoxicated. In some states, for example, Maryland where the National Institutes of Health (NIH) is located, the shipment of alcohol is prohibited. Maryland prohibits the purchase of beer and wine in grocery stores, except for ones grandfathered in. However, Maryland is also one of 17 states that do not allow individual jurisdictions to prohibit the sale of alcohol. In Montgomery County, the local district that contains the NIH campus, alcohol is sold in 25 'Wine and Spirit' stores. Nationwide, some 500 municipalities are 'dry', according to a 2004 survey by the National Alcoholic Beverage Association. Thus, the average alcohol consumption is not the only important component of the environmental landscape in which genes are acting.

Alcoholism is a moderately to highly heritable addiction

Alcoholism and other addictions are moderately to highly heritable (Figure 9.1) (3). This conclusion is based on large, epidemiologically sampled cohorts of twins. The data represented in this figure represent the contributions of multiple studies, totalling thousands of twins. The heritabili-ties of addictions derive from the fact that

monozygotic twins are likely to resemble each other and dizygotic twins are approximately half as likely. Also, the risk of addiction falls further, and proportionately, with further increases in genetic distance to the addicted relative (the proband). Twin studies are subject to certain biases—in particular the problem of shared environment. However, the heritability estimates computed from twin studies have been buttressed by adoption and family studies.

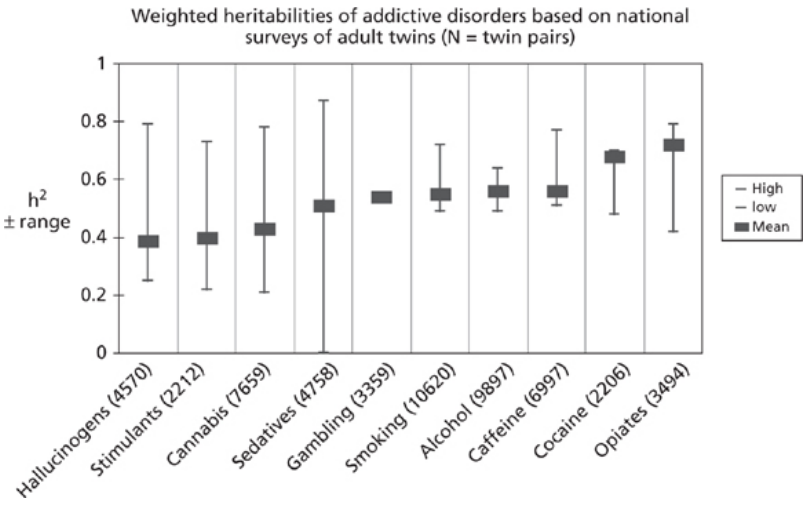

Figure 9.1 Heritabilities of ten addictions, based on a meta-analysis of epidemiologically-based studies comparing concordances of monozygotic and dizygotic twins (3).

What the heritability of addiction does not tell us

1 Heritabilities are correlation-based estimates of the extent to which a trait is influenced by genetic factors, taken as a ratio versus all the factors that influence variation. Other factors include environmental influences shared by children raised in the same family (shared environment), and influences outside the home (unshared environment). They include G × E interactions and measurement error. Heritabilities are population- and cohort-specific.

2 Heritability is a group statistic that does not inform us of individual propensity.

3 Heritability of addiction does not establish that addiction is a disease. Many human characteristics (e.g. height and personality) are moderately to highly heritable.

What the heritability of addiction does tell us

1 People differ in inborn propensity to addictions. The relatively high heritability of alcoholism and other addictions should make us receptive to genetic explanations.

2 Due to genetic individuality, public policy changes that are benign for most people may expose the vulnerability of segments of the population. For example, if the price of alcohol is lowered this may be generally experienced as a consumer benefit, but will contribute to alcoholism in people with innate vulnerability or other risk factors. A goal of genetic studies is to enable people who are vulnerable to limit their exposures, but as yet this prospect is largely theoretical.

3 Addictions are manifestations of events in the brain. Therefore, the heritability of addictions directly leads to the conclusion that these brain events are genetically influenced.

The reductionistic explanation for the heritability of addictions is that inherited DNA variation leads to neurochemical individuality. At the DNA level many functional variants are known, even within the few neurochemical pathways where we have rudimentary inventories (13). Some inherited functional variants alter brain processes and thereby predispose people to seek addictive agents or respond to them differently. Therefore, it should be expected that the effects of genes on brain processes are stronger than effects on behaviours, as, for example, was shown with a functional polymorphism of neuropeptide Y that plays a role in anxiety and problems associated with it, but has stronger effects on molecules and brain responses (14).

Genetics and the disease concept of alcoholism

As discussed, the mere fact that alcoholism is inherited does not mean it is a 'disease'. However, because we do not choose our parents, the inheritance of alcoholism argues that we should regard alcoholism as a phenotype involving choice, rather than as an unmodified choice. It is beyond the scope of this review to make the full argument that alcoholism is both a genetically influenced phenotype and a disease. Nevertheless that argument is soundly based both in the clinical/behavioural phenomenology of alcoholism and in the long-term neuroadaptive changes that are common to addictions. It is these changes more so than genetic

predisposition that trap the addict into punishment-resistant responding for addictive agents. The addicted individual continues to seek the agent even though doing so makes him/her suffer. An alcoholic relapses because of maladaptive changes in brain function, not because he wants to suffer.

Because the same reward circuits are responsible for a variety of rewarding experiences, it is tempting to conflate all pleasurable activities or habits (for example, eating chocolate or horseback riding) with addiction. In this regard, it is important to understand that the neurocircuitry of reward is shared across all agents that are experienced as pleasurable (15), that boundaries are not hard and fast, and that certain drugs placed in the most restrictive categories are placed there for reasons in addition to addictive liability. Other factors that come into play include health hazards (i.e. toxicity) and functional impairments (e.g. impaired decision-making and motor coordination) associated with certain agents. However, addictive liability is an important consideration, because the predictable result of making a highly addictive agent widely available is that many people will become addicted despite the adverse effects of the agent. The adverse properties of the agent, whatever they may be, will thereby be amplified by widespread use. Both neurobehavioural studies and genetic studies strongly indicate that some pleasurable agents (e.g. heroin, nicotine) are highly addictive and others are much less so. Rats will withstand punishment to respond for certain drugs but not others. Furthermore, alcohol and other addictive drugs are themselves psychoactive, leading to an important difference in the significance of initial exposure to a pleasurable substance such as chocolate versus a drug such as alcohol. Repeated exposures to addictive agents lead to

long-lasting neuroadaptations that make it difficult to resist cue-induced or stress-induced relapse and rapid reinstatement.

In addition to these neuroscience-based arguments about addictive liability, genetic findings also have implications for whether alcoholism and other addictions should be defined as diseases and which agents should be more restricted in access. The most informative picture emerges when considering the heritability of various addictions, not just one. Genetic studies reveal a distinction in the addictive liability of different agents experienced as pleasurable. In general, the addictive liability of the agent correlates with the heritability of the corresponding addiction (Figure 9.2) (3). The stronger the addictive liability of the agent, the higher the heritability of the addiction (3). The correlation between heritability and addictive liability is not strong, but some of the most addictive agents (e.g. heroin and cocaine) have the highest addiction heritability. Also, this correlation exists despite the fact that the heritability of certain agents (e.g. amphetamines) is lowered because some people are never exposed, and despite the crudity of estimates of addictive liability. For example, caffeine may actually not be one of the least addictive agents. Another clue to addictive liability is the cross-inheritance of addictions, which will now be discussed.

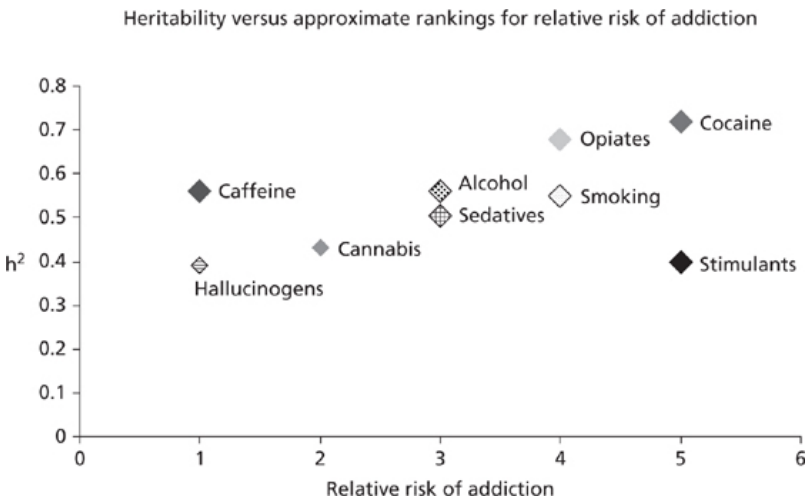

Figure 9.2 The heritability of addiction tends to be predicted by the addictive liability of the agent. Relative risk of addiction, estimated from pharmacobehavioural studies, is indicated on the x-axis and is graphed against heritability of the corresponding addiction. Some of the most highly addictive activities (use of cocaine or opioids) are most heritable. This correlation exists despite the relative crudity of estimation of addictive liability and the many factors that might lower heritability, for example, lack of exposure to a particular addictive agent.

Cross-inheritance of addictions

An important question, to which we know some of the answers, is whether addictions are inherited in agent-specific fashion or whether vulnerability is shared across different addictive agents. If vulnerability is agent-specific, then disease burden will be alleviated proportionately to how we regulate or restrict access to that agent. On the other hand, if vulnerability is general then the addiction burden may be shifted to a different agent, potentially one that is more hazardous. Understanding the relationship between the use of one agent and another is complicated by the gateway phenomenon and by the fact that one thing tends to precede or accompany another, regardless of causal relationship. Genetic studies offer an ability to detect shared inheritance of causation rather than gateway correlation. Shared genetic factors for addictions were discovered by studying the cross-inheritance of addictions in twins (16). In several large studies, including the Virginia, World War II veteran, and Vietnam veteran twin cohorts, it was observed that addiction in a twin
increased the likelihood of addiction to a different agent in a co-twin. Approximately half of the genetic liability to nicotine addiction was shared with alcoholism liability, partially explaining the tendency of alcoholics to smoke. However, as might be expected from the different initial sites of action and mechanisms of absorption and metabolism of addictive drugs, some of the vulnerability is also agent-specific. In this regard, much of the liability to heroin addiction is agent-specific. Addiction liability is, in part, agent-specific, but a substantial portion is general.

Tempering concern about the unevenness of laws governing the purchase and consumption of alcohol and other addictive agents, an individual might use knowledge of personal vulnerability to exploit that environmental variation. This prospect is at this point mainly theoretical; however, it could be helpful to have the option to live in a jurisdiction relatively free of alcohol-related cues and easy access to alcohol. People make lifestyle choices that benefit or place themselves at risk, and increasingly these decisions are informed by medical diagnoses or indicators such as a cholesterol level or even one's weight on a scale. For example, persons with haemolytic anaemia due to G6PD deficiency can avoid oxidants that can trigger a haemolytic crisis. Individuals with a variety of predispositions ranging from lactose intolerance, food allergies, kidney stones, and hypertension abstain from everyday pleasures. An important distinction for the choice to use an addictive agent is the relative rewarding properties of these agents and the contexts in which they are used. Re-emphasizing the relationship shown in Figure 9.2, the stronger the addictive liability of the agent, the higher the heritability of the addiction. For this reason a person predisposed to addiction should be more cautious about initial exposure to agents that are more addictive. From what we know, they may have a problem with heroin or nicotine, which are highly addictive, but not with a drug of lower addictive potential, or with chocolate for example.

For alcoholism and other addictions, the potential benefits of use of knowledge of individual vulnerability are usually not realized. We know this because the risk of alcoholism and

other addictions is elevated severalfold in the offspring of the addicted who have had the opportunity to observe the consequences of alcoholism in their parents and other blood relatives. In such families there are also other risk elements. However, a remarkable finding emergent from classical adoption studies on alcoholism by Michael Bohman and Robert Cloninger and by Donald Goodwin and confirmed by cross-fostering analysis (17) is that the risk of children adopted-away to families without alcoholism was predicted by the alcoholism of the biological parents. Meanwhile, in families with alcoholism, children usually do not learn from the error of the parent, but instead tend to express the genetic risk. This has also been shown by the equivalent effect on risk of having a biological parent with alcoholism or a sibling with alcoholism, and indeed by the fact that alcoholism is not less common in offspring of alcoholics.

Gene × environment correlation and its implications

The apparent inability of people to use a family history of alcoholism to reduce their risk may be partly due to the ways their genotypes influence them to shape their environment, leading to G × E correlation. G × E correlation has been measured in twin studies as the 'genetics of the environment'. Heritabilities of environmental exposures ranging from 7% to 39% have been observed for several categories of environmental factors that play a role in addiction vulnerability: stressful life events, parenting, family environment, social support, peer interactions, and marital quality (18). Children with conduct disorder, a precursor to antisocial personality disorder, tend to seek out antisocial peers. In turn, exposure to antisocial peers increases risks of

antisocial behaviour and addiction (19). G × E correlation also takes other forms. In the passive form of G × E correlation, alleles conferring risk in children also alter the behaviour of the parent transmitting the allele, potentially creating a 'double whammy' effect. Children of alcoholic mothers can be at enhanced risk both via transmitted risk alleles and via less favourable family environment and teratogenic exposures. Another source of G × E correlation is evocative interaction, in which the individual indirectly shapes his/her environment. For example, children with conduct disorder or who just 'won't stop crying' can evoke negative reactions from parents, peers, teachers, and law enforcement, which may in turn promote additional risk. Potentially, these negative interactions might be altered or derailed by genetic and psychophysiologic tests informative for vulnerability. Genetic variations informative for alcoholism have been identified but present knowledge is insufficient to predict vulnerability, and this lack of precise knowledge impairs our ability to define those genetically at risk.

Not all children of alcoholics are at genetic risk of alcoholism

It is usual to state that a child of an alcoholic is at risk for alcoholism. As a group they are at enhanced risk for multiple problems including alcoholism, other psychiatric diseases, and metabolic disease because of stress, abuse, or lowered socio-economic status. However, without genetic or psychophysiogical testing we can maximally estimate the genetic alcoholism risk in an adolescent as about 40%, as compared to a population risk of about 10%. Thus it is also reasonable for the 'genetically at-risk' adolescent to think that

he may be different than his alcoholic parent. Without precise information people are less likely to act and it is difficult to justify treating people as if they were differentially vulnerable. A goal of genetic research including the study of genetically-influenced psychophysiological predictors such as alcohol response, impulsivity, brain reward response, anxiety, and stress resiliency is to advance our understanding of predisposition, providing tools to predict vulnerability and enabling us to more accurately evaluate the origins of an individual's addiction.

Pharmacogenetic predictors

The discovery of pharmaceutical therapies that act on different physiological targets suggests the opportunity to individualize therapy, minimizing deleterious side effects and maximizing efficacy by targeting responsive populations. Improvements in treatment response could transform attitudes towards alcoholism, both within medical settings and in society at large. Classification of addicted patients into more clinical homogeneous subtypes in which aetiological factors including genes tend to be shared represents one first systematic approach to the individualization of treatment and prevention. As discussed this is the well-tested medical model that has proven successful for many other diseases. Again by example, the patient with iron deficiency anaemia is helped by administration of iron and occasionally by blood transfusion. However, even in the absence of aetiological diagnosis, treatments can be targeted using symptoms (symptomatic treatment), signs, clinical history, and individual laboratory findings. Many sorts of individual characteristics represent potential clinical predictors. The use

of a genetic laboratory finding is a pharmacogenetic approach. Other characteristics include age at onset, personality, comorbidity with other psychopathological conditions, familiality, severity, clinical course, and previous response to other treatments. To the extent that these aspects have been defined as genetically influenced they also represent genetic targeting, although they do not involve a laboratory test. Approximately two-thirds of alcoholics (labelled type A or Cloninger type I) have later onset, slower course, and better prognosis, and this general type of alcoholism is less heritable (20). Type B (Cloninger type II) is more familial and marked by antisocial behaviour, earlier onset, rapid course, and poorer prognosis (20). Type I alcoholism thus falls more in the category of internalizing disorders and type II in
the externalizing disorder domain. Treatment might differentially target the strengths and weaknesses of these patients. Thus, ondansetron was found to be more effective in early-onset alcoholics while selective serotonin re-uptake inhibitors may be more effective in alcoholics with anxiety and depression (21). Some genetic variants (e.g. the 5-HT1B receptor (22)) have been shown to confer risk mainly in specific subgroups of alcoholics. An HTR2B stop codon contributes to severe impulsivity, one consequence of which can be alcoholism (23).

Two case studies in the public impact of pharmacogenetic predictors in alcoholism

Common genetic variants in two genes have been identified that appear to alter alcoholism risk and response. Although neither has thus far had a significant impact on diagnosis, treatment, perceptions, or policy, each represents a

still-developing case study. Also, although these genes act in completely different ways—one as a substance-specific factor and the other as a factor that may generalize to other addictive agents—there are common barriers to their widespread appreciation or application.

Aldehyde dehydrogenase 2 (*ALDH2*) Glu487Lys, a functional polymorphism found in 500 million individuals of East Asian descent impedes the metabolism of alcohol. Alcohol is metabolized stepwise to acetaldehyde and then, by ALDH, to acetate. Blockade of ALDH by disulfiram or antimicrobial drugs in the metronidazole class leads to accumulation of acetaldehyde. Acetaldehyde in turn releases histamine, causing an aversive flushing reaction. The *ALDH2* polymorphism Glu487Lys involves a substitution of lysine for histidine. Genetically, the Lys487 allele acts dominantly; one copy leading to loss of most of the activity of the enzyme. Many, or most, Lys487 carriers are aware they have alcohol-induced flushing. However, many drink socially and some become alcoholic. Because flushers are at reduced risk, those who have developed alcoholism presumably have other risk factors. Although alcohol-induced flushing is mainly treated as a curiosity among social drinkers it has recently been recognized that acetaldehyde is a carcinogen as well as an aversive toxin. Acetaldehyde reacts with proteins and DNA in a fashion similar to formaldehyde, its one-carbon cousin. The risk of upper gastrointestinal cancer is greatly amplified in moderate drinkers who carry the *ALDH2* Lys487 variant (24). Advising 500 million carriers of the Lys487 variant to reduce alcohol consumption could reduce rates of cancer as well as rates of alcoholism. Also common in East Asians is a super-active variant of one of the alcohol dehydrogenases, the enzyme that metabolizes alcohol to

acetaldehyde. Genetic epidemiological evidence also ties this *ADH1B* His48Lys variant to oesophageal cancer risk, and it additively interacts with the *ALDH2* polymorphism to reduce the risk of alcoholism (25). Recently it has also been appreciated that polymorphisms of other *ADH* genes, found in non-Asian populations are important in modulating risk of alcoholism, presumably by altering alcohol metabolism. Although none of these alcohol metabolism genotypes is widely used, they illustrate the potential to develop pharmacogenetic predictors that are specific for alcoholism as opposed to other addictions with which alcoholism shares other genetic liability factors.

The mu opioid receptor is a target of endogenous and exogenous opioids. It is the receptor at which opioids such as heroin and methadone act, leading to blockade of pain perception, other psychoactive effects, and in some cases addiction. Blockade of the mu opioid receptor with naloxone can be life-saving in opioid addicts who have overdosed. The mu opioid receptor is also key to the actions of other drugs of abuse. Naltrexone, a long-acting opioid antagonist, is one of a handful of drugs approved for alcoholism, helping patients to reduce drinking by diminishing alcohol-associated reward. The mu opioid receptor gene (*OPRM1*) contains Asn40Asp, a polymorphism involving an amino acid substitution that alters the affinity of the receptor for endomorphin, the endogenous ligand. The Asp40 allele, found in one in five people, predicts better clinical outcome in alcoholics treated with naltexone (26, 27) and as shown by brain imaging of people with different *OPRM1* genotypes the mechanism appears to be altered reward responses to alcohol (28). *OPRM1* Asn40Asp represents an example of a pharmacogenetic predictor associated with response to a specific addiction therapy and it

is a genetic variant that alters reward processes that are shared by other addictive agents.

Underage drinking

A pernicious aspect of alcohol and other drugs of abuse is use by the young, who usually have not attained adult frontal lobe function and decision-making. This interplay between youth and vulnerability is one compelling argument against liberalization of drug access. Frequently, raising widespread concern, drug-intoxicated youth are involved in tragedies, such as vehicle accidents, that are not directly connected to addiction but equally lethal. Thus there is a powerful rationale to restrict children's access to alcohol and certain other drugs. We will also discuss the genetic evidence that bears on whether early exposure to alcohol predisposes to alcoholism, and the surprising answer to that question appears to be no, or perhaps the jury is still out. The age at which drinking is legal is variable, with only 15 states and the District of Columbia in the United States banning underage drinking, outright. There is also variation as to whether a child can enter a liquor store or bar. Since 1984 the minimum age to purchase alcohol in the United States has been 21 years, due to federal law but the minimum age, and other rules governing consumption, differ in many other countries where the sale of alcohol is permitted. For example, in much of Canada the minimum age to purchase alcoholic drinks is 19, and in most countries worldwide the minimum age is 18. Could these laws not only reduce the frequency of alcohol-associated tragedies but also reduce the likelihood that an individual will become alcoholic?

Age of first use of alcohol is a powerful predictor of alcoholism but genetic studies indicate that this effect may be predispositional, or reverse-causal. While early initiation of use is associated with increased risk of developing addiction, this may be another example of G × E correlation, as discussed previously. The odds of lifetime alcoholism are reduced by 9% for each additional year onset of use is delayed (29, 30). However, as would not be obvious from the epidemiology, genetic studies indicate that a major component of the predictive effect is a predispositional pathway of causation. Prescott and Kendler observed that co-twins with late onset of alcohol use had the same risk as siblings with early onset of use (31). Studies on offspring of addicted patients also reveal that different risk factors may be involved at different stages of the development of addiction. This possibility deserves careful attention as we evaluate risk to populations that include children. Furthermore, as discussed, the impact of alcohol on adolescents is potentially devastating, or fatal, regardless of whether they are liable to alcoholism.

Genetic influences on alcoholism and drinking vary across the lifespan

Genetic influences on alcoholism, and probably other addictions, are strongest in later adolescence and young adulthood, which is often the age when alcohol problems first bring people to the courtroom. Kendler and colleagues observed that the heritability of alcohol consumption is remarkably different across different ages. In childhood, heritability of drinking is low, being primarily outside the locus of control of the child. Heritability rises rapidly during adolescence and peaks in late adolescence and young

adulthood. It declines moderately in later years. During adolescence, peer influences are most important for exposure and initial pattern of use, whereas familiality and other psychopathology play a more salient role in transition to problematic use and addiction (32). The change in heritability of alcoholism over the lifespan informs us that the effects of genetic risk variants change across the lifespan, and under different conditions.

Gene × environment interaction

G × E interaction occurs when the effects of gene and environment combine non-additively. Another explanation for deviation from additivity is gene by environment correlation. As discussed, gene and environment are often non-independent, and in such instances we cannot accurately calculate their combined effects by adding the individual effects. G × E is crucial for understanding complex diseases of which alcoholism is one. For alcoholism and other complex diseases such as cancer, diabetes, cardiovascular disease, and infectious disease, genetic variation mediates risk via resiliency and vulnerability to a variety of exposures including mutagens, pathogens, and nutrients. For alcoholism, other addictions, and most other psychiatric disease, stress exposure and stress resiliency play a key role. Childhood trauma and neglect elevate risks of alcoholism and several other psychiatric diseases severalfold but these are group effects—there is wide variation in stress resiliency. Several common functional variants have been identified that partially account for differences in stress resiliency. A number of these variants are found in genes involved in neurotransmitter function, including monoamine oxidase A (33), the serotonin

transporter (*SLC6A4*) (34), and catechol–O-methyltransferase (*COMT*) (35). Others are found at genes involved in the function of the stress endocrine axis; these include neuropeptide Y (*NPY*) (10), an anxiolytic neuropeptide and *FKBP* (36), a gene that encodes a protein that regulates intracellular responses to cortisol, a principal stress hormone.

Psychophysiological indicators of genetic risk and the meaning of an alcoholism diagnosis

Valid and reliable diagnostic criteria for alcoholism have provided a unifying framework for treatment and research, and criteria for alcoholism parallel other addictions. However, alcoholism is a syndromic diagnosis based on symptoms and clinical course, rather than aetiology. Also, alcoholism is in an important sense an end-stage diagnosis reflecting the outcome of addictive processes but failing to address mediating pathology at an intermediate point, or pre-existing vulnerability and events at its beginnings. Alcoholism and other addiction diagnoses are categorical, but many of problems associated with alcohol occur in non-alcoholics (37) and particular problems are more salient in certain alcoholics. For example, binge drinking, characterized by intense bouts of episodic drinking, is a common and deleterious pattern of alcohol use. In certain American Indian communities where binge drinking is prevalent, it generally, but not always, occurs in the context of alcohol dependence but in itself is a strong independent predictor of problems in the major DSM (*Diagnostic and Statistical Manual of Mental Disorders*) symptom areas: social, work, physical, and violence/ lawlessness (38).

In the future, alcoholism and other psychiatric diseases will hopefully be redefined using measures of brain function that more closely reflect vulnerability and present clinical status. Concerning vulnerability, intermediate phenotypes, especially endophenotypes that are disease-associated and heritable (39), identify subgroups of alcoholics who are more homogeneous, and that may ultimately reflect common vulnerability. Several of the most interesting intermediate phenotypes that predict vulnerability to alcoholism are alcohol-induced flushing which reflects alcohol metabolism and predicts aversion to alcohol; low response to the sedative effects of alcohol which reflects neural sensitivity and predicts vulnerability to alcoholism; measures of impulsivity and impaired frontal cortical function which predict vulnerability; measures of stress response and anxiety and differences in the resting electroencephalogram; and responses in the electroencephalogram evoked by specific cognitive stimuli. In several instances where genes have been identified they act through these specific pathways to vulnerability rather than on alcoholism as an inclusive clinical entity. These intermediate phenotypes, and the genes that affect them, also provide clues to the relationship between
alcoholism and other psychiatric disorders. Several 'externalizing disorders' including addictions, attention deficit hyperactivity disorder, and antisocial personality disorder share relatively lower behavioural inhibition, frequently because of comparatively lower frontal executive cognitive control. Redefinition of alcoholism and other addiction diagnoses on a neuropathogenetic basis would have profound public policy implications. It would lead to a better understanding, and integration, of aetiological factors that act across diagnostic boundaries. It should be noted that heritability and gene-level studies both detect evidence of

aetiological factors shared between addictions and other psychiatric diseases. Such genetic findings already appear to place normal personality and psycho-pathology in the same continuum, or at least the same vector space. Alcoholism is aetiologically connected both to other psychiatric diseases and to 'normality'. Although addictions are diseases, both the addicted and the non-addicted are likely to carry some risk and protective elements.

One response to this complexity is to abandon the attempt to make alcoholism (and other psychiatric diagnoses) 'hard' medical diagnoses in the sense of a disease such as cystic fibrosis, which has a defined genetic aetiology (40). However, all hard clinical diagnoses were at one time entrapped within fuzzy entities, which is to say conflated with other problems. Also, hard medical diagnoses are themselves complex and non-discrete, with each patient posing different challenges. Cystic fibrosis for example, can lead to pancreatic insufficiency, pneumonia, and infertility and might have formerly been lumped together with other causes of these same clinical problems. It remains necessary for physicians to make the differential diagnosis, for example, in infants initially presenting with pneumonia, which itself is a more precise and clinically useful label than the presenting complaint of 'fever'. The over-arching diagnosis of cystic fibrosis triggers a regimen of care to prevent future episodes of pneumonia, just as a refined addiction diagnosis may call for certain clinical interventions to prevent future episodes of relapse. Future versions of the DSM may continue to include so-called 'fuzzy', non-aetiological diagnoses such as alcoholism, and may also improve the value of fuzzy descriptions with dimensional indices such as age at onset, years of drug use, frequency of use, and quantity of use.

Based on the current technology and clinical art, including the cost and informativeness of genetic and psychophysiological testing, it appears that medicine will be 'stuck with' non-aetiological addiction diagnoses for the foreseeable future. However, the information already available, including linked genes, strongly indicates that discrete subcategories of vulnerability underlie these general diagnoses.

The nosology of addiction and probably our success treating addictions will not rapidly advance until neurobiological indicators, including genotypes, are integrated. However, neuroscience and genetics have at least taught us that alcoholism is not a lifestyle choice. Instead, alcoholism and other addictions are diseases that can be in part understood, prevented, and ameliorated through an understanding of mechanisms of addiction and predisposition to addiction.

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Chapter 10
Pathophysiology of alcohol addiction

Wolfgang H. Sommer

Introduction

Alcohol is recognized as a causal agent for many illnesses, so it is no wonder that alcoholism has been referred to as the 'great imitator' of other diseases. Yet the key to any alcohol problem lies within the brain and the mind. People consciously drink alcohol with the purpose of altering mood states; the mechanisms behind this and why alcohol may end up becoming an addiction has puzzled researchers for decades. This chapter offers a short review of major findings and concepts in the field of biological alcoholism research. It will address four main points which aim to inform the discussion on alcohol policy and health issues in this book. First, alcohol may be part of our nature, in the sense that alcohol liking and seeking may have been under positive selection during our evolutionary history, which may make alcohol distinctive from other drugs of abuse. Second, individuals vary widely in their innate responses to alcohol; however, the neurobiological mechanisms underlying these differences are likely not the ones causal to addiction. Third, alcohol addiction is not defined by physical dependence, i.e. the emergence of withdrawal symptoms upon cessation of drinking, but rather by its chronic relapsing course, where relapse is triggered by powerful urges or cravings that cause the loss of behavioural control. The phenomenon of craving is at the focus of neurobiological theories of alcohol addiction.

Finally, although substantial knowledge on the neurobiology of alcohol addiction has been accumulated, there is so far little progress in the pharmacotherapy for this disorder; part of the reason for this is that existing pathophysiological concepts are not consequently applied to medication development. Recent reviews on the subject of pathophysiology of alcohol addiction can be found in Sommer and Spanagel (1).

Alcohol is part of our nature

Natural selection for low-level alcohol consumption

From an evolutionary perspective, humans are well adapted to an ethanol-containing diet, which has regularly been provided by ripe fruits, typically below 1% ethanol, sometimes even above 3.5% (2, 3). Humans have evolved the necessary enzymatic functions that provide metabolic tolerance to low amounts of ethanol, thereby preventing intoxication (3). Metabolic utilization of ethanol is facilitated by alcohol dehydrogenases (ADHs), one of the oldest and largest classes of enzymes. The existence of a rapidly evolving ADH system appears to guarantee adaptability to changing internal and external environments. Some variants of ADH and acetaldehyde dehydrogenase cause accumulation of toxic acetaldehyde upon alcohol intake and thereby provide strong protection against alcohol abuse (see Chapter 8, 'Alcohol metabolism and genetic control'). The allelic ADH variants differ between different human populations due to unknown selection pressures. Natural selection for low chronic exposure to environmental stressors often results in a

nutrient–toxin continuum, whereby low concentrations are beneficial and higher concentrations
harmful. For alcohol this has been shown in *Drosophila* species, where longevity is increased at very low concentrations of ethanol, but decreases rapidly with exposure to higher concentration (4). Another example is provided by alko alcohol (AA) and alko non-alcohol (ANA) rats, which are selectively bred and maintained such that AA rats voluntarily consume more than 5 g alcohol per kilogram of body weight per day (g/kg/day), whereas ANA rats consume less than 0.5 g/kg/day alcohol (5). AA rats live longer than the alcohol-avoiding ANA animals, and further in line with findings from *Drosophila*, segregated alleles between AA and ANA rats are strongly clustering on metabolic genes (5, 6).

It should be noted that natural selection of behavioural responses towards alcohol is not restricted to metabolism. It may have acted via various mechanism including olfactory responses, feeding stimuli, reward processes, and by affecting emotional states. Taken together, alcohol preference appears to be an evolutionary inherited trait that came under positive selection in periods of mostly scarce resources. No similar pressure worked on genes protecting against harmful effects caused by higher amounts of alcohol because exposure to such concentrations only became available in the last 10,000 years, a period too short to induce adequate evolutionary counter responses. In this sense, modern alcoholism has been called an ‘evolutionary hangover’ (2), which sets this disorder apart from other substance addictions such as nicotine or other naturally occurring psychotropes.

Molecular and cellular effects of alcohol exposure

While the behavioural consequences to ethanol are well characterized, surprisingly little is known about the molecular mechanisms by which alcohol alters neuronal activity that underlie these effects. Despite alcohol's robust pharmacological effects, its potency is remarkably low. The legal threshold for intoxication in many countries is at 0.05% or about 11 mM ethanol in the blood, and the anaesthetic concentration for humans is about 100 mM. Ethanol's binding to specific proteins is now well established, but these interactions are very different from the interaction of most other psychoactive drugs with their neurochemical targets (7, 8). Despite the low affinity, ethanol binding sites at ligand-gated ion channels such as glutamate receptors of the N-methyl-D-aspartate (NMDA) type increase the sensitivity for alcohol responses at these receptors from the mid to the low millimolar range, implying important cellular and synaptic consequences.

Excitation and inhibition in the central nervous system is determined by the synaptic inputs from the major excitatory neurotransmitter glutamate and the major inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Acute exposure to alcohol in the 1–100 mM range affects both the input and output of the synapses. Generally, acute ethanol potentiates GABA-ergic and inhibits glutamatergic neurotransmission via direct actions at neurotransmitter receptors and intracellular signalling cascades (9, 10). The net effect of acute ethanol on the brain is to dampen neuronal excitability in many regions and to reduce most forms of synaptic plasticity, i.e. long-lasting changes in the efficacy of synaptic transmission.

The initial actions of ethanol on its specific targets at glutamatergic and GABA-ergic synapses cause the subjective effects felt as intoxication signal. Following this first hit, a second wave of indirect ethanol effects on various neurotransmitter and neuromodulator systems is set off, mainly involving monoamines, i.e. dopamine (DA), serotonin, and noradrenaline, as well as opioids and other neuropeptides (11). These effects are crucial for the positive value (reward) that is ascribed by an individual to alcohol and thus underlie the increased motivation for and frequency of its consumption (positive reinforcement). At the same time alcohol reduces the ability for synaptic plasticity, which includes the formation of drug memories. This may explain why the addictive potency of alcohol is relatively low compared to other drugs of abuse and why the development of
alcohol addiction takes a very long time (more than five years from problem drinking to clinical relevant symptoms). It also points out that other mechanisms than alcohol's effects on reward learning are likely to be engaged to commit an individual to the path of addiction.

Chronic exposure to alcohol leads at the synaptic level to functional tolerance, i.e. the response to a certain amount of alcohol has changed because of altered pharmacological interaction of ethanol with its targets (10). This includes tolerance to many GABA-ergic effects including the anxiolytic, sedative, and ataxic effects. On the other hand, chronic ethanol exposure generally enhances the function of NMDA-receptors. With sufficient amounts and exposure time, neuroadaptations at both the cellular and the synaptic level will result in dependence and the emergence of specific withdrawal symptoms. In withdrawal, upregulated NMDA

receptors are hit by strongly increased extracellular glutamate levels, the latter corresponding with the intensity of the withdrawal symptomatology (12, 13). Part of the increased extracellular glutamate may in fact be due to synaptic release, but other mechanisms seem to exist, including decreased glutamate uptake (14).

Why do we like to drink?

Subjective responses to alcohol

When asked what they like about alcohol, people typically report feelings of euphoria, relaxation, or disinhibition as well as reduced stress and anxiety associated with intake. Sometimes these different feelings can be experienced all at once. According to the drug instrumentalization theory, recreational, i.e. non-addicted, drug use in humans is an instrument to alter emotional states, or in other words a learned behaviour to improve the current quality of life by taking a psychoactive drug (15). Drug instrumentalization goals may be improved social interaction, the feeling of well-being, tension reduction, and many others comprising a subject's emotion but also including autonomic activity, motor, and cognitive performance, and behaviour.

Individual responses to alcohol differ widely, depending on an individual's constitution, his/her alcohol use history, and on the conditions of intake. Isolating the various factors has been proven difficult. In fact, a recent laboratory experiment in healthy young social drinkers ingesting one alcoholic drink under standardized conditions demonstrated great variation in the time course of breath alcohol levels and consequently

brain exposure (16). For better control over alcohol administration in laboratory studies, intravenous infusion paradigms have been developed in which subjects receive alcohol at rates determined by an individually tailored, physiologically-based pharmacokinetic computer model (17).

The general subjective effects produced by alcohol are stimulation and sedation (18). Although stimulation and sedation seem to be opposite states, they can in fact be experienced simultaneously. Stimulation is typically experienced at low, but rapidly raising blood alcohol levels soon after intake, while sedation develops slowly and gradually, specifically during the descending limb of the blood alcohol elimination curve. Generally, stimulant effects are more positively labelled than sedative effects, although some sedative effects such as reduced anxiety or tension are positively labelled, and people who experience mostly stimulant effects favour alcohol more than those who report predominantly sedative effects.

Individual differences in the response to alcohol have been implicated in the risk for alcohol addiction. According to the 'low level of response hypothesis' individuals that initially show a low level of response to alcohol may drink more to experience the same psychomotor effects than their peers and thus be at an increased risk for alcoholism (19). This hypothesis has been criticized for two main reasons: intoxication data were mostly obtained by an instrument with a potential
biased towards sedation (20), and subjects are primarily assessed during the descending limb of the blood alcohol curve, when sedative effects are dominating (21). Thus, these findings may primarily show that individuals at risk for

alcoholism are less sensitive to the sedative effects of alcohol. Alternatively, the 'differentiator model' posits that individuals at risk for alcoholism like and drink alcohol more because they are less sensitive to alcohol-induced sedation, but more sensitive to alcohol-induced stimulation (22).

The neurobiological mechanisms mediating the subjective effects of alcohol will be discussed in the next section. Generally, stimulant effects are attributed to activation of the brain reinforcement system, while mechanisms involved in alcohol sedation are less clear but are related to the GABA system. Although the rewarding and stimulant properties of alcohol are under genetic control it is not clear to what extent they impact on the risk for alcoholism.

Circuitry for positive reinforcement and the mesolimbic dopamine system

Investigations into the neurobiological substrates of reward and motivated behaviours (reward system) established that the positive reinforcing properties of most, if not all addictive drugs, originate within a brain circuit comprised of dopamine (DA)-containing neurons originating in the midbrain ventral tegmental area and their release of DA into the ventral striatum, particularly within the nucleus accumbens. An extensive review of such interactions, which formed the basis for the DA theory of addiction, and their pertinence for the treatment of alcohol addiction has been provided by Soderpalm and Ericson (23). Importantly, the role of DA for the actions of alcohol is less clear as for other drugs of abuse. Extensive lesions of the DA system in experimental animals failed to decrease, or even increased an established pattern of ethanol consumption. Such conflicting observations may

result from DA-independent reinforcement implying multiple ways for activation of critical reinforcement circuitry that could be modulated by alcohol's wide range of neurochemical effects. Nevertheless, human neuroimaging studies demonstrated DA release into the ventral striatum as well as activation of this structure after intravenous or oral administration of alcohol in healthy social drinkers (24–27).

Interactions of the DA and opioid systems play an important role in mediating reward; their implications for alcohol and addiction have been reviewed by Spanagel and Heilig et al. (28, 29). Interestingly, genetic variation at the human mu-opioid receptor gene, i.e. an A-to-G substitution within the genetic code, determines the striatal DA release. Carriers of the G allele of this single nucleotide polymorphism are consistently associated with increased experience of euphorigenic effects of alcohol. A combined study in humans and transgenic animals established that the G allele confers much stronger striatal alcohol-evoked DA release compared to the A allele (26), although the underlying mechanism remains unknown. Importantly, while G allele carriers show no established elevation of risk for alcoholism, if addicted they seem to respond better to treatment with the mu-opioid receptor antagonist naltrexone. Understanding this and other genetic heterogeneity in the context of medication response in patient populations will slowly pave the road for an individualized pharmacogenomically driven therapeutic approach to alcoholism (29).

Why do we drink too much?

Alcohol addiction has been defined as a chronic relapsing disorder characterized by compulsive alcohol seeking and drinking, loss of control over limiting alcohol intake, and the emergence of a chronic negative affective state when access to alcohol is prevented (30, 31). The question is then why do addicts relapse? And why does this obviously aberrant behaviour occur even after long periods of abstinence? Relapse is triggered by craving, i.e. an intense urge to drink in response to a memory of the rewarding effects of alcohol. Although craving is easily recognizable both clinically and by the individual, it has been difficult to measure in patients and does not correlate well with relapse in clinical studies (32). Despite these shortcomings, craving is seen as the key factor for the vulnerability to relapse behaviour and consequently all theories of addiction try to explain this phenomenon.

Three main hypotheses can be identified that have been put forward to understand the pathological increased motivation for drug taking in addiction. These vary in their focus on behavioural processes that drive the increased motivation for drug seeking and taking. Each has been associated with distinct but overlapping neural circuits. The first view is based on the function of the classical brain reward circuitry that motivates approach behaviour to obtain natural rewards but is potentially more intensely activated by drugs. The second hypothesis focuses on negatively reinforced drug seeking resulting from pathological activation of the amygdala and other structures involved in negative emotions that normally motivate avoidance when activated by threats or

stressors. The third concept emphasizes loss of control through disrupted 'top-down' influences from the PFC over subcortical structures involved in behavioural output. Even though these concepts cover overlapping aspects of the pathophysiology that leads to drug craving and relapse, it is important to note that each makes different predictions for therapeutic interventions towards relapse prevention.

Reward, incentive sensitization, and the mesolimbic system

Given the key role of the mesolimbic DA system in mediating the positive reinforcing actions of drugs of abuse, alterations in reward system after chronic drug exposure are expected to be important for the transition into addiction. A major hypothesis in the field posits that incentive salience to stimuli present at the time of drug taking is obtained with progressive drug use in as much that in addition to the hedonic responses gained from the immediate drug consumption (described as 'liking') a new motivational quality to the stimuli is added that makes them to desirable goals ('wanting') and thus commands attention (33). Craving is thus explained as pathologically amplified incentive salience in the presence of drug-associated cues that leads to an exaggerated motivation for drugs and probably to compulsive drug taking. According to this hypothesis, brain systems critical for addiction are expected to mediate the 'wanting' rather than the 'liking' component of drug reward. Support for the incentive sensitization hypothesis comes mostly from the psychostimulant literature and focuses on sensitized DA responses, particularly in the nucleus accumbens after repeated drug administration in experimental animals (34). The importance of this brain region in humans was

demonstrated by a recent report on three patients with severe alcohol dependence, high craving, and automated responses that showed a profound reduction of addiction-related symptoms after bilateral deep brain stimulation of the nucleus accumbens (35).

Other researchers emphasize the role of the midbrain reinforcement system in the dysregulation of habit learning. This process normally serves the development of effective, mostly automatic motor responses, but under pathological conditions may disconnect the outcome of a response or action from the stimulus that triggered it, potentially leading to compulsive behaviours. The neuroanatomical substrate of this process was found to be the ventral to lateral compartments of the cortico-striatal circuitry (36). Human confirmation of this concept comes from a recent human neuroimaging study demonstrating higher alcohol cue-induced functional magnetic
resonance imaging (fMRI) activations in the ventral striatum and in prefrontal areas of light social drinkers compared to heavy social drinkers, whereas the latter activated mostly the dorsal striatum in this task (37).

Negative affect, hypersensitivity to stress, and anti-reward systems

Notably, cessation of chronic drug use including alcohol has been associated with hypo- rather than hyperfunction of the mesolimbic DA system (38). Supporting the notion of reduced response to reward or its expectation are human neuroimaging studies demonstrating decreased dopamine D2/ D3 receptor availability and reduced DA release in abstinent alcoholics (39, 40). Clinically, the primary drive for relapse

into excessive alcohol consumption changes from reward craving to relief craving. Based on these and other studies it was postulated that while addiction develops, over time motivational and neural substrates undergo major shifts from initially positive to predominantly negative reinforced drug taking (31, 38). To maintain homeostasis of brain reward mechanisms the initial positive reinforcing effects of a drug are followed by a functional downregulation through postulated 'anti-reward' systems involving the extended amygdala including the central parts of the amygdala and extending rostral into the medial parts of the nucleus accumbens. Upon chronic drug use, the function of the reward system fails to return to normal, but results in a long-term change towards a lower set point ('hedonic allostasis'). Important neurochemical components of the anti-reward system are corticotrophin-releasing hormone (CRH) and its receptor CRHR1 as well as a group of opioid peptides, dynorphins, acting via their cognate kappa-opioid receptor. The progressive recruitment of anti-reward systems mediates exaggerated stress and fear responses that result ultimately in negative reinforcement. In this view, craving is understood as a memory of the rewarding effects of alcohol superimposed on a negative affective state. Supporting this concept, fMRI experiments in alcohol-addicted patients show increased amygdala activation to threatening stimuli when compared to healthy subjects (41).

Learning, impulsivity, and the prefrontal cortex

The third group of hypotheses revolves around the idea of impaired control over behavioural output by prefrontal cortical areas and reflect a 'top-down' view over much of the

same neuronal structures as discussed earlier, namely the striatum and the amygdala. These theories focus on executive cognitive processes underlying the constantly occurring self-monitoring for making split-second decisions between following an impulse and inhibiting it. This self-control is highly important for complex human behaviours and its functioning already during childhood is predictive of a wide range of long-term outcomes that are central to a successful life including the risk for addictive disorders (42). A very recent study showed that impairments in fronto-striatal circuits exist in both addicts and their non-addicted siblings and may act together with other personality traits in determining whether or not an individual will be able to stop or will continue taking drugs (43, 44).

The PFC sends extensive projections to subcortical structures. These glutamatergic synapses could be a substrate for addiction memories via formation of long-lasting changes in synaptic transmission after drug exposure. This plasticity may underlie the persistence of drug-seeking behaviour (45). An additional factor in alcohol addiction contributing to imbalance in glutamate homeostasis and transmission is the pronounced glutamate release during each withdrawal reaction (12, 46–48), which may induce either long-term plasticity, structural damage, or a combination of both. Indeed, alcohol withdrawal produces pronounced long-term changes in
glutamatergic synapses in the PFC which seem to play an even greater role for alcohol addiction and relapse behaviour than changes within the mesolimbic DA system (49). The combined data from cellular, animal, and neuroimaging experiments provide the basis for a glutamate hypothesis specific to alcohol addiction (14, 50) that has offered a strong

rationale for developing antiglutamatergic strategies for relapse prevention and alleviation of withdrawal symptoms (28).

Anaplasticity—a new view on pathophysiological mechanisms in addiction

Animal models are highly important for our understanding of, and for medication development for, addiction. Alcohol researchers have developed a number of tests for modelling relapse behaviour or some aspect of the pathological process in laboratory animals that show good predictive validity. For example, the theoretical framework of anti-reward systems has proven useful for the design and selection of model phenotypes (31) that allowed establishing long-term alterations in amygdala CRH systems in addicted animals (51, 52). However, what is still lacking is a model for capturing vulnerability or resilience to the development and expression of core deficits seen in addicted individuals. As a matter of fact, even after periods with intense alcohol or drug intake, most people do not become addicted. Thus, many of the drug-induced neurobiological processes and deficits, even after chronic exposure, may be neuroadaptations with the ability to revert to normal once drug use is discontinued. This important fact has been captured in an animal model of chronic voluntary cocaine taking in which, as in humans, addiction-like behaviour develops only in a small fraction of cocaine self-administering subjects (53). Addiction-like behaviour was measured according to three criteria similar to the diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV): persistence (difficulties in stopping), highly increased motivation for the drug, and compulsion (continued use despite adverse

consequences). Fulfilling all three criteria was highly predictive for relapse behaviour. Interestingly, animals that progressively develop the behavioural hallmarks of addiction have permanently impaired long-term depression in the nucleus accumbens, whereas long-term depression is progressively recovered in non-addicted rats maintaining a controlled drug intake (54).

What these experiments imply is contrary to what is commonly believed in the field, i.e. addicted animals did not show specific addiction-related neuroplasticity, but were incapable of counteracting initial drug-induced impairments, a phenomenon that the authors called anaplasticity or lack of plasticity. Thus, it appears that the transition to addiction could be mediated by the incapacity to engage active processes that allow control of drug intake. Efforts to adapt this model for alcohol addiction are underway, but so far it has not been applicable for medication testing (55).

Increase consilience about alcohol addiction through pharmacotherapy?

The concept of consilience refers to 'a "jumping together" of knowledge by the linking of facts and fact-based theory across disciplines to create a common groundwork of explanation' (56). The bridge to build here is not so much between different disciplines but between the constructs of alcohol addiction which were developed largely from preclinical research and the experience gained from pharmacotherapy of alcoholic patients. Often in medicine it is found that pharmacotherapy contributes consilience to the understanding of disease mechanisms underlying a distinct

disorder, such as insulin and its importance for treating diabetes mellitus. In the treatment of
tuberculosis the response to pharmacotherapy is even seen as prove of diagnosis in the absence of a positive test for the bacteria. For alcohol addiction such a diagnosis *ex juvantibus* cannot be expected from available pharmacotherapeutics, their efficacy is far too low for providing diagnostic clarity. The question is, however, to what extent available pharmacotherapy for alcohol addiction contributes to our understanding of the pathophysiology of this disorder.

Treatment of acute withdrawal

Sudden withdrawal from alcohol causes central and autonomous hyperexcitability with symptoms ranging from dysphoria and sleep disturbance to severe vegetative disturbances, delirium, and convulsions. In contrast to withdrawal from most other drugs, alcohol withdrawal is a life-threatening condition that requires qualified treatment. Symptoms can be alleviated by reintroducing alcohol. First-line clinical therapy is to use benzodiazepines or other GABA-mimetics with cross-tolerance to alcohol and to taper these off over a few days. Alternatively, antiglutamatergic compounds such as the glutamate release inhibitor lamotrigine, or the glutamate receptor antagonists memantine or topiramate can counter acute withdrawal symptoms in humans (57). Both the GABA-mimetic and the antiglutamatergic strategy are well founded within the earlier discussed findings on the cellular and synaptic actions of ethanol and resulting neuroadaptations that cause physical dependence.

According to the DSM-IV, physical dependence is neither sufficient nor necessary for a diagnosis of alcohol addiction. In fact, even after extensive drinking periods some people do not experience withdrawal symptoms. More importantly, treatment of acute withdrawal seems to have no effect on the relapsing course of the disorder (58). On the other hand, animal studies suggest that hyperglutamatergic states induced by acute ethanol withdrawal may provide the signal for triggering long-term neuroplasticity underlying addictive behaviours (28, 47, 59). Also, humans that have experienced multiple treatments for acute withdrawal show much greater impairment in PFC function and addictive behaviours than patients in earlier stages of their addiction (48). If a link between hyperglutamatergic states during acute withdrawal and subsequent relapse liability could be established, this would provide renewed incentive for medication development in this area (47).

Relapse prevention

The key problem of addiction treatment is to alter the chronic relapsing course of the disorder. Since the mid 1990s, two medications, naltrexone and acamprosate, have been approved by regulatory agencies in many countries for relapse prevention. Both have been extensively studied in clinical trials and their efficacy is well demonstrated, albeit with small effect sizes. According to meta-analyses from trials including about 7,000 patients for either naltrexone or acamprosate these medications significantly reduced the risk of heavy drinking to 83% and 86% of the risk in the placebo group, respectively (60, 61). Although these outcomes are very modest, they provide proof-of-concept for disease-modifying

pharmacotherapy in alcoholism. However, these medications have not changed medical practice, and consequently intense research for new therapeutics that can meet the clinical needs is underway. In this respect, acamprosate and naltrexone have been referred to sometimes as the 'gold standard' to which new compounds should be compared to and which they have to surpass.

Parts of the large variance in treatment outcomes could be attributed to genetic factors such as the A118G polymorphism at the mu-opioid receptor and its role in mediating increased dopamine
release and reward from alcohol described earlier (26, 29). On the other hand, addicts often present reward deficits and chronic negative affect with increased stress sensitivity, which have been identified as defining features of the clinical picture (38). In light of that naltrexone blocks the action of both natural and drug reinforcers, it could equally well increase craving and relapse in many addicts, while exerting a beneficial effect in the relatively small population of 118G-allele carriers (about 20% in populations with European ancestry) which may have a hyperactive reward system. Such opposing actions could well underlie the notoriously high variance in naltrexone outcomes and demands for caution in using it as a standard for new medication trials.

In patients with pronounced reward deficiency it may be necessary to increase mu-receptor function instead of blocking it. This could be achieved by the partial mu-opioid receptor agonist/antagonist buprenorphine, which sustains normal functioning of the reward system by its weak agonist properties, thereby reducing craving, but blocks excessive activation through its antagonist action. This principle is

successfully used in the treatment of opiate addiction. Animal studies have confirmed the decrease in alcohol intake by buprenorphine (62). Obviously, there are substantial drug policy concerns, but the scientific evidence is clearly in favour of such an approach. Buprenorphine is a safe drug even among opioid addicts (63) and is available in a formulation to deter abuse.

Further supporting the anti-reward/negative affect system activation hypothesis are data obtained with nalmefene, a full opioid antagonist that in early clinical trials showed superior results over naltrexone. The distinguishing feature to naltrexone is the stronger kappa-opioid receptor antagonism of nalmefene, which thus may block upregulated dynorphin/ kappa systems that contribute to the chronic negative affective state seen in alcoholic patients (31). Other stress peptides such as CRH are targeted to reduce the stress sensitivity in alcoholic patients. Clinical studies are ongoing for CRH1 receptor antagonist, however, an early clinical trial targeting a similar system, i.e. neurokinin 1 receptors, showed improved clinical outcomes and reduced amygdala responses to stress in alcoholic patients compared to placebo (64).

On the other hand, from the anti-reward/negative affect hypothesis one could predict some level of efficacy of antidepressants in the therapy of addictive disorders. Such an effect, however, is not observed (65), despite negative affective states and compulsivity as seen in addicted patients share substantial symptom overlap with disease categories such as dysphoria, depression, anxiety, or obsessive–compulsive disorders. The mechanism behind this discrepancy is unclear.

Various strategies, including antiglutamatergic substances, aiming to restore the prefrontal function have been suggested (28). Acamprosate does reduce excessive glutamate levels (66), however since the underlying mechanism is unknown, this treatment provides little information on pathophysiological mechanisms. Topiramate is an antagonist at glutamate receptors of the AMPA type. A meta-analysis of several clinical trials demonstrated an at least comparable efficacy of topiramate to naltrexone in relapse prevention, but the treatment suffers from several side effects including cognitive impairments that may limit widespread use (67). Clinical established treatments for controlling impulsive symptoms are available. Particularly atomoxetine, a non-stimulant drug acting on noradrenergic neurotransmission, is effective in adults with attention deficit/ hyperactivity disorder and seems also to reduce alcohol craving (68). Atomoxetine should therefore be considered in the treatment of alcoholic patients. An exciting new avenue in restoring cortical control over behaviour is to specifically interfere with the storage, retrieval, and extinction of drug memories using pharmacological tools. A review of this rapidly emerging field is given in Kiefer and Dinter (69).

In summary, the two available medications for relapse prevention have only modest efficacy and are not strongly embedded in current neurobiological frameworks of alcohol addiction. While
their immediate contribution to improved understanding of the pathophysiological process may appear to be limited, they have undoubtedly inspired a lot of in-depth research into their mechanism of action. In addition, basic research and human laboratory studies have identified many new targets showing promise in the medication development process. Despite these

efforts, no new medications have been brought to clinical approval in the first decade of the twenty-first century. One obstacle may lay in the acceptance of some approaches, e.g. buprenorphine, within the community. Another problem, however, seems to be the expectation that novel treatments should surpass naltrexone and/or acamprosate in head-to-head comparison. Given the uncertainties about the mechanism of action and about the appropriate group of patients, such a rigorous approach seems detrimental to the goal.

Conclusions

What might be the implications of this summarized knowledge for health policy? Our natural and cultural evolution has left us as individuals and as societies with a distinct affinity for alcohol that is different from other drugs of abuse. This should be considered when designing harm reduction strategies. What has been proven successful for other drugs including tobacco may not be applicable in the same way for alcohol.

The individual response to alcohol varies between individuals and strongly influences their behaviour towards this drug, yet it does not seem to be a good predictor of risk for alcoholism. Long-term consequences like substance use disorders are likely to be more influenced by personality traits related to behavioural control. Research has shown that such risk traits can be identified early in development and outcomes can be positively modified by preventing early onset substance and alcohol use (70).

At least three core circuits for developing and perpetuating addictive behaviours have been identified acting interdependently with the ventral striatum/nucleus accumbens being a centre of integration. These circuits are neurochemically closely intertwined, making pharmacologically dissection challenging to the degree that the same pharmacological access point may result in opposing actions and highly variable effects on behavioural output.

Components of this neurocircuitry will be differentially affected by individual alcohol addiction trajectories leading to broad heterogeneity among patient populations that needs to be considered in the choice of the appropriate treatment approach. Further contributing to this heterogeneity are gene variants impacting on the effect of pharmacological interventions. Consequently, there will be no 'magic bullet' to cure alcohol addiction; rather, individualized therapeutic solutions will be required that likely need to target several pharmacological access points simultaneously.

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Chapter 11
Opioid pharmacogenetics of alcohol addiction

Wade Berrettini

Introduction: the role of opioids in alcohol reward

There is growing interest in the relationship between mu opioid receptors and addiction to various substances. Ventral tegmental neurons release dopamine at nerve terminals in ventral striatum and medial prefrontal cortex. Activation of this circuit is a common element of abused drugs, including alcohol (1, 2). Thus, alcohol shares in common with nicotine, cocaine, amphetamine, morphine, etc., this property of enhancing dopamergic transmission in ventral striatum and medial prefrontal cortex. Both animal model and human studies are in agreement on this point (3–5). This release of dopamine in the ventral striatum and medial prefrontal cortex is partially enhanced by stimulation of mu opioid receptors (for which endorphin is the primary ligand) located on inhibitory gamma-aminobutyric acid (GABA)ergic interneurons in the ventral tegmental area. The GABAergic interneurons inhibit the dopaminergic ventral tegmental neurons, whose activation signals reward. Thus, mu opioid receptor agonists enhance the likelihood of ventral tegmental dopaminergic neuron activation (and the experience of reward) by lessening the tonic inhibition of the associated GABAergic interneurons (6–8).

Given this circuitry, it has been consistently shown that endogenous opioids play a role in ethanol reinforcement in

various animal paradigms. Endorphin elevations after alcohol consumption are seen in discrete reward regions of the hypothalamus (9), ventral tegmentum, and ventral striatum (10). It is important to note that endorphin-deficient rats continue to self-administer alcohol, indicating that endorphin is not the sole mechanism of alcohol reward (11). The importance of mu opioid receptor activation as a mechanism for alcohol reward is underscored by the fact that alcohol consumption in alcohol-preferring rats is persistently reduced after inactivating mu opioid receptors in the ventral striatum (12). Similarly, decreased alcohol self-administration is observed in primates after pre-treatment with opioid antagonists (13). C57Bl/6J mice, an inbred strain which prefers alcohol, has increased endorphin release in the hypothalamus after alcohol administration (14). Alcohol-preferring rats have high levels of opioid gene messenger RNA (mRNA) species in the hypothalamus, prefrontal cortex, and mediodorsal nucleus of the thalamus (15), as well as increased mu opioid receptor density in the ventral striatum and medial prefrontal cortex.

Clinical studies of naltrexone in alcoholism

The development of a substantial body of evidence, in the 1980s, that naltrexone (an orally-active mu opioid receptor antagonist) diminished alcohol self-administration in animal models (13, 16–19) led to the first use of naltrexone in alcohol-addicted populations in a controlled clinical trial (19), the promising outcome of which was immediately confirmed in a second controlled
clinical trial (20). Naltrexone was found to reduce alcohol craving and relapse to heavy drinking (operationally defined

as five or more drinks/day for a man, four or more for a woman), but did not change abstinence rates. On the basis of these two controlled trials, naltrexone was approved by the US Food and Drug Administration, in the absence of the usual pharmaceutical industry interest.

In the intervening 20 years, there have been more than 30 clinical trials of naltrexone in alcohol addiction (21–23). While the majority of these clinical trials demonstrate efficacy of naltrexone in reducing risk for relapse to heavy drinking, the effect size is small, with many patients having no benefit. This has resulted in multiple reports in which the naltrexone arm outcomes are not significantly better than the placebo arm outcomes (24). This is an expected outcome, given the tremendous heterogeneity of clinical alcohol addiction. It is likely that important clinical characteristics, such as compliance, severity and duration of alcohol addiction, co-morbidity (both medical and psychiatric), and/or attendance at psychosocial treatment, may influence outcomes.

In this situation, multiple investigators have attempted to define clinical characteristics which might enhance the probability of naltrexone response. Some clinical measures have shown promise in characterizing a naltrexone responder—high alcohol craving (25–27) and strong family history of alcohol addiction (25), but family history of alcohol addiction did not predict response to naltrexone in the COMBINE multicentre trial (28). Alcohol addicts who experience greater euphoria after alcohol may have a better response to naltrexone (29).

A118G *OPRM1* mis-sense single nucleotide polymorphism: molecular and cellular effects

A common mis-sense single nucleotide polymorphism (SNP; rs 1799971) in the first exon of the mu opioid receptor gene, *OPRM1*, was described by Bergen et al. (30), A118G, or N40G, reflecting the fact that the A allele encodes asparagine, while the minor G allele encodes aspartate. The A (asparagine) allele is thought to be N-glycosylated (31), whereas this is not possible for the G (aspartate) allele, as there is no free amino group. Subsequent studies (32–35) revealed large ethnic differences in allele frequencies (Table 11.1).

This allele has been the subject of multiple molecular investigations to determine its functional consequences, in terms of gene expression, protein translation, receptor signalling, and receptor density. Initially, Bond et al. (36) reported that the minor 'G' allele mu opioid receptor resulted in decreased affinity for binding to beta-endorphin, compared to the common 'A' allele receptor. There was no change in binding affinity for alkaloid ligands. This result has not been confirmed in subsequent investigations (37, 38). In one such study transfected HEK293 cells (a fibroblastoid cell type) were used (37), but the 118G allele did not differ in binding affinity for beta-endorphin, compared to 118A. Beyer et al. (37) also reported that the 118G allele was not different from the 118A allele in rate of desensitization, internalization, or resensitization, but 118G had decreased transcription compared to 118A. Ramchandani et al. (38) also did not report differences in kinetics of binding of beta-endorphin to the 118G, compared to 118A. Mahmoud et al. (39), using a

whole-cell patch clamp technique in acutely dissociated trigeminal ganglion neurons, reported that morphine was fivefold less active at the 'G' allele receptor form in activating a Ca^{2+} channel. There was no such difference for fentanyl. Zhang et al. (40) conducted allelic imbalance studies in post-mortem human brain, revealing a marked decrease in 118G allele mRNA. In a second experiment, they showed *in vitro* evidence of a marked decreased translation of the 118G mRNA (40).

Table 11.1 Frequency of G allele for A118G SNP in ethnic groups

Ethnic group	Frequency G	Ethnic group	Frequency G
African	1%	Korean	31%
African American	3%	Chinese	35%
Swedish	11%	Malaysian	43%
European American	15%	Indian	47%

A118G *OPRM1* mis-sense single nucleotide polymorphism: animal model studies

In the murine *OPRM1* gene, there is no equivalent of the A118G naturally-occurring variation. A homologous variation (A112G, with the A allele encoding asparagines and the G allele encoding aspartate, as in the human *OPRM1* gene) was created by bacterial artificial chromosome engineering and murine transgenic techniques by Mague et al. (41). They reported decreased transcription and translation of the G allele in transgenic C57Bl/6 mouse brain, a result congruous with the human post-mortem brain *ex vivo* results of Zhang et al. (40), as well as the *in vitro* results of Beyer et al. (37). There was a blunted locomotor response to morphine in the 112G

mice, as well as decreased morphine conditioned place preference (CPP) in 112G female mice, the latter being a sexually dimorphic response, with 112G males showing the expected CPP response to morphine.

Two other forms of transgenic mice were produced, using homologous recombination to replace the murine *OPRM1* exon 1 with one of the two forms (118A and 118G) of human *OPRM1* exon 1 (38). These investigators conducted *in vivo* microdialysis experiments in the ventral striatum, demonstrating that the 118G mice had the expected elevations in dopamine release after alcohol, while the 118A mice had no significant increase over baseline. These data suggest that the 'G' allele conveys an increased rewarding valence to alcohol, compared to the 'A' allele.

There have been several studies of a similar SNP in the rhesus monkey, the C77G, which results in a homologous amino acid change, asparagine to aspartate (42–44). Both groups report that the G allele monkeys consume significantly more alcohol than the CC monkeys. Further, both groups note that naltrexone significantly decreases alcohol intake in the GG monkeys.

These reports, taken together, are consistent with the hypothesis that the 118G allele (or its equivalent in mouse and primate) conveys a greater rewarding effect of alcohol, a difference which is inhibited by naltrexone. These studies are remarkably consistent, given the species, paradigm, technical, and molecular engineering differences among these studies.

A118G *OPRM1* mis-sense single nucleotide polymorphism: human pharmacogenetic studies of alcohol

There have been several pharmacogenetic reports of the A118G SNP in human laboratory experiments involving alcohol (38, 45–48). In a laboratory investigation of the A118G pharmacogenetics of alcohol reward, Ray et al. (45, 46) demonstrated that the G allele carriers experienced significantly greater euphoria after standard oral doses of alcohol (while controlling for breath alcohol concentration), compared to AA persons. Further, naltrexone significantly blunted the euphoria in the G allele carriers and was without effect in the AA group.

In agreement with this result, Ramchandani reported that G allele carriers had a greater striatal release of dopamine after alcohol (using a raclopride positron emission tomography scan technique), compared to AA participants. In a more naturalistic approach, Ray et al. (47) studied
drinking habits of social drinkers over a five-day period, analysing subjective responses to alcohol by A118G genotype. G allele carriers reported more significantly more 'vigour' and less negative mood after drinking, compared to the AA group. Similarly, Setiawan et al. (48) studied the subjective response to alcohol in social drinkers after a dose of naltrexone. Naltrexone significantly decreased the ethanol-induced 'euphoria' to a priming dose of alcohol in subjects with the G allele, compared to AA participants.

Taken together, these human laboratory studies of the A118G variant on effect of alcohol are remarkably consistent, with the clear conclusion that the G allele permits people to

experience alcohol in a more rewarding manner, compared to AA individuals. It is also notable that naltrexone is able to blunt this euphoria in G allele carriers, but not in AA persons. This latter observation is consistent with subjective reports of the effect of naltrexone in clinical trials for alcohol addiction, in which the medication attenuated alcohol-induced euphoria among responders (29).

Pharmacogenetic studies of naltrexone clinical trials for alcohol addiction

There have been multiple pharmacogenetic studies of naltrexone clinical trials for alcohol addiction published in the last decade. The first such publication (49) was a retrospective analysis of three naltrexone trials of similar design, two conducted at the University of Pennsylvania and one at the University of Connecticut, United States. Compliance was monitored by riboflavin testing and by pill counts. Eighty-two patients (71 of European descent) who were randomized to naltrexone and 59 randomized to placebo (all of European descent) in one of three randomized placebo-controlled clinical trials of naltrexone were genotyped at the A+118G (Asn40Asp) and C+17T (Ala6Val) SNPs in the mu-opioid gene (*OPRM1*). The association between genotype and drinking outcomes was measured over 12 weeks of treatment. For purposes of examining the pharmacogenetics of naltrexone response, the analysis was limited to those subjects with well-defined outcome data who had at minimum six weeks' exposure to the medication. The primary drinking outcome considered was relapse to heavy drinking (≥5 drinks in a single day for men or ≥4 drinks for women). This definition of heavy drinking was the primary

outcome for each of the trials. The timeline follow-back method was employed (along with self-report) to measure alcohol consumption (50). There was a significantly greater proportion of naltrexone-treated subjects with the G allele variant who did not return to heavy drinking (no relapse) compared to those with those homozygous for the A allele (Wald = 4.04, 1 degree of freedom, odds ratio = 3.47 (95% confidence interval: 1.03–11.67), p = 0.045) (Table 11.2).

This finding was confirmed in a larger multisite study of naltrexone, acamprosate, and placebo for alcohol addiction (51). Alcohol-addicted subjects were treated for 16 weeks with 100 mg of naltrexone. All participants received medical management alone or with combined behavioural intervention. When considering only those patients receiving medical management alone, there was a significant effect of naltrexone on 'good outcome' among the 118G carriers, while there was no such effect for the patients receiving naltrexone who were homozygous A118 (Table 11.2). However, there was no such effect in the naltrexone group receiving medical management with combined behavioural intervention. The combined behavioural intervention was delivered by licensed behavioural health specialists in up to 20 flexible participant need-adjusted 50-minute sessions. Combined behavioural intervention, an intensive and specific alcohol intervention, may have compensated for the placebo effect, thereby suppressing the chances of observing a main effect of naltrexone or a genetic interaction. The data presented by Anton et al. (51) are consistent with this thinking. A gene × medication interaction may be observable only in patients who can show obvious benefit from the medication over placebo.

Table 11.2 A118G genotype and good outcome in naltrexone studies (49, 51) of pharmacotherapy for alcohol addiction

Genotype at A118G	(49)		(51)	
	Naltrexone	Placebo	Naltrexone	Placebo
G allele carriers	85%[a]	55%	89%[b]	54%
Homozygous A	56%	46%	56%	50%

[a] P = 0.04, odds ratio = 3.5.

[b] P = 0.005, genotype × medication interaction; odds ratio = 5.8.

In a small Korean study of naltrexone in alcohol addiction (52), subjects adherent to naltrexone treatment with one or two copies of the Asp40 allele took a significantly longer time than the Asn40 group to relapse to heavy drinking ($p = 0.014$). Although not significant, the Asn40 group treated with naltrexone had a 10.6 times greater relapse rate than the Asp40 variant group. There was no effect on abstinence.

In the Veterans Administration multisite study of naltrexone in alcohol addiction, Gelernter et al. (53) reported that the 118G allele did not predict outcome among 149 participants in the naltrexone group and 64 in the placebo group. There are several possible explanations for this result. Firstly, the efficacy of naltrexone is certainly influenced by compliance, and the compliant population was defined as those who opened the medication bottle a minimum of 50% of the time, so that medication compliance was defined liberally. Secondly, it is likely that high levels of co-morbidity influence response to naltrexone. The study population had substantial rates of recurrent unipolar illness, antisocial personality, and anxiety disorders and had severe alcohol addiction of long duration. These factors might overwhelm any genetic predisposition to respond to naltrexone. Thirdly,

the study had limited power: for example, there were only nine 118G carriers in the placebo group.

Coller et al. (54) recently reported the results of a naltrexone and cognitive-behavioural therapy trial in 100 Australian alcohol-addicted persons. They reported an overall effect of naltrexone on relapse to heavy drinking, but no influence of the A188G variants. The absence of a control group makes this study less ideal, as does the small sample size, with 68 study completers.

Taken together, the A118G clinical trials in naltrexone treatment for alcohol addiction remain promising, but there are clear unanswered questions, including the influence of counselling, compliance, and co-morbidity on outcome. Available depot formulations of naltrexone may reduce non-compliance, but the influence of co-morbidity and counselling may be more difficult to resolve. It will be necessary to conduct pharmacogenetic alcohol addiction naltrexone trials, for which participants are randomized by A118G genotype into the naltrexone or placebo arm to reduce possible sources of bias. These trials should be characterized by:

♦ large size (at least about 150 persons per arm, including oversampling of G allele carriers) to ensure adequate power

♦ rigorous assessment of compliance

♦ randomization stratified by genotype

♦ careful assessment of comorbidity

♦ modest psychotherapeutic intervention, so as to mirror 'real-world' clinical practice.

Summary

There is a growing interest in the association between mu opioid receptors and addiction. There are extensive data, across species, to suggest that the 118G form of the mu opioid receptor is characterized by decreased transcription and translation. There are convincing data, from murine, primate, and human laboratory studies, that the 118G (or its species-specific homologue) variant permits alcohol to have a greater rewarding valence, leading to increased alcohol consumption. Further, the human and rhesus data are equally convincing that naltrexone is able to blunt this greater rewarding signal. Lastly, the possibility that A118G alleles can be used clinically to identify alcohol-addicted persons with a greater probability to have a beneficial response to naltrexone is a hypothesis that deserves testing on a large scale, with the characteristics noted earlier.

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Part III
Patterns of consumption

Chapter 12
Tools for estimating alcohol consumption

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Introduction

Measurement of alcohol use cannot be viewed independently of the intended analysis. Four aspects have to be considered: (i) whether alcohol consumption is the dependent or independent variable; (ii) the level of data aggregation; (iii) whether between- and within-individual variation in consumption is of major interest or concern; and (iv) how precise (unbiased) the estimation should be. For example, when considering a legal issue, such as the responsibility for a traffic fatality, self-reported alcohol use will not be the best measure, and objective measures such as blood alcohol concentrations (BACs) are needed. Where the aim is to measure the ratio of male to female alcohol consumption in a particular country, it is sufficient to ask people about their consumption on the previous day (given that interviews are spread out over the whole week) and then to aggregate the results at the country level. In this latter scenario, only a few questions need to be asked and recall bias is small because of the short recall period (1). However, there is the risk that drinkers who did not consume alcohol on the previous day may be misclassified as abstainers. With a longer recall period, misclassification of drinkers can be reduced, but at the cost of recall errors as to the level of alcohol consumption. Systematic errors such as under-reporting are acceptable in correlational analysis if rank order is preserved. However, the

exact level of consumption is important if our aim is to determine how many people exceed a certain consumption level, e.g. to estimate the distribution of different consumption levels in a population.

If intraindividual variability (e.g. occurrence of heavy drinking occasions) is of interest, which is an important consideration for estimating the associations of an outcome with some alcohol-related consequences (see Chapter 2, 'Key studies of alcohol and disease'), more complex measurement instruments are required. Thus, there is no single 'optimal' instrument to measure alcohol consumption, and the choice of instrument depends on the research question (2, 3).

Measurement at the aggregate level

Recorded consumption

Recorded adult per capita alcohol consumption is usually measured at the aggregate level and is defined as the recorded amount of litres of pure alcohol consumed per adult (15+ years) over a calendar year in a country. This indicator only takes into account consumption which is recorded from production, import, export, and sales data, often via taxation data (4). Recorded adult per capita alcohol consumption is calculated as the amount of pure alcohol recorded in a country or region for a given year, divided by the mid-year resident adult population for the
same calendar year. For comparisons between countries, restricting the consumption data to the adult population is advantageous as there are differences in countries' age

structures, especially between high-income and low- to middle-income countries.

Recorded adult per capita alcohol consumption is calculated as the sum of beverage-specific consumption of pure alcohol (beer, wine, spirits, other). The data come from varied, and usually multiple, sources, and the World Health Organization has been collecting and prioritizing these data and publishing the results through the Global Information System on Alcohol and Health (GISAH) (5). Generally, the most accurate data are government statistics of per capita consumption. Increasingly, more governments have been monitoring adult per capita alcohol consumption (GISAH). Generally, next in accuracy are country-specific alcohol industry statistics in the public domain (Canadean, International Wine & Spirit Research (IWSR), Wine Institute; historically data from the industry were published as *World Drink Trends*) and from the intergovernmental International Organisation of Vine and Wine (OIV, L' Organisation Internationale de la Vigne et du Vin), followed by data from the Food and Agriculture Organization (FAO) of the United Nations' statistical database (FAOSTAT). In order to make the conversion of unadjusted volume of alcohol into litres of pure alcohol, the beverage-specific alcohol content (percentage alcohol by volume) is needed. FAO data is considered to be as follows: beer (barley beer 5%), wine (grape wine 12%, must of grape 9%, vermouth 16%), spirits (distilled spirits 40%, spirit-like 30%), and other (sorghum, millet, maize beers 5%; cider 5%; fortified wine 17% and 18%; fermented wheat and fermented rice 9%; other fermented drinks 9%). Of course, government data on pure alcohol consumption may use different concentrations of pure alcohol than are listed here if they have more specific statistical information.

Unrecorded consumption

Although recorded consumption is the major component of total adult per capita alcohol consumption, about one-third of alcohol consumption is unrecorded (see Chapter 15, 'Unrecorded alcohol consumption'), namely either illegally produced or smuggled alcohol, surrogate alcohol (alcohol not officially intended for human consumption, such as perfume), alcohol not registered in the country where it is consumed, or legal unregistered alcohol (e.g. home-made alcohol in countries where it is legal). Obviously, measurement of unrecorded consumption is more problematic than is measurement of recorded consumption and incurs more uncertainty. Three main methods of measurement have been used, and in cases where there are multiple data sources for a country these methods will be used in the following order: first, empirical studies to determine the level of unrecorded consumption (e.g. with general population surveys, or with special studies in regions with high prevalence); second, indirect studies, where other indicators are used (e.g. sugar in Soviet Union, or alcohol poisoning); and third, key informant estimates. While recorded estimates are available on a yearly basis, only a few countries (e.g. Sweden) collect unrecorded consumption data on that frequent a basis. For most countries, unrecorded data are only collected every five years, usually for global studies such as the Comparative Risk Assessment within the Global Burden of Disease Study. Given the high proportion that unrecorded consumption contributes to overall consumption globally, and the potential for more attributable health problems (6), additional research is needed on globally assessing unrecorded consumption and its consequences.

Measurement at the individual level

Alcohol consumption measurement instruments at an individual level can be subdivided into subjective measures (e.g. self-reporting) and objective measures (e.g. BAC). In the case of
self-reporting, respondents are asked to summarize their drinking pattern/behaviour over a predefined period of time, or to report their most recent drinking occasions in a detailed manner.

Measurement of customary drinking habits

'Customary or usual drinking habits' are intended to measure average consumption. Thus, respondents summarize their drinking behaviour in terms of their customary drinking frequencies and the corresponding customary quantity consumed. There are some attempts to add questions which permit the measurement of variability, mainly of different quantities consumed, such as the graduated frequency (GF) approach.

Quantity–frequency index

The most globally used alcohol consumption measure is the quantity–frequency (QF) measure which inquires in two separate questions about usual frequency of drinking and usual quantity when drinking. Answers to these two questions are then transformed into a one-dimensional measure of drinks or grams of pure alcohol per time unit.

Generic alcohol consumption measures assume that drinks contain about the same alcohol content (standard drinks). For these measures response burden is high because respondents average their consumption across different days of the week and for different drinks. The number of standard drinks can vary even for those with the same container size (e.g. cans with different beer strengths) and for drinks consumed in bars or poured into glasses at home. The response burden can be facilitated if graphical material of different drinks and sizes and their number of standard drinks can be presented (e.g. with face-to-face; Internet, or mailed surveys).

QF questions can be asked separately for different drinks (e.g. beer, wine, spirits), and different serving sizes can be used. If questions are administered based on the drink, no typical quantity per drinking occasion can be calculated, because the combination of drinking occasions for different drinks is mostly unknown. It is possible to reduce response burden by asking QF questions separately for work days (Monday to Thursday) and for weekend days (7), or for different drinking situations such as at home or in bars (8), which will provide some information about variability of drinking (weekend versus weekdays), but QF remains a measure of customary (averaged) drinking.

Semi-quantitative food frequency questionnaires

Food frequency questionnaires (FFQs), used in medical epidemiological studies, generally ask only one question concerning alcohol consumption, or one question per drink. Questions concern the frequency of consuming a typical drink, much like the frequency question in a QF, but usually

poorly differentiate the amount consumed at higher alcohol consumption levels (9). FFQs, therefore, provide a more detailed measure of alcohol consumption for daily drinkers.

Use of 5+, 8+, 12+, etc. measures within the quantity–frequency approach, including maximum drinking

The effect of steady versus occasional heavy drinking on mortality and morbidity is established (see Chapter 2, 'Key studies of alcohol and disease', 10), but cannot be measured with customary drinking approaches.

The inclusion of questions concerning frequency of drinking greater quantities, such as drinking 5+, 8+, or 12+ drinks on one occasion or during one day, provides more information than does the classical QF approach on variability of drinking. The usual frequency and the frequency of heavy drinking occasions can be combined to derive overall volume (11). More recently, data concerning
frequencies of heavy drinking occasions have been combined with the maximum amount on any occasion in a given time frame (e.g. during the past 12 months), an approach which seems to capture a certain proportion of the genetic risk for alcohol dependence (12, 13).

Graduated frequency and proportions of occasions

Instead of separately questioning about usual frequencies, frequencies of heavier occasions, and the maximum amount consumed on any occasion, several measures have been suggested to combine volume of drinking and variability of drinking within one instrument. One such suggestion from

Knupfer et al. (14) is called the 'proportion of occasions' approach or 'Knupfer series'; it asks about frequencies of drinking and includes questions on the proportion of different drink quantities, namely five or more, three or four, or one or two units. Proportions are defined on a five-point scale from 'nearly every time', 'more than half the time', 'less than half the time', 'once in a while', and 'never'.

Further developments in this area of alcohol consumption measurement approaches ask about frequencies of days of drinking with particular levels in the past (e.g. past 30 days, past 12 months). This GF approach begins by asking the generic frequency of drinking, and then asks for the maximum amount in the given recall period. Starting with the maximum amount, the instrument then asks a series of questions for the frequencies (every day, five or six times a week, etc.) of different quantities by proceeding negatively from the maximum quantity stated by the respondent in the previous question (e.g. 18+ glasses, 15–17, 12–14, 8–11, 5–7, 3–4, or 1–2). The purpose of the response burden here is to distribute the total number of drinking days correctly over the days where different quantities of alcohol were consumed.

Measurements by listing amounts in recent drinking occasions and diary methods

The difference between these approaches as compared to customary drinking approaches is that respondents provide their consumption details as precisely as possible for a few occasions. Thus, they do not have to average their behaviour; this is the task of the researcher.

Most recent drinking occasion approach

In the last occasion approach, respondents are asked to list all drinking on the last occasion. This can be done in a very detailed way (e.g. with the assistance of a list of different drinks). Response burden and recall errors are reduced because respondents do not have to average and must recall only their latest occasion. As an estimate of an individual's overall volume of alcohol consumption, generic frequency is asked and assumptions must be made about the representativeness of the last drinking occasion for all drinking occasions. This may be questionable if heavier drinking occasions are better recalled than lighter drinking occasions. This measure results in a clearer picture if more than the last occasion is measured, e.g. the two, three, or four previous occasions in a defined time frame. Infrequent drinkers may be overlooked if the time frame is too short. In the 'variable survey period approach' (15) the best matching time period per individual is asked, i.e. either a week for daily and almost-daily drinkers and a year for less-than-monthly drinkers. Then, respondents are asked to list all drinking occasions within this time period. Survey periods are chosen in such a manner as to ensure that around four to five drinking occasions occur in the given interval.

Diaries and timeline follow-back

The survey period approach (fixed for a time frame) can be regarded as a retrospective diary. Since the response burden in diaries is quite high, diaries are commonly used for short recall

periods only (e.g. a week). A particular case is the timeline follow-back (16) that has mainly been evaluated with clinical populations. Supplying the respondents with a calendar, participants provide retrospective estimates of their daily drinking over a specified time period, which usually covers the last month, but which can vary up to 12 months. Several memory aids can be used to enhance recall. For instance, key dates like holidays serve as anchors for reporting drinking. Respondents are encouraged to mark personal key dates such as birthdays, etc. For each day, respondents should give the exact number of standard drinks.

A diary can also be used prospectively, when the respondents monitor their consumption directly when it occurs, in practical reality most often at the end of each day. Thus, the prospective diary can be considered as a series of 24-hour retrospective recalls (17). An example of a diary used in Switzerland is provided in Figure 12.1.

Diaries may provide information on overall frequencies and quantities and beverage-specific frequencies and quantities. Similarly, they may provide a measure of within-individual variability, at least over the reporting period. Diaries have been used with success for periods of more than three months, particularly when derived by innovative reporting technologies such as the ‘interactive voice response’ (18).

Objective measures: blood alcohol concentration and other biological markers

Blood alcohol concentration

BAC is commonly and reliably measured in breath and can be used as a marker for recent alcohol consumption only, since ethanol is eliminated rapidly from the body. Hence, its use in large-scale surveys is limited, as it requires a high level of compliance by respondents within the study to take regular samples with a breathalyser. Its utility, e.g. in conjunction with acute consequences such as traffic accidents, depends on the time between the event and the time the measure is taken. The advantage is an objective assessment that has less measurement error than verbal reports.

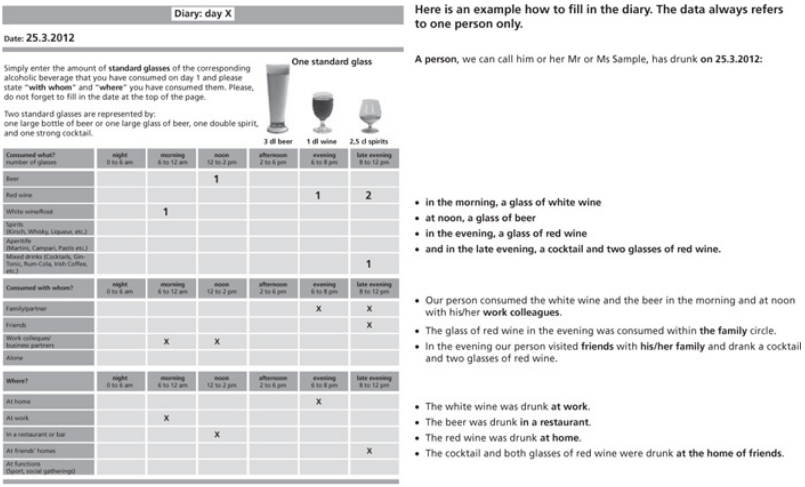
Another objective measure for BAC is to assess transdermal alcohol at the skin surface, where approximately 1% of ingested alcohol is eliminated (19). A main advantage of transdermal measurements is that they are less invasive than methods which require samples of body fluids such as blood or urine. Transdermal measures are intraindividually reliable and provide good measures of variations in intake. So far, however, this measurement approach is less successful at estimating the exact amount of alcohol consumed per episode, and needs calibration with other methods.

Other biological markers

Details of biological markers were reviewed in a special 2003 issue of the journal *Addiction* (20) and by Peterson (21). There have been new developments in biomarkers for alcohol

consumption, especially, but not limited to, biomarkers found in the hair (22). The great advantage of biomarkers is that they are not susceptible to biases introduced by the interviewer or respondent. However, they have disadvantages, namely other factors impact these markers and, thus, the relationship between these biomarkers and average alcohol consumption or frequency of heavy drinking occasions is not as strong as is required for measuring different patterns of alcohol use in the general population.

Traditionally, for longer-term heavy drinking, mean corpuscular volume of red blood cells, and the liver enzymes gamma-glutamyltransferase, aspartate aminotranferase, alanine aminotransferase, and carbohydrate-deficient transferase (CDT), have been used as biomarkers (partially in combination with each other). All of these biomarkers have imperfect sensitivity and specificity but can be used to identify the risk of long-term heavy drinking. These biomarkers also have a clinical role in the detection of complications of drinking, and of co-morbid conditions, which may increase the risk of drinking. Thus, biomarkers are of more value to clinical research, especially in the treatment of alcohol use disorders. Specifically, the advantage of using CDT as a biomarker is that increased concentrations of CDT in plasma can be found after heavy alcohol use (>50–80 g/day) for a relatively short time of a week, and the value normalizes quite quickly after a period of abstinence with a mean half-life of about 15 days (7).



Diary: day X

Date: 25.3.2012

Simply enter the amount of **standard glasses** of the corresponding alcoholic beverage that you have consumed on day 1 and please state "**with whom**" and "**where**" you have consumed them. Please, do not forget to fill in the date at the top of the page.

Two standard glasses are represented by:
one large bottle of beer or one large glass of beer, one double spirit, and one strong cocktail.

One standard glass

3 dl beer | 1 dl wine | 2,5 cl spirits

Consumed what? number of glasses	night 0 to 6 am	morning 6 to 12 am	noon 12 to 2 pm	afternoon 2 to 6 pm	evening 6 to 8 pm	late evening 8 to 12 pm
Beer			1			
Red wine					1	2
White wine/Rosé		1				
Spirits (Kirsch, Whisky, Liqueur, etc.)						
Aperitife (Martini, Campari, Pastis etc.)						
Mixed drinks (Cocktails, Gin-Tonic, Rum-Cola, Irish Coffee, etc.)						1

Consumed with whom?	night 0 to 6 am	morning 6 to 12 am	noon 12 to 2 pm	afternoon 2 to 6 pm	evening 6 to 8 pm	late evening 8 to 12 pm
Family/partner					X	X
Friends						X
Work colleques/ business partners		X	X			
Alone						

Where?	night 0 to 6 am	morning 6 to 12 am	noon 12 to 2 pm	afternoon 2 to 6 pm	evening 6 to 8 pm	late evening 8 to 12 pm
At home					X	
At work		X				
In a restaurant or bar			X			
At friends' homes						X
At functions (Sport, social gatherings)						

Here is an example how to fill in the diary. The data always refers to one person only.

A person, we can call him or her Mr or Ms Sample, has drunk **on 25.3.2012:**

- **in the morning, a glass of white wine**
- **at noon, a glass of beer**
- **in the evening, a glass of red wine**
- **and in the late evening, a cocktail and two glasses of red wine.**

- Our person consumed the white wine and the beer in the morning and at noon with his/her **work colleagues**.
- The glass of red wine in the evening was consumed within **the family** circle.
- In the evening our person visited **friends** with **his/her family** and drank a cocktail and two glasses of red wine.

- The white wine was drunk **at work.**
- The beer was drunk **in a restaurant.**
- The red wine was drunk **at home.**
- The cocktail and both glasses of red wine were drunk **at the home of friends.**

Figure 12.1 Example of a drinking diary.

With respect to the general population, these biomarkers are more likely to be elevated in people aged 30 years and older and in long-term heavy drinkers. Moreover, for determining levels of social drinking, they are of limited value. The same seems to be true with ethyl glucuronide and fatty ethyl esters, both minor ethanol metabolites (22).

Questions of validity and reliability

There are many factors influencing the reliability and validity of self-reports of alcohol consumption. However, it should be noted—as shown for semi-quantitative FFQs—that reliability of alcohol use measures are usually higher than for those of other food intakes. Although not always the case, self-reported survey measures of alcohol use yield lower consumption estimates and have lower validity than do aggregate measures of per capita consumption which are

based, for example, on sales data. There are four reasons why self-reports generally underestimate per capita consumption. First, there may be problems with recall (most people have problems recalling their consumption of several weeks past). Second, many alcohol consumption measures require substantial cognitive efforts, especially if drinking is variable (see 'Measurement at the individual level' section). Third, there may be an effect of social desirability, especially with under-reporting the number of heavy drinking occasions. Fourth, surveys which assess self-reports may incur selective non-response due to (i) an incomplete sampling frame and sample selection bias (inclusion of only those households with a telephone and exclusion of the heaviest consumers in institutions, homeless people, people who are harder to reach, etc.), or (ii) self-selection bias, e.g. heavier consumers—although in the sampling frame—are more reluctant to participate in surveys (23).

Despite being the best measurement of alcohol consumption, aggregate measures come with uncertainty, especially in the measurement of unrecorded consumption (see 'Measurement at the individual level' section). Aggregate level per capita data depend on how precisely unrecorded consumption is measured. Without triangulating per capita data with additional information obtained from surveys, per capita data cannot be used to measure patterns of drinking or consumption in different subgroups (e.g. by age and sex).

An alternative to using survey data or aggregate measures alone is to use both methods in combination through statistical modelling (24). In special applications, especially in heavy drinking populations, survey data, aggregate measures of alcohol consumption, and biological markers

used in combination are hypothesized to provide the best mathematical model to measure alcohol consumption.

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Chapter 13
A global overview of alcohol consumption patterns

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Introduction

Worldwide, alcohol use was identified as the third most important risk factor for the burden of disease in 2004, in terms of disability-adjusted life years lost (1). In middle-income countries (MICs) it was the leading risk factor, and the second most important risk factor in high-income countries (HICs). Only in low-income countries (LICs), where mortality and morbidity is dominated by childhood underweight, maternal undernutrition, unsafe sex, and disease resulting from unclean water and poor sanitary conditions, did alcohol use rank lower as a risk factor (eighth rank) (1). This burden is differential by sex as men experienced five times the amount of harm due to alcohol consumption in comparison to women. This difference is related to differences in volume of consumption as well as patterns of drinking, such as heavy episodic drinking (HED). In the Global Burden of Disease study, alcohol use has been linked to more than 200 three-digit International Classification of Diseases (ICD)-10 codes for disease and injury (2), including liver cirrhosis and cancers, primarily related to volume of drinking and also to homicides and traffic injuries, where drinking patterns, such as heavy episodic drinking, play a larger role.

Besides its impact on disease and injury, alcohol use leads to a wide range of social consequences, impacting on relationships, work, education, and public order and safety (3). Hence, alcohol consumption does not only affect the drinker but creates a great deal of harm to others (4). This chapter provides an overview of the distribution of alcohol use in different regions of the world, including abstention, adult per capita consumption (APC), volume of drinking, and other drinking patterns like HED.

Methods

Data were obtained from the systematic monitoring of the World Health Organization (WHO), whose data are made public on the Global Information System on Alcohol and Health (GISAH) (5). Details of definitions and sources for the various indicators can be found on the GISAH website. In short, the following main sources of information were used: general population surveys for individual-level data, government statistics (sales, production, import, export), and estimations of the Food and Agriculture Organization for aggregate statistics of consumption (6). For sources of unrecorded consumption, please see Chapter 15, 'Unrecorded alcohol consumption'.

Adult per capita consumption

Recorded and unrecorded consumption

Overall in 2004 (estimated as an average of the years 2003–2005) every person aged 15 years or more drank on average 6.1 litres of pure alcohol. Worldwide there is large

variation in APC (Table 13.1), with the highest consumption levels in the developed world, and particularly in the European Region (EUR) (for a list of countries within regions see (7)), and in the former Socialist countries (for country details, see appendix 3 of (7), pp. 273–7). Medium consumption levels are observed in the south of Africa (e.g. South Africa and Namibia) and in North and South America (USA, Canada, Brazil, and Argentina). Low consumption levels are observed in the Saharan and sub-Saharan regions and in the Eastern Mediterranean Region (EMR)—often countries with an Islamic faith—and in many Asian countries such as India and Indonesia.

Of the total APC, 28.6% (1.76 L) was consumed in the form of unrecorded alcohol, e.g. homemade or illegally produced alcohol, with the potential for an increased risk of harm due to often unknown impurities or contaminants (see Chapter 15, 'Unrecorded alcohol consumption'). Generally, the lower the APC the higher the proportion of unrecorded consumption (the correlation being r = –0.73 across all countries in the world: see Table 13.1).

Beverage-specific consumption

In different regions of the world different alcoholic drinks are preferred (Table 13.2). In terms of pure ethanol, globally more than 45% of total recorded alcohol is consumed in the form of spirits, predominantly in the South-East Asian Region (SEAR) and the West Pacific Region (WPR). Alcoholic drinks other than beer, spirits, and wine make up the highest share of total recorded consumption in the African Region (AFR) and in the low-consumption countries of the EMR.

'Other' alcoholic drinks in Africa are mostly fermented drinks made of sorghum, millet, maize, rice, wheat, or fruits, with an estimated alcohol by volume (ABV) of 5%. In Asia, 'other' alcoholic drinks are mostly rice wines (ABV approximately 5%). In most other countries, 'other' alcoholic drinks are mainly fortified and strong wines with an ABV of 17–18% or ciders (5% ABV).

Table 13.1 Total APC, unrecorded consumption in litres and in % of total APC by WHO region for 2004 (average 2003–2005)

WHO Region	Total APC (in litres)	Unrecorded (in litres)	Proportion unrecorded (in %)	Correlation[a] Total APC—proportion unrecorded
African Region (AFR)	6.15	1.93	31.4%	–0.82
Region of the Americas (AMR)	8.67	2.01	23.1%	–0.40
Eastern Mediterranean Region (EMR)	0.65	0.36	56.2%	–0.37
European Region (EUR)	12.18	2.67	21.9%	–0.39
South East Asian Region (SEAR)	2.20	1.52	69.0%	–0.88
West Pacific Region (WPR)	6.23	1.63	26.2%	–0.58
World	6.13	1.76	28.7%	–0.73

[a] Correlations are calculated across countries within each region, and across all countries of the world.

Data from WHO Global Information System on Alcohol and Health (GISAH), Copyright © World Health Organization 2012. Available from <http://apps.who.int/ghodata/?theme=GISAH>.

Table 13.2 Percentage of beverage-specific recorded consumption for 2004 (average 2003–2005)

WHO Regions	% spirits	% beer	% wine	% other
AFR	12.0%	34.1%	5.6%	48.2%
AMR	32.9%	54.7%	12.0%	0.6%
EMR	25.2%	37.8%	5.7%	31.3%
EUR	34.6%	37.1%	26.4%	2.5%
SEAR	71.0%	25.5%	2.5%	1.0%
WPR	54.0%	35.5%	3.6%	6.9%
World	45.7%	36.3%	8.6%	10.5%

Note: percentages of pure ethanol consumed according to drink type.

Data from WHO Global Information System on Alcohol and Health (GISAH), Copyright © World Health Organization 2012. Available from <http://apps.who.int/ghodata/?theme=GISAH>.

At the country level, in most Asian countries and in Eastern Europe spirits are the preferred alcoholic drink (for details, see (7), figure 2, p. 7). Wine is the preferred drink in most of the wine-producing countries of Europe and South America, such as France, Italy, Chile, and Argentina; otherwise wine preference is rare. 'Other' alcoholic drinks (drinks other than wine, beer, and spirits) are preferred mostly in the sub-Saharan region with generally low alcohol use levels. The remainder of the world prefers beer.

Abstention

Lifetime abstention is associated with APC (Table 13.3). Thus, in regions with high APC there are fewer lifetime abstainers. This is also true at the country level (7). Globally, 45% of the world's population has never consumed alcohol (men: 35%; women: 55%). In addition, 13% (men: 13.8%; women: 12.5%) have not consumed alcohol during the past 12 months, but have consumed alcohol at some point in their lives (former drinkers). In regions with high abstention rates, abstainers are commonly lifetime abstainers. In regions with

low abstention rates, a large proportion of former drinkers have abstained during the past 12 months.

The finding of proportionally more former drinkers in regions with higher mean consumption (and lower abstention rates) may be due to what has been called sick quitting (8), i.e. ceasing of alcohol use because of having already experienced alcohol-related diseases. Of course, other factors such as cultural norms and religion contribute to the rate of former drinkers. In EMR, for example, with a prevailing Islamic faith and almost 90% lifetime abstention, not much of the population is left to become former drinkers.

Heavy episodic drinking

Highest per capita alcohol consumption, commonly found in the EUR or other developed countries, does not necessarily mean the highest consumption per drinker. The consumption by past 12 months drinkers, which is particularly high in regions (and at the country level (7)) with moderate or even low APC, is associated with high abstention rates. It may be that stigmatization of heavy drinking or drinking in general (e.g. for religious reasons) may lead to polarization, i.e. that the few drinkers in a country drink a lot because social control does not discriminate between level of drinking, as drinking per se is stigmatized. More research is needed to look into specific relationships underlying HED at the country level, as there are exceptions to this relationship as described next.

Table 13.3 APC and abstention across regions of the world for 2004 (average 2003–2005)

WHO Region	Lifetime abstention	Former drinkers	Past 12-month abstention	% former drinkers among past 12 months abstainers	APC
AFR	57.3%	13.5%	70.8%	19.1%	6.15
AMR	21.5%	20.2%	41.7%	48.4%	8.67
EMR	87.8%	8.7%	96.5%	9.0%	0.65
EUR	18.9%	12.3%	31.2%	39.4%	12.18
SEAR	80.4%	8.9%	89.3%	10.0%	2.20
WPR	29.2%	14.5%	43.7%	33.1%	6.23
World	45.0%	13.1%	58.2%	22.6%	6.13

Note: past 12-month abstention is the sum of former drinking and lifetime abstention; APC represents adult per capita consumption in litres of pure ethanol.

Data from WHO Global Information System on Alcohol and Health (GISAH), Copyright © World Health Organization 2012. Available from <http://apps.who.int/ghodata/?theme=GISAH>.

HED is one of the most important indicators of acute consequences of alcohol use such as injuries, but also is one of the indicators currently unavailable for many countries. HED in the present study is defined as 60 g or more of pure alcohol on at least one occasion in the past seven days and, thus, does not distinguish between HED and chronic heavy drinkers who on average consume 60 g or more of alcohol per day. Worldwide, around 11.5% of drinkers have weekly HED occasions (Table 13.4). HED is a measure which clearly provides additional information pertaining to APC. For example, in EUR with the highest APC, the prevalence of HED among drinkers is the lowest. The percentages of heavy episodic drinkers in Table 13.4 are those among past year drinkers. Globally, HED is high in regions with high abstention rates (AFR, EMR, SEAR), but there are differences at the country level (7). For example, HED is quite high among drinkers in countries with middle to high per capita consumption, such as in Brazil and South Africa, suggesting that APC is driven by frequent HED. On the other hand, in some European countries (e.g. France) with high APC, HED is rather low, suggesting that APC is driven by

more regular but moderate drinking patterns. Another variant of the relationship between APC and HED is observed in North America with more HED in Canada compared to the USA, despite a comparable APC. In a third group of countries with rather low APC, such as Zambia, Malawi, India, and Pakistan, a high proportion of drinkers drank heavily on single occasions, pointing to an 'all-or-none' type of behaviour (9).

Table 13.4 Abstention, APC, average consumption of past 12 months drinkers, and weekly heavy episodic drinking for 2004 (average 2003–2005)

WHO Region	Past year abstention	APC (total population)	APC (past 12 months drinkers)	Weekly heavy episodic drinking[a]
AFR	70.8%	6.15	23.0	25.1%
AMR	41.7%	8.67	16.2	12.0%
EMR	96.5%	0.65	27.7	24.7%
EUR	31.2%	12.18	20.0	11.0%
SEAR	89.3%	2.20	19.1	21.7%
WPR	43.7%	6.23	11.6	8.0%
World	58.1%	6.13	17.3	11.5%

Notes: APC: adult per capita consumption in litres of pure ethanol; [a] percentages of heavy episodic drinking among drinkers.

Data from WHO Global Information System on Alcohol and Health (GISAH), Copyright © World Health Organization 2012. Available from <http://apps.who.int/ghodata/?theme=GISAH>.

Alcohol consumption and economic factors

The wealth of a country is clearly associated with alcohol use in general, but also with the proportion of unrecorded consumption related to total consumption. The higher the income the more alcohol is consumed in general, but the lower the income the higher the proportion of unrecorded consumption.

As shown in Table 13.5 (see Table 13.6 for the classification into higher- and lower-income countries within a region) there are three major findings across regions in the world. First, per capita consumption is higher in the countries with higher income. Second, in countries with higher incomes proportionally less alcohol is consumed in the form of unrecorded alcohol. Third, these associations do not only hold aggregated across countries in a region but also within regions across countries within a region as shown by the correlations between the income status and total APC on the one hand, and income status and the proportion of unrecorded consumption on the other hand. Generally, it can be said that with increasing income alcohol use increases and the proportion of unrecorded consumption decreases. An exception to this rule is EMR, where alcohol use is generally very low and, therefore, there is little variation in consumption explaining generally low associations with other variables.

Table 13.5 APC, unrecorded (in litres) consumption and the proportion of unrecorded consumption in total APC by region and income status of countries for 2004 (average 2003–2005)

WHO Region	Income	Total APC	Unrecorded consumption	Proportion unrecorded	Corr.[a] Income status—total APC	Corr.[a] Income status—proportion unrecorded	Weekly heavy episodic drinking[b]
AFR	Lower	4.27	1.80	42.2%	0.57	−0.52	22.3%
	Higher	8.94	2.13	23.8%	n/a	n/a	28.4%
AMR	Lower	8.12	2.65	32.6%	0.49	−0.78	16.3%
	Higher	9.46	1.10	11.6%	n/a	n/a	8.6%
EMR	Lower	0.66	0.38	57.6%	−0.04	0.00	25.0%
	Higher	0.56	0.22	38.8%	n/a	n/a	22.9%
EUR	Lower	11.96	3.95	33.1%	0.06	−0.75	15.5%
	Higher	12.39	1.46	11.8%	n/a	n/a	8.7%
SEAR	Lower	0.51	0.47	91.5%	0.47	−0.37	9.9%
	Higher	2.45	1.70	69.1%	n/a	n/a	23.0%
WPR	Lower	5.80	1.77	30.6%	0.57	−0.57	7.4%
	Higher	8.79	0.79	8.9%	n/a	n/a	11.3%
WORLD	Lower	5.93	2.00	33.0%	0.05	0.06	10.7%
	Higher	6.39	1.50	23.5%	n/a	n/a	12.7%

Note: [a] correlations are calculated across countries within each of the regions; [b] in past 12 months among drinkers; n/a, not applicable.

Data from WHO Global Information System on Alcohol and Health (GISAH), Copyright © World Health Organization 2012. Available from <http://apps.who.int/ghodata/?theme=GISAH>, and The World Bank, *Country and lending groups*, Copyright © 2012 The World Bank Group, available from <http://data.worldbank.org/about/country-classifications/country-and-lending-groups>.

Table 13.6 Income distinction per WHO Region. For income level (2009) World Bank data were used and dichotomized within regions

Region	Income distinction (proportion of population)
AFR	Low (40.1%) versus lower middle, higher middle, higher (59.9%)
AMR	High (41.4%) versus higher middle, lower middle, low (58.6%)

EMR	Low, lower middle (91.0%) versus higher middle, high (9.0%)
EUR	High (51.7%) versus higher middle, lower middle, low (48.3%)
SEAR	Low (14.6%) versus lower middle, higher middle, high (85.4%)
WPR	Low, lower middle (85.6%) versus higher middle, high (14.4%)

Data from The World Bank, *Country and lending groups*, Copyright © 2012 The World Bank Group, available from <http://data.worldbank.org/about/country-classifications/country-and-lending-groups>.

There is no clear picture of the link between a country's income and the prevalence of HED (Table 13.5). It appears that in the more developed regions, such as Europe or the Americas, HED is more common in the relatively poorer countries, whereas in low- and middle-income countries (LMIC) in Africa and in South-East Asia the relatively wealthier countries show a higher likelihood of HED. In LICs, people have less money for regular alcohol use than do those in MICs and HICs and, thus, people in LICs may engage in HED instead of regular alcohol use. This interpretation, however, remains speculative and needs empirical confirmation.

So far we have relied on cross-sectional comparisons between countries as there are fewer data available for countries which have developed over time. For Thailand, Shield et al. (10) observed that the same relationships prevailed: an increase in economic wealth and transition from LICs to MICs was associated with an increase in per capita consumption and with a decrease in abstention.

Gender differences

As can be seen in Table 13.7, in all WHO regions there are more women than men who are past 12 months abstainers, a fact which has also been observed from surveys in many countries (11). On the other hand, the proportion of former drinkers among past year abstainers is larger for men in all WHO-regions. This suggests a different rationale along gender lines for not drinking alcohol, with more lifetime abstention among women, and more men who cease alcohol use due to sick quitting, i.e. detrimental health aspects provoked or aggravated by former alcohol use.

Table 13.7 Abstention by sex and proportion of former drinkers among past 12 months abstainers, 2005

WHO Region	Gender	Lifetime abstention	Former drinkers	Past year abstention	% former drinkers among past 12 months abstainers	APC 12 months drinkers only	Weekly heavy episodic drinking[a]
AFR	Women	65.2%	12.9%	78.1%	16.5%	15.1	16.2%
	Men	49.1%	14.1%	63.1%	22.3%	27.9	30.5%
AMR	Women	27.4%	22.4%	49.8%	45.0%	9.9	4.5%
	Men	15.2%	17.8%	33.0%	54.0%	21.0	17.9%
EMR	Women	93.4%	4.8%	98.2%	4.9%	14.6	17.9%
	Men	82.4%	12.3%	94.7%	13.0%	28.9	24.9%
EUR	Women	24.6%	13.5%	38.1%	35.5%	12.4	4.6%
	Men	12.6%	11.0%	23.5%	46.5%	26.1	16.8%
SEAR	Women	92.8%	4.2%	97.1%	4.4%	9.3	12.9%
	Men	68.4%	13.5%	81.9%	16.5%	20.6	23.0%
WPR	Women	44.5%	15.1%	59.5%	25.3%	6.0	1.3%
	Men	14.3%	13.9%	28.2%	49.2%	14.7	11.6%
World	Women	55.0%	12.5%	67.5%	18.5%	9.6	4.2%
	Men	34.9%	13.8%	48.7%	28.4%	20.8	16.1%

Note: [a] percentages among past 12 months drinkers.

Data from WHO Global Information System on Alcohol and Health (GISAH), Copyright © World Health Organization 2012. Available from <http://apps.who.int/ghodata/?theme=GISAH>.

Age patterns and youth surveys

Drinking by adolescents and young adults is of special concern in many societies. However, from a global standpoint, the age patterns indicate that lifetime peaks of consumption in late adolescence and early adulthood mainly describe a pattern of drinking in HICs, especially in North America (12). Globally, the most alcohol is consumed in mid life, i.e. the ages of 35–60. This is true for most parts of the world, except for some parts of EUR.

With respect to HED the picture changes and more regions have the highest prevalence of HED in the first part of adulthood. However, in many parts of the world, especially in

LMIC, drinking starts later than in HICs. For example, Thailand has adult per capita consumption above the global average, with 7.1 L APC for 2008, but in the last survey (2007) 75% of male adolescents and 86% of female adolescents in secondary schools were lifetime abstainers (13). In many other LMIC, the situation is similar. One of the reasons may be that alcohol is comparatively more expensive (i.e. the resources necessary to buy a drink in terms of average wages are much higher in LMIC than in HICs), and adolescents cannot afford to buy alcohol. In addition, in many countries there are strong pressures exerted on adolescents and people in early adulthood to abstain.

The situation may change if wealth increases and alcoholic drinks become comparatively less expensive (see (14) for case studies).

Long-term and short-term trends in alcohol use

Long-term trends in alcohol consumption since 1990

Worldwide recorded per capita consumption was stable at around 4.3–4.7 L of pure ethanol between 1990 and 2005 (Figure 13.1). More generally, alcohol use remained more or less stable in all WHO regions. After a slight decrease in alcohol use at the beginning of the 1990s in the EUR, alcohol use increased in that region to a level of 9.5 L, being similar to that observed before the decrease. The initial decline in alcohol use in the 1990s in the American Region has stabilized in the new millennium at about 6.7 L. There was an increase at the end of the last century in the WPR, but

recorded consumption has stabilized since then at around 4.7 L (see (7, figure 3, p. 8)).

Two trends are observed when looking at those countries with a preference for a particular drink (measured by means of most alcohol consumed as pure alcohol). In beer- and wine-consuming countries, the overall decrease in alcohol use is due to a decrease of consumption of the preferred drink, whereas consumption of other alcoholic drinks remained stable. In spirit-consuming countries, the increase in total alcohol use in the early 1990s was due to an increase in spirit consumption, and the more or less stable alcohol consumption after this time can be explained by diverging trends: a decrease in spirit consumption compensated by an increase in beer consumption.

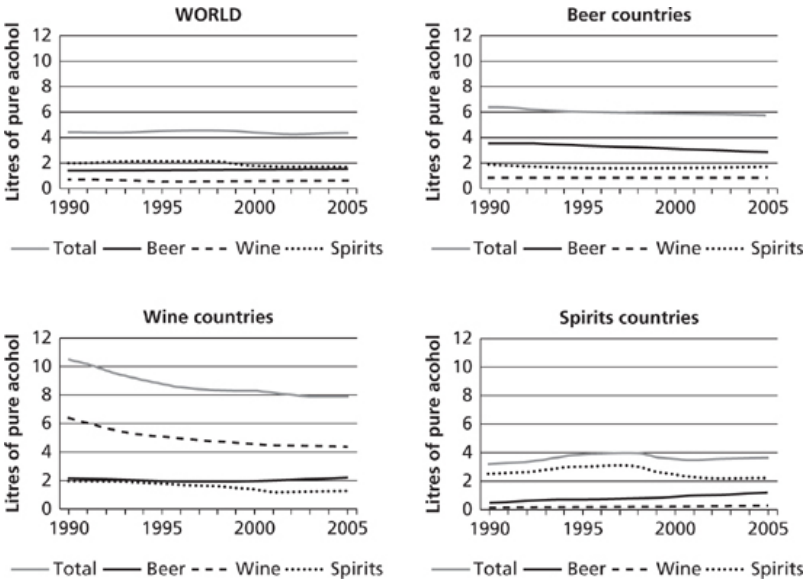

Figure 13.1 Trends in beverage-specific alcohol use in the world, and in beer, wine, and spirit preferring countries, based on preference in 1990, three-year moving averages.

Data from WHO Global Information System on Alcohol and Health (GISAH), Copyright © World Health Organization 2012. Available from <http://apps.who.int/ghodata/?theme=GISAH>.

Table 13.8 Robust estimates of trends (2001–2005) in recorded APC

WHO Region	Five-year trend		
	Decrease	Stable	Increase
AFR	4.5%	70.2%	25.3%
AMR	0.0%	94.7%	5.3%
EMR	13.1%	81.5%	5.4%
EUR	0.6%	87.3%	12.1%
SEAR	<0.1%	31.7%	68.3%
WPR	0.4%	94.5%	5.1%
World	1.6%	74.9%	23.5%

Data from WHO Global Information System on Alcohol and Health (GISAH), Copyright © World Health Organization 2012. Available from <http://apps.who.int/ghodata/?theme=GISAH>.

Robust estimates of change over 2001–2005 in alcohol use

In addition to the trends in recorded consumption, robust estimates were obtained of the change in APC over five consecutive calendar years (2001–2005). With respect to regional estimates (Table 13.8), it appears that besides a more or less stable consumption trend, alcohol use is increasing in SEAR, mainly due to an increase in consumption in India (7). Increasing alcohol use can also be found in some African countries.

Conclusion

Globally there is a large variation in APC with the highest consumption levels in developed countries (particularly in the EUR) and the lowest consumption levels in regions often having an Islamic faith, namely in the Saharan and sub-Saharan regions and in the EMR. Furthermore, 45% of the world's population has never consumed alcohol (men: 35%; women: 55%).

Economic conditions seem to influence alcohol use in many respects. APC is higher and abstention rates are lower in HIC compared to LMIC. The share of total APC consumed in the form of unrecorded alcohol, e.g. home-made or illegally produced alcohol, with the potential for increased risk of harm due to often unknown impurities or contaminants decreases with the increased wealth of a country. Among drinkers, alcohol is more often consumed in the form of heavy drinking occasions in LMIC compared with more regular and moderate use in HICs, suggesting an 'all or none' behaviour where alcohol is less affordable. HED often peaks in early adulthood in HICs, whereas in LMIC abstention rates are very high in this age group as adolescents and young adults in LMIC often cannot afford alcohol.

Trends in alcohol use have been relatively stable since 1990. Total consumption trends within countries were mainly driven by the preferred drinks, e.g. the decrease in alcohol use often observed in countries where wine was the preferred alcoholic drink was primarily due to a decrease in wine consumption, whereas beer and spirit consumption in those countries remained stable or increased. An exception to this can be observed in some countries where spirits have been the

preferred alcoholic drink. In these instances, spirit consumption has been replaced by the consumption of beer. Increases in alcohol use were mainly found in SEAR (predominantly India) or in the AFR.

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Chapter 14
Impact of extreme drinking on mortality

David Zaridze

Alcohol consumption is an important risk factor and cause of death globally. Of all deaths worldwide, 3.8% are caused by alcohol (1). The impact of alcohol is highest in Europe, causing about 6.5% of deaths (men 11%, women 1.8%) although there are important variations in alcohol-attributable deaths within Europe, with the highest proportion in Eastern Europe and Russia (1, 2). It has been estimated that 15% (men 19%, women 7%) of premature deaths under the age of 65 in ten countries of Eastern Europe are attributable to alcohol, while in Russia the proportion of alcohol-attributable deaths is about 20% (men 24%, women 10%) (1).

Alcohol drinking has been implicated in the incidence of and mortality from many diseases and conditions, such as alcohol dependence, cancer of the upper aerodigestive tract, cancer of the liver, cancer of the colorectum, liver cirrhosis, diabetes mellitus, cardiovascular diseases, neuropsychiatric disorders, unintentional injuries, intentional injuries, homicide, and suicide (1, 2).

The alcohol-attributable proportion of deaths and disability is closely related to the average volume and patterns of alcohol consumption. There are some variations in the classifications by amount of pure alcohol consumed per day. Individual alcohol consumption is, however, usually characterized as light (<1 drink/day), moderate (1 drink/day for women and 2

drinks/day for men) and heavy (>1 drink/day for women and >2 drinks/day for men). Light drinking corresponds to <12.5 g pure alcohol/day, moderate drinking to 12.5–25 g/day, and heavy drinking to >25 g/day. The proportion of heavy drinkers varies in different populations (3).

The terms ‘extreme drinking’, ‘hazardous drinking’, ‘binge drinking’, or ‘risky single-occasion drinking’ are used interchangeably to describe intake of large amounts of alcohol (women >4 drinks, men >5 drinks) on a single occasion, which can be characterized as leading to a high blood concentration of ethanol. Gmel et al. (4) chose to define risky single-occasion drinking (or binge drinking or extreme drinking) in terms of pure alcohol consumed, i.e. approximately 60–70 g ethanol for men and 40–60 g for women.

Much interest has focused recently on extreme drinking, particularly in relation to the Russian health crisis. The best estimates, which include unrecorded consumption of alcohol, suggest that total annual per capita ethanol consumption in the second half of the 1990s in Russia was 14 L and 18 L for those aged over 15 (5). According to a Longitudinal Monitoring Survey conducted in Russia in 1994–2004 which included respondents aged over 18 years, frequent drinking increased in men, with the proportion drinking more than weekly rising from 17% to 21%. There was, however, a significant decline in heavy male drinking: consumption of >160 g of pure ethanol in hard spirits per occasion declined from 22% to 12%. The proportion of frequent, heavy male drinkers did not change significantly between 1994 and 2004, remaining steady with 13–14% drinking more than weekly and consuming >80 g of ethanol per occasion. In women,

alcohol consumption more than weekly rose from 2% to 4%. The proportion of female heavy drinkers changed very little, with approximately 8% of women drinking >80 g of pure ethanol per occasion throughout the study (6).

Extreme drinking is a major determinant of high adult mortality rates in Russia and has been linked with increased risk of incidence of and mortality from injuries and several diseases. It has been the object of several descriptive studies (7–10), which analysed the patterns of trends in Russian mortality and alcohol consumption, and its role has been substantiated in analytical epidemiological cohort and case–control studies (11–13).

The changes in Russian mortality rates over the past 20–25 years are unprecedented in any modern industrialized country. The lowest mortality rates were in 1986–1987 following the 1985 Soviet restriction on alcohol production and sales. Following the increase in alcohol consumption after 1987, mortality rates increased sharply, with the highest overall mortality rates recorded in 1994. This increase was followed by a sharp decline between 1994 and 1998 and then a new increase emerged in 1998 and 2002. After 2002, Russian mortality rates decreased slowly but remained high (7–10). Diseases of the circulatory system and external causes were the main contributors to the fluctuations observed in Russian mortality rates (7–10). However, detailed analyses of the disease-specific time trends by subcategories of ischaemic heart disease (IHD) revealed that fluctuations among cardiovascular diseases were chiefly due to ‘other forms’ of acute and chronic ischaemia and to atherosclerotic heart disease, while rates of myocardial infarction were low and relatively constant (10).

It has been estimated that increased mortality during the period 1991–2001 led to 2.5–3 million extra deaths in young and middle-aged Russians (9). According to the death rates for the year 2000, the probability that a 15-year-old man would die before age 35 was almost 10% and the probability that 35-year-old man would die before the age of 55 was 27%. In the United States these probabilities were approximately 2% and 6%, respectively (Figure 14.1) (14, 15).

Alcohol consumption patterns in Russia may be characterized as extreme drinking. As extreme drinking leads to high blood concentrations of ethanol, of interest are the surveys which describe the prevalence (frequency) of high concentrations of ethanol in blood. Analysis of the records of 22,658 forensic autopsies of adults over 15 years of age at death, carried out in the Russian industrial city of Barnaul, found lethal (5 g/L) or potentially lethal (4 g/L) blood concentrations of ethanol in an exceptionally high proportion of autopsies; overall, ethanol was detected in the blood of 60% of men and 53% of women aged between 35 and 69 years. These proportions were particularly high for autopsies of people reported to have died from external causes: in 76% ethanol was detected in their blood, in 25% the ethanol concentration was ≥4 g/L and in 13% it was ≥5 g/L. Among autopsied women who died from external causes, 65% had ethanol in their blood; in 24% the concentration was ≥4 g/L and in 12% it was ≥5 g/L. Among middle-aged men and women who died from alcohol poisoning, 81% had ethanol concentrations of ≥4 g/L, and about 50% had ≥5 g/L (10).

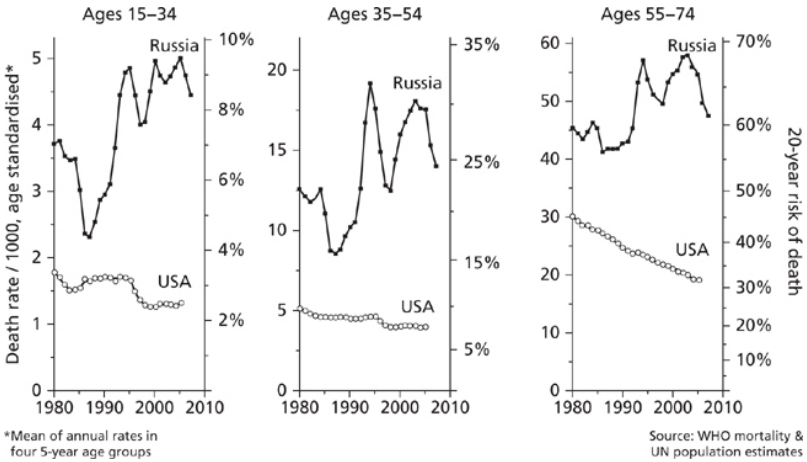

Figure 14.1 All-cause male mortality rates and 20-year risks of death in Russia and the United States, 1980–2007. The graph was produced at the author's request by Jillian Boreham of the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), University of Oxford.

Data from WHO mortality and UN population estimates.

Death due to the toxic effects of acute over-ingestion of alcohol usually involves blood ethanol concentrations of >0.35%, although non-tolerant individuals may die from blood ethanol levels as low as 0.2–0.3% (16). According to the Russian classification, ethanol concentrations in blood ranging from 3 g to 5 g/L cause heavy alcohol intoxication, coma, and are potentially lethal. An ethanol concentration of ≥5 g/L is absolutely lethal (17). It is, however, not realistic to firmly establish a criterion for a lethal blood ethanol concentration, and hence death definitely due to alcohol poisoning.

Few case–control and cohort studies have examined the association between alcohol consumption and mortality in Russia. A cohort study carried out in Novosibirsk included 6,502 men aged 25–64, with follow-up averaging 9.5 years (range 3.1–15.2). The results of the cohort analysis were based on a relatively small number of deaths (815). The frequency of drinking in this cohort was low. Only 8% of men reported drinking three or more times a week, but the main typical dose was high at 91 g, with 55% drinking ≥80 g of ethanol and 16% drinking ≥160 g per occasion (11). The answers to questions concerning the previous week's drinking differ substantially from the answers concerning typical drinking. According to the former, 63% of the cohort members had drunk 80 g of pure alcohol per occasion and 30% ≥160 g. The authors defined binge drinking as consumption of >160 g ethanol per drinking session and, in their analysis of the effects of binge drinking on mortality, they used as reference group those deceased who consumed <80 g of ethanol per occasion, rather than non-drinkers. No association was found between episodic binge drinking (>160 g alcohol) compared to consumption of <80 g of alcohol and death from all causes and cardiovascular disease. However, for a small group of frequent heavy drinkers (5% of all drinkers) who ingested three or more times per week >120 g ethanol per occasion, the risk of dying from all causes, cardiovascular diseases, and external causes was statistically significantly increased. It is noteworthy that in the discussion the authors briefly allude to the separate unpublished results of the analysis which show that the risk of non-fatal myocardial infarction was not raised in frequent drinkers, episodic binge drinkers, or frequent heavy drinkers, suggesting that the increased risk in heavy drinkers is specific to fatal coronary events.

In a retrospective case-control study conducted in Izhevsk (Russia), of 1,750 deceased men aged 25–54 years, 51% were classified as problem drinkers or drinkers of non-beverage alcohols, compared to 13% of controls who were residents of the city. The mortality odds ratio for deceased problem drinkers compared to the living controls, who either abstained or were non-problematic drinkers, was statistically significantly elevated, sixfold or more. The effect was stronger for non-beverage alcohol intake. The mortality ratio increased with an increase in weekly amount of beverage and non-beverage alcohol consumption, although the effect of frequency of consumption was stronger for non-beverage alcohol. A strong direct gradient with mortality was seen for frequency of non-beverage alcohol drinking, independent of the volume
of ethanol consumed. The authors estimated that in this population 43% of deaths of men aged 25–54 years were attributable to hazardous drinking (12).

The largest epidemiological case–control study on the association between hazardous drinking and cause-specific mortality published to date was carried out in three industrial cities of Russia (Barnaul, Byisk, and Tomsk) and included 48,557 deaths (31,504 men and 17,053 women) that occurred between 1990 and 2001 (13). Cases were those who died from causes which were judged beforehand to be substantially affected by alcohol or tobacco. Controls were other decedents. Among male controls, 8% never drank alcohol, 14% were in a reference group or consumed less than half of a 500-ml bottle of vodka per week or equivalent and never more than half a bottle of vodka at one drinking session, and 77% were in higher alcohol consumption categories. Thirty per cent of female controls never drank, 50% were in the

reference category, and 20% in higher alcohol consumption categories. The top category of alcohol consumption (three or more bottles of vodka per week) included 17% and 14% of men and 4% and 2% of women aged 15–54 and 55–74, respectively. On average those in this category drank 4.8 days a week, consuming on average 5.4 500-ml bottles of vodka or equivalent, which corresponds to 1080 g of pure alcohol per week or 225 g of pure alcohol per drinking session, which is nearly four times higher than the binge drinking threshold. The maximum consumption of spirits in one day was reported as one bottle or two bottles (mean 1.4) or 280 g of pure alcohol. Even the men and women who were consuming 1 to >3 bottles per week (1.5 bottles on average), and who drank 2.2 times per week, consumed about 136 g of pure ethanol per occasion, which is more than twice the binge drinking threshold. This category of drinkers included 26% and 29% of men and 6% and 5% of women aged 15–54 and 55–74, respectively. Deaths from the following eight diseases were strongly associated with alcohol consumption: cancer of the upper aerodigestive tract, liver cancer, tuberculosis, pneumonia, liver disease, pancreatic disease, acute IHD other than myocardial infarction, and death from ill-specified disease. For these diseases, relative risks (RR) were elevated more than threefold in the highest category of intake, with $p < 0.0001$ across three categories of alcohol intake (<1, 1 to <3, and 3 or more 500-ml bottles of vodka or equivalent per week) compared to the reference group which included those who consumed less than half of a 500-ml bottle of vodka per week or equivalent and never more than half a bottle of vodka at one drinking session. Some other causes of death were significantly associated with alcohol, for example stroke, but the RRs were less extreme and there was no significant trend in mortality. It is noteworthy that there was only a slight,

statistically non-significant increase in the risk of myocardial infarction. As expected, alcohol consumption was strongly associated with mortality from alcohol poisoning along with other external causes of death, including transport accidents, other accidents, suicide, and assault. The disease groups and external causes that were most strongly associated with alcohol in men were even more strongly associated with alcohol consumption in women. If these associations are causal, then alcohol was responsible for 52% of all deaths at ages 15–54 (men 59%, women 33%) and 18% of those at 55–74 years (men 22%, women 12%) in the study population between 1990 and 2001 (13).

In this study (13) non-beverage alcohol use was strongly correlated with other alcohol consumption and was no more common in those dying from strongly alcohol-related causes than those dying from other causes, suggesting that for a given amount of ethanol consumption its source was not strongly predictive of cause of death.

Zaridze et al. (13) demonstrated that the trend in overall mortality between 1990 and 2004 in the three cities where the study was conducted was affected by deaths from causes strongly associated with alcohol, thus establishing beyond reasonable doubt the important role of alcohol in the fluctuations in Russian mortality between 1990 and 2004.

Can the association between extreme drinking and death from the diseases and conditions which have been found to be strongly related to it be judged causal? The excess mortality from
liver cancer, upper aerodigestive tract cancer, liver diseases, and pancreatic diseases is largely or wholly causal because

the diseases that caused death were induced by alcohol (18–20). The excess mortality from tuberculosis and pneumonia may partly result from increased exposure to infection, reduced immunocompetence, or decreased likelihood of cure. It has been shown that heavy alcohol use strongly influences both the incidence and outcomes of these diseases and was found to be linked to altered pharmacokinetics of medicines used in treatment of tuberculosis, social marginalization and drift, higher rate of re-infection, higher rate of treatment default, and development of drug-resistant forms of disease (21). Some of the excess mortality from stroke and other vascular diseases must reflect the ability of alcohol to increase blood pressure (3).

The strong association between alcohol consumption and ill-specified diseases and acute IHD other than myocardial infarction could be at least partly explained by inadequate post-mortem assessment of causes. In the survey of forensic autopsies described previously (10), 17% of men and 16% of women aged 35–69 years, whose deaths were attributed to acute IHD other than myocardial infarction or acute unspecified IHD as certified causes, had potentially lethal blood ethanol concentrations of >4 g/L, suggesting that these deaths were due to alcohol poisoning rather than vascular disease.

This hypothesis is strongly supported by the extreme fluctuations in mortality from IHD other than myocardial infarction which followed the fluctuations in overall Russian mortality trends, with little variation in the death rates from myocardial infarction (10). In addition, a recently published study from Lithuania has demonstrated that a significant number of alcohol-attributable deaths in Lithuania were

misclassified as coronary deaths, accounting for almost one-tenth of officially registered deaths from IHD in the age range 25–64 (22). Similar results were reported in a smaller study from Kursk (23). The results of another autopsy study, which reported that none of 89 deaths from cardiovascular diseases had alcohol levels >4 g/L, may be explained by the very small sample size (24).

The association between hazardous drinking and excess mortality from accidents could be largely causal (25). The excess death from violence stems partly from the effects of alcohol on behaviour (26). Alcohol can cause depression, impulsivity, and suicidal behaviour (25, 27) and many people who commit suicide have raised blood ethanol concentrations (10).

However dramatic the results of the retrospective mortality studies on the association between extreme drinking and mortality, they still underestimate the alcohol-attributable proportion of all deaths in the study areas, since they were calculated only for people with families still available at the same address years later, and exclude deaths of persons of no fixed abode, who may have lost their homes and jobs because of their drinking habits and who are marginalized from society.

Due to their nature (retrospective mortality study) these studies do not examine the effects of extreme drinking on health in general and the incidence of alcohol-induced disorders and injuries. They exclude many social problems caused by drinking and harm to people other than the drinker. Further studies are needed to fill in these gaps and examine the full societal effects of alcohol.

The results of Russian studies are relevant not only for Russia or Eastern Europe, because in many other societies pervasive heavy drinking can result in public health crises (28).

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Chapter 15
Unrecorded alcohol consumption

Dirk W. Lachenmeier, Gerhard Gmel, and Jürgen Rehm

Introduction

Alcohol consumption can be broadly classified into recorded and unrecorded consumption, i.e. part of which is officially registered and part of which is not. In the last decade unrecorded alcohol consumption has become the focus of increasing attention, as World Health Organization (WHO) estimations have shown that about 30% of global consumption is unrecorded (1).

As the major ingredient of unrecorded alcohol is most typically ethanol, similar to recorded alcohol, all of the health consequences of alcohol consumption described in this book also apply to unrecorded alcohol.

Definition of unrecorded alcohol

Unrecorded denotes alcoholic drinks produced and/or consumed that are not recorded in official statistics of sales, production, or trade. In some countries, unrecorded drinks account for the majority of alcohol consumption (2). Unrecorded alcohol stems from a variety of sources (1, 3): home production, illegal production and sales, illegal (smuggling) and legal imports (cross-border shopping), and other production of alcoholic drinks that are not taxed and/or are not included in official production and sales statistics. A

portion of unrecorded alcoholic drinks derive from different local or traditional drinks that are produced and consumed in the community or homes. The production may be legal or illegal, depending on the strength of the drink. Worldwide, information on these alcoholic drinks and their production or consumption volumes is scarce (1).

Due to the wide diversity of products that may fall under unrecorded alcohol, there has been no consistent definition or usage of this term in the literature. Some authors use the terms illegal, informal, artisanal, home-produced, non-beverage, or surrogate alcohol; however, these terms often only describe subgroups of unrecorded alcohol. The industry prefers the term 'non-commercial alcohol' (4).

WHO provided the following nomenclature and classification (Figure 15.1; see also the Global Information System on Alcohol and Health—GISAH—at: <http://www.who.int>). The term 'unrecorded alcohol' comprises four major categories: (i) illegally produced or smuggled alcohol; (ii) surrogate alcohol, i.e. alcohol not officially intended for human consumption, such as perfume; (iii) alcohol not registered in the country where it is consumed; and (iv) legal unregistered alcohol (e.g. home-made alcohol in countries where it is legal). There are various subcategories within these broad categories. For instance, illegally produced alcohol can stem from the same factory as legal alcohol (i.e. beer factories, distilleries, wineries), but a proportion of the alcohol produced is not declared to the authorities in order to evade taxation. It should be noted that home-made alcohols are usually illegally produced but there are exceptions such as in countries where home production is not illegal but would still be part of unrecorded consumption. Some common

examples of surrogate alcohols include mouthwash, perfumes, and eaux de cologne, which are alcohol products manufactured on a large scale (5, 6). Such alcohols may be produced with human consumption in mind but to evade taxation may be officially classified as ‘shaving water’ or ‘mouthwash’ (7). In Russia (e.g. Savchuk et al. (8)), surrogate alcohols are differentiated based on the type of alcohol that the liquid contains: true surrogate alcohols (i.e. solutions and liquids manufactured from ethanol or containing large amounts of ethanol) and false surrogate alcohols (i.e. ethanol-free liquids, such as methanol, propanol, and ethylene glycol). In some instances alcohols illegally produced for human consumption contain non-beverage alcohols, e.g. to increase alcohol concentration. Thus, beverage alcohol that is offered for consumption on the illegal market could be adulterated by non-drinkable alcohol and consumers may not be aware of the potential risks. Quantitative estimations of the degree of contamination of unrecorded alcohol are currently not available.

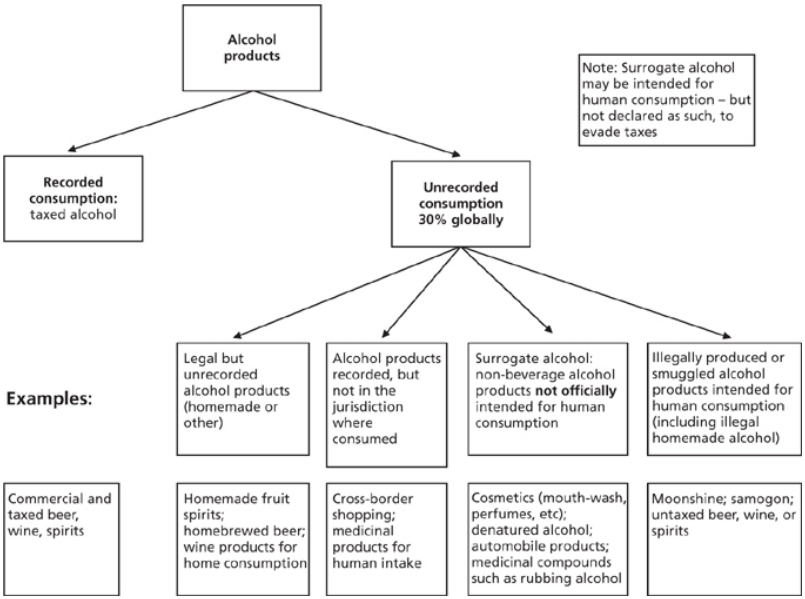

Figure 15.1 Classification of alcohol products.

Reprinted with permission from Lachenmeier DW et al., The composition of alcohol products from markets in Lithuania and Hungary, and potential health consequences: A pilot study, *Alcohol and Alcoholism*, Volume **44**, Issue 1, pp. 93–102, Copyright © 2009, Oxford University Press, DOI: 10.1093/alcalc/agn095.

Similarly, in Russia, it appears that denatured industrial ethanol is used for producing illegal alcohol for consumption since it is possible to—at least partially—eliminate the common denaturing agent diethyl phthalate through simple distillation (8).

Per capita consumption of unrecorded alcohol

While per capita consumption of recorded alcohol is traceable via official statistics based on production, sales, and/or trade data (9), no such data are available for unrecorded alcohol. Therefore, the currently available data are estimates, based on expert opinion or surveys (9), carry substantial uncertainty (2, 9, 10), and have many open questions. Thus, the regional distribution of the four subcategories cannot be quantified. Overall, 30% of global alcohol consumption was estimated to be unrecorded in the early twenty-first century (10, 11) with a high proportion in low- and middle-income countries (LMIC) and in the former Soviet Union, but there are huge regional differences (Table 15.1 and Figure 15.2). As much of the unrecorded alcohol consumption occurs in countries such as India, China, Brazil, Russia, or on the African continent, category iii (alcohol not registered in the country where it is consumed), including cross-border shopping, is not relevant on a global level, but it may still constitute a sizeable portion in some parts of world such as in the Nordic countries (12).

Table 15.1 Global distribution of unrecorded adult per capita alcohol consumption, 2005

WHO Region	Unrecorded adult per capita alcohol consumption in L pure ethanol	Total adult per capita alcohol consumption in L pure ethanol	Proportion unrecorded
Africa	1.93	6.19	31%
Americas	2.01	8.70	23%
Eastern Mediterranean Region	0.34	0.62	55%
Europe	2.67	12.20	22%
South East Asia Region	1.52	2.24	68%
Western Pacific Region	1.63	6.23	26%
World	1.75	6.13	29%

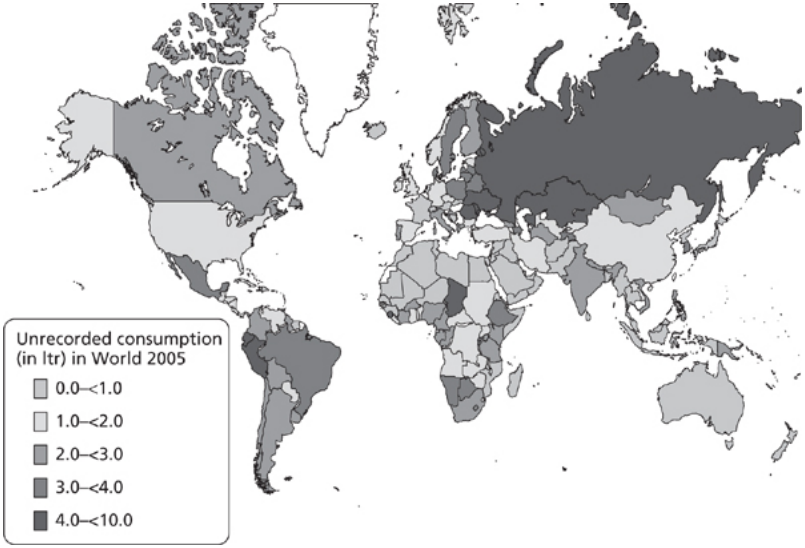

Figure 15.2 Unrecorded adult per capita consumption of pure ethanol in litres, 2005.

Reprinted from *International Journal of Drug Policy*, Volume **22**, Issue 2, Dirk W. Lachenmeier et al., Alcohol under the radar: Do we have policy options regarding unrecorded alcohol?, pp. 153–160, Copyright © 2011, with permission from Elsevier, DOI: <http://dx.doi.org/10.1016/j.drugpo.2010.11.002>.

Socio-economic aspects: who drinks unrecorded alcohol?

In high-income countries, unrecorded consumption amounts to less than 15% of overall consumption. In LMIC, locally produced traditional alcoholic beverages tend to be considerably less expensive than their Western-style, commercially produced counterparts. Local production consists mostly of the fermentation of seeds, grains, fruits, vegetables, sugarcane, or parts of palm trees, and is a fairly simple process. The alcohol content is quite low and the shelf life is usually short—one or two days before the drink is spoiled (1). For this reason, the fermented products are often distilled to produce spirits, which is also possible using simplistic means, e.g. by heating in oil drums over an open fire and applying automobile piping for condensation (13, 14).

In many regions of the world, unrecorded alcoholic drinks are approximately two-to-six times less expensive than commercial alcoholic drinks (15–18) and, thus, are most likely to be consumed by those who are on the margins of society, including very heavy drinkers or alcohol-dependent persons, all of whom are commonly under-represented in surveys (1). Alcohol that is offered for consumption on the illegal market may be adulterated by non-drinkable alcohol

such as methanol, and, thus, consumers are not aware of the potential risks (1). Similar observations of the sale of unrecorded alcohol as counterfeited recorded alcohol are available from Poland (17). However, there is also evidence that some economically disadvantaged heavy drinkers mix drinking alcohol with industrial denatured alcohol (1).

These reasons explain why the fraction of unrecorded consumption is higher in LMIC, and is highest in the poorest regions of Africa, Asia, and South America. In addition, unrecorded consumption is estimated to be relatively high in the Eastern Mediterranean region with predominantly Islamic countries, although the level of overall consumption is very low (1).

Composition and health risks of unrecorded alcohol

The health consequences related to the consumption of unrecorded alcohol can be divided into toxicity specifically due to other compounds found in unrecorded alcohol besides ethanol and other, more general, consequences associated with alcohol use (e.g. cardiovascular disease, cancer). The most noteworthy form of toxicity associated with unrecorded alcohol is accidental poisoning with contaminants such as lead or methanol (5). From a standpoint of public awareness, methanol may be the first and foremost factor of toxicity associated with unrecorded alcohol. Headlines of methanol deaths appear in newspapers with certain regularity, more often than not referring to incidences and outbreaks in low- and middle-income regions of the world (19). We do not want to belittle the tragedy of methanol outbreaks if they occur, however, overall, they do not constitute a major public health

threat, globally or in any region (5, 19). Since methanol was banned from being used as a denaturing substance for industrial alcohol (5), such outbreaks
currently appear only if pure methanol (from chemical suppliers) is added with criminal intent or ignorance to adulterate alcoholic drinks.

Besides these isolated cases of acute toxicity due to methanol, a chronic toxicity of unrecorded alcohol is often assumed to be different from the one of recorded alcohol. However, it is currently not clear whether unrecorded alcohol has a real impact on health above the effect of recorded alcohol if exactly the same amount of ethanol would be consumed with the same drinking patterns (19–21).

In Central and Eastern Europe, and in LMIC, large discrepancies between recorded alcoholic beverage consumption and alcohol-related mortality can be found (1). One example is Hungary where mortality from liver disease is approximately fourfold that of countries with similar per capita consumption of alcohol (22, 23). One reason for this might be the particularly high level of unrecorded consumption which may account for a higher amount of alcoholic drink consumption than from recorded sources (22). Overall, there is a correlation between the level of unrecorded consumption and liver cirrhosis rates, even after controlling for per capita consumption ($r = 0.35$; $t = 2.96$; $p = 0.04$; calculation in (7) based on the numbers displayed in the *Global status report on alcohol and health* (24)). However as alcohol consumption per se has been shown to cause liver cirrhosis as well (25), the specific contribution of unrecorded alcohol is not clear.

Several studies have used chemical analysis to characterize the composition of unrecorded alcoholic drinks with a focus on potentially harmful components (Table 15.2). The evidence so far has only supported a potential impact of a higher concentration of ethanol itself (considerably higher than 40% volume). This may also have a detrimental effect, especially for alcohol poisoning and other injuries. Due to the lack of labelling on unrecorded alcoholic beverages, the necessity of dilution to drinking strength in most cases might be unknown, leading to these drinks being consumed in their original, high-alcoholic strength form.

All other components analysed in the unrecorded alcohols have not been found in the vast majority of unrecorded alcohol at levels known to cause harms to health on a population scale (18).

The exception may be the occurrence of polyhexamethyleneguanidine hydrochloride (PHMG) which was associated with an outbreak of acute cholestatic liver injury in Russia connected to the consumption of unrecorded alcohol (26). The alcohol that was consumed was an antiseptic liquid for indoor disinfection, which contained ethanol (93%), diethyl phthalate (DEP) (0.08–0.15%) and PHMG (0.10–0.14%). PHMG is an effective antiseptic and is commonly used for suppression of hospital infection in the Russian Federation (27) and DEP denatures alcohol (28). Several studies detected PHMG together with DEP in disinfectants that were used as an ethanol source in poisoning cases in Russia (27, 29, 30). On the basis of clinical manifestations and laboratory findings of 579 poisoned patients, Ostapenko et al. (26) concluded that the cholestatic hepatitis was caused by PHMG, while a history of

alcohol-induced hepatitis and cirrhosis contributed to a more severe course of the poisoning. Other factors such as DEP or chronic viral hepatitis may have further contributed to multifactorial liver damage. However, little is known about the alcohol consumed which led to these poisonings, the role of ethanol concentration, or the role of unrecorded consumption. We need to know these facts if we want to seriously look into interventions for reducing alcohol-attributable mortality in Russia. Going beyond this example, we propose to systematically study the impact of unrecorded consumption by conducting case–control studies with cases from alcohol poisoning entries to the emergency room, people treated for liver disease, and alcohol dependence. These studies should include sampling and chemical analysis of the alcohol usually consumed by these groups and matched controls (19).

Table 15.2 Summary of compounds potentially associated with public health consequences in unrecorded alcohol

Compounds in unrecorded alcohol	**Scientific evidence of public health consequences**
Ethanol	Unrecorded alcohol often contains higher ethanol concentrations. This was consistently shown in a number of countries (6, 8, 15–18, 33–36)

Methanol	Several methanol poisoning outbreaks associated with unrecorded alcohol (5)
Higher alcohols (e.g. propanol, butanol, etc.)	Limited and contradictory evidence (8, 15, 16, 22, 33, 34, 37). Research shows that the content of higher alcohols in unrecorded alcohol is similar to recorded distilled beverages (e.g. fruit spirits, rum) (6, 38)
Acetaldehyde	No systematic studies available. Found in some unrecorded alcohols from Guatemala (13, 39). Limited evidence points to public health risk (40)
Ethyl carbamate	No systematic studies available. Found in unrecorded alcohols from Europe (6, 17, 18) and Brazil (41)
Metals (e.g. lead)	No systematic current data available. Metal contaminations were described in moonshine from the United States (5) and Europe (18, 36)

Diethyl phthalate	No systematic data available. Denaturing agent. Detected in several unrecorded alcohol samples from Lithuania (6, 28) and Russia (8, 29)
Biologically active flavourings	Single cases, e.g. coumarin in surrogate alcohol from Lithuania (6)
Polyhexamethylene guanidine	Occurrence in antiseptic liquid for indoor disinfection. Found in several samples of unrecorded alcohol (27, 29, 30). Potentially responsible for a cholestatic hepatitis outbreak in Russia (26)

Policy aspects

In their recent strategies to reduce the harmful use of alcohol (31), WHO stressed reductions in the public health impact of

illicit alcohol and informally produced alcohol and provided some broad policy interventions as potential solutions. These included: (i) good quality control with regard to production and distribution of alcoholic drinks; (ii) regulating the sale of informally produced alcohol and bringing it into the taxation system; (iii) an efficient control and enforcement system, including tax stamps; (iv) developing or strengthening tracking and tracing systems for illicit alcohol; (v) ensuring necessary cooperation and exchange of relevant information on combating illicit alcohol among authorities at national and international levels; and (vi) issuing relevant public warnings about contaminants and other health threats from informal or illicit alcohol.

In view of the amount of unrecorded alcohol consumed worldwide and the fear of an increase due to the economic crisis, it is surprising that almost no policy research at all has been conducted on this topic (7). There is no literature on the effectiveness or implementation costs of the WHO suggestions, probably in part explained by concerns that the systematic evaluation of unrecorded consumption can be seen as supporting the alcohol industry (19). However, from a public health point of view, such an evaluation is necessary, as policy interventions in the area of the harmful use of alcohol as in other areas should be based on evidence in order to minimize attributable harm (7).

It is important for the state to gain effective control over informal alcohol production and distribution, as proposed by Room et al. (32). Gaining such control is not only important to avoid contaminated, low-quality alcohol, but is also crucial for an effective regime of taxation to ensure that the market in

legal alcoholic drinks cannot be undercut by illegal production and distribution (7).

The disparity of consumption levels as well as the close link between some types of unrecorded alcohol and local culture and tradition means that different measures are likely to have different results in different parts of the world. Therefore, a global approach to unrecorded alcohol is neither feasible nor realistic. In Central and Western Europe, the process of gaining control over informal production and distribution took decades or even longer (32) and we can expect a similar time frame is required for Eastern Europe. In less developed regions, such as Africa, Asia, and Latin America, barriers are even higher since basic alcohol policy is only just emerging (7).

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Part IV
Alcohol: gender and age-related issues

Chapter 16
Adolescent and teenage drinking

Ralph W. Hingson and Aaron M. White

Introduction

With 10.4 million underage drinkers, alcohol is the leading substance of abuse among youth in the United States (1). Underage persons frequently binge drink, averaging six drinks per occasion, five times per month (1). Binge drinking corresponds to consuming five or more drinks by the typical adult male and four or more drinks by the typical adult female in about two hours, consumption that brings blood alcohol concentrations (BACs) to 0.08%—the legal threshold for adult alcohol impairment in all states of the United States (2). Being smaller on average, many adolescents require fewer drinks to reach a BAC of 0.08% (3). Yet 92% of alcohol consumed by 12–14-year-olds is through binge drinking (1).

This chapter explores: (i) alcohol use among people under the legal drinking age in the United States, (ii) consequences of their drinking, and (iii) proven prevention strategies.

Adolescent alcohol use

In the United States, it is illegal to sell alcohol to persons under age 21. Although the percentages declined in the past decade (4), in 2010 nationwide 14% of eighth (usually 13-year-olds), 29% of tenth (usually 15-year-olds), and 41% of twelfth (usually 17-year-olds) graders drank alcohol, and

5% of eighth, 15% of tenth, and 27% of twelfth graders reported being drunk at least once per month. Older teens drink more. From 1999 to 2007 among 18–20-year-olds, 38–39% of college students and 31–32% of non-students engaged in binge drinking during the previous 30 days (5).

Nationwide, 12% of underage drinkers consumed 12 or more drinks on their last occasion (1).

The younger the adolescent drinker, the more likely it is that the alcohol was obtained at home (6). Research indicates that young people allowed to drink at home by parents/guardians are more likely to drink excessively and develop alcohol-related problems (7, 8). Among alcohol users aged 12–20 in 2006 and 2007 (6), 29% reported their last drinking occasion occurred in their own home.

Alcohol-related consequences

Frequent binge drinking, high school students (almost one million in the United States) are more likely to engage in a variety of high-risk behaviours (9): driving after drinking, riding with drinking drivers, never wearing seat belts, carrying weapons, unplanned and unprotected sex, and illicit drug use. In the past year, they were more often injured in physical fights and suicide attempts than high school students who did not binge drink frequently.

Starting to drink at an early age has been linked to alcohol-related problems during adolescence and adulthood (10). National surveys indicate that each earlier year before

age 21 that someone begins drinking, the greater the likelihood he/she will experience alcohol dependence (11), dependence before age 25, and chronic relapsing dependence (12). Of all age categories, persons aged 18–20 (11%) and 21–25 (12%) have the highest prevalence of alcohol dependence (1). The association between early-onset drinking and alcohol dependence has been observed after controlling for personal and demographic characteristics, smoking and illicit drug use histories, childhood depression, and family alcoholism history (12), in longitudinal studies (13, 14) and in a study of monozygotic twins discordant on age of first drinking (15). Earlier-onset drinkers are also much more likely as adolescents and adults after drinking to experience unintentional injuries (10), motor vehicle crashes, and physical fights and to injure themselves and others in motor vehicle crashes and in other ways (16). Further, early drinking onset has been linked to suicide attempts (17), violent behaviour (18, 19), dating violence victimization (17), and criminal behaviour (19)—important associations because injuries are the leading cause of death for people aged 1–44 years in the United States, with alcohol the leading contributor (20). Of the 75,000 annual US deaths attributable to alcohol, 40,000 are injury deaths (21).

Alcohol contributes to the three leading causes of death for young people in the United States—injuries, murders, and suicides (22). Between 2001 and 2005, an annual average of 4,492 deaths among persons under 21 were attributed to alcohol (20), including deaths from:

♦ motor vehicle crashes—2,075

♦ homicides—1,227

♦ suicide—480

♦ poisoning—252

♦ drowning—125

♦ fire injuries—41

♦ fall injuries—37

♦ firearm injuries—2.

In addition, half the people who die in crashes involving underage drinking drivers are persons other than the driver (22).

Academic performance

Numerous studies link binge drinking to poorer academic performance (23, 24). One quarter of US college students (4% are under the age of 18, 57% are 18–24, 23% are 25–34, and 16% are aged 35 and over) report academic consequences of their drinking including missing class, falling behind, doing poorly on exams or papers, and receiving lower grades (24–26). A national prospective study (23) reported college binge drinkers were more likely to drop out, work in less prestigious jobs, and experience alcohol dependence ten years later than college students who did not binge drink.

Alcohol and the adolescent brain

Human brain development continues into the third decade of life, raising concerns that heavy adolescent alcohol misuse may produce greater cognitive deficits relative to adults (27). Longitudinal research (28) indicates heavy use of alcohol and other drugs during the teenage years predicts lower scores on tests of memory and attention.

Alcohol overdoses

Consuming large quantities of alcohol can cause death by suppressing brainstem nuclei that control vital reflexes like breathing and gagging to clear the airway (29). An examination of rates of in-patient hospitalizations for overdoses for 18–24-year-olds, between 1999 and 2008, using the Nationwide Inpatient Sample's hospital discharge records from roughly 20% of all hospitals, found hospitalizations for alcohol overdoses without any other drugs involved increased 25%, while hospitalizations for alcohol and drug overdoses in combination rose 76% (30). In 2008, nearly 60,000 young people aged 18–24 were hospitalized for overdoses involving alcohol or alcohol and drugs in combination, one-third of all overdose hospitalizations in that age range.

Strategies for reducing underage drinking

Environmental policies

Legal drinking age of 21

In 1984, when 17 states had a legal drinking age of 21, the US Congress passed legislation that would withhold highway construction funding from states that did not make it illegal to sell alcohol to people below age 21. By 1988, all states adopted the law (31). However, some exemptions exist. In 24 states, individuals under the age of 21 can possess alcohol with parental or guardian consent and/or presence. Parents can legally furnish alcohol to their underage children in 31 states. Only 31 states explicitly prohibit consumption by persons aged under 21. In 47 states, people aged under 21 can serve alcohol (32).

In August 2008, a group of 130 college presidents called for a debate about lowering the drinking age to age 18. Given this widely publicized challenge, evidence about the legal drinking age of 21 warrants review. National surveys (5) indicate that from 1980 to 2010, the proportion who consumed five or more drinks on an occasion dropped from 41% to 23% among high school seniors (mostly 17-year-olds) and from 41% to 28% among individuals one to four years past high school and not in school. Little change (44% to 37%) was seen among college students, those one to four years past high school. Since 1982, among individuals aged 18–20 targeted by the drinking age changes, alcohol-related traffic fatalities declined 63%, more than in any other age group, including 21–24-year-olds (down 44%) (33).

Evidence links a higher minimum drinking age to lower rates of alcohol-related crashes. An examination (34) of data from 1975 to 1993 from the Fatality Analysis Reporting System, Vital Statistics, and annual national surveys, found that lowering the drinking age was associated with a 17% increase among 18–20-year-olds in night-time fatal crashes (those most likely to involve alcohol), the greatest increase of any age group. Daytime fatal crash rates did not change. In the 18–20 age group, there were increases in suicides (10%), past month drinking (17%), and binge drinking (3%). A review of 49 studies revealed that in the 1970s and 1980s, when many states lowered the drinking age among people younger than 21, alcohol-related traffic crashes increased by 10%, whereas when states increased the legal drinking age to 21, alcohol-related crashes decreased by 16% (35). Another review of 48 studies of adolescent drinking and 57 studies of traffic crashes (36) concluded that increasing the legal minimum age for the purchase and consumption of alcohol has been the most successful intervention to date in reducing drinking and alcohol-related crashes among people under 21.

One study (37) found significant declines in traffic fatalities among individuals aged under 21 in states that changed the minimum legal drinking age to 21 prior to the 1984 federal mandate, but not for those who changed it after. While the authors controlled for numerous confounding variables, they did not distinguish whether the traffic deaths involved alcohol. Between 1982 and 2007, there were greater declines in drinking drivers aged 18–20 than 21–24 in fatal crashes in states adopting the age 21 drinking limit both before and after the federal mandate (33).

Examining data from 1982 to 2004 and controlling for numerous potential confounding factors and laws, Fell et al. (31) found adoption of the minimum legal drinking age of 21 was associated with a 16% decline in the ratio of drinking to non-drinking drivers aged under 21 in fatal crashes. Laws aimed at adult drivers, including 0.08% and 0.10% BAC laws, administrative licence revocation, and seatbelt laws were also associated with, respectively, 8%, 7%, 5%, and 3% declines.

An analysis (38) of two national surveys conducted ten years apart found that after controlling for numerous confounding variables, respondents raised in states where they could legally drink prior to the age of 21 were more likely as adults to meet alcohol and drug use disorder criteria.

Zero-tolerance laws

Zero-tolerance laws make it illegal in every state for those under the age of 21 to drive after consumption of any level of alcohol, reducing such behaviour and alcohol-related traffic deaths involving underage drivers (39, 40).

Social host liability

Dills (41) examined national survey data from 1984 to 2004 and alcohol- vs. non-alcohol-related fatal traffic accidents among those aged 18–20 from 1975 to 2005 while controlling for drinking age, several drinking and driving laws, and economic factors. Social host liability laws, adopted in 33 states that hold adults accountable for providing alcohol to

underage persons (other than their children) were independently associated with declines in binge drinking (3%), driving after drinking alcohol (4%), and alcohol-related traffic deaths (5–9%).

Price of alcohol

Recent reviews (42–45), have reported an inverse relation between the tax on or price of alcohol and alcohol misuse and related negative health outcomes. The National Academy of Sciences (42) recommended Congress and state legislatures raise excise taxes to reduce underage drinking and devote the additional revenues to further reduce the problem.

A World Health Organization review (45) concluded:

When other factors are held constant, such as income and the price of other goods, a rise in alcohol prices leads to less alcohol consumption and less alcohol-related harm, and vice versa … Policies that increase alcohol prices delay the time when young people start to drink, slow their progression towards drinking large amounts, and reduce their heavy drinking and volume of alcohol drunk on an occasion.

Alcohol outlet density

Higher alcohol outlet density has been associated with increased alcohol-related problems in cross-sectional and prospective studies, and reducing outlet density may, in turn, reduce those problems (46).

Individual-level interventions

A review (47) of 62 randomized controlled studies of individual-level interventions to reduce college student drinking between 1985 and 2007 reported that intervention participants reduced their quantity and frequency of heavy drinking and alcohol-related problems at 4–195 weeks post-intervention.

Tripodi et al. (48) identified 16 experimental studies testing individually oriented approaches to reduce frequency and quantity of drinks and alcohol problems among 12–19-year-olds. All tested interventions yielded reductions with the largest effects found for brief motivational interventions (with aftercare, adolescents and parents, adolescents only) and multidimensional family therapy.

Normative re-education interventions

College students often overestimate alcohol consumption by fellow students and may consume more alcohol to conform with misperceived group norms. A review (49) of 23 randomized trials tested whether informing college students of their campus' true alcohol consumption norms led to drinking reductions. The review found web/computer feedback interventions produced significant reductions lasting up to 16 months after the intervention into the alcohol problems, the peak BACs, frequency and quantity of drinking, and binge drinking. Individual face-to-face feedback produced declines in frequency of drinking at six-month follow-ups and alcohol-related problems at 17-month follow-ups. Group face-to-face feedback reduced quantity of

drinking and binge drinking for only three months and mailed feedback produced no effect. Campus-wide, social marketing study results were inconsistent.

Recognizing that different interventions may be more developmentally appropriate and effective at different ages, Spoth et al. (50) reviewed over 400 interventions targeting underage drinking. Table 16.1 lists interventions found to have the most promising evidence for persons less than ten years old, 10–15 years old, and those aged 16 to ≥20 years.

Parent initiatives

Pre-college initiatives

Spoth et al. (51) randomly assigned sixth graders (usually age 11) and their parents in 33 schools to the Iowa Strengthening Families Program (ISFP), the Preparing for the Drug Free Years (PDFY), and a control group. ISFP sought to improve parent–child relations, strengthen communication, and increase child coping skills through a seven-session, 13-hour intervention at school. PDFY, offered in five weekly two-hour sessions, sought to enhance parent–child interaction and reduce children's substance initiation. Compared to control group students, when re-interviewed as high school seniors, those exposed to the ISFP were one-third less likely to report drinking to intoxication, and at the age of 21, reported significantly fewer episodes of drunkenness, frequency of alcohol problems, and cigarette and illicit drug use. PDFY and control group differences were smaller during senior year and were not significant at age 21.

Table 16.1 Interventions aimed at different age groups of US adolescents with the most promising level of evidence of effect

Age group		
<10 years of age	**10–15 years of age**	**≥16 years of age**
♦ Linking the interests of Families and Teachers	♦ Keepin' it REAL	♦ Project Toward No Drug Abuse
♦ Raising Healthy Children	♦ Midwestern Prevention Project/Project STAR	♦ Yale Work and Family Stress Program
♦ Seattle Social Development Project	♦ Project Northland	♦ Mississippi Alcohol Safety Education Program and Added Brief Individual Intervention
♦ Nurse-Family Partnership Program	♦ Strengthening Families Program: For Parents and Youth 10-14	

♦ Preventive Treatment Program (Montreal)

Adapted from Spoth R et al., Overview of preventive interventions addressing underage drinking: state of the evidence and steps toward public health impact, *Alcohol Research and Health*, Volume **32**, Number 1, pp. 53–66, National Institutes of Alcohol Abuse and Alcoholism,

College initiatives

Parental influence can extend into college years. Ichiyama et al. (52) tested the effects of sending parents a handbook for talking with college students about alcohol. Comparison group parents received a brochure detailing university alcohol policies and violation penalties. Students who did not drink prior to college whose parents reviewed the handbook were less likely to start, and females already drinking were less likely to show growth in drinking over the freshman year. Turrisi et al. (53) found this parental intervention, in combination with a brief motivational intervention, produced lower levels of alcohol consumption and high-risk drinking among college students compared with a control group.

Campus-wide Internet interventions

AlcoholEdu, a web-based intervention to prevent and reduce college student alcohol misuse, is compulsory for freshmen

under the age of 21 in over 200 colleges and universities It includes personalized feedback to change normative beliefs about alcohol use, education about alcohol's effects on the brain and behaviour, risk awareness, challenges to expectations about effects of alcohol, suggested alcohol-free activities, and strategies to minimize alcohol-related harm (e.g. avoiding drinking games).

Paschall et al. (54) randomly assigned 32 colleges in the autumn of 2007 and 2008 to the intervention receiving AlcoholEdu or control condition (not receiving the intervention). None of the intervention or control colleges had previously implemented an online course.

The two-to-three-hour course had two sessions—one in late summer prior to matriculation and the second 30–45 days later. Students completed online surveys about their drinking practices during each session and again in the spring.

Reductions in 30-day alcohol use, binge drinking, and alcohol problems were observed in the autumn immediately following course completion but not during the spring semester.

Comprehensive community interventions

Several community-based initiatives have successfully reduced drinking- and/or alcohol-related problems among underage individuals and young adults (55):

♦ Communities Mobilizing for Change on Alcohol programme (56)

♦ Community Trials Intervention To Reduce High-Risk Drinking programme (57)

♦ Saving Lives Program (58)

♦ Fighting Back Program (59)

♦ Sacramento Neighborhood Alcohol Prevention Project (60)

♦ Reducing Underage Drinking through coalitions project (61).

Two other programmes, Project Northland (62) (grades six to nine, ages 11–14) and Communities that Care achieved reductions of alcohol use among middle school students (grades five to ten, ages 10–15) (63).

These programmes typically coordinate efforts from multiple departments of city governments: schools, health, police, the Departments of Alcoholic Beverage Control, etc., and concerned private citizens and their organizations, students, parents, and alcohol merchants. The programmes implement multiple intervention strategies, including school-based programmes involving students, peer leaders, and parents; media advocacy; community organizing and mobilization; environmental policy change to reduce alcohol availability to youth; and heightened enforcement of laws regulating sales and distribution of alcohol and reducing alcohol-related traffic injuries and deaths.

Interventions varied by programme. Common interventions included compliance checks to reduce underage alcohol purchases, heightened driving while intoxicated enforcement

often through sobriety checkpoints, Responsible Beverage Service programmes, legal drinking age enforcement, and evidence-based school programmes. Less common interventions included price and tax increases, expansion of screening and brief interventions, and enforcement of traffic laws not specifically focused on alcohol, such as speeding and safety belt laws.

Elements of the comprehensive community-organizing model which have recently been found to reduce drinking or related harms specifically among college students, the population most resistant to drinking reduction (55), include:

♦ A Matter of Degree programme (64)

♦ College community driving under the influence (DUI) enforcement (65, 66)

♦ Western Washington University's Neighborhoods Engaging with Students project (67)

♦ The Safer California Universities Project (68) and Study to Prevent Alcohol-Related Consequences (69) experimental studies which achieved drinking reductions simultaneously at several universities.

In addition to interventions commonly employed in general comprehensive/community programmes, these college/ community programmes commonly added interventions such as police 'wild party' enforcement, substance-free residence halls, alcohol-free recreational activities, social host ordinances, and coordinated college and community judicial processes. They also often monitored college-specific

outcomes, including rates of drinking to intoxication, coerced sexual incidents, intoxication events at off-campus locations, alcohol-related fights, police incidents, alcohol-related injuries, and other consequences to others.

Collectively, these studies underscore the potential for comprehensive multi-component community and college collaborative interventions to reduce underage drinking and related problems in the general underage and difficult-to-reach college student population.

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Chapter 17
Gender and alcohol: consumption and consequences

Richard W. Wilsnack and Sharon C. Wilsnack

Introduction

Why do we need to know about how gender influences alcohol consumption and its effects? For most of the twentieth century, this question was tacitly phrased more bluntly: why do we need to know how women drink? The answer was that we did not need to know. It was assumed that: (i) so few women drank, and drank so little, that any consequences of their drinking could be ignored, and (ii) that when women did consume alcohol, their drinking behaviour and its effects would be the same as men's. As of 1970, only 28 English-language research articles had been published dealing specifically with women's drinking behaviours (1).

Neglect of gender in alcohol research now seems strange because gender differences in alcohol use have been one of the few almost universal patterns in human social behaviour. Nearly everywhere that epidemiological or ethnographic research has been carried out, historically and cross-culturally, men have consumed alcohol more than women have. This pattern has been found in Graeco-Roman and medieval European history (1, 2), in pre-industrial societies on several continents (3), and in recent multinational surveys (4, 5). For a long time, this gender difference was seemingly taken for granted to the extent that there was no

attempt to understand it as more than a local and time-limited phenomenon, and no attempt to ponder its implications.

Since the 1960s, however, there has been a huge increase in research on how gender is related to alcohol use and its consequences; there are now more than a thousand new articles about gender and alcohol published each year. What prompted this growth was a gradual recognition in many branches of medical and behavioural science that to understand alcohol consumption and problems, and how to control them, it is essential to understand the multiple ways they are affected by gender.

Which gender effects have been important enough to stimulate so much attention? First, it has become evident that gender differences in drinking vary greatly (e.g. between societies where it is 'normal' versus 'deviant' for women to drink) and that these differences may change over time (leading to recent debates about whether men's and women's drinking behaviours are converging (6, 7)). Second, there is growing recognition that the consequences of women's and men's drinking may differ physiologically (e.g. in breast cancer), psychologically (e.g. in rates of alcohol dependence), and socially (e.g. in likelihood of driving after drinking). Third, it is now also apparent that causes and conditions affecting men's and women's drinking and related problems may differ in important ways, physiologically (e.g. in alcohol metabolism), psychologically (e.g. in motivations to drink), and socially (e.g. in influences of drinking partners or companions). This chapter aims to summarize the best current knowledge about how women and men differ in their drinking behaviour and in its antecedents and consequences. This knowledge may have implications for how better to prevent

and intervene in hazardous drinking patterns and the problems they create.

How have men's and women's drinking patterns differed?

A fundamental, persistent, worldwide gender difference in drinking behaviour is that women are more likely than men to abstain from alcohol altogether. Furthermore, among drinkers women are more likely than men to quit drinking (more than temporarily) (5). However, gender effects on abstention rates vary greatly cross-culturally. In much of Europe, large majorities of both women and men drink, while in the Middle East and southern Asia, minorities of men drink but much smaller percentages of women drink (or are willing to report doing so) (8). Because of these variations, it is often important to limit gender comparisons of other drinking patterns to men and women who drink at least occasionally (typically within the 12 months preceding a survey).

Generally among drinkers, the higher the level of consumption, the more predominantly the drinkers are men. Thus in multinational surveys, men are much more likely than women to drink five or more times a week, and much more likely than women to consume an average of >23 g of alcohol per day (5). Other surveys consistently confirm that men drink more frequently and in greater quantities per drinking day than women (4), so men have higher levels of total consumption. Men are also more likely than women to engage in heavy episodic (or 'binge') drinking (typically defined as the equivalent of ≥5 drinks or ≥60 g of ethanol in a day) (5, 8). For these reasons, men are much more often categorized as heavy drinkers than women. However, comparisons of

men's and women's rates of heavy drinking and heavy episodic drinking are becoming more uncertain because of increased use of gender-specific thresholds for these measures: for heavy episodic drinking, ≥5 drinks/day for men, ≥4 drinks/day for women; and for heavy drinking, ≥14 drinks/week for men, ≥7 drinks/week for women (9, 10).

Measuring drinking patterns with lower thresholds for women may affect claims that women's and men's drinking patterns are converging (11). Clearly, in many societies roughly equal percentages of men and women drink some alcohol rather than abstain (4, 5). Many longitudinal studies have also found that women's and men's drinking patterns are becoming more similar (6, 12), but convergence may result not only from greater increases in women's drinking but also from greater decreases in men's drinking (7). As yet, women's drinking has equalled or surpassed men's only in subgroups of specific populations, such as among some young adults in the United Kingdom (13).

Effects of alcohol consumption may be modified by other gender influences on drinking behaviour. For example, there is European and North American evidence that drinkers preferring wine are more likely to be women, while those who prefer beer are more likely to be men (14, 15), a pattern that may be associated with a tendency of women to drink more slowly than men (16). Women also often do more of their drinking with meals than men (17), a pattern associated with more benign effects of alcohol (18). Finally, men are more likely to drink alone than women (19), a pattern well-known to be associated with more hazardous drinking. Some evidence indicates that women are likely to be influenced to drink more by heavier-drinking male partners

(20), but in longer-lasting relationships the partners may mutually influence each other's drinking, which may not necessarily lead to heavier drinking (21).

Many analyses of gender influences on alcohol consumption ignore differences within the male and female categories; this is a serious oversimplification. While multicultural data on within-gender differences are scarce, there are clear indications where more research on such differences is needed. For example, although both men and women become more likely to stop drinking at older ages, men are generally likely to persist in drinking longer into old age than women (5, 22). Women drinkers are more likely to engage in heavy episodic drinking if they have more education in low-income countries, but if they have less education in high-income countries (23).

Gender-specific differences in sexual orientation may also affect drinking patterns. In North America, women who identify themselves as not being exclusively heterosexual have higher risks of hazardous drinking (24), although among women elsewhere and among men, associations of drinking levels with sexual orientation are inconsistent (25).

How have the consequences of women's and men's drinking differed?

Beyond gender differences in alcohol consumption, men greatly exceed women in the prevalence of alcohol-related social and behavioural problems. Cross-culturally, men are much more likely to have diagnosable alcohol use disorders (dependence and abuse) (26), high scores on the Alcohol Use Disorders Identification Test (AUDIT) (27), and a diversity of

negative social and behavioural consequences of drinking (28). In particular, men are more involved in alcohol-affected driving and related accidents (29), and men's drinking predicts more severe violence against intimate partners (30). More generally, drinking may facilitate aggressive behaviour in men more than in women (31). Some of the gender differences in alcohol-related problems may now be declining in North America (6), but the extent to which men's alcohol problems exceed women's generally remains larger than gender differences in drinking versus abstaining.

Men may have more alcohol-related problems than women because they drink more and in riskier ways, but women may be more vulnerable than men to alcohol's acute effects. Evidence mainly from US studies indicates that compared with men, women become subjectively intoxicated from fewer drinks (32), are more likely to experience blackouts (33), and show greater cognitive impairment from weight-adjusted moderate doses of alcohol (34). These gender differences have been attributed to women's smaller volumes of body water in which alcohol is distributed, and women's lower rates of first-pass alcohol metabolism that may raise blood alcohol levels, although the role of gastric metabolism is debated (35). However, women also eliminate alcohol from the body slightly more rapidly than men (35), possibly because women have a greater liver volume per unit of body mass (36).

Effects of alcohol on men's and women's health are discussed in other chapters of this book, including both acute effects (injuries) and chronic effects (cardiovascular diseases, cancer, neurological and mental disorders, and effects of alcohol consumption in pregnancy). Therefore, it will suffice here to

emphasize a few general findings. Injuries, mortality, and morbidity from alcohol consumption are generally more common among men because men are more likely to engage in chronic heavy drinking (8). However, for a given level of consumption, women may be more vulnerable to some adverse health effects than men (e.g. liver cirrhosis and strokes (37, 38)). In addition, women's drinking may increase risks of breast cancer and adverse pregnancy outcomes, but men's drinking may increase risks of prostate cancer (39). Apparent health benefits of low to moderate levels of alcohol consumption occur for both men and women, but often at lower levels of consumption for women than for men (40). To summarize, men are riskier drinkers than women, but high consumption levels may be riskier for women than men.

Why have gender differences in alcohol use persisted?

If men continue to drink more heavily and with more associated problems than women, why has this gender gap so widely persisted? The only certain answer is that there are multiple contributing causes. There is no single explanation for the gender differences, but there may be more than sufficient causes to maintain some gender gap. Several hypothetical causes can be summarized here, but it is unclear to what extent any one of them makes men and women drink differently.

Biological differences

It is possible that alcohol consumption is less enjoyable or more unpleasant for women than for men, for biological reasons. Some research has found that the heritability of

alcohol dependence is weaker among women than among men, perhaps because sex-specific thresholds for genetic effects differ, or because heritability may be partially sex-linked (41). However, a sex-linked effect on heritability is not always found (42), it may reflect more than genetic susceptibility, and it has not been assessed for drinking patterns in general. A more likely influence on consumption patterns is that women may drink less than men to experience the same effects of alcohol, as described earlier, because of sex differences in body water and in alcohol metabolism. This hypothesis, however, would not explain women's higher rates of abstaining and ceasing to drink. Some sex-linked influences on abstinence rates might result if women tend to experience more adverse acute physical consequences than men do from drinking the same amount. Studies of acute after-effects of drinking have found that women are more likely to experience hangover symptoms than men from a given level of consumption (43).

Asserting power

Culturally, alcohol has long been valued by men as a symbol and facilitator of male power (44). Consuming large quantities of alcohol, particularly in all-male drinking groups, has often been viewed as a symbol of masculinity (45), particularly if a man can drink large amounts of alcohol without seeming impaired. Also, beliefs that alcohol facilitates physical aggression have been relied on by men seeking to exert power over other men and women (46). For all these reasons, men have typically been more motivated to drink than women. Where women have taken what often used to be considered 'male' jobs, it was thought that women

would also assert the right to drink more like men, explaining declining gender differences in drinking, but the evidence for this effect is weak (44).

Sexual activity

Men's and women's expectations that alcohol will enhance sexual activity have been similar in studies of young adults (47). However, drinking patterns may be influenced by a folk model that differentiates gender effects. In this model, alcohol consumption enables men to be more sexually assertive, but makes women more sexually disinhibited and promiscuous. This creates reasons for men to drink (48), but also creates reasons to condemn or try to limit women's drinking as a moral or physical hazard (49). To the extent that the folk model influences drinking behaviour, it should tend to perpetuate gender differences in alcohol consumption. Hypothetically, women might also limit their own drinking to reduce their related sexual vulnerability (50), but effects of such self-restraint on the gender gap have not been demonstrated.

Risk-taking

Research has consistently found that men are more willing or motivated to take risks than women (51, 52). This gender difference may result partly from biological differences (e.g. testosterone levels) (53) and from sociocultural interpretations that risk-taking demonstrates masculinity while caution is more appropriate for women (52). Alcohol consumption, particularly in large amounts, is not only risky behaviour (in

terms of possible bad outcomes), but as ‘liquid courage’ may also
make it easier for drinkers to ignore risks when called on to display masculinity (54). Consistent with these ideas, recent research has found that risk-taking motivates or enables men to drink more heavily, while women are more likely than men to use risk-reduction strategies when drinking (55, 56). However, risk-taking may help explain gender differences in heavy episodic drinking better than gender differences in abstaining from alcohol.

Social responsibilities

A final hypothesis is that social role responsibilities have had different effects on women’s and men’s drinking. Historically, men have used drinking to symbolize their freedom to disregard responsibilities at work or at home, and as a way to escape from those responsibilities. In contrast, women historically have been less able to relinquish domestic responsibilities (such as childcare), and have often also been obligated to restrain male partners’ drinking and its effects (57). These gender-role differences would increase the gender gap, particularly in heavy drinking. However, when the effects of multiple roles (occupational, marital, and parental) on men’s and women’s drinking are evaluated now, heavier men’s drinking and reduced women’s drinking do not always occur (58). Furthermore, where role responsibilities are becoming less gender-specific, contrasting effects may decline, possibly increasing convergence of women’s and men’s drinking.

Summary and implications

Men continue to consume more alcohol than women, and as a result suffer more adverse effects. This gender difference is smaller for rates of drinking versus abstaining from alcohol, and greater for the heaviest and most problematic drinking patterns. At any given level of consumption, however, women who drink are at greater risk of problems, particularly from health effects. Furthermore, gender differences in consumption and problems are growing smaller in a number of countries. Nevertheless, the multiple possible causes for such gender differences mean that the gender gap is likely to persist to some degree for a long while yet.

This leads back to the initial question: why is it important to know about persistent but possibly dwindling gender differences in drinking and its effects? The findings summarized here suggest at least three reasons why attention to the gender differences is important:

First, cultural processes that perpetuate the perception of heavy drinking as a positive masculinity symbol or a male privilege, such as through the marketing of alcoholic drinks (59), are going to help perpetuate hazardous and harmful alcohol consumption. The effects will occur not only among men, but also among those women who want assert their rights and abilities to drink ‘like men’.

Second, women’s drinking is associated with specific hazards (such as sexual assault, intimate partner violence, and risks of adverse pregnancy outcomes), and women are vulnerable to adverse health effects of alcohol at lower doses than men are. To the extent that women’s drinking is increasing, it is

imperative for women to find and teach themselves more effective ways to prevent their own harm from alcohol (56). Scolding or punishing women will not accomplish this.

Third, if women need to guard themselves against drinking hazards, so do men. This may be the hardest challenge: to help men develop networks of male social support for drinking less, before alcohol disorders develop, and without implying that such behaviour is less masculine. While male support groups have become common, the role of such groups in restraining men's alcohol use is underdeveloped and underevaluated (60). Collaborative male prevention of heavy drinking, however, would be against the economic interests of the alcoholic drinks industry as well as against cultural traditions, and so might face resistance.

Current gender differentiation and its trends seem unlikely to have major positive effects on alcohol consumption and its adverse consequences. The analysis here suggests that beneficial changes will have to be cultural rather than legal, to encourage men and women to think differently about alcohol. At present, it is difficult to foresee if or how or when this will happen.

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Chapter 18
Alcohol use in the elderly

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Introduction

The older population is one of the most-rapidly growing demographics. It is expected that by 2030, 20% of the world's population will be over the age of 60 (1). Many older adults drink alcohol and some have alcohol abuse and dependence problems (2). Due to the physiological changes that accompany ageing, the effects of alcohol on organ systems are different in older adults, and potentially more harmful (3). In addition, ageing introduces different life stressors than those common in early and middle adulthood, which can lead to changes in drinking patterns among older adults.

Perhaps of most concern for elderly drinkers is the lack of effective assessment tools for their age group (4). Whereas the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) criteria are useful for identifying those adults with problematic drinking who have responsibilities such as employment or childcare, or who are DUI (driving under the influence) offenders, elderly drinkers often do not have the same characteristics, and are thus missed by such assessments. In this chapter, we detail the patterns and prevalence of alcohol use among the elderly and discuss diagnosis and treatment options for those with alcohol use problems.

Prevalence

Prevalence rates indicate that older adults have lower rates of problematic drinking than do younger individuals, and that there is an inverse relationship between age and alcohol consumption such that as age increases, alcohol use decreases (5). Moderate drinking prevalence rates range from 27% to 39% among men and from 22% to 32% among women, and heavier drinking rates are about 10% for men and 2.5% for women (6). However, a significant proportion of adults over age 65 still appear to be at-risk drinkers (13% of men and 8% of women), or binge drinkers (14% of men and 3% of women) (7). Among the elderly, hazardous drinking is described as four or more drinks per day for men and three or more drinks per day for women, with the frequency of drinking ranging from twice a month to three times per week (8).

Drinking patterns

Epidemiological studies have detailed several patterns of drinking in the elderly. For example, men drink more than women, Caucasians drink more than other racial groups, college graduates drink more than those with less education, and higher income, living in an urban environment, being employed, and being married are all independent predictors of increased drinking (9).

The two largest epidemiological studies used to measure drinking behaviour, the National Longitudinal Alcohol Epidemiologic Survey (NLAES) and the newer National Epidemiologic Survey of Alcohol and Related Conditions

(NESARC) both show relatively low prevalence rates for alcohol use disorders (AUDs), abuse, and dependence among North Americans age 60 or over (10). The NLAES was used in the early 1990s, and replaced by the NESARC in the early 2000s. Although the two measures produce similar data regarding prevalence rates among those aged 60 or over, the NESARC shows higher rates of lifetime AUDs, as well as alcohol abuse than did the NLAES. Rather than being a time-based effect, where such rates are actually increasing, the change appears to be due to self-reported hazardous use changes that are not mirrored by concomitant changes in outcomes of hazardous use as reported by other measures (10). Across both surveys, it appears that less that 5% of the population age 60 or over meet current (past 12-month) AUD, abuse, or dependence criteria. This is considerably lower than the prevalence rates for younger individuals surveyed. What is unclear from the results of such epidemiological studies is whether the prevalence of drinking-related problems is actually lower in older adults, or if the measures used do not adequately capture the drinking behaviours and associated problems of the elderly.

Overall, the NESARC data provide evidence that moderate drinking, that is, drinking one to two drinks per day, has protective effects for the elderly (11).

The NESARC findings (11) show the following:

1 Moderate alcohol use (one drink per day or less) by older women has beneficial health effects.

2 Alcohol use does not increase emergency room visits or hospitalizations of men or women.

3 Alcohol abuse and dependence by older adults does not increase utilization of health care.

4 There is a weak association between alcohol use and injury in older women.

5 Current drinkers are healthier than former drinkers.

Smaller sample studies reveal similar patterns with alcohol consumption decreasing as a function of increasing age. In a study of adults aged 65 to 89, 66% of participants drank alcohol at least once a month (12). Among those who drank, consumption rates in the oldest group (≥80 years old), were half that of the younger cohorts (aged 65–69 and 70–74). Based on current knowledge of body water and tolerance, it seems likely that such patterns of decreasing use with increasing age are indicative of dose titration such that as they continue to age, elderly adults may need less alcohol to produce the same effect.

A recent study of elderly drinkers (n = 3,308) indicated that roughly one-third of adults over the age of 60 were at-risk drinkers, meaning they were at risk from their alcohol consumption (quantity or frequency consumed, or driving after drinking), or the combination of alcohol and health co-morbidities, or the combination of alcohol and other medications (e.g. antidepressants) (13). Among these at-risk individuals, approximately 60% were in each of these risk categories. Similar to the findings of Goodwin et al. (12), alcohol consumption was significantly lower in those over 80 years of age.

Early versus later onset drinking

There appear to be two major patterns to alcohol drinking among older adults. First, there are those who have been drinking for many years and continue to drink as they age. These early-onset drinkers may have a current or prior alcohol problem, and often worsen as they age due to a decrease in external contingencies on drinking (e.g. no job to get to or no living spouse to monitor alcohol intake) (14). The second group—late-onset drinkers—are those individuals who did not begin to drink until later in adulthood, usually in response to a specific stressor, such as the death of a spouse (15).

Men and women often change their drinking patterns in older adulthood, with men decreasing heavy drinking, while moderate drinking behaviour remains stable, and women decreasing moderate drinking while heavier drinking stays stable (6). This suggests a gender difference in the malleability of alcohol use behaviours. In addition, drinking behaviour between ages 55 and 65 is correlated with drinking behaviour at ages 75 to 85, suggesting that changes in drinking among the elderly are subtle rather than extreme (16).

An additional issue is that many older adults use alcohol as a sleep aid, either alone or in combination with other sleep aids. In a small study of older women (age 80 and above), over half of the sample (n = 91) drank three or more drinks per night as a sleep aid, and among those who used both alcohol and sleep aids (n = 33), two-thirds drank three or more drinks per night (17). As it is well-known that alcohol is not an effective sleep

aid, this suggests an opportunity to educate elderly individuals on sleep-related issues.

Protective effects of alcohol

Moderate drinking appears to convey several benefits to older adults. In moderate doses (no more than two drinks per day for men and no more than one drink per day for women), alcohol has demonstrated cardioprotective effects (18). In addition, those who drink alcohol at low to moderate levels have better mental health, better functional and cognitive test results, and more social support than do those who do not drink (19). In fact, moderate drinkers tend to be overall healthier than those who do not drink at all (20). This includes self-reported perceived health status and functioning as reported on the short-form (SF)-36 health survey, as well as direct tests of memory. However, the relationship between drinking and cognition is non-linear, as cognitive performance declines at and above four drinks per day (21). This again supports the potential benefit of light to moderate drinking in later adulthood.

Evidence in support of this comes from a longitudinal study of alcohol intake and survival in New South Wales which revealed a cardioprotective effect of alcohol in both men and women, as well as increased longevity for moderate drinkers (one to seven drinks per week) only as compared to teetotallers (22). However, the increases in longevity were 7.6 months for men and 2.7 months for women, suggesting that the gains were modest at best.

Harmful effects of alcohol

Older adults will show more effects from the same amount of alcohol than will younger adults. This is due in large part to age-related declines in lean body mass and total body water, the body spaces where alcohol is distributed (23).

Drinking beyond the low to moderate level however, can lead to or exacerbate existing medical problems and cause additional complications. In a sample of Medicare (a national social security programme) beneficiaries across the United States, alcohol-related hospitalizations accounted for only 1% of all hospitalizations among the elderly, but over one-third of those hospitalizations led to an alcohol-related diagnosis, and almost 50% of those were a diagnosis of alcohol dependence (24). Medicare beneficiaries are almost entirely older adults, and the vast majority of US individuals age 65 and older (>95%) are covered by Medicare, thus this sample would represent the vast majority of the elderly US population. In combination with the NESARC findings described earlier, this suggests that the elderly are hospitalized for alcohol-related problems relatively late in their drinking.

Although the evidence linking atrial fibrillation to drinking is unclear, there is at least an association between excessive drinking and acute episodes of atrial fibrillation. As the rate of atrial
fibrillation increases 100-fold between ages 40 and 90, rising from 1.1 in 1000 to 105 in 1000, the potential impact of alcohol on atrial fibrillation is greater in the elderly (25). Alcohol is also known to exacerbate cognitive impairments, liver disease, ulcers, and hypertension, making even moderate drinking risky for elderly individuals with these disorders.

In addition, elderly individuals who fit the definition of 'problem drinkers', meaning they drink three or more drinks per day, report higher rates of limitation as well as higher rates of SSDI and SSI receipt (26). SSDI and SSI are US federal benefits available only to those with impairment or health problems that prevent or limit paid work in those individuals. As such, SSDI/SSI receipt serves as an objective measure of limitation, and appears to agree with self-reported limitation.

Gender differences in alcohol use and alcohol effects

Women have less body mass and thus less body water at all points in the lifespan, making them more susceptible to the harmful effects of alcohol, as well as to intoxication at lower levels of consumption. In addition, sex steroid hormone levels are reduced with menopause, exacerbating alcohol's harmful effects on body tissues. Of particular concern for older women is the relationship between alcohol and breast and other cancers (27). A meta-analysis revealed that the relative risk for breast cancer among women increases 7.1% for every 10 g of alcohol consumed per day (28).

In addition, women with a history of regular alcohol use were 2.2 times more likely to have impaired activities of daily living than those who had no regular alcohol use history (29). This is a greater impairment that that seen from age, smoking, or stroke, and indicates the breadth of the problem that results from chronic alcohol consumption.

Elderly Caucasian women show higher rates of drinking than do Hispanic or African American women in the same age

group, many of whom report no drinking (30). However, this drinking is at light to moderate levels, not heavier or at-risk drinking, suggesting that overall, elderly women drink at or below moderate levels.

Alcohol-related problems among the elderly

Among the elderly admitted to the hospital for alcohol-related problems (acute intoxication, falls, etc.), a large number (>90%) drank over the recommended level for light to moderate drinking (31). As their presentations at intake were widely disparate, identifying at-risk alcohol use among the elderly can be extremely complicated.

Testing for problematic alcohol use among older adults

The goal of alcohol testing or screening is to identify at-risk drinkers (those who could likely develop an AUD), as well as those who already have an AUD, and to determine the need for further assessment, and eventually treatment if necessary (27).

Older adults often have already stopped working due to retirement, may have suffered the loss of spouse and friends due to death, thus reducing their social interactions, and may have stopped driving due to difficulties with vision or mobility (32). In addition, behaviours that would identify younger drinkers such as frequent falls or unexplained bruises or injuries are often viewed as age-related among the elderly rather than as alcohol-related. As such, the common criteria for assessing alcohol abuse and dependence are less relevant

and less diagnostic in the aged population than in younger adults (33).

Older adults often live alone, relatively isolated from family and friends, and thus it may be difficult to gather accurate, or even any, collateral information on drinking behaviour (34). With no
one there to see drinking behaviour, alcohol purchases, or falls and injuries related to intoxication, older adults may have alcohol problems that remain undiagnosed. In addition, the social isolation of many older adults may result in family members, caregivers, and medical professionals being unaware and unsuspecting of alcohol problems in elderly individuals.

The CAGE assessment can be helpful as a brief evaluation of drinking behaviour among older adults (19). By asking questions that begin with the assumption that the individual drinks at least occasionally (which describes the majority of older adults), the CAGE is four yes/no questions about drinking behaviour. Answering yes to two or more of these questions indicates a need for further assessment of drinking behaviour and a possible alcohol abuse/dependence diagnosis. In older adults, there is some suggestion that answering yes to even one question on the CAGE points to the need for further investigation of drinking behaviour (19). Self-report data, on the whole, probably underestimates alcohol use in the elderly (35). However, self-report is the current gold standard for gathering alcohol use data and as such is used to determine drinking patterns. Daily diaries for tracking alcohol usage have been found to be a more effective means to track consumption of alcohol in the elderly as compared to

quantity–frequency measures, which require recall over longer periods of time (36).

Those older adults who are at-risk drinkers show poorer mental health functioning than do low-risk drinkers, as measured by the short-form-36 health survey (SF-36). The SF-36 is a 36-item instrument measuring self-reported mental and physical functioning (37). Among the elderly, there do not appear to be gender differences in SF-36 outcomes, although women do score better than men, most likely due to higher social functioning (e.g. more friendships, better connection to family) (37). In addition, abstainers score significantly lower than do low-risk drinkers, and even high-risk drinkers. From the data, it is unclear whether the abstainers are abstainers due to a prior alcohol problem. As such, the poor health of abstainers could be due to prior drinking problems, rather than to current behaviour. However, regardless of any prior problems, the findings regarding low-risk drinkers again underscore the potential benefit to moderate drinking in later adulthood.

Treating elderly individuals for alcohol abuse/dependence

The current recommendations for alcohol treatment do not differ for older adults as compared to young and middle-aged individuals. As already mentioned, older adults have reduced body water and altered metabolism which impacts the absorption and pharmacokinetics of potential alcohol treatment medications such as benzodiazepines. As such, dosing becomes increasingly critical for older adults undergoing alcohol treatment. In addition, careful monitoring of liver and kidney function during alcohol treatment allows

both for assessing any harmful effects of medication treatment and for capturing any recovery-related improvements, particularly in liver function.

In a study by Ray, Weisner, and Mertens (37), it was apparent that older individuals (age 50 or over) were less likely to use psychiatric addiction treatment services as part of follow-up care after diagnosis and treatment for an AUD than were younger individuals. This lack of follow-up care makes older individuals more likely to relapse to alcohol use within five years after treatment, but it is unclear why older adults demonstrated a lack of follow-up service utilization. Similarly, elderly individuals hospitalized for alcohol problems have been shown to underutilize out-patient follow-up care, although it is indicated upon discharge (38).

Other possible medications for use among elderly individuals with alcohol problems are the same as those used to treat drinking in younger individuals, including topiramate and naltrexone (39). For some elderly individuals, the injectable form of naltrexone (Vivitrol®) may be the best choice as it is a once-monthly dosing and thus has fewer compliance issues than oral medications.

Choosing a medication requires careful investigation of the patient's drinking history, as different medications appear to be more effective in either those with an early onset or a late onset of drinking (39). Regardless of choice of pharmacotherapy, all patients would benefit from at least a brief motivational intervention where the practitioner speaks to the patient about reducing or stopping their drinking, and about ways to do so.

Co-morbidities

There is little data available on the co-use of alcohol and other medications (licit and illicit) (27). However, as medical problems and thus medications increase with increasing age, it is reasonable to assume that the majority of elderly individuals require medications. As such, it is important that elderly individuals are made aware of potential interactions between medications and alcohol, particularly where alcohol use directly influences medication efficacy.

Depression and anxiety

Many older adults complain of depression and some of its common symptoms such as loss of libido and insomnia, but these may be primarily related to ageing and not to alcohol use as they often are in younger adults with AUDs (40). There is evidence that depression and alcohol use co-occur among the elderly, although the vast majority of the drinking is light to moderate, rather than heavy or problem drinking (41). In older adults, anxiety does not appear to drive drinking behaviour or to co-occur with alcohol problems as it does in younger adults (42). However, there is strong evidence that among elderly individuals with chronic mental or emotional health disorders, drinking can lead to decreased functioning (43).

Conclusions

The largest group of older adults, the ‘baby boomers’, many of whom used illicit drugs in the 1960s and 1970s, are now reaching age 65, and their prior use histories could lead to

increased risk for problem drinking in their later years (44). This group will be of particular interest to alcohol researchers and treatment providers as they move through older adulthood.

The majority of the available evidence reveals that many elderly individuals can drink at light to moderate levels with no negative effects for at-risk drinking (45). However, it is still essential to screen elderly individuals for AUDs and such screening requires moving beyond the typical signs of escalating problematic use in younger individuals. As such, it is important to tailor typical alcohol-use questions to be more appropriate to elderly individuals.

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Part V
Alcohol, injury, and violence

Chapter 19
Alcohol consumption and injury

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Introduction

The purpose of this chapter is to assess the risks of unintentional injuries in relation to alcohol consumption and how these risks vary, based on characteristics of those injured and the context of the injury. The association between alcohol and intentional injuries, as well as motor vehicle collisions, will be reviewed in subsequent chapters. We will draw conclusions on variations in the risks related to alcohol consumption for various causes of injuries (e.g. falls, fires, poison), severity of injuries, type of injury (i.e. concussion, cut, internal injury, or a broken bone), location of injuries (both at a micro level, such as recreational or leisure location, and a macro level, such as different countries), patterns of drinking, and demographics.

Methodological approaches and issues

There is a vast amount of scientific evidence from experimental research and field studies which assess the effect of alcohol in causing injuries. In this section we outline the methodological approaches and issues of these studies before discussing the results of various studies in the following sections. Experimental research involves the administration of various amounts of alcohol followed by the

measurement of performance in controlled environments. While experimental studies are extremely informative for understanding the acute (i.e. immediate) effects of alcohol, the findings may not accurately reflect real-life conditions.

Conversely, field studies are useful for determining the actual amount and proportion of individuals drinking among those who are injured and to assess the likelihood that alcohol may be causally related to injuries. To assess causality, the strength and significance of a statistical relationship between drinking and injury is first determined, usually by calculating odds ratios (ORs) where the proportion of those who have consumed alcohol in the injury group is compared to the proportion in a non-injury group. Confounders, such as sex, age, or risk-taking propensity, are ruled out as possible explanations for the results by matching cases and controls in the design of the study, or by multivariate statistical analyses.

Sources of data

Several sources of data from various populations have been used to study alcohol and injuries. Most commonly, these include: (i) the deceased, usually by examination of coroners' reports, (ii) injured people assessed at emergency departments (EDs), and (iii) population surveys where respondents are asked to recall injury events. Coroners' reports measure actual blood alcohol levels (BALs) of the deceased following trauma, giving accurate estimates of alcohol consumption at the time of death. A methodological strength of these studies is that estimates of the prevalence of alcohol intoxication are not biased from people choosing not participating in the study. However, such studies can be

biased in jurisdictions where coroners do not routinely test for alcohol and only test cases where alcohol is suspected. A common limitation is that these studies typically do not include a control group, so risk levels cannot be assessed. Furthermore, important information, such as psychosocial measures of the victims, often remains unknown.

By contrast, ED studies typically include non-injury ED patients or external controls as a comparison group. Unfortunately, challenges still exist for deriving unbiased estimates of risk in such studies. For example, accurate aggregate accounts of alcohol intoxication can be biased in studies that exclude people who are too intoxicated or severely injured. Furthermore, refusals are likely more common for injuries where liability may be an issue, and it is possible these cases are more likely to involve alcohol, causing underestimates of risk. A strength of ED studies is that events connected to the injury and drinking are easily remembered because they occurred recently. By comparison, population surveys require respondents to recall events that could have occurred long ago and they may have partially forgotten. However, population surveys capture a wider range of people than ED studies; therefore, the findings can be more generalizable to a larger group.

Studies utilizing administrative hospital data rely on several classification systems to describe the mechanism, type, and severity of injuries. Most hospitals worldwide use external cause of injury codes (known as E codes or Y codes) to define the environmental events, intent, location, and circumstances that resulted in an injury. Injuries are also classified according to the type of injury (e.g. laceration) using nature of injury codes (known as N codes or T codes). Finally, injuries are

classified according to severity using anatomic criteria such as the Injury Severity Scale (ISS) or Abbreviated Injury Severity Scale (AISS), or physiological criteria such as the revised trauma score (RTS). Unfortunately, classification schemes vary by hospital, region, and country. No consensus has been reached among injury experts as to which coding systems are best—a considerable limitation for comparing results across studies. Furthermore, although cause and severity of injury is typically recorded for patients who are admitted to hospital or who die because of an injury, this information is often not recorded for the majority of patients who have less severe injuries and are treated and released from the ED.

Study designs

Three major types of study designs are most commonly used to assess the level of risk of injury from alcohol consumption: cross-sectional, case–control, and case-crossover. The first, a cross-sectional design, collects data from a group of people at one point in time, allowing comparisons to be drawn between people with different characteristics. A population survey employs a cross-sectional design, as do studies of ED patients with injuries who are compared to those without (typically those with medical conditions) in terms of alcohol involvement.

A possible limitation of the ED cross-sectional approach relates to the inclusion criteria for the control subjects. For example, alcohol use may have caused the medical condition(s) (e.g. liver diseases) for which they are seeking care, resulting in underestimates of ORs. Alternatively, the

medical condition(s) may have created reductions in drinking, resulting in inflated ORs. Additionally, medical patients are often older, which may inflate ORs because older people tend to drink less than younger people. In order to adjust for differences in sex and age between the injured and non-injured groups, multivariate statistical approaches are frequently used to correct for these effects in predicting injury.

In comparison, the case–control design improves this limitation as control subjects are purposefully selected to be similar to cases (injury subjects) on known factors related to consumption of alcohol, such as age and sex. However, case–control studies have other methodological limitations. For example, selecting controls from the general population could introduce bias due to selection of the relevant time period to question participants regarding alcohol consumption. Bias may also be introduced by differential response rates in the two groups, for example, by recruitment of injured subjects by face-to-face interviews in an ED setting with a high response rate compared with recruitment of control subjects in a telephone survey with a much lower response rate. Differential response rates are a limitation that may distort ORs.

Finally, the case-crossover design was introduced as an approach that avoids the problem of fixed confounding factors, such as age, sex, health status, and personality, since each injury subject acts as his own control. In this type of study, injury patients are typically asked to report their alcohol consumption just before the injury event and at the same time usually one week before the event. The main shortcoming of this approach is that people tend to forget

events over time and would therefore be more likely to under-report alcohol consumption a week prior to the injury event—a bias that will result in overestimating the risk of alcohol involvement in injuries (1). Furthermore, in this approach case–control pairs, where drinking or abstinence occurs at both the injury event and one week prior, are ignored, creating a potential selection bias that favours recruitment of episodic drinkers.

Experimental evidence

An expansive volume of controlled experimental research, largely from the 1980s to the late 1990s, has been conducted on the effects of alcohol on human behaviour. Reviews of this time period highlight that acute alcohol consumption impairs psychomotor performance, including poorer coordination, balance, reaction time, hand–eye coordination, memory, and intelligence (2). The psychomotor effects of alcohol have been demonstrated, differentially, at both high and low levels of drinking and follow a dose–response relationship. The threshold for negative effects on psychomotor tasks is generally found at BALs as low as 20 mg% (3). Higher alcohol consumption at BALs of 80–100 mg% has been shown to slow reaction time by about 10% and greater effects are evident with larger doses. In addition, psychological effects of alcohol intoxication also contribute to injury by increasing risk-taking behaviour, which alters expectations about negative consequences (4).

Field study evidence

Cause of injury

Cause of injury, also known as mechanism or mode of injury, refers to how a victim was hurt, such as from a fire or fall. Excluding traffic accidents, the most frequently cited causes of alcohol-related unintentional injuries are those caused by drowning, falls, and fires (5). Studies have suggested alcohol consumption as the strongest risk factor for death by fire (6, 7), and reaffirmed by Smith et al. (5) who reported approximately 40% of unintentional fire and burn deaths involved intoxication of the victim, with other studies have reported rates as high as 61% (6).

Given the psychomotor effects of alcohol, it is not surprising that injury from falls and drowning is also highly associated with alcohol consumption. An early review conducted by Hingson and Howland (7) in the late 1980s found alcohol was associated with 15–53% of injuries from falls and 21–77% of fatal falls in over 20 studies. Stahre and Simon (8) more recently investigated non-fatal
hospitalizations for injuries in California, United States, for the year 2006, and found that 56% of alcohol-induced unintentional injury hospitalizations were due to falls (21,616 hospitalizations). Kool et al. (9) conducted a meta-analysis and determined that people who had been drinking had a threefold increase in risk (OR = 3.0) of fall injury compared to sober controls, and for people with BALs of 160 mg% the OR increased to over 60. Staggering risks like these are also seen in drowning cases: persons with a BAL of 100 mg% have about ten times the risk of death by drowning during

aquatic activity, increasing risk with higher BALs. It is estimated that 30–70% of persons who drown during aquatic activity have consumed alcohol (10).

Alcohol poisoning is another form of unintentional injury that has been examined. In 2009, alcohol was listed in 51,909 drink poisonings reported to a participating poison control centre in the United States (11). Most of these were not fatal cases. Of them, 2,640 cases were listed as unintentional, and in many cases another substance was co-ingested (11). Among others, Yoon et al. (12) suggests that although death from alcohol poisoning is documented in the alcohol epidemiology literature, it is underreported and not routinely checked as a cause of death by medical examiners. Despite popular assumptions, alcohol poisoning death is more common among experienced drinkers (i.e. alcoholics) than among inexperienced users of alcohol (e.g. youth and occasional or moderate social drinkers) (12).

Type of injury

Injury type is usually considered in two dimensions: nature of injury (e.g. fracture) and body part injured (e.g. upper extremities). In terms of the involvement of alcohol in both these dimensions, relatively little research has been conducted (13). In a recent study of ED patients at 45 locations worldwide, researchers found BALs of at least 80 mg% for various types of injuries as follows: 15% of concussion/head injuries; 12% of bruise, cut, sting, bite, or penetrating injury; 9% of internal organ injuries; 7% of sprain fractures or dislocations; and 3% of burns (14). The body part injured also varies by amount of alcohol consumed with head injuries

most commonly associated with greater amounts of alcohol (14). One prospective cohort study in Ireland reported injured patients with low alcohol concentration mostly suffered from soft tissue injuries of the extremities, whereas progressively higher alcohol consumption was associated with significantly higher rates of extremity fractures and head injuries (15). Although variations in the likelihood undoubtedly occur for different types of injury, the reasons for this variation are not properly understood.

Location of injury

Unintentional injuries from alcohol consumption vary by the situational location where injury occurred, such as at home, work, or during leisure or recreational activities. The analysis of 45 worldwide ED studies indicates that alcohol-related injuries are most likely to occur at a restaurant/bar and least likely at school/workplace (14). Studies of injuries occurring in the home have proposed a 12-fold increase in risk of injury after three drinks (16). As mentioned, alcohol appears to be a risk factor for injuries due to falls and many falls occur at home.

For injuries occurring during recreational and leisure activities, the importance of alcohol largely depends on the type of activity. Alcohol has been implicated in up to 41% of leisure activities (17), including skiing (18), bicycle riding (19), team sports (17), snowmobiling (20), all-terrain vehicle use (21), and, more frequently, aquatic-related activities (10). For instance, a study in 2001 found that boaters with a BAL between 50 and 100 mg% were 2.8 times more likely to incur a fatal accident, and boaters with a BAL greater than 100

mg% were 12 times more likely to die than those who had not been drinking (22).

Outside of leisure activities, work-place injury involving alcohol has been reviewed (23, 24). However, the proportion of individuals with positive BALs in work-related accidents remains relatively low compared to those occurring at other locations (25). While some workers may not drink on the job, alcohol may be more indirectly implicated in occupational injury the day after drinking (18). In addition, particular work sites may have greater risks of alcohol-involved injury, such as remote construction and oil sands sites, and other predominantly male, high-risk injury jobs.

Severity of injury

ED studies support the conclusion that injury severity increases with alcohol involvement, depending on injury mechanism (15, 26). Macdonald et al. (14) found that the more severe types of injuries, such as head injuries, were most likely to be associated with BALs over 80 mg%. Furthermore, the number of body regions injured and their severity were both significantly related to alcohol impairment.

Within certain types of injuries, alcohol consumption appears more common among fatalities than those with less serious injuries. For example, Levy et al. (25) found that alcohol involvement was significantly higher among persons killed in fires than among survivors (30.6% versus 11.0%). One explanation for these findings is the adverse psychomotor effects of alcohol intoxication may impede a victim's ability to escape from a fire once it has started (6).

Dose–response

The dose–response relationship between alcohol use and unintentional injury based on field studies has recently been analysed. In a systematic review and meta-analysis, Taylor et al. (27) concluded acute alcohol consumption and injury risk increase together. The risk of injury was found to increase non-linearly for unintentional injuries (excluding crashes) and linearly for falls. At approximately 14 g of ethanol (approximately one standard drink) the odds of injury increased slightly (OR = 1.30), but at 140 g the risk of injury increased substantially (OR = 24.2).

Pattern of drinking

Pattern of drinking has been used to describe different aspects of drinking, such as frequency, quantity, and contexts associated with unintentional injury. An analysis of EDs across seven countries showed frequent drinkers, who reported never indulging in heavy episodic drinking, were five to six times more likely to present at the ED with an alcohol-related injury, compared with infrequent drinkers (28). However, when controlling for dose of alcohol, more frequent drinkers have been found to be at lower risk than less frequent drinkers at all BAL levels (29).

It appears that the quantity of alcohol consumed on a given occasion, rather than the usual frequency, is a more powerful predictor of injuries. Indeed, many studies and literature reviews have confirmed that an increased risk of injury is associated with episodic binge drinking (30). For example, Stallones and Xiang (31) found a significant effect: those who

drank alcohol on average three or more times per week had about 3.2 injuries per 10,000 person-work-days, compared with 1.9 injuries per 10,000 person-work-days for non-drinkers. As mentioned earlier, research suggests that some types of fatal injuries, such as those caused by drowning, falls, and fires, appear more likely to involve alcohol than less serious injuries.

Demographic characteristics

Most ED studies indicate that patients seeking emergency care for alcohol-related injuries are disproportionately males, younger, and frequent heavy drinkers (25). Further, in terms of ethnic background, Yoon et al. (12) found more specifically that Hispanics and non-Hispanic black males in the United States have a higher risk for accidental alcohol poisoning mortality than non-Hispanic white males.

Substantial research also supports a disproportionate risk of alcohol-related injuries among the youngest and oldest age groups (i.e. <19 and >65 years of age). Although drinking, and especially heavy drinking, is less common among the elderly, those who do drink are more susceptible to alcohol-related injury (32). Approximately 30% of falls occur in the oldest proportion of the population (1%) where alcohol consumption is the lowest (33). However, one prospective cohort study examined whether early age of drinking onset was associated with respondents unintentionally injuring themselves or others when under the influence of alcohol (34). Interestingly, respondents who began drinking at an early age were more likely to unintentionally injure themselves and others when drinking. These disproportionate

rates of injury related to alcohol use among the young and old could be due to greater susceptibility to the effects of even moderate amounts of alcohol in these groups.

Aside from which groups are most likely to be involved in alcohol-related injuries, described previously, some evidence shows that this dose–response relationship between alcohol and injury risk for males and females may be different. In a case–control study, the risk of injury at greater than 60 g of alcohol was significantly higher for females (OR = 9.6) than for males (OR = 2.1) (29). One explanation for this is the metabolic and weight difference between men and women.

Regional variations

Large variations exist in terms of the involvement of alcohol in different cultures and there appears to be large degree of variation across studies from different countries worldwide (35). Rehn et al. (36) also found a high burden of unintentional alcohol-related injuries geographically disproportionate in the most eastern regions of Europe, particularly eastern Russia. In post-Soviet society, alcohol poisoning mortality is occurring on an unprecedented scale and has been increasing linearly from 1970 to 2002, particularly among young women (37).

Variations in drinking and injury rates by region are a product of laws, society, and culture. Often researchers refer to differences in drinking cultures as ‘wet’ and ‘dry’ cultures. Gmel and Daeppen (38) write:

Greater alcohol involvement has been found in those regions considered ‘dry,’ which exhibit more pro-temperance

sentiment with higher rates of abstinence, but also higher rates of infrequent but heavy drinking, compared to those regions considered 'wet,' where alcohol is more likely to be consumed frequently but in smaller amounts and with meals, more typical of 'wine-drinking' cultures.

Variations across communities or regions are likely attributable to a number of factors, such as socio-demographics, socio-cultural factors, and drinking patterns in the community that comprised the catchment area for the study.

Conclusions

A dose–response relationship is found between higher doses of alcohol and reductions in psychomotor capabilities from experimental studies, and correspondingly increases in the amount
of alcohol consumed is related to a higher likelihood of injuries, based on field studies. Research shows that across different cultures that males, younger people, and heavy drinkers are most likely to be involved in alcohol-related injuries. Large variations in the size of these risk relationships between alcohol intoxication and injuries are related to sex, age, severity, cause, situational location, and cultural context.

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Chapter 20
Alcohol and road traffic injury

James C. Fell and Robert B. Voas

Introduction

The problem

There is ample evidence that alcohol impairs the ability to drive a motor vehicle. The World Health Organization (1) estimated that 268,246 people were fatally injured in alcohol-related traffic crashes worldwide in 2004. This represented 11.9% of the 2.2 million alcohol-attributable deaths in the world in 2004, the second leading cause of such deaths. Of the estimated 75,000 alcohol-attributable deaths in the United States in 2001, motor-vehicle crashes were the leading cause of death (13,764), exceeding alcoholic liver diseases, liver cirrhosis, and other alcohol-related injury deaths (2). Although alcohol impairment plays a major role in traffic crashes around the world, this chapter will use alcohol and road traffic injury in the United States as a case study.

Alcohol-impaired driving resulted in 10,839 traffic crash fatalities in 2009, accounting for 32% of traffic fatalities in that year in the United States (3). Although alcohol-impaired driving fatalities recently decreased 7.4% from 2008 to 2009 (from 11,711 to 10,839), fatalities not involving an alcohol-impaired driver decreased more (10.7%), from 25,712 in 2008 to 22,969 in 2009. At least an additional 200,000 people were injured in impaired-driving crashes in 2009, and

impaired-driving crashes of all severities (i.e. property damage, injury, fatal) cost US citizens at least $51 billion that year (in year 2000 dollars) (4).

A 2007 nationwide roadside survey of night-time weekend drivers indicated that 2% of the drivers on US roads had illegal blood alcohol concentrations (BACs) (5). Each year for the past decade, an estimated 1,400,000 drivers were arrested for driving while intoxicated (DWI) or driving under the influence (DUI) (6). This number reflects only those apprehended by the police; however, research indicates that police only detect about 1 in 88 drivers on the roads who have an illegal BAC (7). A nationally representative telephone survey of more than 10,000 licensed drivers showed that US drivers admitted to 85.5 million drink-driving trips in the past 30 days in 2008 (8).

Alcohol and driving impairment

BAC is the standard measurement of alcohol in the body. An average male weighing 73 kg (kilograms) will reach a BAC of about 0.02 g/dL (grams per decilitre) after consuming one standard drink on an empty stomach. One standard drink is defined by National Institute on Alcohol Abuse and Alcoholism and the National Highway Traffic Safety Administration (NHTSA) as (converted from ounces to ml) 354.88 ml (millilitres) of beer at 5% alcohol (354.88 × 0.05 = 17.74 ml of alcohol); 147.87 ml of wine at 12% alcohol; and 44.36 ml of liquor at 40% alcohol (80 proof). Alcohol is absorbed by diffusion, metabolized mainly in the liver, with a small amount eliminated in urine and expired air. Alcohol's

immediate effects are due to its depressant effect on the brain, and chemical tests of
blood drawn from a vein or capillary are the preferred indirect way of estimating alcohol concentration in the brain in live humans. However, the most common way of estimating the concentration of alcohol in the blood for motor-vehicle drivers is by testing air expired from the lungs.

A person's performance in tracking and divided attention tasks is degraded at BACs considerably lower than 0.05 g/dL (9). Further, information processing, perception, and psychomotor skills are impaired at BACs of <0.10 g/dL but generally >0.05 g/dL. Moskowitz and Fiorentino (10) reviewed 87 experimental studies of skills performance at low BACs. They reported thresholds as low as 0.01 g/dL for the deterioration of some skills, and as high as 0.06 g/dL for others. Other reviews of experimental studies have also concluded that alcohol can cause significant impairment at low BACs. For example, a review of the international literature of the effects of low levels of alcohol on driving ability found that most studies showed that low alcohol levels (BACs of 0.025–0.08 g/dL) can significantly impair the psychomotor performance, compromising driving safety (11).

Tests of actual driving performance conducted in on-the-road settings or in driving simulations offer more realistic estimates of the effects of alcohol. As noted by Linné et al. (12), driving impairment is typically measured by increased lateral deviation (lane maintenance), but other measures are also used (e.g., speed maintenance). Technological advances in recent years have made driving simulators and measurement techniques more sophisticated and more sensitive to alcohol effects. These advances have resulted in

an overall increase in sensitivity to degradations of behaviours due to alcohol, as determined in laboratory experiments and in tests of actual driving performance. In a recent experiment using the National Advanced Driving Simulator (NADS) at the University of Iowa, alcohol-impaired driving based upon driver performance and vehicle measurements was identified within eight minutes of the simulator drive (13), mainly via lane maintenance and lane deviation measures. Consequently, behaviours related to driving are known to be impaired at lower BACs than was previously believed, with increased impairment of many behaviours clearly occurring at BACs in excess of 0.05 g/dL.

Drinking in relation to driving

How many US drivers drink and drive at night?

Our knowledge about the impaired-driving problem in the United States has been augmented by National Roadside Surveys (NRSs) from which we can estimate the prevalence of drink-driving over time in the contiguous 48 states by randomly selecting drivers from the road and requesting breath samples. The first NRS was conducted in 1973, the second in 1986, the third in 1996, and the fourth in 2007 (14). Figure 20.1 summarizes and compares the results of the four NRS studies of weekend night-time drivers. The percentage of drivers in all BAC categories decreased in succeeding decades, except for an increase in the percentage of drivers with BACs of 0.05–0.079 g/dL between 1986 and 1996. However, the overall percentage of positive BAC drivers decreased between 1986 and 1996. The 2007 NRS indicated

that about 8% of night-time drivers were drinking and 2% were alcohol impaired.

What proportion of US drivers admit to drink-driving?

In a 2001 telephone survey of more than 6,000 people aged 16 and older in the United States, 23% reported driving within two hours of drinking alcohol (15). In the same survey, problem drinkers were estimated as 29% of the past year's drinking drivers, accounting for about 46% of all drink-driving journeys. 'Problem drinkers' were defined as having two or more positive responses to the CAGE instrument (an abbreviation for the four questions asked in the questionnaire—Cut back, Annoyed, Guilty, and Eye-opener) (16). These problem drinkers accounted for 343 to 491 million drink-driving trips reported in 2001.

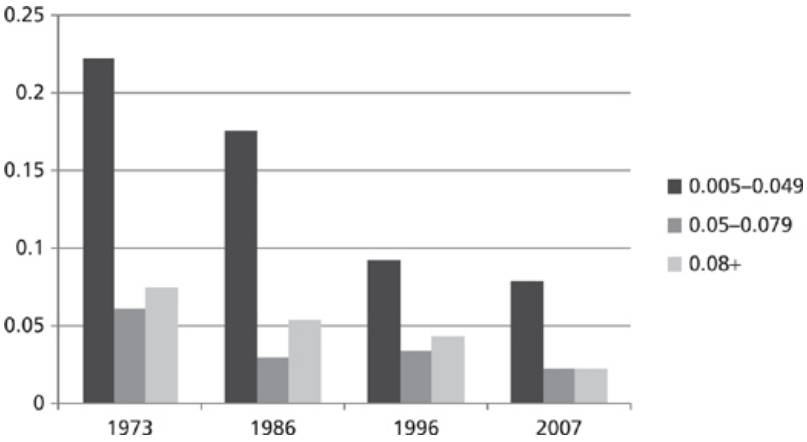

Figure 20.1 Proportion of drivers on US roads on weekend nights with various blood alcohol concentrations.

Reproduced from John H. Lacey et al., *2007 National Roadside Survey of Alcohol and Drug Use by Drivers: Alcohol Results*, National Highway Traffic Safety Administration, Washington, DC, USA, 2007, p. 4. NHTSA documents are public information and not copyrighted.

How many drivers are arrested each year for DWI in the United States?

About 1.4 million drivers have been arrested annually for DWI (6)—more than are arrested each year for larceny or theft, assaults, weapons charges, or vandalism, as examples. In 2006, this DWI arrest rate was about one DWI arrest for every 138 licensed drivers in the United States. When combined with drink-driving surveys, this amounts to one DWI arrest for every 772 reported episodes of drink-driving (7).

How many drivers killed in traffic crashes were drinking alcohol?

According to NHTSAs Fatality Analysis Reporting System (FARS) (17), 38% of fatally injured drivers in 2009 were drinking (BAC ≥0.01 g/dL), 33% were illegally intoxicated (BAC ≥0.08 g/dL), and 15% had very high BACs (≥0.20 g/dL).

Risk of a crash at various BAC levels

The risk of a driver being involved in a crash while at various BAC levels was determined recently in a case–control crash risk study (18). Drivers involved in property damage and injury crashes were given breath tests to measure their BACs.

One week later, at the same crash location, same time, same day of the week, two drivers on the roads were stopped and breath tested for their BACs. This allowed researchers to determine the relative risk of being in a crash at different BAC levels. The relationship is shown in Table 20.1, which displays the rise in crash risk as the BAC increases based on the study (see also (19)). The risk of being involved in a crash was significantly elevated at BACs of 0.05 g/dL and higher. Such relative risk studies (see also (20)) have encouraged the adoption by national legislatures in European countries and by state and provincial legislatures in the United States, Canada, and Australia of so-called illegal per se laws. These laws make it an offence to drive with a BAC at or higher than a specific limit, such as 0.08 g/dL (United States, Canada, and United Kingdom) or 0.05 g/dL (Australia, most of Europe) or 0.02 g/dL (Sweden).

Table 20.1 Relative risk of a driver being involved in a traffic crash by BAC level

Driver BAC (g/dL)	**Relative risk of being in a crash (relative to BAC = 0.00)**
0.00	1.00
0.01	1.03
0.02	1.03

0.03	1.06
0.04	1.18
0.05	1.38[a]
0.06	1.63
0.07	2.09
0.08	2.69
0.09	3.54
0.10	4.79
0.11	6.41
0.12	8.90
0.13	12.60
0.14	16.36
0.15	22.10

0.16	29.48
0.17	39.05
0.18	50.99
0.19	65.32
0.20	81.79
0.21	99.78
0.22	117.72
0.23	134.26
0.24	146.90
0.25+	153.68

[a] Statistically significant beginning at this BAC.

Data from Compton et al., Crash risk of alcohol impaired driving, in Mayhew DR and Dussault C (eds) *Proceedings of Alcohol, Drugs & Traffic Safety—T 2002: 16th International Conference on Alcohol, Drugs & Traffic Safety*, August 4–9,

2002, pp. 39–44, International Council on Alcohol, Drugs and Traffic Safety (ICADTS), Montreal, Copyright © 2002 and *Journal of Safety Research*, Volume **40**, Issue 4, Blomberg et al., The Long Beach/Fort Lauderdale relative risk study, pp. 285–292, Copyright © 2009, Elsevier.

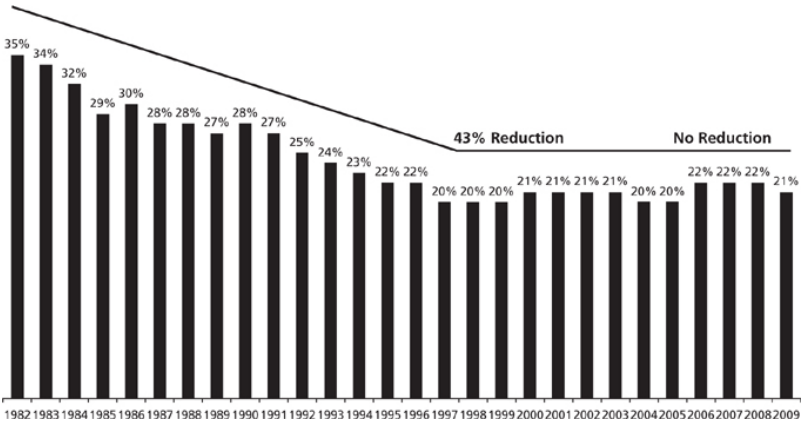

Figure 20.2 Percentage of all drivers involved in fatal crashes estimated to have been legally intoxicated (BAC ≥0.08 g/dL), 1982–2008.

Data from *Fatality Analysis Reporting System (FARS): Detailing the Factors Behind Traffic Fatalities on our Roads*, National Highway Traffic Safety Administration, Washington, DC, USA, 2011. NHTSA documents are public information and not copyrighted. Available from <http://www.nhtsa.gov/FARS>.

Drinking and driving resulting in fatal crashes

Alcohol has historically been involved in a substantial proportion of fatal crashes in the United States. The BACs of drivers in fatal crashes has provided the best system for measuring drink-driving trends over the last three decades, which clearly show progress in reducing the problem. All fatally injured drivers with alcohol levels higher than the current legal limit in the United States (BAC ≥0.08 g/dL) dropped from 49% in 1982 to 32% in 1997—a 35% relative decline. Since 1997, that percentage has remained at 32–33% through 2009. A similar decline occurred for fatally injured drivers with extremely high BACs (≥0.20 g/dL), with stagnation between 1997 and 2009. The ratio of drinking drivers to non-drinking drivers in fatal crashes, a common research measure of the problem, declined from 0.69 in 1982 to 0.32 in 1997—a 54% decline. That ratio has remained at 0.32–0.35 from 1997 to 2009.

Another important measure of the impaired-driving problem in the United States is the proportion of all drivers (fatally injured and surviving) involved in fatal crashes with BACs ≥0.08 g/dL. Although that proportion decreased substantially between 1982 and 1997 (by 43%), it has remained at 20–22% since (Figure 20.2) (17).

Approaches to reducing impaired driving

In the early 1980s, the public's attitude toward drink-driving was substantially transformed. Citizen activism, expressed through organizations such as Remove Intoxicated Drivers and Mothers Against Drunk Driving, is usually credited for

this change that stimulated the passage of key drunk-driving legislation by the states and by the US Congress (21). Among the laws initiated or expanded during the 1980s and 1990s that have proven effective in reducing impaired-driving fatal crashes are (i) administrative licence revocation laws providing for swift suspension of the
driver's licence upon arrest for DWI; (ii) laws lowering the legal BAC limit for driving from 0.10 to 0.08 g/dL; (iii) laws raising the minimum legal drinking age (MLDA) to 21 nationwide; (iv) zero-tolerance laws that make any measureable BAC illegal for drivers aged 20 and younger; and (v) vehicle sanction laws providing for vehicle immobilization, impoundment, or forfeiture for a DWI conviction. The failure of the proportion of fatally injured drivers with 0.08 g/dL BACs to decline since 1997 indicates the need for increased attention to impaired driving. Opportunities to reduce alcohol-related road injuries and deaths are discussed under three broad headings: primary, secondary, and tertiary prevention.

Primary prevention: reducing risky drinking

Except for the studies on the effect of raising the MLDA to 21, traffic safety policy-makers in the United States have mostly neglected the opportunities to reduce impaired driving by reducing risky drinking. Recent research suggests that at least two areas can potentially influence risky drinking and merit more attention by policy advocates.

Problems related to early onset of drinking

Grant and Dawson's (22) and Hingson et al.'s (23) studies of young people who began regular alcohol consumption in their early teens (aged 13–14) found they are at a substantially higher risk of becoming alcohol dependent and of being involved in alcohol-related crashes than youth who start drinking alcohol later. This higher risk of early-onset drinking has been supported by the research on brain development, indicating that brain cells continue to grow and differentiate into the early twenties (24). This continued development of the brain up to about age 25 is also linked to a lower perception of risk by youth. The growing understanding of the risk of underage drinking, especially early-onset drinking, may provoke new attention and energy to enforcement strategies that reduce underage drinking.

Brief interventions to reduce risky drinking

Screening and brief interventions (SBI) in primary medical care facilities (25) and in college health clinics (26) have been shown to result in at least short-term behavioural changes regarding risky drinking. The potential benefits of SBI have been constrained by the limited time physicians have to conduct them. This problem can be reduced by a change in Medicare (US national social insurance) rules that will let physicians charge for such interventions and by having the SBI conducted by nurses and other caregivers. This area clearly has outstanding potential for reducing risky drinking in the near future.

Secondary prevention: reducing drink-driving

Preventing drinkers from driving after consuming risky amounts of alcohol remains a difficult problem. Two general deterrence legislative initiatives and an enforcement initiative have some potential for reducing alcohol-related driver deaths.

Graduated driver licensing for novice drivers

The high crash rate of novice drivers in the first few months of driving has led to the development of a three-staged entry system into full licence status that has effectively reduced driver fatalities among 16- and 17-year-olds. Evidence indicates that this graduated driver licensing (GDL) system effectively reduces all types of crashes during the first year of driving (27). The demonstrated effectiveness of GDL should stimulate states to enhance their current laws to ensure they contain
all the recommended GDL elements, which can lead to increased benefits in the future (e.g. nighttime driving restrictions and teen passenger limitations). To obtain maximum effectiveness, GDL laws rely on parental supervision.

Lowering the legal BAC limit to 0.05 g/dL

Lowering the legal BAC limit has led to a reduction in alcohol-related fatalities (28). This has been demonstrated by the successful reduction of the BAC limit to 0.08 g/dL in the United States and to 0.05 g/dL in Australia (29).

Increased use of high-visibility enforcement

Overall, the proportion of drivers in fatal crashes who are intoxicated has not declined significantly since 1997, suggesting we need either more effort or improved methods to increase the general deterrent effect of enforcement. Two programmes appear to have promise: (i) community efforts to enforce alcohol policies and laws against serving alcohol to underage drinkers and obviously intoxicated patrons, and (ii) mini-checkpoints (with fewer officers) using passive alcohol sensors, accompanied by publicity (30). Effective DWI enforcement programmes require substantial support for traffic law enforcement by both the community and the local government.

Many research studies funded by NHTSA—the federal agency leading the national effort to reduce impaired driving—have been published as governmental reports. Several procedures and devices that enhanced the efficiency of the criminal justice system have developed from these projects. For example, a list of vehicle manoeuvres which alert officers that drivers are possibly intoxicated was developed (31), as was a three-component standardized field sobriety test (SFST) that could be used at the roadside and has come into use nationwide (32).

Tertiary prevention: reducing impaired-driving recidivism

Although appropriate treatment remains the key to recovery for drivers with alcohol-abuse problems, the most promising measures have focused on strategies that keep repeat convicted DWI offenders from driving while impaired by

alcohol. These strategies include impounding the vehicles of convicted DWI offenders, assigning alcohol ignition interlocks to the vehicles of convicted DWI offenders (33), and monitoring offenders' alcohol consumption through intensive supervision probation (34) or through technology (e.g. alcohol-monitoring systems based on transdermal alcohol sensing) (35).

Vehicle sanctions

Vehicle impoundment legislation as a sanction for DWI and DWS (driving while suspended) offenders has effectively reduced recidivism and crash involvements (36).

Alcohol ignition interlocks

There is extensive evidence that alcohol ignition interlocks (AIIs) are effective in reducing recidivism by 65% while on the offender's vehicle (33). However, many convicted DWI offenders either do not have a vehicle or claim not to own a vehicle; thus, the AII is not installed. Evidence suggests that it will be necessary to threaten to impose a less desirable sanction, such as house arrest, as the alternative to the interlock to motivate most eligible offenders to install the AII units (37). If the low rate of participation in the interlock programme can be overcome, this technology shows promise for producing a significant reduction in DWI recidivism.

Traditionally, alcohol consumption has been monitored through breath or urine tests. During the last decade, however, methods have been developed for measuring the approximately 1% of ingested alcohol that is lost through perspiration on the skin. This has opened the possibility of continuous monitoring of drinking (38, 39). One such device—the SCRAM™—is already used with more than 10,000 offenders in the United States and Canada according to the manufacturer, Alcohol Monitoring Systems, Inc. Currently, the technology is relatively expensive, and although tested in a laboratory setting (35), it has not been used long enough in the field to determine whether it reduces recidivism. Devices of this type can potentially keep DWI offenders from impaired driving, yet minimally affect their employment, their families, and their lifestyle.

Other drugs

There is growing evidence that drugs other than alcohol are also contributing to road injury in the United States and around the world. There is strong evidence that drugs other than alcohol can impair skills related to driving (40). The data come from laboratory studies (41), from studies of crash-involved drivers (42), and from individuals with medical conditions (43). However, the relative risk of crash involvement for specific substances, particularly illegal drugs, such as those on the US National Institute on Drug Abuse (NIDA) Schedule I, have yet to be determined in a case–control study. Thus, although there is strong reason to believe that use of Schedule I drugs by drivers increases their

crash risk, the extent of the problem has not been defined (44).

The future of alcohol-impaired driving

New technological developments promise vehicle systems that may eventually make alcohol-impaired driving extremely rare. One of the passive monitors for alcohol in the breath of the driver makes it unnecessary for the driver to blow into an interlock breath tube (45). Another developing technology measures BAC passively through the skin, providing a substitute for blowing into the interlock (46). A consortium of government and private industry is funding the development of such systems called the 'Driver Alcohol Detection System for Safety'.

These systems may have value as a method for activating a driver interlock system when detecting a drinking driver in the vehicle. Thus, the near future offers the possibility of equipping all new vehicles with a system that would make impaired driving unlikely. If such technology were to become available, several issues would need to be resolved. Would the marketplace and consumer demand dictate its widespread use? Would the government be willing to mandate such devices on all vehicles? Would such units containing relatively sensitive equipment prove to be reliable over a new vehicle's typical life in the United States? Regardless of whether such devices come to fruition, advanced alcohol-sensing technology will clearly contribute significantly to alcohol safety in the future.

Conclusions

The United States has demonstrated that alcohol-impaired driving traffic injuries and deaths can be substantially reduced. Between 1982 and 1997, the ratio of drinking to non-drinking drivers in fatal crashes decreased by 54%, but since then, progress has ceased. As reported by an expert study committee sponsored by the Transportation Research Board (47), the United States has fallen behind many countries in its countermeasures for impaired driving. Lowering the legal BAC limit
to 0.05 g/dL has been accomplished by many countries without any economic crises (as US alcohol and hospitality industries claim). Random breath tests are routinely conducted in Europe and Australia, yet few US states and communities conduct sobriety checkpoints with any frequency. Automated speed enforcement using cameras reduced traffic fatalities in France by 50%, within three years, including alcohol-related fatalities. The United States must face reality: progress in reducing impaired driving depends upon the adoption of some of the measures described.

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Chapter 21
Alcohol and suicide

Alexander E. Crosby, Victoria Espitia-Hardeman, LaVonne Ortega, and Briana Lozano

Introduction

Excessive alcohol consumption is associated with multiple adverse health outcomes, including unintentional injuries and violence, and ranks third among modifiable behavioural risk factors contributing to mortality (1, 2). Fatal and non-fatal suicidal behaviour presents major challenges to the public's health throughout the world. In the United States for instance, suicide has ranked among the top 12 leading causes of death since 1975; in 2010, it was the tenth leading cause of death overall, responsible for 38,364 deaths (rate: 12.1 per 100,000 population) or approximately one death every 15 minutes (3). The National Electronic Injury Surveillance System collects data on non-fatal injuries treated in a nationally representative sample of hospital emergency departments in the United States. During 2010, an estimated 487,770 persons were treated in the United States for non-fatal, self-inflicted injuries (rate: 159.6 per 100,000 population) (3). Self-report data are also useful in understanding morbidity. The National Survey of Drug Use and Health asks respondents aged 18 or older about suicidal thoughts and behaviour. Annual averages of combined 2008 and 2009 data found an estimated 8.3 million adults aged 18 or older (3.7% of the adult population) reported serious thoughts of suicide in the past year and 1.1 million (0.5%) reported attempting suicide (4). The Youth

Risk Behavior Surveillance System, a school-based system, has measured health risk behaviours (including suicidal thoughts and behaviour) among high school students in grades 9–12, aged approximately 14–18 years. In 2011, 15.8% of students in the United States reported that they had seriously considered suicide and 7.8% had made a suicide attempt during the 12 months before the survey (5).

Alcohol consumption has been consistently shown in research as one of the most important risk factors for suicidal behaviour (6) and its effect reaches across the range of demographics in US society (7). The Alcohol-Related Disease Impact (ARDI) system is one method of estimating the number of alcohol-attributable deaths (AADs) and years of potential life lost (YPLLs) due to alcohol. ARDI estimates AADs by multiplying the number of deaths from a particular alcohol-related condition by its alcohol-attributable fraction. YPLLs, a commonly used measure of premature death, are then calculated by multiplying age- and sex-specific AAD estimates by the corresponding estimate of life expectancy. From 2001 to 2005, an estimated annual 79,646 AADs and 2.3 million YPLL were attributed to the harmful effects of excessive alcohol use (8). An estimated annual 7,266 AAD and 243,018 YPLL were associated with suicide specifically (8).

Theories and empirical studies linking alcohol and suicidal behaviour

While many authors agree that both acute and chronic alcohol use are associated with suicidal behaviour, the explanation for this association is still debated. Rogers (9) presents a

comprehensive model for understanding the relationship between alcohol consumption and suicidal behaviour, which includes its pharmacological effects, its social environmental consequences, its influence on cognitive processes, and the interactions of these three components. Steele and Josephs (10) discuss the concept of 'alcohol myopia' to explain the diverse consequences of alcohol consumption defined as alcohol's general impairment of awareness and reflection that happens when alcohol is consumed. This cognitive effect of alcohol consumption is evident even at low blood alcohol levels, indicative of moderate social drinking, and is exacerbated with increasing consumption. Sher (11) elaborates on the concept that impulsivity and aggression are strongly implicated in suicidal behaviour. Constructs related to aggression and impulsivity confer additional risk for suicidal behaviour in people with alcohol dependence.

The description of the association between acute alcohol use and suicide also has multiple theories including the following: decedents of suicide have high rates of positive blood alcohol; intoxicated people are more likely to attempt suicide using more lethal methods; and alcohol may be important in suicides among individuals with no previous psychiatric history (12). Cherpitel et al. recommend that several confounding factors must be considered in examining the effect of acute alcohol consumption, with or without intoxication, on suicidal behaviour, such as alcohol dependence, concurrent use of other substances, and co-morbid psychiatric disorders (12). Huf-ford (13) proposes the concept of alcohol distal and proximal risk factors for suicidal behaviour. Distal risk factors include alcohol dependence, psychological disorders, and negative life events (interpersonal loss), which may precede suicidal behaviour.

The concept states that proximal risk factors determine the timing of suicidal events by translating the statistical potential of distal risk factors to action. Without proximal risk factors, distal risk factors may never be realized and will remain a statistical abstraction. Possible mechanisms explaining how alcohol intoxication increases the proximal risk of suicidal behaviour include increased psychological distress, increased aggressiveness, suicide-specific alcohol expectancies, and cognitive constriction which impairs the generation and implementation of alternative coping strategies.

Prevention and intervention

Some theories point to alcohol as a moderator for suicidal behaviour due to its link with psychiatric illness, depression, social isolation, and other significant suicide-related risk factors (9). These ideas make alcohol-related interventions a valid target for suicide prevention and intervention measures. Previous studies and systematic reviews have assessed the efficacy of alcohol reduction interventions. However, most of the study designs that have examined violence as an outcome have primarily focused on evaluating alcohol's effects on interpersonal violence such as assaults, intimate partner violence, homicide, and child maltreatment, or unintentional injuries like motor vehicle collisions; very few have examined effects on suicidal behaviour.

Clinical research shows that brief interventions in a variety of settings, such as primary care, emergency departments, prenatal care, criminal justice system, and college, can decrease alcohol consumption, and these work in a variety of populations—younger and older adults, men and

women (14). In addition, the US Task Force on Community Preventive Services (Community Guide) recommends increasing alcohol taxes as a strategy to prevent excessive alcohol consumption (15, 16). A study conducted by Markowitz et al. (17) suggested that as little as a 5.5 cent increase in the US beer tax would save one adolescent or young adult male life from being lost to suicide per year in each state. A similar intervention in Australia supports this model (18). Reducing alcohol use in problem drinkers is also effective. A one-year experimental, extended aftercare intervention of discharged patients from a hospital-based alcohol treatment facility in the United States, demonstrated reduced suicide attempts in participants (19).

Other effective alcohol reduction strategies recommended by the Community Guide are enhanced enforcement of laws prohibiting sales to minors, maintaining limits on hours and days of alcohol sales, and dram shop liability (historically, a dram shop referred to any establishment where alcohol was sold). These Community Guide recommendations are specific for reducing alcohol use but implementation of similar strategies has reduced suicides. In Slovenia, establishing a minimal purchasing and drinking age of 18 and limiting the locations and times of alcohol sales resulted in a 10% reduction in male suicides (20).

Conclusion and public health implications

Excessive alcohol consumption is a contributing factor to many forms of violent behaviour (18). The two public health concerns of excess alcohol consumption and suicidal behaviour pose direct threats to the individuals involved and

to their families, community, and society. Though much research has been conducted establishing the association between alcohol use and suicidal behaviour, further studies are needed to fully understand the mechanisms through which alcohol influences this behaviour and the specific effect of alcohol-related interventions on suicidal actions (18). These areas of research may benefit prevention efforts by showing the potential dual impact of reducing alcohol-related suicide and decreasing non-suicide-related alcohol health problems.

In the section 'Prevention and intervention', evidence-based clinical and community level interventions for alcohol reduction have been described. This suggests that prevention approaches can integrate both alcohol and suicidal behaviour prevention efforts. A few programmes have demonstrated reductions in suicidal behaviours and alcohol consumption (21) but there have been few efforts to measure suicide-related outcomes from other proven alcohol interventions. A major obstacle to an integrated prevention approach that addresses both alcohol-related problems and suicidal behaviour is topic-specific funding and research which can hinder collaboration across fields. Increasing collaboration across disciplines can help facilitate research and programme development which, in turn, may lead to progress on multiple health problems that can be addressed by comprehensive prevention efforts.

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Chapter 22
Alcohol and intimate partner violence

Megan R. Gerber

Introduction

Intimate partner violence (IPV), defined as physical, sexual, or psychological harm by a current or former partner or spouse (1), is a critical global public health concern (2). IPV can occur among heterosexual or same-sex couples and does not require sexual intimacy. Worldwide, IPV is the most common form of violence against women; a World Health Organization (WHO) multi-country study estimated that 15–71% of women have experienced abuse in their lifetimes (1, 3).

Although IPV affects both men and women and is present in same-sex relationships, the overwhelming majority of incidents and injuries occur between men and women, with women more likely to be victims (4) and to sustain more serious injury (5–7). Female-perpetrated IPV tends to be motivated by self-defence or fear, while male perpetrators more frequently have control as a motive (7). IPV impacts persons from all socio-economic classes and some work suggests higher prevalence among certain ethnic groups (8). In the National Survey on Drug Use and Health (NSDUH), black and Hispanic participants were more likely to have experienced IPV in the preceding year (9).

IPV has well-established adverse physical health effects that include acute traumatic injuries as well as more chronic presentations including chronic pain syndromes (10–12), irritable bowel syndrome (13), and poor pregnancy outcomes (14, 15). Mental health sequelae include depression, posttraumatic stress disorder, anxiety disorders, and suicide (16–19). IPV has long been associated with substance use, most notably alcohol use, and indeed may be the type of violence most strongly linked to alcohol (20). Alcohol use appears to increase the occurrence, chronicity, and severity of IPV (8, 21–26).

The link between alcohol use and IPV is consistent internationally and across cultures. When one or both partners had problems with alcohol, both the WHO multicountry study (27) and the 13-country Gender, Alcohol and Culture Study (GENACIS) (28) found higher rates of IPV across the sampled sites. The relationship between alcohol and IPV has been demonstrated in both population samples (8, 18, 22, 25) and clinical studies (29–31).

Despite the evidence supporting the association between alcohol and IPV, it remains a challenge to establish causality. Moreover, the alcohol and IPV relationship is controversial due to challenges in study design and concern among advocates about absolving perpetrators from accountability or misleading victims into inferring safety when no alcohol is consumed (26).

Background

Alcohol is a known risk factor for many forms of aggressive and violent behaviour (26). While many episodes of IPV appear to involve alcohol, it can be difficult to establish the temporal relationship between alcohol consumption and the abuse, in part because studies rely on self-report by victims and perpetrators and because many studies have used cross-sectional study design which cannot establish causality (24). Measurement of alcohol use also varies; history of use may indicate
an alcohol problem while incident use anchors alcohol intake to the specific IPV occurrence (32). Methodology that collects data from both partners may reduce under-reporting of IPV (8).

Estimates of alcohol use in the setting of IPV vary widely between 25% and 50% of incidents (25, 33). A meta-analysis confirms that alcohol and IPV are associated for both genders (26); at the time of an assault, men are drinking 6–57% of the time and women 10–27% of the time (34). Higher rates are seen in alcohol treatment populations; the rate of IPV in alcoholic males in the year prior to entry to alcohol treatment is 44–60% (35–37). In medical settings, problem drinking is a marker for IPV; the predicted probability of IPV when problem alcohol use was reported was 21% for 12-month and 43% for lifetime abuse (38). Thus, while alcohol has not been definitively identified as causal in IPV, it is clearly a correlate and provides potential points of intervention and prevention (33).

Conceptual models underlying the association

The neurobiological mechanisms of the relationship between alcohol and aggression are numerous and complex; detailed discussion is beyond the scope of this review. Alcohol use and abuse are well-known risk factors for multiple forms of violent and aggressive behaviours (26). Laboratory studies have consistently demonstrated the link between alcohol and aggression (39–41). Numerous conceptual models have been advanced to explain how alcohol consumption might increase aggression, and thus IPV; a brief review is included here.

The disinhibition (or proximal effects) model holds that human aggressive tendencies are normally held in check by inhibiting forces. Alcohol is thought to increase the likelihood of aggressive behaviour through direct pharmacological effects on the brain (26, 33, 42). Although alcohol has been shown to directly affect parts of the brain involved in impulse control, experimental studies do not support the hypothesis that alcohol's pharmacological effects alone increase aggressive acts (41). The multiple threshold model, holds that alcohol may have a variable psychopharmacologic impact on individuals with differing personality traits thus resulting in shifting likelihood of IPV after alcohol consumption (26). Individuals with few risk factors will have a minimal association between alcohol and IPV while those with moderate risk may experience enough disinhibition with drinking alcohol to engage in IPV. Those with high levels of risk may be above threshold without drinking and intoxication may increase the likelihood of severe IPV (43).

The cognitive impairment/distortions model (33) postulates that alcohol contributes indirectly to increased aggression by

causing cognitive, emotional, and psychological changes that may reduce self-awareness, alter judgement, or result in inaccurate assessment/perception of risks (33, 41).

Another commonly applied construct is the indirect effects model (26) which asserts that alcohol has a causal relationship with aggression that is mediated by other variables, such as the quality of the marital relationship. Studies have shown that the alcohol–IPV relationship persists after controlling for marital discord, a finding that undermines the strength of this model (44). While these theories are variably supported by basic and social science research, further study is necessary to better understand the mechanisms by which alcohol consumption is associated with IPV.

IPV perpetration and alcohol use

In a study of abuse of multiple substances, alcohol disorders were the most prevalent use disorders among IPV perpetrators (21). An examination of IPV-related homicides demonstrated alcohol in forensic toxicology data for 70% of suspects (44). While alcohol is associated with IPV perpetration for males (MFPV) and females (FMPV) (8, 26), more attention has been focused on MFPV. Approximately one-third of IPV incidents involve alcohol use by men who are more often drinking than women (8). Increase in both number of IPV assaults and severity has been associated with incident drinking by a male perpetrator (44, 46). A number of studies support the concept that quantity of alcohol consumed significantly determines IPV perpetration; in a metaanalysis, problem drinking was more closely associated with IPV than

alcohol use itself (26). In alcoholic and known batterer samples, the odds of IPV aggression were eight to 11 times higher on days of drinking even after control for personality traits and relationship discord (44). It follows that alcohol use also figures prominently in IPV recidivism; the most influential risk factor for re-assault after entry to a batterers' programme was a man's intoxication and not drinking per se (47).

FMPV similarly shows a clear trend towards increased risk of assault with alcohol use. A metaanalysis found a small but significant effect size for alcohol use and FMPV (26). As with MFPV, quantity consumed increases risk of FMPV. In one large population-based study, binge drinking was associated with perpetration by women but not by men (21). In an urban emergency department, the adjusted odds of an abused woman drinking while perpetrating IPV increased 1.4 times for every five drinks consumed weekly (48).

Some data suggests that ethnicity plays a role in alcohol use and IPV perpetration. In the National Alcohol Survey (8, 22), both MFPV and FMPV were examined across ethnic groups. Black couples exhibited the highest rate of both and alcohol consumption was higher among them (22). These relationships persisted after control for other sociodemographic variables, but may not generalize across cultures.

IPV victimization and alcohol use

As with IPV perpetration, alcohol is the most commonly found substance use disorder among victims (21). Female

alcohol use increases the risk of MFPV (25) and female IPV victimization is frequently recurrent and associated with heavy alcohol use (14). Perpetrator alcohol use is associated with an increased probability of injury to the victim (49). It has been suggested that alcohol problems may be a consequence of IPV victimization and that alcohol use can increase over time after abuse (50) as a form of self-medication (29). Conversely, other studies have demonstrated a relationship between IPV and baseline problem drinking among abused women and their partners (44, 51).

Alcohol use figures prominently in reports of female and male IPV victims. In the United States' population-based National Violence Against Women Survey (NVAWS), 33.6% of female IPV victims reported partners' alcohol use during the assault, while one-fifth of male victims (21.8%) reported incident use by partners. The male victims reported using alcohol themselves 20.8% of the time. Female victims were more likely to be physically injured if their partners had been drinking alcohol (32).

Findings from an urban emergency department demonstrated that abused women who drank while victimized consumed more alcoholic drinks per week and were more likely to be alcohol dependent than victims who were not drinking at the time of victimization (48). Abused women generally drink more, report feeling more intoxicated, and have higher blood alcohol levels on days of victimization (52). Quantity consumed has an impact: the odds of an abused woman drinking while victimized increased 1.3 times for every five drinks consumed weekly (48).

Relationship dynamics also play a key role; injured women admitted to a trauma centre demonstrated a gradient of 12-month IPV prevalence based on drinking in the dyad. When both partners were non-problem drinkers the prevalence of severe IPV was 4.9%; when the woman was the only problem drinker rates increased to 28.6%; and when the male partner was the only problem drinker rates were reported at 35.7%. Finally, when both partners had alcohol problems,
the rate jumped to 73.7% (31). In other studies, victims' alcohol use is frequently correlated with that of the abusive partner (8). Binge drinking has been related to IPV victimization for both genders (21).

Researchers have also examined the impact of alcohol use on reporting IPV to the police, since reporting can result in improved psychological well-being and safety (32). Alcohol use by a perpetrator has been found to increase the likelihood that a victim will report an abusive episode (53). Overall, women report IPV to police at higher rates than men (32).

Finally, it is important to emphasize that these data demonstrating associations between alcohol use and victimization do not imply that victims are culpable but rather demonstrate vulnerability (54) and a potential point of intervention to reduce violence and injury.

IPV in alcohol treatment

Examination of IPV in alcohol treatment settings has elucidated potential opportunities to intervene. The majority of treatment studies have been conducted in the United States.

Evidence suggests that IPV is positively associated with seeking treatment for alcohol problems. In the NSDUH the prevalence of alcohol treatment was greater by nearly twofold among those reporting any IPV when compared to respondents who were negative for IPV exposure (9). Victimization was correlated with treatment seeking but perpetration was not, potentially suggesting that victims may blame themselves for the violence or feel that they can control it by improving their own behaviour (9).

In a multisite study of alcoholic men seeking treatment (37), 44% reported one or more acts of IPV in the preceding year. Only 17% received a referral to an IPV treatment programme from their alcohol treatment provider. Of those referred, only 13% actually enrolled in IPV treatment; all of those complying were involved in the criminal justice system. Importantly, the authors concluded that the lack of referrals likely stemmed from assessment failures rather than failure to refer when IPV was detected (37).

Alcohol interventions have been shown to produce decreases in IPV even without specifically targeting the violence or relationship discord (55, 56). A study of an intensive partial hospital treatment programme for alcohol dependence and use among alcoholic women and their male partners demonstrated both a decrease in alcohol use and reductions in both MFPV and FMPV (57). A similar study demonstrated reductions in IPV among males treated for alcohol dependence (56). These studies also demonstrated an association between relapse and continued IPV. A year after treatment, recovered alcoholic men had a violence rate comparable to the comparison (non-drinking) group, while relapsed alcoholics had more than double the rate (55).

The observation that risk of IPV appears to increase when there is concordance in drinking patterns among partners (51, 58) has led to couples' interventions. Hesitations regarding this approach are understandable; in a qualitative study of barriers to entry to couples treatment for alcohol problems, some participants feared that treatment would increase risk of IPV (59). Use of behavioural couples therapy (BCT) is controversial due to concerns about increasing IPV risk, so this intervention is usually employed in couples engaging in low-to-moderate levels of IPV (54). BCT teaches communication and problem solving skills to reduce conflicts that may escalate to violence. In this model, clinicians inquire about IPV and set goals to reduce future occurrences (54).

A number of studies have demonstrated promising reductions in IPV after alcohol treatment combined with BCT (36, 55). In a randomized trial with alcoholic women and their non-substance-abusing male partners, those who received BCT along with standard individual alcohol treatment reported fewer days of drinking in the subsequent year and reduced IPV (60).

Another promising intervention is community reinforcement and family training (CRAFT) which examines both the antecedents and consequences of IPV for the victim and is increasingly used in Europe and the United States (61). Victims are taught coping skills to avoid escalating stressful situations. The training encourages active family participation and enables intimate partners to play an important role in persuading substance-using IPV perpetrators to enter and remain in treatment (61).

Prevention

The association between alcohol and IPV suggests that men and women who misuse alcohol may be an ideal target audience for violence prevention efforts (62). A number of universal and selected prevention programmes have targeted general violence reduction among alcohol abusing populations suggesting that this strategy could be useful in preventing IPV (62). Improvement in IPV assessment and referral practices within alcohol treatment settings is clearly needed, although the finding that men given such referrals rarely follow through suggests that combining IPV and alcohol treatment whenever possible may be a more effective strategy (37).

Restriction of alcohol availability has had promising results. A law enacting earlier closing hours for bars in Brazil was correlated with a reduction in IPV-related homicides and a trend toward reduced IPV (63). Conversely, alcohol taxation has not been shown to reduce IPV (64).

An expanding body of work that examines alcohol context—where alcohol is consumed—may also inform prevention efforts. A study in St Petersburg, Russia, demonstrated that those who drank publically on streets or in parks had over five times the odds of perpetrating IPV (65). Ecological research demonstrates a relationship between IPV and density of alcohol outlets (66–68). A number of social mechanisms may underlie this connection providing potential opportunities for public health and policy intervention through possible changes in zoning, law enforcement, and community action/education (67).

Conclusion

The relationship between IPV and alcohol is irrefutable and complex. The association significantly impacts both IPV perpetration and victimization. Promising interventions include combining behavioural couples treatment with alcohol treatment when appropriate. Legal and zoning interventions to limit availability and access to alcohol may provide important temporizing effects as well. Expanding awareness of the alcohol and IPV link will hopefully fuel further intervention trials and prospective studies while promoting study of prevention efforts globally.

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Chapter 23
Alcohol and crime

Stephen K. Talpins, Robyn Robertson, Erin Holmes, and Matthew Dunagan

Introduction

When most people think about alcohol and crime, they think of impaired driving—and with good reason; in 2009, an estimated 22% of people killed in motor vehicle crashes in the United States—approximately 10,839 people—were killed in crashes where at least one driver had a blood alcohol content (BAC) of 0.08 g/dL or higher (1). However, alcohol is frequently a factor in the commission of many other types of crimes. Indeed, alcohol plays a role in a significant percentage of crime, particularly violent crimes, worldwide (2). This has important implications for the strategies applied to mitigate and minimize criminal behaviour.

Historically, there have been two equally important goals of the justice system—to deter future offending through the application of sanctions and to encourage offender rehabilitation and behaviour change. In reality, a much greater emphasis has been placed on the use of sanctions and deterrence, frequently to the detriment of rehabilitative efforts. As evidence of this, offenders are inconsistently screened, assessed, or treated for substance misuse issues. This, in part, has contributed substantially to the extraordinarily high recidivism rates in the United States and elsewhere. This chapter summarizes the magnitude of alcohol

misuse-related crime and describes new approaches that hold considerable promise to better achieve the objectives of the justice system by striking a balance between its competing goals.

The relationship between alcohol and crime

Alcohol does not cause or commit crime—people do (the majority of those who consume alcohol do so responsibly) (3). However, many offenders have significant alcohol misuse issues that contribute to offending behaviour. Unfortunately, most countries are not well equipped to measure the magnitude of the problem for a variety of reasons. Nonetheless, based on available data, the World Health Organization estimates that approximately 20–30% of homicides committed around the world are alcohol misuse-related (4). Not surprisingly, the rates are highest where alcohol consumers are most apt to drink to intoxication (2). For example, 60% of those arrested for homicide in Scotland in 2002 'were drunk at the time of the offence' (5), while almost 75% of those arrested for homicide in the Russian Federation in 1995 consumed alcohol prior to the offence (4).

Studies and surveys in the United Kingdom and United States provide significant insight into the problem. In the United Kingdom, a 1997 study estimated that 63% of sentenced males and 39% of sentenced females were drinking at 'hazardous' levels in the years before entering custody (5). Furthermore, 15% of the inmates participating in the 2003 Crime and Justice Survey reported

that they had consumed alcohol at the time of the offence (17% reported having taken alcohol and other drugs) (5).

In the United States, offenders report alcohol misuse issues at a similarly alarming rate. In a 2002 survey (6) of inmates serving time in local or county jails, over 46% indicated that they suffered from alcohol dependence or abuse, almost 40% reported having recurrent social or interpersonal problems (including 'arguments/problems with spouse, intimate, family or friends or get[ting] into physical fights') because of alcohol misuse, and 33% admitted drinking at the time of their offence. In a 2004 survey of state and federal prisoners serving time for a violent offence, almost 37% indicated that they were under the influence of alcohol at the time of the offence (7).

While it is impossible to fully measure the extent of alcohol-related criminal behaviour, much less to appreciate the pain and devastation wrought by offenders who misuse alcohol, it is evident that estimates of the economic cost are substantial; alcohol misuse-related crime in many Western countries often costs their societies the equivalent of over $1 billion a year (8). In the United States, estimates approach an astonishing $84 billion (9).

Unfortunately, rehabilitation and treatment often are not priorities in sentencing. Despite the fact that justice professionals provide more referrals for treatment than any other source in the United States—they constitute an estimated 40–50% of referrals to community-based treatment programmes (10)—offenders with substance misuse issues are still identified inconsistently and treatment strategies are not uniformly applied (11–13). To illustrate, it has been

suggested that the current treatment capacity requires a fourfold increase to accommodate all offenders referred for treatment (14).

Unsurprisingly, without treatment interventions to address alcohol misuse in relation to offending behaviour and support long-term risk reduction, recidivism rates are extraordinarily high. In the United States, for example, researchers reviewed data relating to approximately 300,000 prisoners released from 15 states in 1994. Approximately 52% of the offenders returned to prison within three years of their release (67.5% were rearrested) (15). In 2011, the Pew Charitable Trusts examined recidivism data from 1994 to 2007. It found that the three-year return rate hovered around 40% when it excluded California (16). Although we cannot attribute the high recidivism rate exclusively to the failure to treat offenders' substance misuse issues, the general failure to adequately address offenders' needs on a larger scale cannot be overlooked.

Alcohol misuse cannot be understood or addressed in isolation; offenders who misuse alcohol typically have co-occurring problems and may also suffer from drug abuse or other psychiatric disorders, often depression, anxiety, or post-traumatic stress disorder. There is no convincing data that allows us to determine what percentage of alcohol-misusing offenders have coexisting mental health challenges, but there is little doubt that many do (17). In the United States, almost one-third of offenders who were under the influence of alcohol at the time of their offences were also under the influence of illicit drugs (9). In Canada, 14% of federal inmates reported having been under the influence of

both alcohol and illicit drugs during the commission of their most serious offence (18).

Solving the problem

Incarceration alone, while a valuable tool, does not change most offenders' behaviour as evidenced by the aforementioned recidivism rates. It is known that a strong nexus exists between alcohol misuse, crime, and violence. If we effectively lower the amount of alcohol misuse, we can make great strides in further reducing crime. The debate on how to do this is usually a battle between more enforcement and increased penalties, or the need to increase funding for treatment and
rehabilitation. To sustain success in addressing the crime problem it is not necessary to substitute rehabilitation for law enforcement, or vice versa, but instead it is important to get punishment for offenders right and the way to do this is through focused deterrence. The good news is that justice professionals are now finding success through innovative community corrections programmes that successfully balance supervision, monitoring, and rehabilitation. This approach to offender management involves a requirement that offenders abstain from using alcohol and drugs, the incorporation of appropriate and meaningful treatment strategies, and the application of alcohol testing and monitoring technologies.

In the United States, three programmes have emerged that illustrate this new approach and hold tremendous promise—driving while intoxicated (DWI)/drug courts, Hawaii's Opportunity Probation with Enforcement (HOPE) programme, and the South Dakota 24/7 Sobriety Project.

Although ongoing research is needed to increase understanding of these programmes and extend our knowledge of effective delivery strategies, they appear to work well and have been identified as model programmes by the National Partnership on Alcohol Misuse and Crime (NPAMC), a public–private partnership that promotes evidence and consensus-based solutions.

Driving while intoxicated/drug courts

In 1989 in Miami-Dade County, Florida, Chief Judge Gerald Wetherington, Judge Herbert Klein, State Attorney Janet Reno, and Public Defender Bennett Brummer created the nation's first formal drug court acting as a treatment and accountability-based programme. In 2011, there were over 2,000 drug courts and their success is well documented. Participants appear in court regularly, are evaluated for alcohol and drug problems, are required to participate in treatment, and are tested regularly for drug use. Those who violate programme rules are subjected to a variety of sanctions, including incarceration. Five independent meta-analyses demonstrated that drug courts reduced recidivism by between 8% and 26% (19). The success rate of individual courts varies according to fidelity to the model and the ten guiding principles developed by the National Association of Drug Court Professionals' (NADCP) National Drug Court Institute. The most effective courts are those that are dedicated to the offenders most in need and adhere most closely to NADCP standards.

Building on the success of drug courts, judges and advocates developed DWI courts focusing on 'hard-core' impaired

drivers in the 1990s. DWI courts are operated like drug courts. However, because DWI offenders are particularly dangerous, judges tend to be less forgiving of violations. Currently, there are almost 200 DWI courts and 400 hybrid DWI/drug courts. DWI courts have not been studied as extensively as drug courts. However, three studies, including one sponsored by the National Highway Traffic Safety Administration (NHTSA), demonstrate that properly administered DWI courts can dramatically reduce recidivism (20–22). Consequently, DWI courts have been endorsed by numerous national organizations and supported by NHTSA as a promising sentencing practice (23).

HOPE

The HOPE programme is a coordinated effort between Judge Steven Alm, local probation officers, prosecutors, defence lawyers, and police that ensures immediate and rational sanctions for probation violations. Participants are not permitted to use alcohol or illegal drugs; compliance is monitored through frequent and random urine drug testing. Participants are assigned a colour and call in every day. If their colour is selected, they must appear at the local probation office and provide a urine sample. Participants are given an opportunity to engage in treatment, but are not forced to do so. Participants who violate programme rules are sentenced to short jail terms.

Those who demonstrate that they cannot or will not control their alcohol or drug abuse are required to undergo treatment—a process described as ‘behavioural triage’ (24).

A significant component of HOPE is that it greatly economizes the use of treatment resources. Unlike most treatment-based programmes, including drug courts, HOPE does not require that every participant participate in treatment. By not mandating that all drug offenders have to receive treatment at the beginning of supervision, the programme opens up scarce and expensive treatment slots for the substance abusers who are in the most need of and who are more likely to benefit from those services.

Critics of HOPE predicted the project would be a disaster—the judge would overcrowd the jail, probation officers would be swamped by having to write too many violation reports, prosecutors and public defenders would never be able to keep up with a full docket of cases and have the time to address issues that arise with modification hearings. However, none of these scenarios occurred. This feat was achieved partly by sheer will, but mostly due to the power of teamwork. The judge, probation officers, prosecutors, public defenders, and local law enforcement raised their concerns and, through open discussion, streamlined the existing processes and resolved the matters before HOPE commenced. This teamwork approach fostered positive perceptions of the programme among staff who were involved in its daily operations. Indeed, the highest levels of satisfaction with HOPE were reported by judges and probation officers (25).

Researchers compared HOPE probationers with a randomly assigned control group under a grant from the National Institute of Justice (NIJ). HOPE participants tested positive for illegal drugs far less frequently than the controls (13% versus 46%), recidivated less than half as often (21% versus

47%), and ultimately served much less time in custody (138 versus 267 days on average) during the study (26). This research shows that when offenders violate probation and the consequence for their violation comes shortly thereafter, not several months later, offenders are more likely to change their criminal behaviour. More importantly, the response to a violation does not have to be as severe as a state prison sentence.

In 2009, the Institute for Behavior and Health recognized Judge Alm for developing the programme. NIJ is funding the addition of four pilot sites on the mainland to determine the extent to which the programme and its impressive results may be replicated in other jurisdictions. As Dr. Mark Kleiman, a proponent of replicating HOPE-style probation in other jurisdictions noted, 'It would be tragic if the politics proved prohibitive, but it would be genuinely criminal if we didn't even try'.

South Dakota 24/7 Sobriety Project

The South Dakota 24/7 Sobriety Project was created by former South Dakota Attorney General Larry Long. Unlike DWI/drug and HOPE court programmes, the 24/7 Project is a state-wide programme. Current Attorney General Marty Jackley administers the programme, which is operated on the local level by the sheriffs.

Repeat DWI offenders and others with significant alcohol misuse issues may participate in the programme during pre-trial release or while on probation or parole. Participants are required to abstain from alcohol and illegal drugs. Compliance is monitored through vigorous alcohol and illegal

drug testing. Participants are required to appear at their local sheriff's department twice daily for breath alcohol testing or to wear a continuous alcohol monitoring (CAM) bracelet. In addition, they submit to regular urine drug testing or wear a drug patch. Those who test positive are incarcerated immediately, typically for one or two nights. The programme does not provide treatment. However, offenders who are convicted of DWI are required to undergo assessment for alcohol and drug problems and given treatment through alternative mechanisms under state law.

Table 23.1 South Dakota 24/7 Sobriety Project compliance rates

Twice daily breath testing	Continuous alcohol monitoring (CAM) testing	Urine drug testing	Drug patch testing
As of 18 February 2011	**As of 6 December 2010**	**As of 18 February 2011**	**As of 18 February 2011**
• 17,960 participants	• 2,603 participants	• 1,789 participants	• 82 participants
• 3,709,113 tests administered	• 367,587 total days monitored (testing occurs every half an hour)	• 39,270 tests	• 958 patches (each worn for up to seven days)
• 3,682,372 (99.28%) passed tests	• 78.5% are fully compliant	• 97.11% pass rate	• 86.43% pass rate
• 55% of participants were 100% compliant, 83% never violated or only violated two times or less			

Data from Loudenberg R, *Mountain Plains Research* (2008 data provided to NPAMC by then Attorney General Long; 2009 data provided to NPAMC by Attorney General Marty Jackley).

The programme began as a small pilot. However, anecdotal reports of its success spurred almost immediate state-wide expansion. Today, approximately 90% of the state participates in the programme. Individuals participating in the programme know that they are very likely to be caught and incarcerated if they use alcohol or illegal drugs. Accordingly,

most abide by programme rules. Table 23.1 summarizes their compliance rates.

Preliminary data suggests that participants recidivate significantly less often than offenders who do not participate. Data suggests that repeat offenders who participated in the twice daily testing regimen recidivated approximately 35–50% less than controls during years one, two, and three (27).

Offenders are required to pay for their testing. Remarkably, the programme is reaching the point where it will be self-sustaining. Two national organizations, the Institute for Behavior and Health and the Council of State Governments as well as NHTSA have recognized General Long's efforts to develop this programme. In June 2011, the National Sheriffs' Association formally recognized the programme's efficacy and voted to endorse it.

While this programme has undergone one evaluation with promising results, a second, more comprehensive evaluation is being conducted by Dr. Beau Kilmer and the RAND Corporation, with funding from the National Institutes on Alcohol Abuse and Alcoholism (NIAAA). More research is needed to inform understanding of how this programme can best be utilized and under what conditions it can be most effective.

Conclusion

It is clear that a significant number of offenders have alcohol misuse problems and that this is an important factor in

offending behaviour. While the justice system has traditionally struggled to address their needs, rehabilitative efforts have often been sacrificed in the pursuit of deterrence models. However, the development of these non-traditional models that attempt to achieve a better balance between deterrence and rehabilitation signals a shift in philosophy and our approach to the management of these offenders through the justice system. The three examples of efforts
to better address the risks and needs of alcohol misuse offenders previously described offer tremendous promise. While they are different in their application and delivery, they collectively strive to address offender needs; require abstinence; monitor compliance; impose swift, certain, meaningful, and proportionate sanctions for violations; and provide opportunities for meaningful treatment as appropriate.

It is believed that these programmes may be even more effective if their collective strengths can be leveraged to develop a continuum of appropriate monitoring, rehabilitation, and supervision, and taken to scale. This process has already begun. For example, South Dakota Judge Lori Wilbur presides over a DWI court that uses 24/7 monitoring (28). Additionally, DWI and drug courts around the country employ random urine drug testing, CAM bracelets, at-home breath alcohol testing, and ethyl glucuronide and/or ethyl sulfate tests for alcohol. We can easily envision a tiered system where:

♦ every offender who needs a DWI or drug court is placed in one that uses HOPE style drug testing and 24/7 style alcohol monitoring

♦ every serious or violent felon who does not qualify for a DWI or drug court is placed in a HOPE programme with 24/7 style monitoring

♦ each of the participants can be moved in or out of the tiers based on their performance.

Burgeoning correctional budgets and lack of security do not have to go on in perpetuity. With funding in short supply, focused-deterrence programmes based on swift and certain sanctions for non-compliance are the best way to improve public safety by giving judges a reliable alternative to incarceration of drug and alcohol offenders. Such a system would better utilize limited resources and result in better outcomes, delivering what is often called 'Smart Justice'. While the justice system is not well-suited to prevent crime, with some adjustments it can be the best vehicle for managing the risk and addressing the needs of those who offend.

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Part VI
Alcohol and cancer

Chapter 24
Alcohol and carcinogenesis: mechanisms and biomarkers

C.J. Peter Eriksson

Introduction

Alcohol consumption has been associated with cancers in a variety of locations, including upper aerodigestive tract, stomach, intestinal tract, liver, pancreas, bladder, lung, prostate, and female breast. However, because of inconsistencies between studies and/or other lacks of established causality, alcohol consumption has, so far, been officially categorized by the World Health Organization's International Agency for Research on Cancer (IARC) to Group 1 (sufficient evidence of carcinogenesis) only in relation to cancers of upper aerodigestive tract, colorectum, liver, and female breast (1). In addition, alcohol is also categorized to Group 2 (limited evidence) in relation to pancreatic cancer (1).

Throughout the years it has become increasingly evident that alcohol drinking-related cancer is not caused by alcohol per se. Instead, the mechanistic explanations include the metabolism of alcohol, other ingredients in the drink, and/or more indirect pathways related to lifestyle factors associated with alcohol consumption. Genetic epidemiology research is becoming a more and more important tool in assessing the aetiology and biomarkers of alcohol-related cancers. The aim

of the present overview is to briefly summarize the current knowledge regarding these aspects.

Mechanistic considerations

The fact that all alcohol-related cancers are located in the first passage of the alcoholic drink and/or in regions with active alcohol metabolism indicates that alcohol concentration, other constituents of the drink, and/or metabolism of alcohol and possible other constituents may be crucial aetiological factors. Acetaldehyde, the first metabolite of alcohol, has emerged as the pivotal agent standing for a considerable part, if not most, of the carcinogenicity of alcohol drinking. Acetaldehyde is derived by endogenous alcohol oxidation primarily in the liver, by exogenous microbial alcohol oxidation in the upper aerodigestive and gastrointestinal tracts, and as a constituent of the alcoholic drink.

After alcohol intake, normal peripheral blood acetaldehyde concentrations in non-alcoholic Caucasian populations is not detectable (<1 μM) (2) in men and about 0–5 μM in women, depending on oestrogen status (3). In Asian populations with reduced aldehyde dehydrogenase (ALDH) activity venous acetaldehyde levels may increase to about 10–270 μM (2). In Caucasians, considerably higher acetaldehyde levels, up to 40–80 μM at alcohol concentrations of 20–40 mM (4, 5), are formed in the saliva as the consequence of microbial alcohol oxidation. In both Caucasian and Asian populations, genetic factors (6), smoking (7), and poor oral hygiene (4) further elevates the acetaldehyde levels in the upper aerodigestive tract.

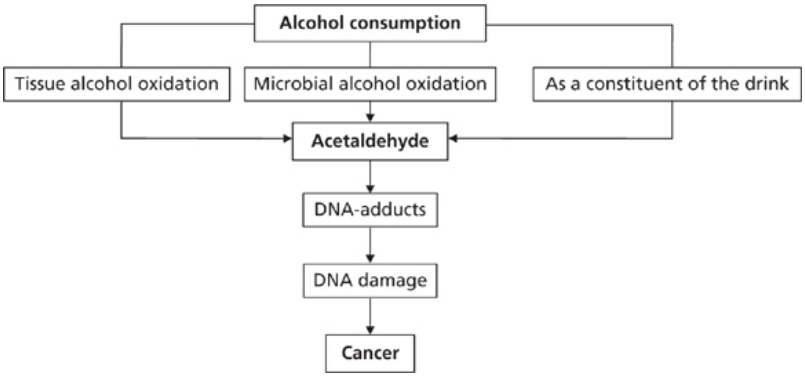

Figure 24.1 Aetiology of the carcinogenic effect by acetaldehyde.

A general pathway scheme for the aetiology and potential mechanisms of the carcinogenic effect by acetaldehyde is outlined in Figure 24.1.

Metabolic acetaldehyde as the primary agent in the initiation of alcohol-related cancers

The evidence and indications for acetaldehyde being directly involved in the causation of cancer are the following:

1 Compelling genetic epidemiological evidence linking acetaldehyde elevation by polymorphism of acetaldehyde metabolizing aldehyde dehydrogenase (ALDH2) to cancers in the upper aerodigestive tract. Especially, regarding oesophageal cancer, the numerous studies are conclusive and, thus, acetaldehyde, associated with alcohol consumption, was recently categorized by IARC to Group 1 regarding this cancer site (1).

2 Although, not yet officially categorized by IARC, the inactive ALDH2 allele has also significantly (and without contradictory results) been associated to increased risk of cancer in the lungs (8).

3 A number of studies in Asian populations have demonstrated associations between the polymorphism of the alcohol dehydrogenase ADH1B and upper aerodigestive tract cancer, which have been explained by less active ADH causing prolonged actions of the remaining ethanol-derived acetaldehyde (9).

4 Sufficient evidence of carcinogenicity in experimental animals (10).

5 The location of active endogenous (liver, breast, and pancreas) and microbial (upper aerodigestive and gastrointestinal tracts) alcohol oxidation (i.e. acetaldehyde formation) fits well with the location of alcohol-related cancers.

6 Acetaldehyde is a cytotoxic, genotoxic, mutagenic, and clastogenic compound (11) and it has been shown that consumers of alcoholic drinks have a higher frequency of chromosomal aberrations and sister chromatid exchange (12). In addition, elevated micronucleus formation (general tumour biomarker) has been observed in lymphocytes of ALDH2*2 individuals after alcohol drinking (13).

7 After alcoholic drink consumption, carriers of the inactive allele of the ALDH2 display increased lymphocyte levels of micronucleus formation and three different forms of acetaldehyde-derived mutative DNA-adducts

(N2ethyl-2′-deoxyguanosine, alpha-S- and alpha-R-methyl-gamma-hydroxy-1, N2-propano-2′-deoxyguanosine) (14).

The carcinogenic role of external acetaldehyde in alcoholic drinks

Acetaldehyde derived in alcohol metabolism is carcinogenic, indicating that acetaldehyde as a component of alcoholic drinks may also be carcinogenic. The mechanistic considerations that support this statement can be summarized as follows:

1 The acetaldehyde content of many alcoholic drinks exceeds the systemic acetaldehyde levels during normal ethanol oxidation, i.e. without inhibition of ALDH activity or increased alcohol oxidation rate. The mean levels (and ranges) of the acetaldehyde in different groups of alcoholic drinks vary between 9 μM (0–63 μM) for beer, 34 μM (0–211 μM) for wine, 66 μM (0–1200 μM) for spirits, and 120 μM (12–800 μM) for fortified wines (15). Consequently, in addition to acetaldehyde levels derived by endogenous and microbial alcohol oxidation, further initial elevations, up to several hundred μM, have been detected in saliva during alcoholic drink intake (6, 16).

2 The most solid associations between alcohol-related cancer and polymorphism in the alcohol and acetaldehyde metabolizing systems occur at the sites with direct first contact with the alcohol ingested, i.e. the upper aerodigestive tract.

3 Regions with increased frequency of oesophageal cancer seem to correlate with the culture of drinking alcoholic drinks

with high acetaldehyde content, e.g. the situation with the apple brandy Calvados in the north-west regions of France (17, 18).

Further studies will be needed to fully assess the carcinogenic role of the drinks containing acetaldehyde, the limits for safe acetaldehyde concentrations in the drinks, and the need for new acetaldehyde regulations and directives for the alcohol industry.

Other mechanisms for alcohol-related tumour initiation, promotion, and progression

The role of alcohol metabolism in tumour initiation, promotion, and progression is implied by a number of associations between different forms of cancer and polymorphisms in genes involved in the oxidation of ethanol. Whether, or to what degree, these associations are explained by other metabolic factors than acetaldehyde has not been established. Such possibilities will now be considered.

Oxidative stress

The alcohol-induced CYP2E1 enzyme produces various reactive oxygen species (ROS), which lead to the formation of lipid peroxides such as 4-hydroxy-nonenal and the condition of oxidative stress. Increased ROS and oxidative stress, which damage the DNA and its repair, have been associated with ethanol-induced carcinogenesis in organs, such as the breast (19), liver (20), and pancreas (21).

Toxicokinetics

Many findings show that alcohol, by inhibiting the breakdown of several carcinogens such as nitrosamines, urethane, vinyl chloride, and benzene as well as many other solvents, may potentiate effects of these carcinogens (22).

Induction of polyunsaturated fatty acids

The metabolism of alcohol may produce an excess of oxygen free radicals and lipid peroxidation, which may lead to increased cell proliferation and outgrowth of carcinogen-initiated cells (23).

Induction of mitogen-activated protein kinases

Alcohol-induced oxidative stress may increase the mitogen-activated protein kinase (MAPK) signalling cascade, which is essential in cell proliferation and differentiation, apoptosis, stress, and inflammatory responses. Such MAPK events have been associated with breast cancer (24).

Vitamin A (retinol)

Alcohol oxidation may interact on retinol metabolism, which could lead to disturbed cell-cycle regulation and consequently to carcinogenesis (25).

Insulin-like growth factors

Excessive alcohol consumption has been associated with effects on the insulin-like growth factors (regulators of cell proliferation, differentiation, and apoptosis), which thus could promote carcinogenesis, e.g. in the breast (26).

Folate metabolism

Folate metabolism is linked to DNA methylation and synthesis, which are two crucial steps in carcinogenesis. Folate deficiency is associated with different forms of cancer, of which colon cancer is the most commonly described (27).

Alcohol and sex hormone elevation

Oestrogens and androgens are well-known activators of cellular proliferation, which is associated with an increased risk for carcinogenesis. Alcohol consumption in women causes an increase in the levels of oestrogen and/or androgen, which may promote the development of breast cancer (28).

Cirrhosis

Alcohol-related hepatocellular carcinoma without pre-existing cirrhosis is rare, which indicates that the pathogenic events that lead to cirrhosis precede those that cause cancer (29).

Alcoholic intake increases immunodeficiency and immunosuppression, conditions that facilitate carcinogenesis by silencing immune-related defence mechanisms in various organs (30).

Biomarker considerations

Little is known about biomarkers exclusive for alcohol-related carcinogenesis. Although specific cancer biomarkers for alcohol-related tumour initiation, promotion, and progression are not yet established, genetic and phenotypic biomarkers may also be applied for defining increased risk of carcinogenesis, as exemplified in the preceding sections. Currently, the most important phenotypic biomarker for high risk of acetaldehyde-related upper aerodigestive tract cancer is the facial flushing reaction (vasodilation plus skin heating effect), often followed by nausea (and tachycardia at higher alcohol consumption). This reaction, which is caused by impaired genetic capacity (by the *ALDH2*2* allele) to oxidize acetaldehyde, is very common, with a frequency of about 40% in East-Asian populations. The risk for oesophageal cancer in these individuals is extremely high,
with odds ratios up to about eight in high alcohol consumers (31). The recent understanding of this serious cancer risk and of the decision of IARC to classify the acetaldehyde-related cancer to Group 1, may lead to massive health programmes regarding this danger (32), which, hopefully, could save millions of lives for the years to come.

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Chapter 25
Upper aerodigestive tumours: mouth, pharynx, larynx, and oesophagus

Mia Hashibe, Binh Y. Goldstein, Lin Cai, and Zuo-Feng Zhang

Introduction

Upper aerodigestive tract (UADT) cancers include malignancies of the oral cavity, oropharynx, hypopharynx, larynx, and oesophagus. Worldwide, more than one million UADT cases and 700,000 deaths due to UADT are estimated to occur each year (1). Smoking tobacco products including cigarettes, cigars, and pipes is the major risk factor for UADT cancers (2). Additional UADT cancer risk factors are chewing betel quid and areca nut, for oral cavity cancers (3); a family history of cancer (4); asbestos and inorganic acid mists (occupational), causing laryngeal cancer (5, 6); and genetic variants in the alcohol metabolism genes *ADH1B* and *ADH7* (7). The major histological type of oral cavity, pharyngeal, and laryngeal cancers is squamous cell carcinoma (SCC), while the proportion of adenocarcinomas to SCC varies by geographic region for oesophageal cancers (8, 9). Although the UADT incidence rates have been decreasing with the decreasing prevalence of tobacco smoking in most regions over the last few decades, the incidence rates for tonsil and tongue cancers overall (10) and for the oral cavity and pharyngeal cancer among young women (11) have been increasing in the United States. The alarming trend for oropharyngeal cancer might be due to human papillomavirus

(HPV) infection, a recognized cause of oropharyngeal cancer (12). In North America, 40–80% of oropharyngeal cancer cases are HPV positive (13). Oesophageal SCC incidence is in decline in most developed countries, whereas adenocarcinoma of the oesophagus, linked to gastro-oesophageal reflux and obesity, is increasing (8, 9).

Alcohol drinking, aside from tobacco smoking, is a major risk factor for UADT SCC. Relative to other alcohol related cancers, the risk conferred by alcohol drinking is thought to be strong for UADT cancers (14). Consuming 50 g of alcohol per day may increase the risk of oral cavity and pharyngeal cancers by approximately threefold, the risk of laryngeal cancer by twofold relative to non-drinkers (15), and the risk of SCC of the oesophagus by fivefold (16). In contrast, alcohol drinking was not strongly associated with oesophageal adenocarcinomas (17).

Independent effect

The effect of alcohol drinking has been demonstrated to be independent of tobacco smoking, in studies focusing on alcohol drinking among never-smokers. Individual level data on never-tobacco users was pooled for 1,072 head and neck cancer cases (including oral cavity, pharynx, and larynx) and 5,775 controls from 14 case–control studies by the International Head and Neck Cancer Epidemiology (INHANCE) consortium (18). Never-drinking in general was not associated with head and neck cancer risk. However, heavy drinking of ≤3 drinks per day was associated with an approximate twofold increase in head and neck cancer risk. Across the head and neck cancer subsites, the risks associated

with higher frequency of alcohol drinking were most pronounced for pharyngeal cancers and laryngeal cancer, compared to oral cavity cancer. There have been few studies reporting on alcohol drinking frequency among never-smokers for oesophageal SCC. Kato et al. reported a RR of 8.6 (95% confidence interval (CI): 2.1–6.0) for drinking 30 ml or more per day compared to <30 ml day in a cohort study including eight oesophageal cancer cases (19). Odds ratios (ORs) for never-smokers from a case–control in Italy including 17 cases are shown in Table 25.1 (20). In a large case–control study of oesophageal cancer in the Chinese population with 415 (187 male, 228 female) never-smoking cases and 1,549 (824 male, 725 female) never-smoking controls, the adjusted OR was 1.4 (95% CI: 1.0–2.0) for men who ever drank alcohol and 1.4 for both men and women who consumed at least 500 ml ethanol per week (p for trend = 0.043) (21). According to these studies, heavy alcohol drinking appeared to be a risk factor for oesophageal SCC, independent of tobacco smoking.

Table 25.1 Alcohol drinking and the risk of UADT cancers in never-tobacco users

	Oral cavity	Pharynx	Larynx		Oesophagus
Reference	**(15)**	**(15)**	**(15)**		**(20)**
Cases/controls	**383/5,775 (INHANCE)**	**369/5,775 (INHANCE)**	**121/4,602 (INHANCE)**		**17/289**
	OR[a] (95% CI)	**OR[a] (95% CI)**	**OR[a] (95% CI)**		**OR[b]**
Frequency:				Frequency:	
Never drinkers	1.00	1.00	1.00	<35 drinks/week	1.0
<1 drinks/day	1.14 (0.8–1.63)	1.39 (0.99–1.96)	0.92 (0.5–1.69)	35–59 drinks/week	0.8
1–2 drinks/day	1.64 (1.19–2.25)	1.66 (1.18–2.34)	1.26 (0.77–2.07)	60+ drinks/week	7.9
3–4 drinks/day	1.11 (0.57–2.15)	2.33 (1.37–3.98)	1.24 (0.62–2.45)		
≥5 drinks/day	1.23 (0.59–2.57)	5.50 (2.26–13.36)	2.98 (1.72–5.17)		
P trend	0.032	<0.001	<0.001		

[a]ORs were adjusted for age, sex, race/ethnicity, and education level.

[b]ORs were adjusted for age, area of residence, years of education, and occupation.

Data from Franceschi et al., Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy, *Cancer Research*, Volume **50**, Issue 20, pp. 6502–6507, Copyright ©1990 American Association for Cancer Research.

Dose–response

Between 1988 and 2007, the International Agency for Research on Cancer (IARC) monograph on alcohol reported that there were five cohort studies on oral cavity and pharyngeal cancers, eight case–control studies on oral cavity cancer, nine case–control studies on pharyngeal cancer, 19 case–control studies on oral cavity/pharyngeal cancers combined, 18 case–control studies on laryngeal cancer, 16 cohort studies on oesophageal cancer, and 14 case–control studies on oesophageal cancer (15). Most of these studies showed dose–response relations between alcohol drinking frequency and the risk of UADT cancers with adjustment for tobacco smoking, consistently across
various geographic regions including Europe, Asia, North America and Latin America. On the other hand, the IARC monograph reported that there was little information on the duration of alcohol drinking and the risk of laryngeal cancer.

Additionally, no dose–response relations were observed between duration of alcohol drinking and the risk of oral cavity, pharyngeal, and laryngeal cancer among never-smokers by the INHANCE consortium (18). For oesophageal cancers, most of the studies had focused on the frequency of alcohol drinking. Among the studies that reported on duration of alcohol drinking and the risk of oesophageal SCC, approximately half showed dose–response relations (15). A recently published large-scale case–control study of 1,520 cases and 3,879 controls in China showed strong dose–response associations with respect to duration, frequency, and ethanol concentration (21).

Cessation of alcohol drinking

Quitting drinking for 20 years or more was reported to reduce the risk of oral cavity cancer (OR = 0.45, 95% CI: 0.26–0.78) and laryngeal cancer (OR = 0.69, 95% CI: 0.52–0.91) based on the INHANCE consortium pooled analysis of 9,167 head and neck cancer cases and 12,593 controls (22). A reduced risk for quitting drinking 20 or more years was suggestive for pharyngeal cancer (OR = 0.74, 95% CI: 0.50–1.09). Quitting drinking for 10 years or more was also reported to be beneficial in reducing oesophageal cancer risk in three separate case–control studies (15).

Types of alcoholic drinks

Previously, the overall consensus was that the most common type of alcoholic drink type in a specific region conferred the greatest risk of UADT cancers. The highest UADT cancer risks were observed for beer in North America, wine in

Europe, and hard liquors in Latin America (15). However, a recent INHANCE consortium analysis examined alcoholic drink types among individuals who reportedly drank only one type of alcoholic drink and did not observe large risk differences (23). Head and neck cancer risks were fairly consistent among individuals who drank increasing frequencies of beer only, liquor only, or wine only (Figure 25.1), supporting ethanol and its metabolites as the principal carcinogen rather than other components in the each specific alcohol type. Drinking >30 alcoholic drinks per week resulted in head and neck cancer risk increases of fourfold for liquor, fivefold for beer, and sixfold for wine. In North America, the head and neck cancer risk estimates for liquor and beer appeared to be slightly higher, whereas the risk estimates for wine were higher in Europe and Latin America. For oesophageal SCC, three cohort studies and three case–control studies investigated differences in alcoholic drink types. Though there were suggestions of higher risks of oesophageal cancer for wine in a Japanese cohort study (24) and for wine and wine + spirits in an Italian study (25), neither of these studies showed significant risk differences in oesophageal SCC risk due to alcoholic beverage type.

Tobacco and alcohol

Numerous epidemiological studies have examined interactions between tobacco and alcohol for UADT cancers, but many reports assessed interactions only descriptively, without applying formal statistical testing (2). While some studies tested for interactions on the additive scale, others tested on the multiplicative scale, and different categories were used for tobacco use and alcohol use. Overall, the

majority of these studies demonstrated a joint effect between alcohol and tobacco consumption (26).

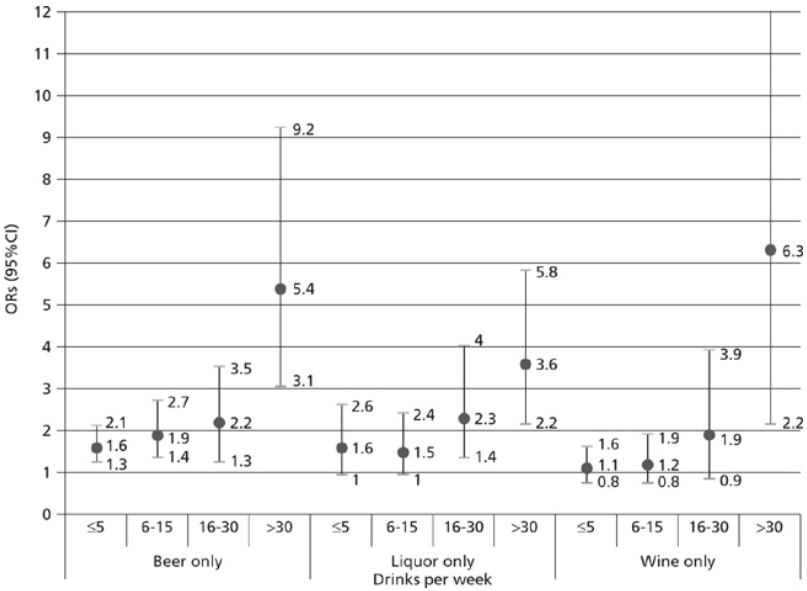

Figure 25.1 Types of alcoholic drinks and the risk of oral cavity, pharynx, and laryngeal cancer.

Data from Purdue et al., Type of alcoholic beverage and risk of head and neck cancer—A pooled analysis within the INHANCE Consortium, *American Journal of Epidemiology*, Volume 169, Issue 2, pp. 132–42, Oxford University Press, Copyright © 2002, DOI: 10.1093/aje/kwn306.

In the INHANCE consortium pooled data analysis, multiplicative interaction parameters were estimated for tobacco and alcohol drinking as shown in Figure 25.2 (27). When the multiplicative interaction parameter is greater than

1 and the 95% CIs do not cross the null value of 1, an interaction on the multiplicative scale is suggested. Interactions were suggested for oral cavity and pharyngeal cancers. The estimate for laryngeal cancer was not significant; though a more than additive interaction was confirmed (27). For head and neck cancer, regardless of the subgroups by gender, age, or geographic region, a clear interaction on the multiplicative scale was demonstrated. Similarly, interactions on the multiplicative scale have also been reported in nine case–control studies and two cohort studies for oesophageal cancer (15, 21).

Attributable risk

The proportion of head and neck cancer cases attributable to alcohol alone appears to be fairly small, based on INHANCE consortium analysis (Figure 25.3) (27). These results may suggest that the mechanism of action for alcohol in carcinogenesis is that it acts as a solvent for tobacco carcinogens. However, this does not take away from the fact that alcohol is an independent risk factor for UADT cancers among never-smokers. Alcohol alone appeared to play a larger role in pharyngeal cancer than for oral cavity or laryngeal cancers. In combination with tobacco, alcohol accounted for large proportions of head and neck cancer cases, ranging from 24.3% of head and neck cancer in women to 46.5% of head and neck cancer cases in Europe. The proportion of oesophageal cancer cases attributable to alcohol have been reported as 48.6% in Japan (28), 42.5% in Western Europe (3.6% alcohol alone, 38.9% alcohol + tobacco) (29), 47% in China (15.6% alcohol along and 31.4% alcohol + tobacco) (30), and 72.4% in the United States (31).

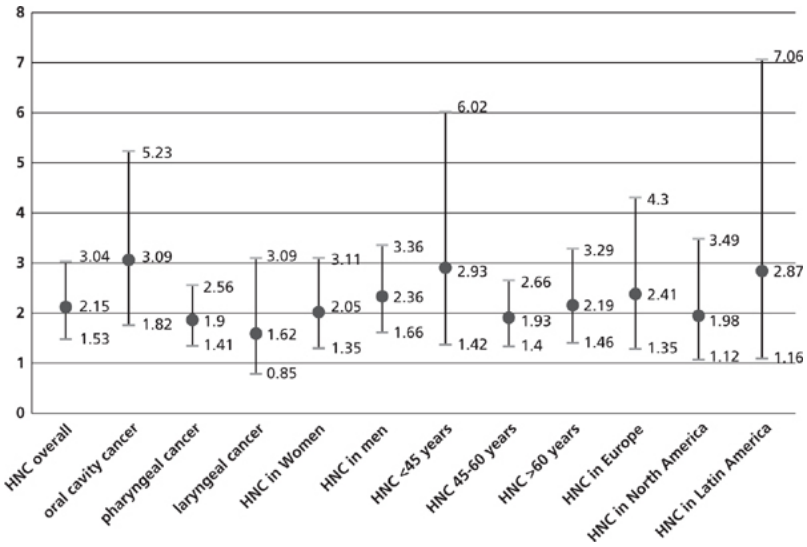

Figure 25.2 Multiplicative interaction parameters for tobacco and alcohol on the risk of head and neck cancer (HNC) by subgroups.

Data from Hashibe M et al. Interaction between Tobacco and Alcohol Use and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium, *Cancer Epidemiology, Biomarkers and Prevention*, Volume 18, Number 2, pp. 541–50, Copyright © 2009 American Association for Cancer Research.

Summary

Alcohol is clearly a major risk factor for SCC of the UADT. While tobacco smoking is the most important risk factor for SCCs of the UADT, studies focusing on never-smokers have

demonstrated an independent effect of alcohol. Dose–response relations between the risk of UADT SCC and alcohol frequency are very prominent, whereas the dose–response with the years of alcohol drinking appeared to be important only for oesophageal cancers. Though previously it was believed that the most common type of alcoholic beverage in a particular geographic region was responsible for the greatest UADT SCC risk, an updated review of the evidence suggests that significant differences in risk by alcoholic beverage type are not present. The interaction between alcohol drinking and tobacco smoking on UADT cancer risk is substantial, with attributable fractions suggesting that alcohol mainly plays an important role in carcinogenesis together with tobacco rather than alone. While numerous epidemiological studies have contributed to elucidating the role of alcohol in UADT SCC development, the collaborative efforts of pooling data within the INHANCE consortium for oral cavity, pharyngeal, and laryngeal cancer have been highly beneficial. Similar efforts for oesophageal SCC would be invaluable in further contributing to the research.

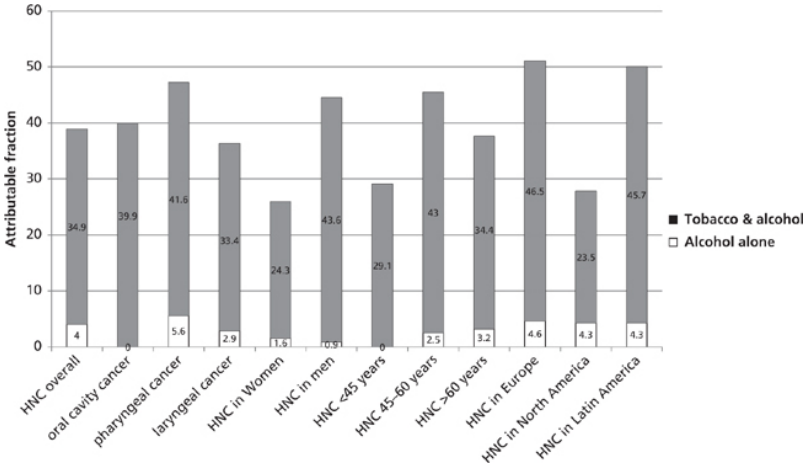

Figure 25.3 Attributable fractions for alcohol alone and tobacco and alcohol for head and neck cancer (HNC).

Data from Hashibe M et al. Interaction between Tobacco and Alcohol Use and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium, *Cancer Epidemiology, Biomarkers and Prevention*, Volume 18, Number 2, pp. 541–50, Copyright © 2009 American Association for Cancer Research.

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Chapter 26
Gastrointestinal tumours

David Zaridze

Gastric cancer

Despite a steady decline in incidence and mortality over recent decades, gastric cancer remains one of the most common cancers worldwide, with an estimated 934,000 new cases per year (1). The bacterium *Helicobacter pylori*—a major risk factor for gastric cancer—is estimated to be responsible for 63% of all cases of non-cardia gastric cancer worldwide. It has been suggested that smoking and alcohol consumption are associated with an increased risk of gastric cancer, while consumption of fruit and vegetables decreases the risk. The distinct time trends shown by gastric cardia cancer (its incidence rates show a strong increase in some industrialized countries) is an indication that its aetiology is different, namely it is associated with obesity, gastro-oesophageal reflux, and Barrett's oesophagus (2).

The working group of the International Agency for Research on Cancer (IARC) which met in Lyon in 1988, considered uncertain the existing epidemiological evidence on the association between alcohol consumption and gastric cancer (3). In 2007, the IARC working group reassessed the carcinogenicity of alcoholic drinks for stomach cancer and concluded that, although significantly increased risks were reported in some studies, confounding by socioeconomic

status and low intake of fresh fruit, vegetables, and various micronutrients could not be ruled out (4).

The working group reviewed 12 cohort studies, conducted in general populations in China, Denmark, Japan, Sweden, the United Kingdom, and the United States, which examined the association between alcoholic drink consumption and stomach cancer. Two studies, one Japanese and another Chinese, reported significantly increased risk. In both studies the relative risks (RRs) were significantly increased in heavy drinkers. In the Japanese study the RRs were adjusted for sex and age, while in the Chinese study the RRs were not adjusted (4).

The working group also reviewed 25 case–control studies. In 11 of them an association was found between alcohol consumption and risk of stomach cancer. These studies were conducted in China, Germany, Italy, Japan, Poland, Portugal, Russia, Uruguay, and Venezuela. The size of three of them was considered too small. Thus, although formally statistically significant positive associations were found in 11 case–control studies the results of only eight were weighed in the assessment. In most of these studies RRs were adjusted for age, sex, education, and smoking. In only two of them, in addition to these variables, RRs were adjusted for fruit and vegetable consumption and in only one for *H. pylori* infection status. One study reported gastric cancer risk associated with vodka consumption among *H. pylori*-positive and *H. pylori*-negative subjects. The RRs for an association between alcoholic drink consumption and stomach cancer were between 1.6 and 3.5 for medium and heavy drinking.

Some investigators have considered the role of different types of alcoholic drink. Vodka consumption was found to be strongly associated with risk of gastric cancer in Polish and Russian
studies (5, 6). A case–control study conducted in Uruguay (7) found that consumption of alcoholic drinks, particularly of hard liquor and beer, increased the risk of stomach cancer nearly threefold. Several studies reported on the joint effects of alcoholic drink consumption and tobacco smoking, especially in relation to the gastric cardia (5, 6, 8).

A meta-analysis of cohort and case–control studies on alcohol drinking and gastric cancer, which included all relevant articles published in English up to June 2010, provided evidence of a lack of association between moderate alcohol drinking and gastric cancer, but a positive association with heavy alcohol drinking (9). The overall RR, based on 44 case–control studies and 15 cohort studies was 1.07 (95% confidence interval (CI): 1.01–1.13). The summary RRs were 0.94 (95% CI: 0.78–1.13) for gastric cardia and 1.07 (95% CI: 0.91–1.26) for gastric non-cardia. The RRs for drinkers versus non-drinkers were 1.02 (95% CI: 0.95–1.09) among Asian and 1.12 (95% CI: 1.01–1.24) among non-Asian populations (P for heterogeneity = 0.138). The overall RR for heavy alcohol drinking, based on 13 studies, was 1.20 (95% CI: 1.01–1.44). The RR for heavy drinking was 0.90 (95% CI: 0.65–1.25) among Asian and 1.39 (95% CI: 1.14–1.69) among non-Asian populations (P for heterogeneity = 0.026). The analysis of dose–response relationships showed an increase in RRs with increased ethanol intake: RRs were 0.95 (95% CI: 0.91–0.99) for 10 g/day ethanol, 1.01 (95% CI: 0.96–1.06) for 25 g/day, 1.14 (95% CI: 1.08–1.21) for 50 g/day, 1.30 (95% CI: 1.19–1.40) for 75 g/day, 1.45 (95% CI:

1.31–1.62) for 100 g/day, and 1.62 (95% CI: 1.42–1.85) for 125 g/day ethanol.

The companion meta-analysis of 24 case–control and cohort studies provided definite evidence of an absence of association between alcohol drinking and gastric cardia adenocarcinoma risk (10). The RR for drinkers versus non-drinkers was 0.89 (95% CI: 0.76–1.03). The RR for heavy alcohol drinking was 0.98 (95% CI: 0.78–1.23). The dose–response analysis showed no significant increase in risk at any level of alcohol intake.

The results of these meta-analyses (9, 10), particularly concerning Asian populations, are in accordance with an evaluation based on a systematic review of epidemiological studies in the Japanese population conducted by Shimazu et al. (11). According to this review, of the 11 cohort studies evaluated, nine showed no association between alcohol drinking and gastric cancer, and only one showed a strong positive association among men. In all 11 evaluated case–control studies no association between alcohol consumption and stomach cancer was observed.

The most recent cohort study conducted in China, and not included in the discussed meta-analyses, found that light and moderate alcohol consumption is not associated with increased risk of gastric cancer whereas heavy drinking is. They found that RR for moderate drinkers (<4 drinks/day) compared with non-drinkers is 0.94 (95% CI: 0.76–1.18) and 1.46 (95% CI: 1.05–2.04) for heavy drinkers (>4 drinks/day) versus non-drinkers (12).

Colorectal cancer

Incidence of colorectal cancer ranks fourth in men and third in women of all cancers, with over one million new cases occurring every year worldwide (1). It has been suggested that dietary factors are important in the aetiology of colorectal cancer—animal foods are associated with increased risk and foods of plant origin have a protective effect. Among lifestyle factors, obesity and lack of physical activity have been shown to be associated with the risk of colorectal cancer. Cigarette smoking and alcohol consumption are other avoidable risk factors linked with cancer of the colorectum (2).

Several meta-analyses and overviews have supported a positive association between alcohol consumption and colorectal cancer. Cho et al. (13) pooled data from eight large cohort studies
conducted in Europe and North America. The analysis included 4,600 cases of colorectal cancer among 490,000 men and women. The multivariate analysis was adjusted for age, gender, tobacco smoking, body mass index (BMI), height, physical activity, use of anti-inflammatory drugs, energy intake, and diet. The RRs for colorectal cancer across the five increasing categories of alcohol intake were 0.94, 0.97, 1.01, 1.16, and 1.41 respectively (p for trend = 0.001). The differences between types of alcoholic drinks were not statistically significant, nor were the associations significantly different among anatomical subsites.

In a meta-analysis of 16 prospective studies, Moskal et al. (14) observed that the average RR associated with an increase in consumption of 100 g ethanol per week was 1.19. Other meta-analyses and overviews also found a positive

association between alcohol consumption and colorectal cancer risk (15, 16).

In 2007, the IARC working group examined the carcinogenicity of alcoholic drinks in relation to colorectal cancer and concluded that the occurrence of malignant tumours of the colorectum is causally related to the consumption of alcoholic drinks. This evaluation was based on more than 50 prospective and case–control studies which reported on the association between alcohol consumption and the risk of colon, rectal, and colorectal cancer, and results of pooling and meta-analysis. Regular consumption of about 50 g/day alcohol is associated with an RR of 1.4 compared with non-drinkers. Based on available data the working group suggested that the association is similar for colon and rectal cancer and does not vary by type of alcoholic drink. The working group inferred that the association does not appear to be confounded by age, gender, ethnicity, BMI, physical activity, or diet. The working group added colorectal cancer to the list of cancers causally related to alcohol, which previously consisted of oral cavity, pharynx, larynx, oesophagus, and liver cancer (4).

The most recent meta-analysis of 27 cohort and 34 case–control studies confirmed the causal association between alcohol consumption and colorectal cancer (17). Of these studies, 22 reported fully adjusted risk estimates and 36 reported risks adjusted for tobacco smoking. Summary results did not materially change when studies with no adjustment for potential confounders were excluded. The summary RRs, compared to non-drinkers, were 1.12 (95% CI: 1.06–1.19) for any drinkers, 1.00 (95% CI: 0.95–1.05) for light drinkers, 1.21 (95% CI: 1.13–1.28) for moderate drinkers, and 1.52

(95% CI: 1.27–1.81) for heavy drinkers. The RRs were higher for rectal cancer for any drinkers and light drinkers, but about the same for moderate and heavy drinkers. There was no significant heterogeneity in RRs by colon subsites among any and light drinkers. There was, however, a non-significant increase in risk of cancer of the distal colon compared to the proximal colon among moderate and heavy drinkers. Men had statistically significantly higher risk than women among any drinkers (P = 0.001) and moderate drinkers (P = 0.02). For heavy drinking, the association was stronger in Asian studies (RR = 1.81, 95% CI: 1.33–2.46; p heterogeneity = 0.04). Dose–response meta-analyses showed that, compared to non-drinkers, RRs for those who consumed 10, 24, 50, and 100 g/day alcohol were 1.07 (95% CI: 1.04–1.10), 1.18 (95% CI: 1.12–1.25), 1.38 (95% CI: 1.28–1.50), and 1.82 (95% CI: 1.41–2.35), respectively. The increase in risk (7%) associated with light drinking (10 g/day alcohol) has not been reported before. However, the authors' comments on this finding suggest that the differences between the dose–response analysis and meta-analysis for light drinking may likely be due to the different methods used. The results of dose–response analyses based on modelling have certain limitations intrinsic to the method, including exposure misclassification.

The proportion of colorectal cancer incidence attributable to alcohol in eight European countries, based on results from the European Prospective Investigation into Cancer and Nutrition (EPIC) prospective cohort study, is estimated to be 17% (95% CI: 10–25%) in men and 4% (95% CI: 1–10%) in women (18).

Conclusions

Moderate alcohol consumption is not associated with increased risk of stomach cancer. There is, however, a positive association between heavy alcohol drinking and non-cardia gastric cancer. Moderate and heavy alcohol consumption is causally associated with colorectal cancer. The risk of colorectal cancer increases with increasing alcohol intake.

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Chapter 27
Liver and pancreatic tumours

Patrick Maisonneuve

Epidemiology of liver and pancreatic cancer

Worldwide, for both sexes combined, liver cancer represents the fifth most common form of cancer and the third leading cause of cancer death with respectively 750,000 estimated new cancer cases and 700,000 deaths in 2008 (1). Liver cancer is much more frequent in less-developed areas where the prevalence of hepatitis B (HBV) or hepatitis C (HCV) virus infection is high, with more than half of the new cases and deaths occurring in China (Figure 27.1) (1, 2). Overall, liver cancer is more common in men than in women with a sex ratio of 2.4:1. Hepatocellular carcinoma (HCC) represents the major histological subtype, accounting for 70–90% of all liver cancers. Other histological subtypes include intrahepatic cholangiocarcinomas that arise from the epithelial lining of the bile duct. The great majority of HCCs are associated with liver cirrhosis, the major causes of which are HBV and HCV infection and heavy alcohol consumption. Other risk factors include ingestion of food contaminated with aflatoxin B1, haemochromatosis, tyrosinaemia, or non-alcoholic fatty liver diseases (3).

Unlike liver cancer, pancreatic cancer is relatively infrequent, but because it has a very poor prognosis, pancreas cancer is a common cause of cancer death. As pancreatic cancer is strongly age-related with less than 10% of all patients

developing the disease before the age of 50 years, it represents a very uncommon form of cancer in most developing countries where life expectancy is short (Figure 27.1) (2–4). Conversely, it now ranks as the fourth or fifth most common cause of cancer death in developed countries, with an estimated burden of 160,000 deaths for both sexes combined in 2008 (1). Smoking is the most established risk factor for pancreatic cancer, causing 20–25% of all tumours. Many factors associated with the metabolic syndrome, including over-weight and obesity, impaired glucose tolerance, or long-standing diabetes, also increase the risk of the disease, while a small proportion, no more than 10%, of pancreatic tumours have a genetic origin (4).

Alcohol, inflammation, and cancer

Alcohol is known to promote inflammation of both the liver and the pancreas, leading to liver cirrhosis and pancreatitis (5, 6). These two chronic conditions have been in turn associated with increased risk of liver and pancreatic cancer (5–7). While liver cirrhosis precedes the development of liver cancer in most of the cases, long-standing chronic pancreatitis precedes pancreatic cancer in a very small proportion of the cases. Therefore, the contribution of heavy alcohol intake on the risk of developing cancer, mediated by chronic inflammation, varies widely for both organs.

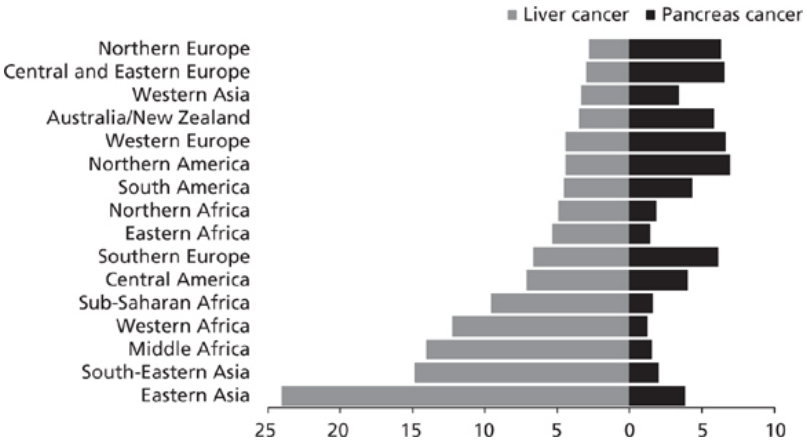

Figure 27.1 Age-standardized incidence of liver and pancreatic cancer in selected regions, both sexes, all ages, 2008 (per 100,000), using data from GLOBOCAN 2008.

Data from Ahmedin Jemal et al., Global cancer statistics, *CA: A Cancer Journal for Clinicians*, Volume **61**, Issue 2, pp. 69–90, John Wiley & Sons, Inc., Copyright © 2011 American Cancer Society, Inc. and Ferlay et al., GLOBOCAN 2008 v1.2, *Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10*, Lyon, France, International Agency for Research on Cancer, Copyright ©2010, available from: <http://globocan.iarc.fr>.

Alcohol and liver cancer

In 1988, the International Agency for Research on Cancer (IARC) published its first monograph on the evaluation of the carcinogenic risk of alcohol drinking to human (8). Based on results from four cohort studies and ten case–control studies, the working group concluded that there was 'sufficient

evidence for the carcinogenicity of alcoholic beverages' and that 'the occurrence of malignant tumors of the liver was causally related to consumption of alcoholic beverages'. A large number of epidemiological and experimental studies have been published since then, pushing IARC to perform a revision of this volume in 2010 (9). Additional results from cohort studies, including cohorts of heavy drinkers, and numerous case–control studies from many regions of the world, confirmed that the consumption of alcoholic beverages is an independent risk factor for primary liver cancer with no substantially different effects for the various types of alcoholic drink consumed.

While chronic infections with HBV and HCV are the major causes of liver cancer worldwide, the increased risk associated with alcoholic drink intake has been consistently found among individuals infected with hepatitis viruses as well as among uninfected individuals (10). It should, however, be noted that, even in low-endemic areas where alcohol abuse is generally thought to be the major cause of liver cancer, HBV and HCV infection have a foremost role (11). Modelling of the dose–effect relation between alcohol drinking and liver cancer revealed a steady linear increase in the risk of liver cancer for increasing alcohol intake, for values of >60g of ethanol per day, with no substantial differences between men and women. A synergism between alcohol drinking and either HBV or HCV infection was also found, as heavy alcohol drinking doubles the risk associated with hepatitis virus infection (10).

While cirrhosis generally precedes the development of HCC, a minority of patients develop cancer in the absence of cirrhosis but with evidence of chronic liver disease. Again,

HBV and HCV infection and heavy alcohol intake are the main determinants of liver cancer in the absence of cirrhosis, supporting the hypothesis that chronic liver disease and liver cancer develop in parallel following exposure to the same agents (12, 13).

An increasing number of studies suggest an interaction between genetic susceptibility and alcohol drinking on cancer risk. Associations between single nucleotide polymorphisms in the methylenetetrahydrofolate reductase (*MTHFR*) gene and in the aldehyde dehydrogenase 2 (*ALDH2*) gene and liver cancer have been reported but, so far, results are inconsistent (14–16).

Alcohol is known to induce steatosis, steatohepatitis, and cirrhosis but the mechanism by which it increases the risk of liver cancer is not fully understood. Among the potential mechanisms, production of acetaldehyde and free radicals during alcohol metabolism, induction of cytochrome p4502EI, modulation of cell regeneration, or alterations of the immune system have been proposed (3).

Alcohol and pancreatic cancer

Unlike for liver cancer, the initial evaluation in 1988 by the IARC monograph working group based on 29 studies suggested that consumption of alcoholic drinks was unlikely to be causally related to cancer of the pancreas (8). In fact, most early studies have found either no or only a weak association between alcohol consumption and pancreatic cancer. The second revision published in 2010 was based on evidence from papers published until 2007 (9). Overall the

working group concluded that the evidence for an association between consumption of alcoholic drinks and pancreatic cancer risk was sparse and/or inconsistent. Only a few cohort studies reported an excess risk among those with a frequent intake after adjustment for age and smoking (17, 18) while initial data from two large US cohorts (the Health Professionals Follow-Up Study and the Nurses' Health Study) did not support any overall association between alcohol intake and risk of pancreatic cancer (19). Most of the 29 published case–control studies with quantitative data found no association between alcoholic drink intake and the risk of pancreatic cancer. Several studies, however, suggested that heavy alcoholic drink consumption (≥15 drinks/week) may be associated with an increased risk of pancreatic cancer (20–24). The working group, however, warned that the difference in findings may be partly due to differences in study design, and subject to substantial exposure misclassification and/or recall bias.

Results from several large-scale studies have been published since then, providing new interesting information; while a pooled analysis of 14 cohort studies supported a weak relationship, but only for women consuming in the highest alcohol consumption category (>30 g of alcohol/day) (25), and an analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) study failed to find an association between ethanol intake and the risk of pancreatic cancer (26), some investigators focused their attention on the association between high levels of alcohol consumption and pancreatic cancer risk. Data from the US National Institutes of Health-AARP Diet and Health Study (27) suggested a moderately increased pancreatic cancer risk with heavy alcohol use, particularly with liquor. The relative risks of

developing pancreatic cancer were 1.45 (95% confidence interval (CI): 1.17–1.80) for heavy total alcohol use (≥3 drinks/day) and 1.62 (95% CI: 1.24–2.10) for heavy liquor use, compared with light drinkers (<1 drink/day). A subsequent meta-analysis of the dose-relation between alcohol drinking and pancreatic cancer risk identified heavy alcohol consumption (three or more drinks per day or >30–40 g of alcohol/day) to be associated with a 22% increased risk of pancreatic cancer (28). Given the moderate association limited to heavy drinking and concerns due to the strong relationship between smoking and alcohol consumption, which could lead to residual confounding, alcohol would be responsible for only a small fraction of pancreatic cancers.

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Chapter 28
Alcohol consumption and breast cancer risk

Peter Boyle

Introduction

Alcohol consumption has been associated with a variety of different forms of human cancer for several centuries. The evidence linking alcohol drinking to cancer risk has been reviewed recently (1–3). There is convincing epidemiological evidence that the consumption of alcoholic drinks increases the risk of cancers of the oral cavity, pharynx, and larynx and of squamous cell carcinoma of the oesophagus (Chapter 25). The risks tend to increase with the amount of ethanol consumed, in the absence of any clearly defined threshold below which no effect is evident.

Alcohol drinking is also strongly associated with the risk of primary liver cancer (Chapter 27); the mechanism, however, might be mainly or solely via the development of liver cirrhosis, implying that light or moderate drinking may have limited influence on liver cancer risk. An increased risk of colorectal cancer (Chapter 26) has been observed in many cohort and case–control studies, which seems to be linearly correlated with the amount of alcohol consumed and independent from the type of alcoholic drink.

Evidence regarding an association between alcohol consumption and breast cancer risk has come to the fore during the past quarter century. The association had been

hinted at in several case–control studies but the potential recall bias and, in particular, when dealing with a small increase in risk, weighed against making any firm conclusions regarding the association. The breakthrough publication came from the prospective Nurses' Health Study in 1987 (4)—breakthrough in the sense that it was a well-designed, prospective study which clearly demonstrated the association between breast cancer risk and moderate alcohol consumption. The authors concluded that these data, and previously published case–control studies on the topic, suggest that alcohol intake may contribute to the risk of breast cancer.

There are now over 100 epidemiological studies conducted using a variety of study designs, in a variety of international settings, which provide a striking and consistent body of evidence about the association between moderate levels of alcohol consumption and risk of breast cancer in women. Consequently, alcohol consumption has been recognized as a risk factor for breast cancer by the International Agency for Research on Cancer (1, 2).

It is not useful to provide a detailed review of all published studies of alcohol consumption and breast cancer risk but it would be appropriate to look at some of the key studies and monitor the evolution of the accumulation of the evidence of association and public health responses (5).

Throughout the following chapter, one drink, whether a glass of beer, a standard glass of wine, or a shot of spirits, will be considered to contain 10 g of ethanol.

Selected key studies

The Nurses' Health Study in the United States was initially based on 89,538 United States Nurses aged 34–59, with no history of cancer, who completed an independently validated dietary questionnaire, that included the use of beer, wine, and liquor, in 1980. During the first four years of follow-up, 601 cases of breast cancer were diagnosed among cohort members (4).

Among the women consuming 5–14 g of alcohol daily (about three to nine drinks per week), the age-adjusted relative risk of breast cancer was 1.3 (95% confidence interval (CI): 1.1–1.7). Consumption of 15 g of alcohol or more per day was associated with a relative risk of 1.6 (95% CI: 1.3–2.0) and there was evidence of a highly significant increase in risk with increasing reported alcohol consumption. Among women without risk factors for breast cancer who were under 55 years of age, the relative risk associated with consumption of 15 g of alcohol or more per day was 2.5 (95% CI: 1.5–4.2) (4).

While there had been several previous case–control studies reported, this study was the first well-designed, large study which was free from the issues of recall bias which plague retrospective case–control studies, particularly on this topic. In addition, it provided in a clear manner data on what is a small value of relative risk which is at the limit of what can be reliably detected by epidemiological studies. This study served to launch epidemiological research into this association.

Another key, early study of this association was a meta-analysis of case–control studies conducted by Howe et al. (6). Howe assembled data from six case–control studies which had been conducted to examine the relationship between diet, nutrition, and breast cancer risk. Data from 1,575 cases and 1,974 controls were analysed with respect to alcohol intake.

There appeared to be a highly statistically significant and consistent elevated risk of breast cancer for drinkers of 40 g or more of alcohol per day, for whom the relative risk, as compared with that of non-drinkers, is 1.69 (95% CI: 1.19–2.40) (6). This association was not due to confounding by a number of diet-related factors, including total calories, fat, fibre, and vitamin C.

By the early 1990s, the association between alcohol consumption and the risk of breast cancer had been reported fairly consistently in a growing number of studies. In order to clarify the situation, Longnecker (7) undertook a meta-analysis of 38 epidemiological studies which had reported information on alcohol consumption and breast cancer risk. This meta-analysis reported a risk, relative to non-drinkers, of 1.1 (95% CI: 1.1–1.2) for one drink per day, 1.2 (1.1–1.3) for two drinks per day, and 1.4 (1.2–1.6) for three or more drinks per day.

Smith-Warner and colleagues (8) undertook an analysis of six prospective studies, conducted in four countries, which met a priori criteria and were included in a pooled analysis. Information about 4,035 cases of breast cancer derived from studies of 322,647 women was available. The pooled multivariate Relative Risk associated with an increment of 10

g/day (about one drink per day) was 1.09 (95% CI: 1.04–1.13) (8).

The Collaborative Group on Hormonal Factors in Breast Cancer (9) assembled over 80% of the relevant information on alcohol and tobacco consumption and breast available worldwide. Analyses were based on 58,515 women with invasive breast cancer and 95,067 controls from 53 studies. The average consumption of alcohol reported by controls from developed countries was a modest 6.0 g per day, i.e. about half a unit/drink of alcohol per day, and was greater in ever-smokers than never-smokers (8.4 g per day and 5.0 g per day, respectively).

Compared with women who reported drinking no alcohol, the relative risk of breast cancer was 1.32 (95% CI: 1.19–1.45) for an intake of 35–44 g per day alcohol, and 1.46 (95% CI: 1.33–1.61) for consumptions ≥45 g per day alcohol (9).

The relative risk of breast cancer increased by 7.1% (95% CI: 5.5–8.7%) for each additional 10 g per day intake of alcohol, i.e. for each extra unit or drink of alcohol consumed on a daily basis the risk of breast cancer increased by around 7%. This increase was the same in ever-smokers and never-smokers (7.1% per 10 g per day in each group). By contrast, the relationship between smoking and breast cancer was substantially confounded by the effect of alcohol (9).

When analyses were restricted to 22,255 women with breast cancer and 40,832 controls who reported drinking no alcohol, smoking was not associated with breast cancer (compared to never-smokers, relative risk for ever-smokers = 1.03 (95% CI: 0.98–1.07), and for current smokers = 0.99 (0.92–1.05)).

The findings for alcohol and for tobacco did not vary substantially across studies, study designs, or according to 15 personal characteristics of the women; nor were the findings materially confounded by any of these factors. If the observed relationship for alcohol is causal, these results suggest that about 4% of the breast cancers in developed countries are attributable to alcohol. In developing countries, where alcohol consumption among controls averaged only 0.4 g per day, alcohol would have a negligible effect on the incidence of breast cancer (9).

The Million Women Study (United Kingdom) is a large initiative which has published some detailed findings about breast cancer risk factors in women, including on the association with alcohol consumption (10). A total of 1,280,296 middle-aged women in the United Kingdom enrolled in the Million Women Study were routinely followed for incident cancer. A quarter of the cohort reported drinking no alcohol and 98% of drinkers consumed fewer than 21 drinks per week and an average of 10 g alcohol (one drink) per day.

Low to moderate alcohol consumption in women increases the risk of certain cancers. Every additional drink regularly consumed per day contributes 11 breast cancers per 1,000 women up to age 75 (10).

During an average 7.2 years of follow-up per woman, 68,775 invasive cancers occurred. Increasing alcohol consumption was associated with increased risk of breast cancer (12%, 95% CI: 9–14%) (P trend <0.001). The trends were similar in women who drank wine exclusively and consumers of other types of alcohol (10). The authors calculated that for every

additional drink regularly consumed per day, the increase in the incidence of breast cancer up to age 75 years was estimated to be 11 per 1000 for women in developed countries.

In the United States Women's Health Study (1992–2004) data was also collected regarding alcohol consumption (11). During an average of ten years of follow-up, 1,484 cases of total breast cancer (1,190 invasive and 294 *in situ*) were documented among 38,454 women who, at baseline, were free of cancer and cardiovascular disease and provided detailed dietary information, including alcohol consumption, for the preceding 12 months.

Higher alcohol consumption was associated with a modest increase in breast cancer risk; the multivariable relative risks for ≥30 g/day of alcohol versus none were 1.32 (95% CI: 0.96–1.82) for total breast cancer and 1.43 (95% CI: 1.02–2.02) for invasive breast cancer.

An increased risk was limited to oestrogen receptor (ER) and progesterone receptor (PR) positive tumours; the multivariable relative risks for an increment of 10 g/day of alcohol were 1.11 (95% CI: 1.03–1.20) for ER+/PR+ tumours (804 cases), 1.00 (95% CI: 0.81–1.24) for ER+/PR–tumours (125 cases), and 0.99 (95% CI: 0.82–1.20) for ER−/PR− tumours (167 cases) (11).

The National Institutes of Health–AARP Diet and Health Study (1995–2003) consisted of 184,418 postmenopausal women aged 50–71 years. During an average of seven years of follow-up, 5,461 breast cancer cases were identified (12).

Alcohol consumption was significantly positively associated with total breast cancer—even a moderate amount of alcohol (>10 g/day) significantly increased breast cancer risk. In a comparison
of >35 g versus 0 g/day, the multivariate relative risks were 1.35 (95% CI: 1.17–1.56) for total breast cancer, 1.46 (95% CI: 1.22–1.75) for ductal tumours, and 1.52 (95% CI: 0.95–2.44) for lobular tumours.

The multivariate relative risks for ER+/PR+, ER+/PR−, and ER−/PR− tumours were 1.46 (95% CI: 1.12–1.91) for >35 g versus 0 g/day, 1.13 (95% CI: 0.73–1.77) for >20 g versus 0 g/day, and 1.21 (95% CI: 0.79–1.84) for >20 g versus 0 g/day, respectively (12).

Further follow-up of the prospective observational study of 105,986 women enrolled in the Nurses' Health Study followed up from 1980 until 2008 focused on an early adult alcohol assessment and eight updated alcohol assessments (13). During 2.4 million person-years of follow-up, 7,690 cases of invasive breast cancer were diagnosed among the participants. Increasing alcohol consumption was associated with an increased breast cancer risk that was statistically significant at levels as low as 5.0–9.9 g per day, equivalent to three to six drinks per week (RR = 1.15; 95% CI: 1.06–1.24).

Binge drinking, but not frequency of drinking, was associated with breast cancer risk after controlling for cumulative alcohol intake. Alcohol intake both earlier and later in adult life was independently associated with risk. Chen et al. (13) concluded that low levels of alcohol consumption were associated with a small increase in breast cancer risk, with the most consistent measure being cumulative alcohol intake

throughout adult life. Alcohol intake both earlier and later in adult life was independently associated with risk.

Public health response

Evidence of an increase in risk of breast cancer associated with moderate levels of alcohol consumption is consistently found in a variety of study designs, using differing methodologies, conducted in a wide range of countries around the world, with quite similar findings including evidence of an increase in risk with increasing alcohol consumption. On this basis, independent assessments of carcinogenicity have concluded that alcohol consumption, even at moderate levels, increases the risk of breast cancer.

Even if the increased risk is small, the habit is so widespread in the population that the attributable risk could be substantial.

Boffetta et al. (14) estimated that a total of 389,100 cases of cancer are attributable to alcohol drinking worldwide, representing 3.6% of all cancers (5.2% in men, 1.7% in women). The corresponding figure for mortality is 232,900 deaths (3.5% of all cancer deaths). This proportion is particularly high among men in Central and Eastern Europe. Among women, breast cancer comprises 60% of alcohol-attributable cancers. Boffetta and Hashibe (3) estimated that in Europe in 2002, 28,300 cases of breast cancer, representing 7.7% of all breast cancers, were attributable to alcohol consumption.

An exercise was conducted to estimate the attributable fraction of breast cancer in France in 2000. It was estimated that 10.7% of breast cancer cases could be attributed to the use of hormone replacement therapy and oral contraceptives, 10.1% to physical inactivity, 9.4% to alcohol consumption, and 5.4% to changes in reproductive factors since 1930 (15).

Clearly, moderate levels of alcohol consumption can explain a substantial proportion of breast cancer cases. Knowledge of such a risk factor needs to be turned into public health policy.

The European Code Against Cancer was initially developed in the late 1980s as the basis of the ambitious Europe Against Cancer programme of the European Commission. Against this background of cancer as an important public health problem and one of the commonest causes of premature and avoidable death in Europe, the European Code Against Cancer was introduced in
1987 as a series of recommendations which, if followed, could lead in many instances to a reduction in cancer incidence and also to a reduction in cancer mortality.

The European Code Against Cancer was originally drawn-up, and subsequently endorsed by the European Commission high-level Committee of Cancer Experts, in 1987. Revisions of the Code took place in 1994 (16) and again in 2003 (17) by groups of international experts. These revisions were jointly funded by the European Commission and the European School of Oncology in 1994 (16) and by the European Commission and the European Institute of Oncology in 2003 (17).

The second revision, to produce the third version, of the European Code Against Cancer, was completed in 2003 (17). This involved 125 European scientists from different disciplines working in 18 subcommittees. The launch took place on 16 June 2003 in the European Institute of Oncology.

All evidence which became available since the previous version (16) was evaluated and modifications were made to the Code. In particular, in view of the mounting evidence of an increased risk of breast cancer with moderate consumption of alcohol, it was recommended under point 5 of the Code that 'If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a man and one drink per day if you are a woman'.

Summary

The association between alcohol consumption and the risk of breast cancer has been reported fairly consistently in numerous studies. Willett et al. (4) reported a significant association in the first prospective study with detailed exposure information. Howe et al. (6) demonstrated an association in a meta-analysis of six case–control studies designed to investigate nutrition and cancer.

In a meta-analysis of 38 epidemiological studies, the pooled risk estimates were 1.1 (95% CI: 1.1–1.2) for one drink per day, 1.2 (1.1–1.3) for two drinks per day, and 1.4 (1.2–1.6) for three or more drinks per day, relative to non-drinkers (7). A pooled analysis of six prospective studies reported similarly modest increases in risk, with a dose–response trend between alcohol consumption and breast cancer risk, after taking into

account the major risk factors (8). In another pooled analysis of 53 epidemiological studies with 58,515 cases and 95,067 controls, for each additional 10 g per day increase in alcohol intake, an increase in breast cancer risk of 7.1% (standard error, 1.3%) was reported in never smokers (9). Differences in risk due to alcohol drink type have not been observed (18). The association is consistent among both premenopausal and postmenopausal women although there is evidence emerging that the effect may be greater in (or confined to) ER+ve/ PR+ve breast cancer.

The third version of the European Code Against Cancer (17) incorporated the growing body of evidence into point 5 of the Code, recommending that women limit their alcohol consumption to one drink per day in view of the risk of breast cancer. This level was one half of the recommended daily limit for men.

On the basis of the growing body of evidence, the International Agency for Research on Cancer convened a Working Group to prepare the Monograph on Alcohol Drinking in February 2007. It was concluded that there was sufficient evidence that the risk of breast cancer was increased by alcohol consumption (2).

Very recent studies, notably from the Million Women Study, have strengthened knowledge of the impact of moderate alcohol consumption levels on increasing the risk of breast cancer. In view of the increasing widespread habit of binge drinking in younger women, it is of considerable importance that Chen et al. (13) have highlighted that the risk of breast cancer is associated with this type of drinking and that the

risk of breast cancer is increased by alcohol consumption patterns at
younger ages. Berkey et al. (19) also concluded that higher amounts consumed, and more frequent consumption of alcoholic drinks in adolescence may increase the occurrence of benign breast disease in young women.

Conclusions

A number of key questions arise when considering the association between alcohol consumption and breast cancer and have been addressed previously (5), but are worthwhile emphasizing once again.

Does even moderate consumption of alcohol increase the risk of breast cancer? There is a large body of evidence which is consistent with alcohol consumption increasing the risk of breast cancer and there is consistent evidence from large, prospective studies indicating that even moderate alcohol consumption increases the risk of breast cancer.

Does the risk of breast cancer increase with increasing alcohol consumption? The relative risk of breast cancer associated with alcohol consumption is quite small and it has taken the establishment of large, well-conducted studies to identify the risk. Most studies have confirmed a gradient of increasing risk of breast cancer associated with increasing levels of breast cancer, even at moderate levels of consumption.

Is alcohol consumption an important cause of breast cancer? Even although the increased relative risk is quite small, there

is such a large proportion of women who consume moderate amounts of alcohol. In France, 9.4% of breast cancer is attributable to alcohol consumption and 7.7% of all breast cancers in Europe are attributable to alcohol.

What is the effect of stopping or reducing alcohol consumption on breast cancer risk? It is unknown at the present time whether the increased risk of breast cancer associated with alcohol consumption declines when consumption is reduced or stopped altogether.

Is the mechanism by which alcohol consumption causes breast cancer known? The mechanism of action whereby alcohol consumption increases the risk of breast cancer is unknown at the present time. However, it is starting to appear as though the risk is stronger in (or confined to) women with ER+ve/PR+ve breast cancer. This could have the potential to focus attention on the search for a mechanism particularly now that the subtypes of breast cancer are becoming more clearly defined, although epidemiological knowledge of the aetiology of these subtypes is still lacking (20).

Irrespective of a lack of a strong biological mechanism, it is clear that alcohol consumption even at moderate dose levels increases the risk of breast cancer in women. Limiting or restricting daily consumption levels will reduce the risk of developing breast cancer.

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Chapter 29
Bladder and genitourinary tumours

Claudio Pelucchi and Carlotta Galeone

Introduction

Acetaldehyde, the primary breakdown product of ethanol in the body, is classified as carcinogenic to humans (1, 2) and is present in the urine after drinking alcohol (3). Besides acetaldehyde, several other components and metabolites of alcoholic drinks are excreted through the urinary tract. Alcoholic drinks have a diuretic effect; consumption of beer and other alcoholic drinks may increase the frequency of voiding, reducing the period of exposure of the bladder epithelium to potential carcinogens. Thus, a mechanistic role of alcohol consumption in the aetiology of genitourinary cancers is plausible.

In this section, we review the relation between alcohol and genitourinary cancers, with particular focus on the bladder. A large amount of data on the issue has been made available since the 1970s. We identified over 40 epidemiological studies providing information on alcohol and bladder cancer, 35 on kidney, and over 70 on prostate cancer. Further, recent meta-analyses provided detailed quantification of the associations with these neoplasms, reporting summary relative risks (RRs) at different levels of alcohol consumption and for various types of alcoholic drinks (4–7).

Bladder cancer

The association between alcohol consumption and bladder cancer has been widely investigated (8). Most data were given by case–control studies, but a few large cohort investigations are also available. In particular, the Million Women Study, a United Kingdom cohort study including about 1.3 million women and 928 bladder cancer cases, recently reported no significant association at any level of alcohol drinking (9). Similar findings emerged in three earlier United States cohort studies (10–12), whereas the Netherlands Cohort Study (13) reported an increased bladder cancer risk in men drinking ≥30 g/day of alcohol (RR = 1.63), however with no clear trend in risk. Case–control studies were also generally consistent, indicating a lack of meaningful associations. However, a few investigations found both decreased (14, 15) or increased (16–18) risks of bladder cancer. A large study in the United States, including 1,586 cases and 1,586 controls (14), reported a reduced risk in heavy drinkers (odds ratio, OR = 0.68) as well as in those with duration of consumption over 40 years (OR = 0.66). On the other hand, an Italian analysis (16) found a strong increase in risk for current alcohol drinkers, both in men (OR = 2.1) and women (OR = 3.4). A meta-analysis summarized the evidence on the issue by pooling data of studies adjusted at least for age, sex, and smoking habit (4). Eighteen studies were included, obtaining a pooled OR of 1.00 (95% confidence interval (CI): 0.89–1.10) for alcohol drinkers. The estimates were consistent across different study designs, varying little from 0.99 for cohort to 1.00 for hospital-based and 1.04 for population-based case–control studies.

Dose–risk relation

Another meta-analysis published in 2001 and based on two cohort and nine case–control studies of bladder cancer examined the dose–risk relation with alcohol drinking (19). After controlling for tobacco smoking, no significant excess risk was found, with pooled RRs of 1.02 for 25 g/day, 1.04 for 50 g/day, and 1.09 for 100 g/day of alcohol. Subsequent studies generally reported no meaningful trend in risk between alcohol consumption and bladder cancer (13, 20), though a large US population-based case–control study found a decreasing relation (14). Pelucchi and colleagues (5) performed an updated meta-analysis of epidemiological studies published up to October 2010, with specific focus on heavy drinking and dose–risk relation. Nineteen studies and over 11,000 cases of bladder cancer were included, but only nine investigations reported data for consumption of three or more alcoholic drinks/day. The pooled RR for heavy drinkers was 1.02 (95% CI: 0.78–1.33), with significant heterogeneity between studies. This was at least in part explained by different results across geographic areas, European studies showing higher risk estimates than US and Asian studies. However, a sensitivity analysis showed that a single study determined most of the elevation in risk in European studies. In conclusion, the evidence suggests no dose–risk relation, nor any association at high levels of consumption, between alcohol and risk of bladder cancer.

Type of alcoholic drink

A quantitative meta-analysis (4) examined the relation between alcohol and bladder cancer according to different

types of alcoholic drinks. Consumption of beer (pooled OR = 0.86, 95% CI: 0.76–0.96, based on ten studies) and wine (pooled OR = 0.85, 95% CI: 0.71–1.00, based on ten studies), but not spirits (pooled OR = 1.01, 95% CI: 0.87–1.15, based on nine studies) was inversely associated with bladder cancer risk. However, these results were based on a small number of investigations and, more importantly, significant heterogeneity was found between studies in both the meta-analyses of beer and wine drinking.

When examining the identified studies, no consistent pattern of risk is apparent with beer, wine, and spirits, with (for each beverage type) a few studies reporting positive and others negative associations (8, 14, 20–22). Given these considerations, and bearing in mind results for most other neoplasms (1), it appears that there is no difference in bladder cancer risk across different alcoholic drinks.

Confounding from tobacco smoking

Tobacco smoking, a recognized risk factor for bladder cancer, is positively correlated to alcohol drinking in several populations. Therefore, smoking habits generally act as a confounder in the alcohol–bladder cancer relation, leading to an over-estimation of the real associations. Most, though not all, of the identified studies were, however, adjusted for tobacco smoking. In the meta-analysis from Bagnardi et al. (19), an excess risk of bladder cancer for high alcohol intake emerged, but this result vanished after controlling for tobacco smoking. Similarly, in the Pelucchi et al. meta-analysis the pooled RRs among heavy drinkers were 1.38 in studies not adjusted and 0.97 in studies adjusted for tobacco smoking (5).

Kidney cancer

Data on the association between alcohol consumption and kidney cancer were provided by several epidemiological studies, mainly cohort studies. A recent International Agency for Research on Cancer (IARC) monograph stated that there was evidence of lack of carcinogenicity between alcohol consumption and kidney cancer (2). However, the role of alcohol consumption is still unclear as a number of studies found no association, but several others found a protective effect, especially of moderate and heavy drinking. A pooled analysis of 12 cohort studies on alcohol intake and renal cell cancer (23), including a total of 1,430 cases, found a significant inverse association for moderate to heavy consumption (i.e. ≥15 g/day), the reduction in cancer risk being about 30%, with no difference by sex. A similar reduction in cancer risk was found in the Million Women Study (9) for the highest category of alcohol consumption (i.e. >20 g/day). In a recent meta-analysis (6) which included 20 observational studies (one pooled analysis, four cohort, and 15 case–control studies), the estimated RRs, as compared to non-drinkers of alcohol, were 0.85 (95% CI: 0.80–0.92) for overall consumption, 0.90 (95% CI: 0.83–0.97) for light drinkers (i.e. 0.01–12.49 g/day), 0.79 (95% CI: 0.71–0.88) for moderate drinkers (i.e. 12.5–49.9 g/day), and 0.89 (95% CI: 0.58–1.39) for heavy drinkers (i.e. ≥50 g/day). The role of type of alcoholic drink, amount and duration of alcohol consumption, and the consequences of drinking cessation are other aspects which are still unclear. In particular, findings from the pooled analysis of 12 cohort studies did not suggest that intake of any specific alcoholic drink was more strongly associated with a reduced risk of renal cell cancer (23).

Prostate cancer

Two large cohort studies on alcohol consumption and prostate cancer have been made available during the last five years (24, 25), providing relevant information that added to about 70 other epidemiological studies. The first study, conducted in various European countries, included over 140,000 men and a total of 2,655 prostate cancer cases (24). No association was found between various measures of alcohol drinking and prostate cancer risk. Several analyses were conducted to investigate the role of amount of drinking and of different types of drinks, as well as to clarify whether results differed according to stage and grade of prostate cancer, but no meaningful association emerged. The second study, conducted in the United States, included 294,707 men and a total of 17,227 prostate cancer cases, 1,900 of which had advanced stage and 514 were fatal (25). Results differed according to the stage of disease. A modest positive association was found with non-advanced prostate cancer, with RR of 1.25 (95% CI: 1.13–1.37) for consumption of ≥6 drinks/day versus non-drinkers. On the other hand, no association was found with advanced disease (the corresponding RR was 0.97, 95% CI: 0.73–1.29) and an inverse relation emerged with fatal disease (RR = 0.45, 95% CI: 0.25–0.81).

The most updated meta-analysis on alcohol and prostate cancer was conducted during 2011 and included the results of both studies already described (7). The summary RR for alcohol drinking, based on a total of 50 case–control and 22 cohort studies, was 1.06 (95% CI: 1.01–1.10), in the presence, however, of significant heterogeneity between studies. No

significant increase in risk of prostate cancer was found for heavy drinkers (i.e. ≥4 drinks/day, RR = 1.08, 95% CI: 0.97–1.20), as compared to non- or occasional drinkers.

Conclusions

No material association emerged between alcohol drinking and bladder cancer in a revision of about 40 epidemiological investigations. This conclusion is further supported by two meta-analyses that recently provided definite quantitative evidence on the issue (4, 5). Results were somewhat inconsistent between studies, possibly because of different drinking patterns and correlates—mainly tobacco smoking—among different populations. However, residual confounding by smoking might explain the moderate increase in risk of bladder cancer reported in some studies.

Increasing evidence from large cohort studies indicates a protective role of moderate alcohol drinking on kidney cancer. This has been explained through the effects of alcohol on insulin sensitivity (26), or through a role of fluid and/or antioxidants intake contained in alcoholic drinks. The risk appears to level-off in heavy drinkers.

Results for prostate cancer are somewhat heterogeneous. Overall, the available evidence suggests no meaningful role of alcohol consumption. In particular, no trend in risk was observed with increasing alcohol consumption, as heavy drinkers showed no meaningful excess risk in most studies. Potential differences in the alcohol–prostate cancer relation according to stage or grade of disease remain unclear and should be further investigated.

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Part VII
Alcohol and non-malignant disease

Chapter 30
Cardiac disease

William H. Frishman

Introduction

Alcohol (ethyl alcohol, ethanol, liquor) holds a special place among substances of abuse. Unlike the others, its use in moderation is accepted by society and, in fact, its consumption is often encouraged for health reasons (1). Many cultures and religions have traditional ceremonies which not only incorporate, but actually require the use of alcohol, especially wine. However, similar to the other substances of abuse, alcohol also causes many medical problems, most notably, liver disease. This chapter discusses another common alcohol-related problem—that of alcohol-induced cardiovascular disease.

Over the past 20 years, alcohol has increasingly been viewed as a potential ally in the war against coronary heart disease (CHD) (2–6). Many investigators have reported on the beneficial effects of routine alcohol intake, and non-scientific journals have provided these data to the lay public. Therefore, the positive effects of alcohol will also be discussed.

Alcohol has also been linked to some specific detrimental effects on the cardiovascular system. These include alcoholic cardiomyopathy (ACM), systemic hypertension, and arrhythmia.

Alcoholic cardiomyopathy

In 1884, Bolinger described cardiac enlargement in persons who had habitually consumed excessive amounts of beer. Later, in 1893, Steel recognized a clinical syndrome of heart failure in the same population (7). Since then, the definition of ACM has been refined to include cardiomegaly, ventricular chamber dilation, myocardial contractile abnormalities, and pathological alterations in the heart muscle involving both ventricles in patients whose sole causative agent is ethanol consumption of >80 g/day for ten years or more (8). Some recent surveys suggest that less, but still significant, consumption of alcohol may play a part in some 'idiopathic' cases (9). Symptoms generally become clinically evident between 30 and 60 years of age. Symptomatic heart failure is typically of sudden onset (7). ACM is a leading cause of secondary CM in the United States. In 1987, 4.2% of reported deaths resulting from CM were due to alcohol (10).

For decades, the nature of ACM was obscured by its confusion with beri-beri, a disorder that originates from thiamine deficiency. ACM, however, is a low output form of heart failure, unlike beri-beri which is characterized by peripheral vasodilation and high output failure. In 1956, ACM was described in well-nourished alcoholics (7). Since then, the association of ACM and excessive alcohol consumption has been well established (11, 12). In fact, a direct correlation of lifetime alcohol dosage with left ventricular (LV) mass and an inverse correlation with ejection fraction (EF) have also been established (13). Timmis et al. (14) studied parameters of myocardial contractility in volunteers who were stratified according to their previous alcohol exposure. The results

showed a progressive decline in ventricular function in response to ethanol exposure. The authors suggested
that this finding implies some degree of chronic myocardial impairment which is proportional to the degree of ethanol exposure. Also, the low prevalence of clinical nutritional deficiency in patients with ACM and the infrequency of heart disease in patients with cirrhosis support the contention that cardiac abnormalities are not dependent on malnutrition (11). It has been shown that the vulnerability to cardiomyopathy (CM) among chronic alcohol abusers is partially genetic and related to the presence of the angiotensin-converting enzyme (ACE) DD genotype (15).

In early stages the disorder tends to be subclinical. Cardiac hypertrophy and dilatation are clinically evident by non-invasive means only. LV end-diastolic pressure is increased and LVEF decreased (7, 16). Up to one-third of all chronic alcoholics have a depressed EF (13).

In experimental models, it has been shown that rats given 30% of calories as ethanol every day for eight months displayed haemodynamic effects similar to those seen in humans with long-term alcohol intake. Systemic arterial pressure, LV peak systolic pressure, and myocardial contractility were decreased with an unchanged heart rate. The alcoholic rats demonstrated a 5.2-fold elevation in LV end-diastolic pressure. Finally, ventricular chamber volume was increased through myocardial remodelling, with decreased LV thickness. These alterations resulted in a 571% increase in the diastolic volume (17).

Those who succumb to the disease have hearts which weigh up to 900 g (normal 300–325 g), dilated and hypertrophied

atria and ventricles, and irregular foci of thickened, fibrotic endocardium, which is often overlaid by mural thrombi. Microscopically, diffuse interstitial fibrosis, interstitial chronic inflammation, and hypertrophic, as well as atrophic, myocytes are present (7).

Although ACM is more common in men due to their higher frequency of alcoholism, women are actually more sensitive to the cardiac effects of ethanol (7). In a large, cross-sectional study (18), alcoholic women were compared to both alcoholic men and non-alcoholic women regarding myopathy and CM between the sexes. They found that although female alcoholics had a mean lifetime dose of alcohol which was only 60% that of male counterparts, they suffered myopathy and CM just as frequently. The threshold dose for the development of CM and myopathy was considerably less in women than in men. Also, the decline in EF with increasing alcohol dose was significantly steeper. Kupari and Koskinen (19), however, found that in alcoholic women, indices of LV function were affected to the same extent as men when adjusted for body surface area and other indices of systolic or diastolic dysfunction.

Although the exact mechanism has not been elucidated, the development of ACM has been attributed to the increased stimulation from the peripheral sympathetic nervous system. Alcohol may augment obstruction in hypertrophic CM by this mechanism. Excess catecholamines and adrenal hypertrophy have been identified in rats receiving excessive alcohol, and subsequently developing cardiac hypertrophy (20, 21). Prazosin, given concurrently with ethanol in experimental rats, did not prevent, and actually enhanced the cardiomegaly seen in rats given ethanol alone, suggesting that postsynaptic

alpha-1-adrenoceptor stimulation is not an important contributor to ethanol-induced cardiomegaly (20). In contrast, when similar rats were first exposed to metoprolol, a beta-adrenergic blocker (in high levels only—100 mg/kg thrice daily), it prevented the previously seen cardiac hypertrophy, suggesting there is a beta-adrenoceptor-mediated link in the cardiac hypertrophy induced by ethanol (21).

In early cases of ACM the heart may return to normal following discontinuation of alcohol use (22). Demakis et al. studied the natural course of ACM from time of diagnosis for an average of 40.5 months (22). They divided patients into groups based on progression—clinical improvement, remained unchanged, and symptoms deteriorated. The two most significant factors in improvement of symptoms and prolonged outcome were abstaining from alcohol, and a short duration before beginning symptomatic treatment (i.e. digitalis, diuretics). Even patients with New York
Heart Association class IV heart failure have demonstrated an improvement in symptoms as well as objective criteria (LVEF) with abstinence (23). Previous studies showed some benefit of prolonged bed rest; however, only 21% of patients with improvement maintained the benefit upon returning to exercise (22).

Abstention is the cornerstone to treatment of patients with ACM (24). As already stated, this is the only true hope for reversal of the process. However, Nicolás et al. (25) showed that both abstinence and controlled drinking of up to 60 g of ethanol per day (four standard drinks) were comparably effective in promoting improvement in cardiac function. Patients should also receive treatment for heart failure

including diuretics, ACE inhibitors, angiotensin II blockers, beta-blockers, and digoxin, as with all forms of dilated cardiomyopathy (DCM) (26).

Patients with ACM and signs and symptoms of heart failure have an average life expectancy of less than three years (7). However, in comparison, patients suffering from ACM have a significantly better long-term prognosis than patients with idiopathic DCM. In one study, the actuarial survival of a patient with idiopathic DCM was only 30% versus 81% in ACM. The transplant-free survival was 20% and 81%, respectively (27).

Coronary artery disease

The influence of alcohol on the development of coronary artery disease (CAD) has been evaluated in many large epidemiological investigations (28–31). Unfortunately, there are some inherent difficulties in studying the relationship between alcohol use and CAD (32, 33).

The Honolulu Heart Study looked at Japanese-American men, 47% of whom were non-drinkers (29). They reported a six-year age-adjusted incidence of acute myocardial infarction (MI) which was 34% lower among all drinkers, and five times greater in non-drinkers than in those who drank >40 ml/day.

In a study of 85,001 patients examined over a four-year period and followed for evidence of CAD, 756 patients were subsequently hospitalized for CAD. The data were adjusted for age, sex, race, smoking, and caffeine intake (31). A significant and progressively lower risk of CAD was found in

drinkers of alcohol when compared to controls (lifelong abstainers). The relative risk in alcohol users was between 0.29 and 0.70 for acute MI, chronic ischaemic heart disease, and other acute coronary syndromes. The protection became apparent at one to two drinks daily. In the Auckland Heart Study—a case–control study of 295 patients—a 40% lower incidence of acute MI was seen with all levels of alcohol intake compared to lifelong abstainers (28). Animal models have also been used to demonstrate benefit. Rats given ethanol and induced to have an MI actually had longer survival rates than controls not fed alcohol (34). This may relate to the vasodilatory and antiplatelet effects of alcohol which are described later in this section.

Epidemiological studies like those described in this chapter, showing benefit of moderate alcohol consumption on CAD, were often criticized for a possible bias due to a self-imposed avoidance of alcohol relative to pre-existing conditions. Because of this, the association between self-reported alcohol consumption and CAD was studied prospectively in 51,529 male health professionals (35). The authors reported a relative risk for CAD (fatal or non-fatal MI or coronary artery bypass graft/percutaneous transluminal coronary angioplasty) which was between 53% and 71% for those reporting alcohol intake of >5.1 g/day. This was in comparison to a relative risk of 1.0 in non-drinkers. These results were adjusted for other coronary risk factors including dietary intake of fat and fibre. Also, patients were excluded if they had pre-existing conditions such as hypertension, diabetes, or gout, which would make them less likely to use alcohol (35). Other studies support the ‘U-shaped’ or ‘J-shaped’ curve of light-to-moderate alcohol consumption set forth in the earlier studies (36–40).

Surprisingly, this seems to hold true even for patients with type 2 diabetes (41). The use of alcohol in diabetics should be strictly monitored as glycaemic control can be compromised (42).

Whereas a protective effect of alcohol intake was demonstrated on a long-term basis in the previously mentioned studies, an acute protective effect of alcohol was suggested in a case–control study designed to investigate the hypothesis that alcohol acutely increases the risk of both non-fatal MI and coronary death in the 24 hours after drinking (43). The results actually reflected a lower estimated risk of CAD in patients who reported drinking alcohol in the previous 24 hours (odds ratio 0.75 for non-fatal MI in men to 0.46 for coronary death in women). The risk was not significantly changed according to how many drinks were reported (between one and four). In contrast, a study by Mukamal et al. did not show an association between recent alcohol consumption and the occurrence of MI (44). Zhou et al. demonstrated that moderate to heavy alcohol consumption increased the risk of CAD in Chinese men (45).

While the benefits of moderate alcohol intake are now accepted (46, 47), the exact mechanism for the benefit is still not totally resolved, and may not be seen in younger patients (48). The actual cause for benefit is probably multifactorial in aetiology. The two most commonly cited actions of alcohol which probably contribute to a benefit in CAD are its favourable effects on haemostatic factors and the lipid profile (49, 50).

Congestive heart failure

In contrast to what was presented at the beginning of this chapter regarding the CM effects of alcohol, recent studies have shown that there may be a potential benefit from moderate alcohol use in patients with pre-existing LV dysfunction. In a long-term follow up observational study published by Abramson et al. (51) there was a correlation between moderate alcohol consumption and a lower heart failure incidence, unrelated to a reduction in MI risk. It was found that in persons without heart failure, the relative risk of developing symptomatic congestive heart failure was 1.00, 0.79, and 0.53 for those who consumed no alcohol, 1–20 oz., and 21–70 oz. per month, respectively. Even after adjustments for age, sex, and incidence of MI, this relationship held. These findings were independent of the type of alcohol consumed (51).

In patients with documented ischaemic CM (EF <35%), a similar reduction in the relative risk of both all-cause mortality (85%) and MI (55%) was observed among patients reporting light-to-moderate alcohol consumption versus those reporting none. There was no difference in the two groups with regard to death from ischaemia, arrhythmia, or progressive heart failure (52).

Conclusion

Alcohol is a dichotomous substance of abuse. On the one hand, it can cause devastating, untimely myopathic disease in rather young patients when used in large amounts. On the

other hand, it may reduce the risk for developing CAD and congestive heart failure when used in moderation.

It is important to remember, however, that alcohol is still an addictive substance which can cause unfortunate consequences related to its use that go beyond the scope of this presentation. As clinicians, we must be careful in our advocacy of the use of alcohol (53–55). We must stress the principles stated earlier, that while a moderate amount of alcohol may be helpful, patients should be made to understand that more is not better.

Finally, although it was discussed how alcohol moderation in patients can be helpful in avoiding heart disease, it is not our only means for providing benefit. Promoting other lifestyle modifications in alcoholic patients can help reduce risks and promote an all-around sense of well-being at
the same time. Exercise, better eating habits, smoking cessation, and compliance with medication (i.e. antihypertensives) can go a long way to improving clinical outcomes, and should not be ignored when treating the alcoholic patient.

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Chapter 31
Vascular disease

Kenneth J. Mukamal

Introduction

Consistent evidence over four decades (1) has addressed the relationship of alcohol consumption with coronary heart disease (CHD). However, the associations of alcohol consumption with other forms of vascular disease have not been nearly as well characterized. Among these vascular diseases are hypertension, cerebrovascular disease (including ischaemic and haemorrhagic stroke), peripheral arterial disease (PAD), abdominal aortic aneurysm (AAA), and venous thromboembolism (VTE). As might be expected from the diverse pathophysiologies and vascular beds involved, these diseases are heterogeneous, even within a single disease, and subtypes do not always have similar associations with alcohol intake. However, a few common mechanistic threads help to place these associations into perspective.

Hypertension

Perhaps the most important and yet most perplexing vascular complication of alcohol intake is hypertension. This association has been recognized for decades (2), yet its mechanisms remain elusive.

Consistent alcohol intake above recommended limits—typically three drinks per day or more—increases the

risk of hypertension (3). Studies worldwide have found similar results (4–6), suggesting it is unlikely to be related to a single drink type. Although estimates vary, some 5–10% of cases of hypertension may be attributable to excessive alcohol use (3, 7).

Whether alcohol consumption within recommended limits (i.e. two drinks per day for men, one for non-pregnant women) also causes hypertension remains uncertain. A direct association has been proposed in meta-analyses with few prospective studies, with higher risk even within recommended limits (8), but in a few cases, moderate alcohol consumption has been associated with a lower risk of hypertension (9, 10). One hypothesis for this inconsistency is that the higher risk observed among moderate drinkers may reflect underreporting, with higher risk limited to individuals whose true consumption exceeds two drinks per day (11).

Why alcohol raises blood pressure is not entirely clear; it is not a vasoconstrictor or sympathomimetic. In intervention studies (12), there are biphasic effects of blood pressure, with lower blood pressure shortly after drinking (consistent with a vasodilating effect) that rebounds above baseline later. In circadian studies, alcohol consumed in the evening leads to lower blood pressure soon afterward, an effect that wanes by morning, but with a sustained increase in heart rate (13). Thus, the inconsistencies in effects of alcohol on blood pressure may reflect variability based on timing of blood pressure measurement.

Genetic differences may contribute to heterogeneity in effects of moderate drinking. African Americans appear more likely

to have increased risk of hypertension with moderate drinking than
do white Americans (5, 14), perhaps pointing to the *ADH1B*3* polymorphism (which increases conversion of alcohol to acetaldehyde) as a contributor to higher risk (15). One intriguing observation that points to the causal role of alcohol in hypertension is the consistent association of *ALDH2*2* alleles (16) with lower risk of hypertension, even when compared with heterozygotes. Because variant homozygotes consume very little alcohol, these studies establish alcohol as a risk factor for hypertension, but do not clearly define whether a safe level of intake for blood pressure exists.

Stroke

Stroke—or cerebrovascular accident—represents a heterogeneous mix of subtypes with complex associations with alcohol. There are two main types of stroke—ischaemic and haemorrhagic—and a few subtypes of each (i.e. atherothrombotic, lacunar, embolic, subarachnoid haemorrhage, and intracerebral haemorrhage). Perhaps the easiest way to reconcile the different associations of alcohol with these various types is to review four important stroke risk factors.

As noted, alcohol intake above recommended limits clearly increases the risk of hypertension, a strong risk factor for all types of stroke. Even moderate intake may have blood pressure-raising effects, although this is less consistent and dramatic. An important protective factor for vascular disease is high-density lipoprotein cholesterol (HDL-C), which

alcohol consumption increases in a dose-dependent manner (17). However, HDL-C is a less strong protective factor for ischaemic stroke than for CHD. Further, heavy alcohol consumption, even episodically, raises risk of atrial fibrillation (18), an extremely strong risk factor for ischaemic stroke. Finally, alcohol intake directly inhibits platelet function (19), acting as an antithrombotic agent that may have both beneficial and detrimental effects.

Ischaemic stroke, the most common type in Europe and the Americas, occurs when intracerebral arteries become acutely occluded, either through thrombosis or distal embolism and often at the site of existing stenoses. Given that hypertension and atrial fibrillation are particularly strong risk factors for ischaemic stroke, and that both of these are associated with heavy drinking, it could be anticipated that heavy drinking would increase risk of ischaemic stroke. Moreover, because even moderate drinking may raise blood pressure hours later, the expected benefit on ischaemic stroke from higher HDL-C among moderate drinkers might be anticipated to be blunted by higher blood pressure.

Indeed, this has been observed, as the apparent inverse association of light alcohol intake with ischaemic stroke risk occurs at a lower dose of alcohol consumption (typically less than daily drinking) and with less risk reduction than does the corresponding association with CHD risk (20, 21). One meta-analysis reported that consumption of <12 g/day was associated with a relative risk of 0.82, but that consumption of 60 g/day or more was associated with higher risk (22). In a large study of American men, the lowest risk of ischaemic stroke occurred among men who consumed one drink every

3–4 days (23); the lowest risk for CHD in the same study occurred among men who drank daily (24).

Even ischaemic stroke has important subtypes whose associations with alcohol may differ (25). Thrombotic stroke occurs when thrombotic occlusion occurs *in situ*, while embolic stroke reflects distal embolization, often from atrial fibrillation. Small amounts of alcohol might be anticipated to reduce clotting but not necessarily to alter risk of atrial fibrillation, while heavy drinking would be anticipated to increase the latter risk as well. In the large study of American men previously noted, the hazard ratio associated with intake of less than one drink per day was 0.76 for thrombotic stroke, suggesting a trend toward lower risk. In contrast, risk was doubled (albeit not significantly) for embolic stroke. Larger studies of ischaemic stroke subtypes are needed to confirm these findings.

Not surprisingly, heavier drinking clearly increases the risk of ischaemic stroke (22, 23), presumably because of its marked effect on blood pressure. Interestingly, even single episodes of consumption of three or more drinks or drinking to intoxication may acutely trigger ischaemic stroke (26, 27).

The second stroke type is haemorrhagic stroke, which is most common in Asia. It comprises subarachnoid and intracerebral subtypes (i.e. bleeding around or into the brain). The major risk factors for haemorrhagic stroke are hypertension and bleeding tendency, both of which are associated with alcohol intake in a dose-dependent manner. A meta-analysis of cohort studies of subarachnoid haemorrhage found increased risk restricted to heavier intake (>150 g/week), with a summary relative risk of 2.1 (28), but a comparable meta-analysis of

case–control studies of intracerebral haemorrhage found odds ratios of 2.05 for intake ≤56 g/day and 4.11 for intake >56 g/day (29). Thus, light drinking may reduce risk of thrombotic but increase risk of haemorrhagic stroke, while heavy drinking increases risk of all types of stroke.

Peripheral arterial disease and abdominal aortic aneurysm

PAD, most commonly localized to the lower extremities, is widely prevalent, particularly in older adults, and a major cause of disability and loss of mobility. The pathophysiology of and risk factors for PAD provide some context for its association with alcohol intake. PAD occurs with progressive atherosclerotic accumulation in arterial walls, particularly in the iliac beds and below; in the aorta, aneurysmal dilatation is the more common manifestation. However, acute vascular insufficiency is uncommon in the legs. In addition, it is uniquely particularly strongly related to cigarette smoking and, to a lesser degree, hypertension. The association with cigarette smoking is so strong (30) that it likely colours the evidence for alcohol and PAD because alcohol consumption and cigarette smoking tend to co-occur frequently.

Not surprisingly, the evidence relating alcohol intake to PAD is not as extensive as that for either stroke or CHD; no meta-analyses have been conducted and only a few prospective studies are available. The Framingham Heart Study (31) demonstrated hazard ratios for risk of claudication of 0.67 for consumption of 1–2 drinks per day for men and 0.44 for 0.5–1 drinks per day for women. A similar magnitude of lower risk was observed in the Physicians

Health Study for intake of seven or more drinks per week (32). A study among diabetic adults found no association of alcohol intake with risk of PAD (33), but in a cohort of older adults, U-shaped relationships of alcohol intake with two measures of PAD were found, with lowest risk among consumers of 1–13 drinks per week (34).

Little is also known about the relationship of alcohol consumption with risk of AAA, a form of vascular disease classically related to hypertension and most common among men. Among male smokers, a Finnish study found a U-shaped relationship (35), but a large study of American men found a direct relationship of alcohol intake with higher risk, consistent with effects of alcohol on blood pressure, with 65% increased risk among men consuming two or more drinks per day (36).

Venous thromboembolism

VTE and arterial forms of vascular disease differ in key ways. Although some cardiovascular risk factors, such as diabetes and obesity, increase risk of VTE, most others do not (37). As such, the most important contribution of alcohol may be its effects on clotting. Alcohol intake tends to be associated with lower levels of procoagulant factors (17) and prolongs bleeding time (38). Thus, one might anticipate that alcohol intake would tend to be associated with lower risk of VTE.

To date, studies on alcohol use and VTE remain mixed. Some large case–control and cohort studies have suggested a dose-dependent lower risk of VTE related to alcohol intake (39–41), while others have observed no effect (37, 42).

Cumulatively, these results are inconclusive but suggest a possible inverse association with alcohol consumption.

Conclusion

There are complex relationships between moderate and heavy alcohol consumption and vascular disease, reflecting their heterogeneity and the multiple mechanisms by which alcohol consumption can influence vascular disease. Heavy alcohol consumption clearly increases risk of hypertension, all forms of stroke, and probably AAA. For moderate alcohol consumption, relationships differ. It has a less pronounced effect on blood pressure and appears to be associated with a lower risk of ischaemic stroke, at least among light drinkers, and possibly a lower risk of PAD and VTE. These relationships concord with known effects of alcohol intake on cardiovascular risk factors, and until randomized trials are performed (if ever), stand as our best evidence regarding the effects of alcohol on vascular disease.

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Chapter 32
Benign diseases of the gastrointestinal tract

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Introduction

Alcohol consumption has non-neoplastic effects on the gastrointestinal (GI) tract by directly impacting the GI mucosa and by actions mediated following absorption into the bloodstream. Mild to moderate alcohol consumption may enhance bactericidal action in the stomach and deliver antioxidant nutrients to the GI mucosa. Acute or prolonged heavy alcohol consumption interferes with the normal structure and function of the GI tract, often damaging the epithelium and contributing to life-threatening conditions such as GI bleeding.

The oesophagus

Heartburn and gastro-oesophageal reflux disease

The oral cavity and oesophagus are exposed to alcohol immediately after its ingestion. Chronic alcohol abuse decreases the secretion of saliva by damaging salivary glands, causing tooth decay, gum disease, glossitis, stomatitis, and parotid enlargement (1, 2). Of significant consequence in the developed world is mucosal inflammation of the distal oesophagus, colloquially referred to as heartburn. When objective signs of mucosal damage, such as erosions, are also present, the diagnosis of reflux oesophagitis is made (3).

Presenting symptoms of reflux oesophagitis include chest pain, substernal or mid sternal burning sensation, difficulty swallowing, coughing, water brash, and hoarseness. Gastro-oesophageal reflux disease (GORD; GERD in the United States), is one of the most common conditions among adults and is the most common GI symptom treated in ambulatory clinics in the United States. Lifestyle modifications, such as losing weight, eating earlier in the day, and abstaining from alcohol and cigarette smoking, may improve symptoms, although no controlled studies have specifically evaluated the effect of such modifications (4, 5). More than 60 million prescriptions for GORD medications were filled at US retail pharmacies in 2004, the majority of which were for proton pump inhibitors (PPIs) (6, 7). There is no gold standard diagnostic test for GORD; evaluations include upper GI endoscopy, radiological assessment, ambulatory 24-hour oesophageal pH monitoring, manometry, and trials of PPIs.

GORD is initiated and maintained by the reflux of gastric contents, including acidic chime or bile, into the oesophagus. GORD typically occurs because the lower oesophageal sphincter does not maintain adequate tone at rest or because it relaxes inappropriately allowing the retrograde movement of gastric contents into the oesophagus (4). A single alcoholic drink can cause relaxations of the oesophageal sphincter (1). GORD may be exacerbated if oesophageal peristalsis is disordered so that gastric contents are not cleared from the oesophagus or if the motor function of the stomach is impaired so that it does not empty in a timely fashion. Left untreated,
ongoing mucosal damage may lead to oesophageal stricture (5). Decreased salivary bicarbonate and alcohol-induced

peripheral neuropathy contribute to diminished oesophageal acid clearance. The intensity of reflux and the presence of oesophagitis correlate with the dose and duration of alcohol consumption. In addition, the noxious effects of alcohol may continue even after consumption has ceased, revealing that it may sensitize the mucosa to damage (8).

As early as 1978, a small clinical trial demonstrated that even modest amounts of alcohol consumption—180 ml of 100-proof vodka—induced GORD in 11 of 12 healthy adult participants after ingesting a standard meal (9). Studies note that a high proportion of alcoholics have GORD and it may go undiagnosed. In a Romanian study of 86 chronic ethanol abusers, reflux was symptomatic in 62% of the participants and 30 patients (35.7%) presented with oesophagitis with columnar epithelial metaplasia (10). Other studies have found similar high incidence of Barrett's metaplasia in alcoholics (1). Alcohol-induced generation of nitric oxide may be the major contributing factor to diminished sphincter tone because nitric oxide mediates smooth muscle relaxation (11). Plasma nitrite and nitrate levels are higher in moderate alcoholics than in abstainers; this increase is more pronounced in heavy alcoholics (12).

Alcohol also contributes to the development of GORD by causing peristaltic dysfunction of certain portions of the oesophagus and slowing both oesophageal motility and gastric emptying (3, 5). High-amplitude contractions in the middle third of the oesophagus coupled with a decrease in the lower/middle-amplitude ratio are pathognomonic of excessive alcohol consumption, and tend to improve with abstinence (8, 13). Strong, simultaneous contractions provoke disturbed clearance due to failed peristalsis, which is worsened by the

occurrence of repeated reflux events into the oesophagus when the pH is still acidic from previous reflux episodes (14). Chronic alcoholics are also more prone to spontaneous sphincter relaxations (13). Moderate alcohol consumption does not appear to exacerbate GORD when a PPI is administered. In one placebo-controlled crossover trial, gastric emptying was not delayed in beer drinkers who concomitantly received esomeprazole (15). Patients with GORD should be advised to avoid alcoholic drinks since alcohol consumption induces reflux in healthy volunteers and increases it in patients with GORD (15).

The stomach

Alcohol consumption has been implicated in diseases of the stomach by its inflammatory and erosive effects. By stimulating acid production, alcohol contributes to structural dyspepsia and creates an environment of hyperacidity which perpetuates tissue vulnerability. Human and animal studies have shown that alcohol concentrations of 10% or greater disrupt the gastric mucosal barrier and increase the mucosa's permeability (1). Alcohol may also decrease prostaglandins and induce mucosal injury. These mucosal insults contribute to pathological conditions including superficial gastritis, chronic atrophic gastritis, and peptic ulcer disease (5). Alcoholic gastritis, just similar to gastritis induced by non-steroidal anti-inflammatory drugs (NSAIDs) or other drugs, presents as dyspepsia (5). Chronic alcoholics are also usually cigarette smokers and the combination of heavy drinking and cigarette smoking, creates the 'perfect storm' for ulcers to develop and to resist healing (16). In a study of 1,020 consecutive patients who were admitted for alcohol

detoxification in New York City, United States, peptic ulcer disease recognized on endoscopy was present in (23.8%) of all patients and upper GI mucosal inflammation was present in all patients (17).

The hormone gastrin is synthesized and released from G cells in the gastric antrum. Its regulation is tied to neurocrine stimulation via the vagus nerve, paracrine inhibition by somatostatin, luminal food content, and luminal acidity. Dose and type of alcohol consumed affect stomach actions. Lower ethanol content drinks such as beer and wine cause gastrin to be released; higher ethanol concentration drinks (hard liquor/ spirits) may actually be inhibitory and stimulate neither gastrin release nor gastric acid secretion (18). Non-alcoholic constituents of beer and wine may be responsible for the stimulatory actions of both drinks on gastric acid secretion and release of gastrin, although there is no consensus on current aetiological theories (18). Other researchers have demonstrated that fermented, but not distilled drinks induce elevations in the hormone gastrin leading to greater acid release (8). Alcoholics and binge drinkers are noted to have delayed gastric transit and gastric emptying with drink type and quantity affecting motility (5, 19). Low-dose alcoholic drinks appear to accelerate gastric emptying and bowel motility while higher-dose drinks delay emptying while reducing bowel motility (20, 21). Both wine and beer are rich in phytochemicals, including flavonoids, phenolic acids, and hydroxycinnamates, which have numerous biological and antioxidant properties that may influence gastric acid secretion and motility. Many studies have shown that *Helicobacter pylori*—the main culprit in peptic ulcer disease—is less frequently discovered in regular drinkers and that moderate alcohol consumption may favour suppression

and eventual elimination of *H. pylori* infection (8, 22). At higher levels of alcohol consumption, the antimicrobial effects of alcoholic drinks may be opposed by adverse systemic effects, such as derangements of immune defences (22).

Upper gastrointestinal bleed

National Hospital Discharge Survey (United States) data from 1992–1999 found an annual hospitalization rate for upper GI (UGI) bleeding of 149–172/100,000 (23). Despite recent advances in endoscopic therapy, mortality associated with GI bleeding remains significant at 5–11% (23). Acute GI bleeding may present as haematemesis or haematochezia with or without haemodynamic instability. Individuals with chronic GI bleeding may have asymptomatic iron-deficiency anaemia or haemoccult-positive stool on screening for colorectal cancer. As in the general population, occult blood loss in the stool of alcoholics is an important marker for colorectal neoplasia and faecal occult blood should not be attributed to alcohol ingestion without the exclusion of coexistent pathology (24). Factors associated with mortality due to UGI bleeding identified in prospective studies include liver disease and liver failure which are characteristic features of chronic alcoholics.

UGI bleeding is more common in NSAID users and NSAID users are often more likely to be alcoholics (25). The combination of alcohol and NSAID use potentiates the likelihood of developing a UGI bleed and, not surprisingly, GI bleeding is more lethal in the heaviest of drinkers. In a European study of 330 individuals who presented with UGI

bleeding, compared to non-NSAID users, individuals who took NSAIDs included a significantly greater proportion of alcohol abusers (P = 0.01), whose bleeds occurred predominantly from erosive gastritis (25). Additionally, in a recent US study of 128 patients who underwent emergency surgery for peptic ulcer disease, half of patients were cigarette smokers and 34% were abusing alcohol, while 53% were current NSAID users (26). Notably, perioperative mortality in this study was 12.5%.

Conversely, in a study of 727 patients evaluated by the gastroenterology consultative service at a large US inner-city hospital presenting with UGI haemorrhage, 212 of whom were classified as chronic alcohol users (80 g or more per day for at least one month), peptic ulcer disease was the most common cause of bleeding (60%) while gastropathy was aetiological in only 32 patients (4%) (17). Comparing the causes of bleed between drinkers and non-drinkers in this study, drinkers were more likely to bleed from varices ($p = 0.024$) or other portal hypertension-related causes ($p < 0.01$), whereas peptic ulcer was more common in non-drinkers compared with chronic drinkers (67% versus 53%; $p < 0.01$). Antioxidants in wine and beer may also affect coagulation. The polyphenol resveratrol, a constituent of red wine, inhibits platelet reactivity and has vasodilatory actions which could promote UGI bleeding (27).

Mallory–Weiss syndrome

First described in 1929 by Mallory and Weiss as the triad of ‘vomit, alcohol, and hematemesis’, Mallory–Weiss syndrome today is characterized by massive bleeding subsequent to

tears in the GI mucosa at the junction of the oesophagus and the stomach (28). About 10–15% of all UGI bleeds are due to these tears (1); in most cases, they are the consequence of elevated gastric pressure caused by repeated retching and vomiting due to excessive alcohol consumption, often in the setting of binge drinking (29). In about 40–50% of cases, the underlying aetiology for Mallory–Weiss syndrome is alcohol consumption, either acutely or chronically (1, 29). About a quarter of individuals who suffer this type of tear may have a complicated course and complications are more common in those with heavy alcohol consumption as well as coagulopathies—a frequent consequence of decreased clotting factor synthesis noted in alcoholic cirrhotics (29). They are more fatal in alcoholics and alcoholics are more likely to experience a re-tear (28). In a US study of 34 individuals evaluated endoscopically for Mallory–Weiss tear, 30-day mortality included four deaths, all of whom had multiorgan system failure due to varices or bleeding ulcer(s), and all of the deaths were in patients who had a history of alcohol abuse (30).

The small intestine and colon

Maldigestion, malabsorption, and diarrhoea

Alcohol impacts the nutritional status of heavy drinkers, mainly through diminished intake and malabsorptive effects in the small intestine and colon (31). Alcoholics frequently manifest disaccharidase deficiency in the form of lactose intolerance (8). In a study of alcoholics without liver failure or serious illness who presented with symptoms of dyspepsia, nausea, or diarrhoea, C-D-xylose breath test results mirrored

those of untreated coeliac disease patients, consistent with malabsorption (32). Alcoholics demonstrate reduced absorptive area due to pathology of microvilli which correlates to histology noted in lactase deficiency (19). Even in the absence of overt malnutrition, chronic alcohol ingestion decreases intestinal disaccharidase activities (33). Alcoholics also show reduced duodenal absorption of proteins, fats, and carbohydrates (21). Significant maldigestion and malabsorption of nutrients including folic acid, calcium, zinc, vitamins B12, C, D, and E, as well as glutathione and selenium have been demonstrated in very heavy drinkers (34–36). These deficiencies compromise critical enzymatic functions and lead to ineffective immune function that promotes deleterious and compounding health issues (37). It is not surprising that individuals with inflammatory bowel disease note worsening of GI symptoms after alcohol consumption (38).

The aetiology of macronutrient and micronutrient deficiencies among alcoholics is multifactorial, and includes dietary folic acid and protein deficiency, pancreatic insufficiency, abnormalities of biliary secretions, and direct effects of alcohol on the GI tract (31). Initially, intestinal microvilli are damaged by sustained exposure to ethanol. Data derived from animal studies supports the theory that ethanol acutely disrupts nutrient transport by changing microvillus membrane lipid fluidity; the absence of adaptive changes in membrane composition and fluidity may explain the persistent absorptive defects observed with chronic alcoholism as well as increased intestinal permeability (39). Secondly, heavy drinkers often develop chronic pancreatitis and the characteristic diminished release of pancreatic enzymes results in the loss of macronutrients—notably fat and

protein—in the stool along with micronutrients (1). Nonetheless, even alcoholics without chronic pancreatitis have been shown to malabsorb fat and protein (8). Thirdly, gastric dysmotility due to the toxic effects of alcohol may cause early satiety, abdominal pain, bacterial overgrowth, and sitophobia (40); coupled with nausea and vomiting, the result is often diminished food intake. Maldigestion is augmented by inadequate bicarbonate delivery to the duodenum, with secondary inactivation of enzymes and bile acids by gastric acid. Diminished bile salts contribute to nutrient maldigestion and malabsorption and augment the greater incidence of diarrhoea (i.e. bile salt diarrhoea) by causing colonic secretion of fluid. Finally, studies show that chronic alcohol consumption causes marked reductions in water and sodium absorption in the jejunum and ileum in both healthy individuals as well as alcoholics (1, 21).

Additionally, chronic alcoholics have an altered metabolism which may result in significant weight loss. Compared to social drinkers, alcoholics demonstrate lower body weight and body mass index (BMI) due to decrements in fat mass, a higher resting energy expenditure value normalized by fat-free mass, and the preferential utilization of lipids as an energy substrate (41). Mean BMI, basal metabolic rate, lipid oxidation, and carbohydrate oxidation were abnormal during the period of heavy drinking in a study of 32 alcoholics, but each of these metabolic parameters normalized after three months of abstinence from alcohol. Normalization is postulated to be related to regression of the functional alterations of the microsomal ethanol oxidizing system and of mitochondria which occur secondarily to chronic ethanol abuse (42). Many absorptive abnormalities are reversed when

alcoholics are given a nutritious diet, even with continued intake of alcohol (31).

Distal colonic motility has been shown to be increased in alcoholics with notably decreased transit time. Transit time increases markedly following abstinence from alcohol, which may help to alleviate colonic diarrhoea. Hazardous drinking and cigarette smoking are also common and important risk factors for increased rates of complications after surgery. Post-surgical wound healing especially can be compromised by heavy alcohol consumption. Surgical complications such as anastomotic leak are more frequently observed in heavy drinkers and alcoholics, likely due to compromised immune functioning. For instance, in a study of 333 unselected consecutive patients in a Danish surgical department who underwent colonic or rectal resection with anastomosis, relative risk of anastomotic leakage was over seven times greater in alcohol abusers compared to abstainers (43). In a separate study of 32 male heavy drinkers (≥60 g of alcohol/ day) and 32 controls (<25 g of alcohol/day) who underwent colorectal surgery and who were matched with respect to operative procedure, diagnosis, age-complicating cardiopulmonary diseases, weight, and smoking habits, general postoperative complications following surgery and increased length of hospital stay were significantly more common in the heavy drinkers (44).

Summary

Alcohol lowers oesophageal sphincter pressure, reduces acid clearance, and alters oesophageal epithelial function, contributing to an increased incidence of GORD. Dyspepsia,

chronic atrophic gastritis and delayed gastric emptying are characteristic of chronic alcoholics. UGI bleeding in heavy drinkers is more commonly a consequence of variceal bleeding due to portal hypertension than to gastritis, while peptic ulcer disease and *H. pylori* infection have been shown to have a lower incidence in individuals who consume alcohol than abstainers. Finally, malnutrition in heavy drinkers is common and is due to the combined effects of diminished intake, decreased digestion, bacterial over-growth and bile salt diarrhoea. Immunological effects of heavy alcohol consumption, such as delayed or deficient healing from colorectal surgery, should also be a major concern for health care providers.

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Chapter 33
Liver disease

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Introduction

In popular culture the liver is believed to be the prime organ damaged by alcohol. However, the majority of people who drink alcohol in excess of recommended limits do not develop liver disease. Alcohol-related liver disease (ALD) represents a spectrum of liver damage caused by excessive alcohol consumption. The spectrum ranges from reversible fatty liver through to alcoholic hepatitis (AH), alcohol-related cirrhosis, and hepatocellular carcinoma. This chapter will outline the mechanisms of alcohol-related liver damage and the clinical consequences this leads to.

Alcohol metabolism

Alcohol excretion is mainly by catabolism in the liver, small amounts are excreted unchanged in urine and breath. Three catabolic mechanisms operate: alcohol dehydrogenase (ADH) which reduces alcohol to an acetaldehyde, the microsomal ethanol oxidizing system (MEOS) which is based on cytochrome P450 2E1 in the endoplasmic reticulum, and catalase which makes a minor contribution to alcohol metabolism. The two major products of alcohol metabolism that are potentially toxic to the liver are acetaldehyde and the oxidative stress manifest as reactive oxygen species (ROS).

Pathology

There is a spectrum of histological change associated with alcohol-related liver damage. Many patients consuming excess alcohol will have no light microscopic changes to the liver. The most common pathological change is macrovesicle steatosis, large droplets of lipid visible in the cytoplasm of the cells. Sometimes microvesicle steatosis can also be evident and up to 50% of the liver can be composed of fat. This change is not specific to alcohol excess, also being associated with obesity and diabetes mellitus (1). A source of confusion is that the term alcoholic hepatitis can be used to describe both a histopathological appearance and a clinical syndrome. Patients can have histological features of AH without the clinical syndrome. AH occurs as a distinct pathology with either steatosis or cirrhosis as a background pathology. The steatosis is accompanied with neutrophil infiltration around foci of hepatocyte necrosis with changes in hepatocyte cytoskeleton, termed Mallory's hyaline and fibrosis. The end-stage pathology of alcoholic liver disease is cirrhosis, a disruption of the normal architectural relationships between portal triads and central veins, with rounded nodules of regenerating hepatocytes surrounded by collagen bands.

Mechanisms of liver damage

Alcohol can damage the liver by many mechanisms, though the evidence for some of these mechanisms in humans is weak. The plethora of mechanisms may not all interact at the same time or

in the same way in individuals, making for controversy, but this complex of mechanisms in part explains the variability of alcohol toxicity in humans (2).

Fatty liver

Fatty liver was believed to be the first step in hepatocyte damage, however this is now doubted, and it could be viewed as an adaptive defence response. There are multiple mechanisms of fat accumulation in the liver due to alcohol; however, the fat droplets are composed of triglyceride and esterified cholesterol. These are inert, lacking the cellular toxicity of their components: glycerol and free fatty acids. Studies of non-alcoholic fatty liver disease suggest that the conversion of free fatty acids to triglyceride, stored as intrahepatic steatosis, is a protective mechanism against oxidative stress. Many lipid synthesis pathways are up-regulated by antioxidant defence regulators such as Nrf2 or cell survival factors such as NFκB. Thus rather than being a pathological pathway, simple isolated hepatic steatosis may be a marker of successful adaptation to oxidative stress.

Dietary fat directly contributes to hepatic steatosis; additionally alcohol increases circulating free fatty acids via adipose tissue lypolysis. Critical to fatty acid metabolism is transcriptional factor peroxisome proliferator-activated receptor alpha (PPARα) which regulates mitochondrial, microsomal, and peroxisomal fatty acid oxidation; ethanol decreases its transcription and activity (3). Methionine deficiency due to diet or consumption by stress response also causes steatosis (4). Ethanol directly inhibits methionine synthetase causing hyperhomocysteinaemia which increases

expression of SREBP-1c which induces the expression of lipogenic genes.

Failure of hepatic export of lipid is due to down-regulation by ethanol of microsomal triglyceride transfer protein (MTP), the enzyme for packaging triglycerides and apolipoprotein b into very low-density lipoprotein for export from the liver.

Oxidative stress and lipid peroxidation

The principal cause of damage in the liver is excess oxidative stress in the form of ROS from the metabolic consequences of alcohol from the MEOS/CYP2E1 system, the mitochondrial electron transport train, and nitric oxide synthase, both within hepatocytes and kupffer cells. These ROS cause peroxidation of polyunsaturated fatty acids within cell membranes and lipoproteins (5). This leads directly to cell death or to the release of reactive aldehydes with potent pro-inflammatory properties. The first line of response is intracellular glutathione, which is rapidly consumed; dietary deficiencies due to alcohol consumption can reduce glutathione stores exaggerating the effect. Ethanol and ROS inhibit many enzyme systems regenerating glutathione.

Acetaldehyde

Acetaldehyde—the metabolite of ethanol metabolism by alcohol dehydrogenase—can form shift-bases with cellular proteins forming protein adducts. There are two damage mechanisms—disrupting protein structure losing function or causing formation of antigenic structures that trigger immune-mediated reactions. It has also been suggested that

acetaldehyde can induce damage by reduction of mitochondrial glutathione, increasing hepatocyte sensitivity to TNFα, as well as possibly via changes in mitochondrial membrane cholesterol content through an action of acetaldehyde on SREBP-1c which up-regulates cholesterol-synthesizing enzymes.

The immune system

Auto-antibodies to acetaldehyde and other reactive species that form protein adducts due to ethanol metabolism occur in humans, but a pathological role has not been proven. However the innate
immune response to translocated endotoxin from the gut, due to ethanol-induced increased intestinal permeability, is stimulated when the endotoxin circulates via the portal vein to the liver. Hepatic kuppfer cells respond to endotoxin via CD14 and Toll-like receptor 4 to produce a battery of cytokines including IL-6 and TNFα; production of these cytokines leads to a full-blown inflammatory response (6). The most promising clinical research interventions centre on inhibiting this pathway.

Fibrosis

The clinical syndromes of ALD relate to the consequences of hepatic repair by fibrosis. The mechanisms of damage described lead to an inflammatory response. This activates hepatic stellate cells to become myofibroblasts causing proliferation and collagen formation, laying down bands of collagen that disrupt hepatic architecture and lay the foundations for cirrhosis (7).

The individual response to alcohol

The majority of heavy drinkers will not develop ALD despite apparently consuming similar amounts of alcohol in similar circumstances. The cause of this variation is probably multifactorial, and the combinations of factors differ between individuals, but accumulate to cross a threshold of response.

The impact of dose of alcohol

Epidemiological studies show a dose response between alcohol intake and risk of ALD. The risk of ALD starts with alcohol consumptions of a little over 30 g/day, with a 5% risk increasing to 10% at 60 g/day; this may increase disproportionately at higher levels (8). Studies suggest that continuous drinking is worse than binge drinking. There are suggestions that wine is less toxic in comparison to its alcohol content, but the studies are confounded by obesity which is associated with beer and spirit drinking (8).

Diet

Dietary deficiencies—calorific or specific—such as selenium, antioxidants, vitamins A, C, and E, or co-enzyme Q are common in ALD but not causal. They may exacerbate the degree of damage. A strong association is evident for alcohol toxicity and obesity; for any given level of alcohol consumption the obese have an excess risk of ALD (9).

Gender and the risk of ALD

It is recognized that women develop ALD at a lower intake of alcohol than men. This has been ascribed to higher blood alcohol concentrations per unit of alcohol consumed due to reduced body mass index and relative increased fat mass. Some recent evidence suggests that oestrogen may change gut permeability, increasing endotoxin exposure (10).

The influence of genes

The search for genes causing ethanol susceptibility has yet to bear fruit. Studies have used candidate gene approaches focused on polymorphisms of alcohol-metabolizing, fat metabolism, or oxidative stress response genes. These pathways are polymorphic with much redundancy and epigenetic mechanisms operating. As such, it is unlikely that single genes are going to be causal in most patients (11). With the expansion in genomic technologies, application to a well-phenotyped population of sufficient size should answer this question.

Clinical consequences of ALD

People who consume more alcohol than their body can tolerate come to medical attention with a wide variety of symptoms, signs, and laboratory abnormalities.

Epidemiology

Several long-standing observations regarding the epidemiology of ALD remain true today. Men are twice as

likely as women to have alcohol-related cirrhosis. Black people are more likely than Caucasians to suffer. The incidence of ALD-related cirrhosis is declining in most countries with several factors thought to be contributing to this observation. An increased awareness of ALD, increased participation in alcohol support groups coupled with increased use of pharmacological methods to assist abstinence, and changes in the consumption of certain types of alcohol have been shown to influence the decline in alcohol-related liver deaths since the 1970s in many countries in Europe and North America (12), the exception to this is the United Kingdom—Scotland in particular.

Diagnosis

The diagnosis of ALD is largely dependent on a sound clinical history including alcohol consumption. Ideally, this should always include a corroborating history from family members or friends. Biochemical investigations are limited in their ability to accurately diagnose ALD. Markers such as a raised mean corpuscular volume and raised gamma-glutamyl transpeptidase can be suggestive of ALD, but fall short of accurately diagnosing this condition. Radiological investigations are similarly disappointing—abdominal ultrasound may reveal the non-specific finding of a bright liver (hyperechogenic). Histological assessment is rarely required, but if performed, typically shows features of alcohol damage including steatosis, lymphocytic infiltrate, and ballooning of hepatocytes—features all seen in non-alcoholic fatty liver disease. This further emphasizes the importance of a detailed history as the cornerstone of diagnosing ALD.

Prognosis

ALD-related deaths accounted for 4.4/100,000 persons in the United States in 2003—a reduction from 6.9/100,000 a decade previously (13); this trend has been observed throughout the developed world, with the exception of the United Kingdom. UK Department of Health statistics reveal an increase in overall hospital admissions for alcohol-related disease. Alcohol-related cirrhosis accounts for approximately 7% of all liver transplants carried out in the United Kingdom—the third most common indication (14), however most ALD patients would not be candidates.

Surrogate presentations

General practitioners and many specialists need to be aware of the possibility of alcohol as the underlying cause of the problem when the patient has non-specific symptoms such as fatigue, nausea, or dyspepsia. More specific clinical situations as diverse as falls, neuropathy, morbid jealousy, depression, marital discord, pancreatitis, hepatomegaly, and acne rosacea are all signals of a possible issue relevant to alcohol consumption; failure to respond to treatment in gout or hypertension also raises the possibility. Front-line clinicians may use a range of questionnaires to determine whether patients are being adversely affected by alcohol. Examples include the CAGE questionnaire, the Alcohol Use Disorders Identification Test (AUDIT), and the Severity of Alcohol Dependence Questionnaire (SADQ) (15). Laboratory tests undertaken to investigate signs and symptoms, or merely for monitoring therapy, which most commonly prompt consideration of

alcohol problems are abnormal liver function tests and macrocytosis on a full blood count or film. These all present opportunities for intervention before serious complications occur.

Clinical consequences of cirrhosis

The clinical consequences of cirrhosis secondary to alcohol are numerous and potentially life threatening. Most patients with cirrhosis have compensated disease—sufficient residual liver function to show no clinical signs or symptoms of liver failure. The clinical consequences of alcohol-related cirrhosis arise mainly as a consequence of portal hypertension, the splanchnic circulation becoming hypertensive due to reduced outflow of blood due to the hepatic vascular disruption related to cirrhosis and a hyperdynamic systemic circulation increasing inflow. This leads to three clinical syndromes—ascites, variceal bleeding, and hepatic encephalopathy, any or all of these indicate decompensated liver disease. Ascites is the presence of free fluid in the abdomen often up to 20 litres, debilitating the patient with its weight and mass; it may also become infected—spontaneous bacterial peritonitis. This condition has an associated mortality in the region of 40% (16). Portal hyper-tension also leads to the development of abnormal blood vessels; varices are usually oesophageal but also at ectopic sites. These are a major cause of massive gastrointestinal bleeding and death in patients with alcohol-related cirrhosis. Acute confusional states and inebriation can be mistaken for hepatic encephalopathy (HE), a clouding of consciousness associated with failure of clearance of gut and metabolic toxins by the cirrhotic liver. Episodes of HE can be short lived, responding

to therapy, or can develop into a chronic state. ALD can also presented as end-stage liver disease, often provoked by infection, where the consequences of portal hypertension will be in evidence but also synthetic liver failure with jaundice, wasting, and coagulopathy.

Treatment

The main aim of treatment is alcohol abstinence. Removal of the precipitant allows liver recovery and avoidance of complications. Abstinence is often difficult to achieve and often requires the support of a multidisciplinary team. Support groups, therapy, and in some instances in-patient detoxification programmes are useful tools in the armoury. Chemical treatments should be used only in conjunction with these methods. Disulfiram has been shown to improve the time to relapse in the short term, although is best used in a supportive and supervisory environment (17). Treatment of decompensated liver disease is beyond the scope of this review but focuses on removing the cause (alcohol), treating infection, dealing with ascites with diurectics or paracentesis, stopping bleeding using endoscopic or radiological interventions, and treating encephalopathy with agents to reduce gut toxins and manage ammonia and glutamine metabolism. End-stage liver disease secondary to alcohol damage can be treated with liver transplantation. ALD is the second most common indication for liver transplant in Europe (18). Prior to transplantation, close attention and assessment of ongoing alcohol consumption should be made. The societal issues of allocating donated organs that are over-subscribed—causing a 25% mortality in those on the transplant waiting list—to ALD patients also has to be

considered, as it may have a detrimental effect on organ donation.

Alcoholic hepatitis

Although part of the ALD spectrum of disease, AH is often considered a distinct clinical entity due to its very poor short-term prognosis, in contrast to the much improved prognosis of its abstinent survivors, which is very different to those with end-stage liver disease. AH is an acute condition, however almost 50% of patients presenting with AH have established cirrhosis and the rest have fatty liver disease with a history of alcohol consumption (19).

Epidemiology

A recent population study from Denmark suggests an increasing incidence of AH over the past decade (20). Overall, 1,951 patients were recorded as having AH within the ten-year study period—the incidence for men rose from 37 to 46 per 10^6 population and from 24 to 34 per 10^6 for women. The true prevalence of AH is unknown, as a substantial proportion of cases are asymptomatic, although in the study of Naveau and colleagues, approximately 20% of 1,604 individuals with alcoholism undergoing liver biopsy had evidence of AH (21), but we have already commented on the difference between clinical and pathological AH. The volume of alcohol required to cause AH is unknown. Episodes of AH are more common with large amounts of alcohol consumption, following binge drinking and concomitant malnutrition (22).

Diagnosis

Diagnosing AH remains a challenge and is largely a clinical diagnosis, the differential being infection on a background of alcohol-related end stage liver disease. A robust alcohol consumption history is key to the diagnosis, often requiring corroborating history from relatives. Clues from physical examination may include features of liver cirrhosis, jaundice in severe cases, fever unexplained by infection, and the presence of a hepatic bruit (23). Laboratory investigations are largely non-specific for the diagnosis of AH. Serum bilirubin, prothrombin time, and serum creatinine form part of prognostic calculators, however have limited diagnostic utility. Aminotransferases are often moderately elevated with an aspartate aminotransferase: alanine aminotransferase ratio in excess of 1.5 (23). Liver biopsy has a controversial role in the diagnosis of AH, as it has an excessive mortality and is frequently not diagnostic. Imaging modalities are often helpful in the exclusion of alternative pathologies, i.e. hepatocellular carcinoma, but not in making a positive diagnosis.

Risk stratification/prognosis

Several scoring models exist for the risk stratification of AH. Each aims to identify those patients at the severe end of the spectrum and therefore those with the highest mortality rates. The original Maddrey discriminant function (mDF) score was developed in 1978 (24) and modified in 1993 (25). The mDF score comprises serum bilirubin and prothrombin time—scores greater than 32 indicate severe AH and are associated with an untreated 28-day mortality rate of 35%

(25). Alternative scoring models have been used in predicting mortality in severe AH. The model for end-stage liver disease (MELD) score is comparable to the mDF in predicting 30-day and 90-day mortality in AH (26). The Glasgow alcoholic hepatitis score (GAHS) was developed in 2005 and shown to be superior to the mDF in predicting 28-day outcome (27). A GAHS ≥9 is indicative of severe AH and is associated with a 28-day survival of 46%.

Treatment

The treatment of AH is multifactorial. Effort should be made to correct electrolyte and vitamin deficiencies, as well as close monitoring of fluid balance and renal function. Alcohol withdrawal should be considered and addressed where appropriate. Specific therapies, other than alcohol abstinence, centre largely around two options: corticosteroids and pentoxifylline. Corticosteroids have long been used in the treatment of severe AH (number need to treat for survival at 1 month = 7). Several randomized controlled trials have shown a significant benefit in treating with corticosteroids versus placebo (28). A recent Cochrane review of five clinical trials of pentoxifylline showed a probable treatment benefit of this drug, although no firm conclusion could be reached (29). Pentoxifylline was associated with reduced all-cause mortality, however one trial suggested increased serious and non-serious adverse events with pentoxifylline. A small study from India compared corticosteroids head to head with pentoxifylline for the treatment of severe AH and found reduced mortality as well as a renoprotective effect in the pentoxifylline group (30). Large-scale studies comparing corticosteroid and pentoxifylline are awaited.

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Chapter 34
Pancreatitis

Dhiraj Yadav

Introduction

Alcohol has been linked to pancreatitis for over a century. Unlike many chronic diseases (e.g. heart disease) where alcohol is considered to be a risk factor, it is implicated as a direct aetiological factor for pancreatitis. The costs of treating pancreatitis are substantial. In 2004, pancreatitis was the seventh most common gastrointestinal disorder in terms of admissions to non-federal US institutions and the estimated costs for in- and out-patient care for pancreatitis were over US$3.5 billion (1). Although empiric data are not available, based on contribution to pancreatitis aetiology, about 40% of these costs may be attributable to alcohol. Given its low prevalence, most literature on the relationship between alcohol and the pancreas until recently was limited to observations from case series. In contrast to pancreatitis, data on the association between alcohol and pancreatic cancer are weak. The role of alcohol in other benign and malignant diseases of the pancreas is limited. The present chapter will focus on emerging data on disease burden, association and risk of pancreatitis with alcohol consumption, disease recurrence, progression, and opportunities for altering the natural course of disease.

Definitions

Acute pancreatitis is defined as sudden onset of upper abdominal pain with elevation of serum pancreatic enzymes to three or more times the upper limit of normal and/or evidence of inflammatory changes in and/or around the pancreas on imaging studies. Chronic pancreatitis is a chronic, usually progressive inflammatory disorder characterized by abdominal pain, episodes of acute pancreatitis, and scarring of the pancreas resulting in a loss of function characterized by exocrine and/or endocrine insufficiency.

Burden of pancreatitis

Until recently, there were limited data on population-based estimates for pancreatitis. Numerous studies in the past three decades from different regions have described the incidence and outcomes of acute pancreatitis. Data on chronic pancreatitis still remain scarce and are available only from a few countries.

The incidence of acute pancreatitis in most Western countries in the past two decades ranges from 20 to 50 per 100,000 population (2–4). This incidence of acute pancreatitis has been rising rapidly. As an example, the number of hospitalizations with a primary in-patient discharge diagnosis of acute pancreatitis in non-federal US institutions more than doubled from 101,000 in 1988 to 210,000 in 2002 (5). Two main reasons that account for this include an increase in the incidence of gallstone-related acute pancreatitis from rising obesity rates, and increasing rate of serum

pancreatic enzyme testing (3, 6). Other suggested factors include an increase in the number of endoscopic procedures like endoscopic retrograde cholangiopancreatography, and the availability of newer medications which can result in pancreatitis as a side effect (3). An increase in the incidence of acute pancreatitis related to alcohol has been reported only from select countries (7–9).

The incidence of chronic pancreatitis is much lower than acute pancreatitis and ranges from four to nine per 100,000 in Western countries (10–13). Time trends are available only from Olmsted County in the United States (13). During the period 1977–2006, although the overall incidence (i.e. cases diagnosed clinically or only on autopsy) was stable, an increase in the incidence of clinical cases, mainly from an increase in the diagnosis of alcohol-related chronic pancreatitis, was observed. Prevalence data are available only from Japan and the United States. The prevalence in Japan was 29 per 100,000 (45 in males, 12 in females) in year 2000, while in Olmsted County it was 42 per 100,000 (52 in males, 34 in females) in 2006 (12, 13).

Alcohol's contribution to pancreatitis aetiology

Alcohol is the second most common cause of acute pancreatitis after gallstones, accounting for about 19–32% of cases (3). Alcohol is the single most common cause of chronic pancreatitis and accounts for at least 50% of patients. The proportion of chronic pancreatitis patients with alcohol aetiology was as high as 70–90% in earlier studies (14–17), while in two recent large multicentre studies and a population-based study from Olmsted County, United States,

about 50% of patients were attributed to alcohol (13, 18, 19). The reasons for these observations have not been explored but could be related to widespread use of highly sensitive cross-sectional imaging studies that can detect milder changes in the pancreas and a higher proportion of women in the US studies (13, 20).

The demographic profile of alcohol-related pancreatitis differs from other causes in that these patients are more likely to be middle aged (35–55 years), male (about two-thirds), and black (compared with whites).

Natural history of alcohol-related pancreatitis

The clinical presentation and short-term outcomes of alcohol-related acute pancreatitis is similar to other aetiologies. However, the risk of recurrences and progression to chronic pancreatitis after the first attack of acute pancreatitis are more common in the setting of alcohol. About one in three patients with alcohol-related acute pancreatitis develops recurrent acute pancreatitis and one in five patients progresses to chronic pancreatitis.

The clinical presentation and natural history of alcohol-related chronic pancreatitis differs from the idiopathic form, especially the late-onset type of disease. Patients with alcoholic chronic pancreatitis are more likely to have abdominal pain, acute pancreatitis episodes, and complications like pseudocysts.

Assigning alcohol's role as a cause for pancreatitis

There is no standardized definition for alcohol-induced pancreatitis. The relationship between alcohol and pancreatitis has traditionally been considered to be dichotomous. The threshold to assign alcohol as a cause of pancreatitis varies from 50 g to 80 g/day (i.e. 4–7 drinks/day) without or with (>2–5 years) a specified duration of consumption. Such an assignment is often circumstantial in a pancreatitis patient who also happens to be a 'drinker' and does not have another obvious cause. The amount of self-reported alcohol consumption by chronic pancreatitis patients varies widely. In a recent US study of 540 patients, 25% patients (13% males, 35% females) were lifetime abstainers, 25% (38% males, 11% females) very heavy drinkers, 13% (12% males, 13% females) heavy drinkers, while the remaining reported light or moderate drinking during the period of maximum drinking in their life (20). In an Italian study of 893 patients, no alcohol consumption was reported in 37% (23% males, 74% females), 1–79 g/day in 19% (22% males, 12% females), and ≥80 g/day in 44% (55% males, 12% females) (19). Data are now emerging on the risk of pancreatitis based on alcohol consumption.

Alcohol and the risk of pancreatitis

Determination of pancreatitis risk from alcohol has been difficult for two main reasons. First, alcohol consumption is fairly common with ever- and current-drinking self-reported by 86% and 72% of men and 73% and 60% of women respectively (21). Secondly, the prevalence of pancreatitis in the general population is very low. Thus, most data on the

relationship between alcohol and pancreatitis were derived from observations made in case series from centres with specific interest in the disease. Recent studies have quantified the risk of pancreatitis from alcohol consumption.

The absolute risk of clinical pancreatitis in alcoholics using prevalence as a surrogate was evaluated in a cross-sectional study of a large cohort of US veterans (22). Among veterans who received an alcoholism diagnosis, the prevalence of diagnosis codes for pancreatitis was 5.9%, which was about sixfold higher when compared with veterans with no alcoholism diagnosis. In a subset of male veterans who attended the detoxification programme, pancreatitis was confirmed using strict criteria on chart review in 3%. In a cohort study from Denmark consisting of 17,905 subjects followed for a mean of 20.1 years, pancreatitis diagnosis was received by 2.5% of subjects who self-reported drinking 35 or more drinks/week when compared with 1.3% of subjects who were non-drinkers at the time of ascertainment (23).

The absolute risk of pancreatitis has also been quantified using prevalence of histological changes in autopsy specimens. In a recent study of 620 alcoholic subjects, the prevalence of histological changes of chronic pancreatitis on autopsy was 14% which is three- to fivefold higher than clinical pancreatitis (24).

A multicentre case–control US study classified subjects into five drinking categories based on the amount of self-reported alcohol consumption during the maximum drinking period of life. After controlling for demographic factors (age, gender, body mass index) and smoking, the risk of chronic pancreatitis increased significantly (odds ratio 3.1, 95%

confidence interval (CI): 1.87–5.14) only at the very heavy drinking level (i.e. five or more drinks/day) (20). In the Danish cohort noted previously, the estimates of relative risk were similar to the US study at the very heavy drinking level, but the overall relationship between alcohol and pancreatitis was dose-dependent (23). A meta-analysis using published literature determined the threshold for risk of pancreatitis to be four drinks/day (25).

The risk of acute pancreatitis based on amount, type, and frequency of alcoholic drink was evaluated in a Swedish cohort study of 84,601 subjects, followed for ten years. The risk of acute pancreatitis increased in a dose-dependent fashion with consumption of each five drinks of sprits on an occasion (relative risk 1.52, 95% CI: 1.12–2.06). The study did not find any association for other alcoholic drink type (wine, beer), amount of monthly consumption, or frequency of consumption (26).

Individual susceptibility to alcoholic pancreatitis

Not all subjects who drink excessively develop organ damage or clinical disease indicating that other environmental and/or genetic factors exist. The risk of pancreatitis is much lower than many other diseases. As an example, the risk of alcoholic cirrhosis with heavy alcohol consumption is
much higher (5–10%) when compared with pancreatitis (2–5%). Subjects who drink heavily often have concurrent damage in more than one organ indicating that common cofactors (environmental and/or genetic) or mechanisms are responsible for disease at least in a subset of patients. As an example, in an autopsy study, 39% of patients with chronic

pancreatitis also had cirrhosis while 18% of patients with cirrhosis also had features of chronic pancreatitis (24).

About two-thirds of patients with alcohol-related pancreatitis are men. This is likely related to a higher prevalence of alcohol consumption in men since the rate of pancreatitis with equal amounts of consumption appears to be similar in both sexes. Black people have a two- to threefold increased risk of pancreatitis when compared with white people due to reasons that are unclear at this time (27, 28).

There is paucity of data on cumulative alcohol consumption, lifetime drinking trajectories, and alcoholic drink type in pancreatitis patients. The susceptibility to pancreatitis by drink type was different in two recent cohort studies—while the risk of acute pancreatitis was increased by spirits in one study, beer drinking was associated with chronic pancreatitis in the other. It is difficult to draw definite conclusions from these observations due to limited number of subjects at the heavier drinking levels (23, 26). Although it is possible the degree of risk varies by drink type, pancreatitis has been described in all drinking populations and from all geographical areas.

Drinking and smoking habits frequently coexist and most heavy drinkers are also heavy smokers. Therefore, smoking has gained considerable attention as a potential co-factor for alcohol-related pancreatitis. Smoking has now been well established as an independent dose-dependent risk factor for acute and chronic pancreatitis (29). Its magnitude of association is similar to that of alcohol. The association of smoking with pancreatitis is stronger in alcohol-related pancreatitis and it is possible that this relationship is

synergistic (20). Smoking has been linked with disease progression, with heavy smokers being four times more likely to progress from acute to chronic pancreatitis after controlling for alcohol consumption (30). Patients with chronic pancreatitis who are smokers are diagnosed at a younger age than non-smokers, and are more likely to develop pancreatic calcifications, or diabetes (31).

Genetic linkage and candidate gene studies have identified six pancreas-targeting factors that affect susceptibility to acute and/or chronic pancreatitis. These genes target the acinar cells through a trypsin-dependent pathway (*PRSS1*, *PRSS2*, *CTRC*, *CASR*, *SPINK1*) or the duct cells (*CFTR*) (32). Of these, modest association has been noted for *SPINK1* and *CTRC* genes with alcohol-related pancreatitis. However, the association of these genes is much stronger for non-alcoholic forms of chronic pancreatitis. This indicates that although trypsin-dependent injury may play a role in alcohol-related pancreatitis, other pathways may also be equally important in driving the disease process (33).

Can the natural course of alcoholic pancreatitis be altered?

Although acute pancreatitis is a common occurrence in patients with chronic pancreatitis, until recently there was ambiguity on whether and how often acute pancreatitis recurs or progresses to chronic pancreatitis. In a German study (30), during a mean follow-up period of about eight years, the overall risk of recurrence was 18% in patients after the first attack of acute pancreatitis and it was highest in the setting of alcohol aetiology (33% versus 11%). Progression to chronic

pancreatitis was infrequent (overall risk 4%) and was seen only in patients with alcoholic aetiology. In another study from Japan, the overall risk of recurrent acute and chronic pancreatitis was 20% and 15%, respectively. The risk of recurrences and progression to chronic pancreatitis was higher among patients with alcohol aetiology (34).

The Japanese study also evaluated the risk of recurrences and progression based on alcohol consumption during the follow-up period (34). About one-third of patients stopped drinking, one-third decreased drinking, and one-third continued at the same level. The risk of recurrences and progression was about threefold among patients who continued drinking at the same level compared with patients who abstained from drinking altogether. Another retrospective study from Finland also indicated a substantially lower risk of recurrences after discontinuation of drinking (35). Finally, a proof-of-concept randomized controlled trial on the role of aggressive alcohol intervention in preventing disease recurrences was recently published (36).

There are limited data on the role of smoking cessation on disease course. In a retrospective study, Talamini et al. found that the risk of developing calcifications in subjects who stopped smoking after diagnosis returned to baseline (i.e. similar to non-smokers), while the risk was increased about twofold in patients who continued smoking after diagnosis (37).

Conclusion

Data from recent studies have clarified the role of alcohol in pancreatitis in terms of the risk, threshold associated with increased risk, recurrences, and progression to chronic pancreatitis. Empiric data demonstrate the benefits of alcohol abstinence in preventing disease progression thereby providing an opportunity to alter the natural course of the disease. Incorporating aggressive counselling for both alcohol and smoking should be included in the routine management of all patients with pancreatitis, and efforts are needed to improve physician education on the benefits of counselling in achieving these aims.

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Chapter 35
Diabetes

Dolly Baliunas

Review of evidence that alcohol is a risk factor for incident type 2 diabetes

There is growing evidence that alcohol consumption is a risk factor for incident type 2 diabetes. On the whole, most studies find a U- or J-formed association curve between alcohol consumption and the risk of developing type 2 diabetes (1). Subjects with low to moderate daily alcohol consumption have the lowest risk of developing type 2 diabetes compared to total abstainers and persons with a larger daily alcohol intake.

The results of individual studies vary. Some studies have found a linear inverse relationship association between alcohol consumption and incidence of type 2 diabetes (2). In the Nurses' Health Study, alcohol consumption was associated with a lower risk of type 2 diabetes compared to abstention (3). The Health Professionals Follow-Up Study in males found a similar inverse association between alcohol consumption and type 2 diabetes (4, 5). The Physician's Health Study corroborates that consumption of alcohol in men has an inverse linear association with type 2 diabetes (6). An Australian study revealed an inverse dose–response curve in women, while no association was seen in men (7). Not all studies, however, find an inverse association between alcohol consumption and risk of type 2 diabetes. In a

population-based study no association between alcohol consumption and incidence of type 2 diabetes was found (8). In contrast, Holbrook et al. found a positive association between alcohol consumption and incidence of type 2 diabetes in men (9). A study in middle-aged men who consumed a substantial amount of alcohol (greater than 21 drinks per week) found a 50%-increase in relative risk of type 2 diabetes compared with their counterparts who drank up to one drink per week (10).

Several reviews and meta-analyses have now been conducted on this topic. Narrative reviews have suggested a U-shaped relationship or a protective effect of moderate consumption with some question about the effect of higher levels of alcohol consumption (11–14).

In addition to more narrative reviews, three quantitative reviews have been conducted. Carlsson et al. (15) included data from 13 cohorts, and categorized consumption into predetermined moderate- and high-consumption groups and used current abstainers or low consumers as the reference group. In their analysis, moderate consumption was associated with a 30%-reduced risk of diabetes among men (relative risk 0.72 (95% confidence interval (CI): 0.67–0.77)) and women (relative risk 0.68 (95% CI: 0.61–0.75)). The risk associated with high consumption was described as being unclear. In another meta-analysis, in which alcohol consumption was treated continuously, a risk reduction of approximately 30% was observed for those with a daily consumption of 6 g to 48 g of alcohol (16). Heavy drinkers (greater than 48 g alcohol daily), however, were found to have a relative risk of type 2 diabetes corresponding to that of non-consumers, 1.04 (95% CI: 0.84–1.29). In this analysis, a

more protective effect of moderate consumption was observed for women.

The most recently published meta-analysis confirms the U-shaped relationships between average amount of alcohol consumed per day and risk of incident type 2 diabetes among men and women, although a more protective effect of moderate consumption was found for women (17). For women, the protective effect at moderate consumption and hazardous effect at higher consumption were both statistically significant. For men, the protective effect was statistically significant, but for higher consumption the confidence interval did not exclude a relative risk of one. This most recent meta-analysis addresses several of the methodological concerns of previous reviews. A sensitivity analysis was conducted using self-reported diabetes outcomes to determine if, as suggested by Koppes et al. (16), a more protective effect would be found relative to studies which objectively measured for diabetes. Self-reported diabetes status did indeed impact the risk relation with volume of alcohol exposure but only for men; there was no effect for women. Accordingly, the analyses were repeated separately for self-report versus no self-report in men and found a linearly decreasing dose–response relationship in the studies with self-report, as well as a model similar to the main analysis in the rest of the studies. The result in the group based on self-report was mainly influenced by two studies (4, 6) that accounted for 81% of the observations. This meta-analysis also addressed what is known as the sick-quitter effect (18) by using lifetime abstention from alcohol consumption as the reference group. In previous reviews, the reference group was composed of former drinkers and lifetime abstainers. Due to health concerns, former drinkers may abstain from alcohol

consumption, and thus may actually be at increased risk of developing diabetes. In comparison to the previous meta-analyses, this most recent analysis included 20 cohort studies in total: an additional six studies not included by Koppes et al. and an additional ten not included by Carlsson et al. The meta-analysis by Koppes et al. used a total of 15 studies. That by Carlsson et al. included 13 studies. Thus, there was substantial overlap in the data included in the respective analyses.

Most studies on alcohol consumption and the risk of type 2 diabetes are observational and thus are subject to residual confounding. The meta-analyses which rely on the data from individual studies are subject to the same potential limitations precisely because they take their data from these previously published individual studies. In the published literature on alcohol consumption and risk of incident type 2 diabetes, different studies do not use the same definition of diabetes or of a unit of alcohol. Diabetes status can be self-reported or based on administrative data. In some studies it is based on fasting plasma glucose values and in others on a 2-hour oral glucose tolerance test. While the variety of outcome and exposure measurements is a methodological limitation to attempts to summarize the published literature, one may nevertheless take confidence from the fact that the overall findings have been similar despite these variations in measurement.

Role of pattern of consumption and type of alcoholic drink

Most prospective studies measure alcohol consumption at only one point in time which assumes intake is fairly stable over time. Alcohol consumption, and the resulting health effects, are more complex than mere volume of consumption measured at one point in time. Alcohol consumption is dynamic, especially over longer periods of follow-up (19). Changes in alcohol consumption over time have been associated with subsequent changes in risk of cardiovascular diseases (20) and mortality (21), although some inconsistency exists (22, 23). Though several individual studies of the association between alcohol consumption and risk of type 2 diabetes measured alcohol more than once (2, 24–27) only one study used more than one alcohol measurement in its main analysis (28). Additional alcohol measurements would add weight to the validity and relevance to the alcohol measure because it is long-term consumption that tends to be of medical and public health concern.

The way in which alcohol is consumed (i.e., with meals or bingeing on weekends) affects various health outcomes (29). Therefore, it is possible that the risk of diabetes associated with heavy alcohol consumption is due to consumption mainly on the weekend as opposed to the same amount spread over a week. Some individual studies have measured drinking pattern in addition to volume of consumption (4, 7, 28), but while these did not present sufficient data to permit a combined analysis of pattern with volume, they did present some analysis of pattern of consumption. Hodge et al. found that consumption of more than 210 g alcohol over three days

increases the risk of type 2 diabetes fivefold, while consuming the same amount of alcohol distributed over a week does not influence the risk (7). Conigrave et al. found that frequent consumption of small amounts of alcohol (preferably at least five days a week) has the most pronounced inverse association with risk of type 2 diabetes compared to the same amount of alcohol taken once (4).

The impact of the type of alcoholic drink is controversial. In the studies of Conigrave et al. (4) and Djoussé et al. (2) the type of drink did not play a role, indicating that the impact on the risk of developing type 2 diabetes is mainly due to ethanol per se. However, Kao et al. found an increased risk of type 2 diabetes in heavily drinking men with spirits being more harmful than wine and beer (10). In the Melbourne Collaborative Cohort Study it was shown that consumption of wine lowers the risk of type 2 diabetes, while there is no association to consumption of beer and spirits (7).

Biological mechanisms

Different mechanisms behind the diabetes protective effect of moderate alcohol intake have been proposed. The biological mechanism is uncertain, but there are several factors that may explain the relationship, including increases in insulin sensitivity after moderate alcohol consumption (30, 31), changes in levels of alcohol metabolites (32), increases in high-density lipoprotein (HDL) cholesterol concentrations (5), or via the anti-inflammatory effect of alcohol (33). In line with the suggestion that moderate alcohol consumption increases insulin sensitivity, the protective effect of alcohol is primarily observed in overweight subjects where alcohol

probably counteracts the obesity-induced insulin resistance (34).

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Chapter 36
Neurological and mental disorders

Tarakad S. Ramachandran

Introduction

Sixty-seven per cent of American adults consume alcohol (1) and acute ethanol intoxication is increasingly associated with road traffic accidents, falls, subdural haematoma, drowning, infection, meningitis, seizures, domestic violence, homicide, and suicide. It is reported that approximately 20–25% of US emergency department patients have been drinking (2). Acute and chronic effects of alcohol abuse result in significant morbidity and mortality worldwide. Alcohol has a preferential, diverse, and deleterious effect on the nervous system. The central nervous system (CNS) and peripheral nervous system may be damaged by the direct or indirect effects of alcohol, or both.

Mechanism

Alcohol variously induces changes in many receptors including gamma-aminobutyric acid (GABA), glutamate, opioid, adenosine, dopamine, and serotonin (3). Ethanol inhibits excitatory glutamate receptors by glutamate receptor up-regulation and facilitates inhibitory GABA receptors, by GABA receptor down-regulation (4). Hence, abrupt abstinence after prolonged or binge drinking can result in tremor, hallucinations (visual, auditory, or tactile), seizures, or delirium tremens, with severely constricted attentiveness,

fluctuating levels of alertness, agitation, and autonomic instability. It is possible, moreover, that repeated binges and withdrawals cause not only early abstinence symptoms but also glutamate-induced excitotoxicity and permanent neuronal damage, in turn contributing to more lasting neurological disorders, including dementia.

Thiamine deficiency causes excessive glutamate release and thus like ethanol has the potential to cause excitotoxic neuronal damage. The potential for excitotoxicity is likely to be compounded when thiamine-induced glutamate release is combined with ethanol-induced glutamate receptor up-regulation. Treatment with the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist memantine has reportedly shown cognitive improvement in patients with probable ethanol-related dementia in an open label study (5). Benefit from memantine therapy has also been shown in Wernicke–Korsakoff syndrome (6).

Atypical alcohol dehydrogenase (ADH) enzyme, which is present in 85% of East Asians and is about five times faster than the normal ADH, converts ethanol to acetaldehyde. Acetaldehyde is metabolized by aldehyde dehydrogenase (ALDH) to acetic acid then oxidized to carbon dioxide and water. Due to faster metabolism, consumption of alcohol by these individuals results in accumulation of acetaldehyde, with resultant facial flushing, vasodilation, and tachycardia. Alcohol flush reaction is also known as ‘Asian glow’, as one in three East Asians tend to experience it with drinking. Thus, the differences in individual’s responses to alcohol intake are in part due to the varying availability and efficiency of ADH and ALDH (7).

Acute alcoholic intoxication

In the United States about 12% of the population drink alcohol daily and become intoxicated several times a month. The lifetime prevalence of alcohol dependence is about 14%, and at any given six-month period, 5%. Signs and symptoms of acute ethanol intoxication vary with severity and can include slurred speech, nystagmus, disinhibited behaviour, incoordination, unsteady gait, memory impairment, stupor, or coma. Hypotension and tachycardia may occur as a result of ethanol-induced peripheral vasodilation, or secondary to volume loss. Alcohol is uniformly a CNS depressant. It causes impairment of divided attention and loss of restraint on speech and behaviour; it results in euphoria, loquacity, and an increase in self-confidence; and it causes a reduction in neuromuscular coordination, gait, manual dexterity, and visual acuity. Reaction time is prolonged and memory, insight, and concentration are impaired. Alcohol intoxication causes a complex multifaceted deterioration of human postural control. Low blood alcohol levels in the presence of profound coma should point to another concurrent pathology and all patients should receive thiamine supplementation. Alcohol idiosyncratic intoxication may follow in a small group of individuals following ingestion of a small to substantial amount of alcohol, associated with excitability, combativeness, and destructive behaviour. The attack is usually followed by deep sleep and the patient may remain amnestic to the whole episode. The person with such idiosyncratic reaction to alcohol is considered temporarily insane and it does have medico-legal importance.

Amnestic syndromes

Alcohol-related blackouts are characterized by periods of amnesia for portions of the drinking episode. This usually involves young individuals, chronic drinking is not a requirement, and during these spells, the person appears 'normal' and coherent, without alteration in consciousness. Various explanations including malingering, repression, and toxic effect of alcohol on short-term memory have been proposed without valid proof.

Chronic ethanolism

Genetics play a strong role showing high rates of alcoholism in first-degree relatives. Identical twins have a higher concordance than do non-identical twins (8). Gene encoding for alcohol-metabolizing enzymes shows that they are protective against alcoholism. Presence of the *ADH2*2* allele in Asians might explain the lower prevalence of alcohol disorders among them. 'Sensitivity' to alcohol might also be a factor, and those with a lower 'sensitivity' tend to drink more to achieve the desired effect. 'Learning' is another factor with children imitating their parents' drinking; boys are more encouraged to drink than girls. With chronic alcoholism, mucosa of the mouth, tongue, and salivary glands reveal changes with leucoplakia, dysplasia, hyperplasia, acinar and ductal hyperplasia, reduction of the adipose tissue mass, predominance of T lymphocytes, and B lymphocytes with the absence of plasma cells (9).

Mental disorders

Alcohol taken in small amounts results in disinhibitory effects and reduction in anxiety, while intermediate amounts cause ataxia and sedation, and in larger amounts, anaesthesia and coma. Depression occurs in about 60% of alcoholic patients (10), with an increased risk of suicide in 2–3% of alcoholics, more so after the loss of an intimate relationship (11).

Forty per cent of alcoholic men on psychiatric wards have a psychiatric disorder unrelated to substance abuse including a high incidence of drug dependence, antisocial personality disorder,
schizophrenia, and mood and anxiety disorders. Forty-five per cent of alcohol-dependent adults develop one or more additional psychiatric conditions during their lifetime, and antisocial personality has a prevalence of 30%. Up to 17% of all alcoholics eventually die by suicide (12, 13).

Alcohol withdrawal seizures (‘rum fits’)

Alcohol withdrawal seizures occur 7–38 hours after the cessation of drinking and peak at 24–48 hours. There can be single or multiple seizures. Status epilepticus is rare. It is estimated that 20–40% of patients with seizure who present to an emergency room have seizures related to alcohol abuse. There are three types of seizure related to alcohol; convulsive inebriation corresponds to a seizure during severe acute alcohol intoxication and alcohol withdrawal seizures follow a partial or complete sudden withdrawal of alcohol, resulting in delirium tremens (DT). The third, known as the alcoholic epilepsy, consists of recurrent seizures in patients with

alcohol abuse without previous history of epilepsy and without relationship to alcohol withdrawal or acute alcohol intoxication.

Delirium tremens

Uncomplicated alcohol withdrawal (‘the shakes’) begins 12–24 hours after the cessation of drinking and peaks at 24–48 hours, then subsides within five to seven days, even without treatment. It may be accompanied by anxiety, tremors, nausea, vomiting, palpitations, and increased blood pressure.

Delirium is derived from Latin, meaning ‘off the track’, and in the year 1813, Sutton coined the term delirium tremens (14). DT is a complex neuropsychiatric syndrome with disturbances of cognition, perception and sensorium, alertness, sleep/wake cycle, and psychomotor behaviour, and associated seizures. Since alcohol withdrawal is prevalent among general hospital patients, prompt recognition is paramount. Treatment consists of therapy with benzodiazepines, alcohol, other cross-reacting agents, beta-blockers, and alpha-2 agonists, in addition to thiamine, intravenous fluids, nutritional supplementation, and multivitamins.

Alcohol hallucinosis

Hallucinosis consists of vivid, unpleasant, auditory, visual, or tactile hallucinations with a clear sensorium, usually within 48 hours of reduction or withdrawal from alcohol. They usually linger for seven to ten days or might enter a chronic

phase. This condition should be differentiated from visual release hallucinations or Charles Bonnet syndrome. Charles Bonnet reported this condition in 1881, which is defined by a triad of complex hallucinations and associated visual deterioration due to coexistent ocular pathology and normal cognitive status (15).

Wernicke's encephalopathy

Carl Wernicke first described this acute neuropsychiatric condition characterized by mental confusion, ophthalmoplegia, and gait ataxia (16). This classical triad can be seen only in one-third of the patients with Wernicke's encephalopathy. The eye findings frequently include bilateral abduction deficits due to VI nerve palsies eventually leading to ophthalmoplegia, vertical or horizontal gaze-evoked nystagmus, and rarely, primary position upbeat nystagmus. Mental features include inattentiveness, abulia (apathy), and impaired memory, progressing in the absence of treatment to coma. Wernicke's encephalopathy had been reported in other conditions of malnutrition, in non-alcoholic patients, including anorexia nervosa or dieting (17), hyperemesis gravidorum (18), prolonged parental nutrition without proper supplementation (19), prolonged starvation, poor unbalanced nutrition, especially with refeeding (20), gastrointestinal surgery, particularly including bariatric surgery (21), transplantation, haemo- or peritoneal dialysis, and AIDS.

Even though thiamine is mainly absorbed in the duodenum, SLC19A2, one of the high-affinity thiamine transporters, shows greater expression in the stomach more than in the

duodenum (22). Apart from the stomach's greater role in thiamine absorption, patients on proton pump inhibitors for peptic ulcer may develop hypomagnesaemia (23), which can cause suboptimum thiamine phosphorylation (24). Because of the involvement of hydrogen cations in the absorption of thiamine, prolonged use of antacids may also interfere with thiamine absorption.

Abnormal magnetic resonance imaging (MRI) signals are typically seen in the medial thalami, mammillary bodies, tegmentum, periaqueductal region, and tectal plates. Less commonly involved sites include the dorsal medulla, red nuclei, cranial nerve nuclei, cerebellum, corpus callosum, and frontal and parietal cerebral cortex, though they are more frequently involved in non-alcoholic patients. In addition, mammillary bodies and inferior colliculi may show enhancement with contrast.

Typical autopsy findings include punctate haemorrhages around the third and fourth ventricles and the aqueduct, which are observed in 0.8% to 2.8% of the general population in the West, and 12.5% of alcohol abusers. Its relationship to Korsakoff's psychosis was appreciated later by other investigators.

Treatment consists of timely replacement of thiamine.

Korsakoff's syndrome

Russian psychiatrist Sergei Korsakoff described this chronic amnestic syndrome which results from thiamine deficiency associated with alcohol dependence. Patients have

anterograde and retrograde amnesia, with an inability to form new memories and retain new information. They have marked deficits in anterograde and retrograde memory, apathy, confabulation in some, and otherwise, relative preservation of cognition (25, 26). Attention, sensorium, and societal skills are left relatively intact, while they are totally unaware of their illness. Involvement of anterior thalamus contributes to the memory impairment.

Central pontine myelinolysis

Dilution of serum sodium in chronic hypotonic alcohol (beer) drinkers results in hyponatraemia (27). When severe, this can result in nausea, vomiting, ataxia, seizures, coma, and even death. CPM is one of the serious sequelae of chronic ethanolism and even the most conservative correction of hyponatraemia has been associated with central pontine myelinolysis (CPM) (28). In addition to decreasing levels of consciousness, CPM may be associated with horizontal gaze paralysis, pseudobulbar palsy and quadriplegia. MRI shows the characteristic changes with a hyperintense lesion in the pons with sparing of the ventrolateral and corticospinal tract on T2-weighted images, and bright high-signal intensities in the corresponding area on the diffusion-weighted image. In severe hyponatraemia, the rate of correction with saline infusion should be cautiously adjusted to avoid the development of central pontine myelinolysis, especially in those with risk factors. Treatment consists of infusion of hypertonic saline (3% sodium chloride) and restriction of intake of fluids. But serum sodium level should not be increased at a rate of more than 0.5 mmol/L per hour, and not to exceed 10 mmol/L in the first 24 hours and 18 mmol/L in

48 hours. Dilution should be used if sodium rises faster than these recommended rates. One should aim to avoid the use of hypertonic or isotonic saline to make the correction (29).

Marchiafava–Bignami disease

Marchiafava–Bignami disease is a rare neurological complication of chronic alcoholism, causing mania, depression, paranoia, dementia, seizures, paresis, and ataxia, often progressing to coma and death within a few months; symptoms are not readily explained by the prominent corpus callosum demyelination and necrosis, which is the pathological hallmark of this poorly understood disease. Patients may show 'crossed avoiding reaction', characterized by the inability to grasp objects presented to the right visual half-field with the left hand, or to respond to contralateral somaesthetic stimuli with either of the upper limbs. This phenomenon is attributed to the inability of one hemisphere to respond to visual or somaesthetic stimuli projected to the other hemisphere (30). MRI on fluid-attenuated inversion recovery images reveal symmetric hyperintensity signals in the genu of the corpus callosum, hemispheric white matter, frontoparietal cortex, middle cerebellar peduncles, and internal capsules (31). Histology often reveals necrosis of the corpus callosum and of the anterior commissure and cortical and subcortical infarctions. Diffuse cortical lesions of the laminar sclerosis type and lacunae in the basal ganglia and the pons are also evident.

Alcoholic dementia

Alcoholic dementia represents 10% of all cases of dementia. This condition occurs in the absence of other indirect causes of injury to the brain including nutritional, traumatic, and metabolic aetiologies. It is often a slowly progressive, global intellectual impairment. Degradation of frontal lobe integrity will result in an alcoholic behaviour characterized by blunted affect, impaired judgement, decreased motivation, social withdrawal, distractibility, poor insight, and cognitive dysfunction (32, 33). Ethanol is a direct neurotoxin, by several mechanisms, including glutamate excitotoxicity and oxidative stress, exacerbated in some cases by thiamine deficiency and in sufficient dosage can cause lasting dementia. Diagnostic criteria include dementia for at least 60 days after last exposure to ethanol, alcohol intake of minimum 35 standard drinks weekly for males and 28 for females exceeding five years' duration and significant ethanol intake within three years of the onset of intellectual impairment (34, 35). Injury to brain is dose related and recurrent binge drinking is likely to produce more cognitive damage to the brain (36). Fifty to 70% of chronic alcoholics have deficits on neuropsychological evaluation, though unequivocal evidence for chronic ethanolism as a sole causative aetiology is lacking. Imaging studies (computed tomography, MRI) reveal cortical atrophy with ventriculomegaly and enlargement of sulci, though consistent correlation between chronicity of ethanolism and severity of cognitive dysfunction is lacking.

Ethanol has effects on cognition indirectly by recurrent intoxication, withdrawals, brain trauma, CNS infection,

hypoglycaemia, hepatic failure, Wernicke's encephalopathy, Korsakoff's psychosis, and Marchiafava–Bignami disease.

Alcohol causes damage to pontocerebellar and cerebellothalamocortical systems, cerebral white matter, the superior frontal association cortex, hypothalamus, and cerebellum, and less consistently the hippocampus, amygdala, and locus coeruleus (37). The prefrontal cortex has been shown to be especially vulnerable by spectroscopy (38).

Alcoholic cerebellar degeneration

The cerebellar cortex and Purkinje neurons (39) are particularly vulnerable to alcoholic intoxication. Atrophy of the cerebellar vermis is well known, particularly with heavy drinkers (40). Alcoholic cerebellar degeneration causes persistent instability of gait and balance, predisposing to falls. This is often associated with selective atrophy of anterior superior vermis of the cerebellum (41).

Patients exhibit abnormal stance and gait, with lower extremity incoordination. Tandem gait is typically not possible. Arms may be involved, only mildly, showing impaired hand writing, coarse, rhythmic 3–5-Hz postural tremors. Global dysarthria may be evident. Cessation of drinking, nutritional supplementation, and supportive care with physical therapy, canes, walkers, and wheelchairs are helpful in maintaining mobility.

Peripheral neuropathy

Peripheral polyneuropathy due to thiamine deficiency alone was predominantly a large-fibre, motor dominant, rapid, sensory-motor neuropathy, while polyneuropathy in alcoholics without thiamine deficiency was due to small-fibre axonal loss mixed-neuropathy, sensory dominant, and slowly progressive. Thiamine-deficient alcoholics tend to have a mixture of the two types. Though the association of peripheral neuropathy is well established in chronic ethanolism, demonstration of a direct neurotoxic effect still remains elusive. In addition to sensory loss to touch, pain and vibratory sense, burning pain, paraesthesiae, skin changes, atrophy, hair loss, and loss of deep tendon reflexes, distal motor weakness also occurs. Compression palsy causing neuropraxia is also a well-known occurrence. Autonomic neuropathy, either purely parasympathetic, or a combined sympathetic and parasympathetic, is well known in chronic alcoholics (42) and in those with cirrhosis of the liver. The severity of the autonomic neuropathy could be influenced by the severity of the coexisting cirrhosis (43).

Myopathy

Acute myopathy is associated with weakness, pain, tenderness, and swelling of the affected muscles, symptoms occurring in relation to a binge, developing over a course of hours to days. While the distribution can be focal or asymmetric, symmetrical proximal myopathy is common. Cardiomyopathy, increased creatine phosphokinase (CPK), myoglobinuria from rhabdomyolysis, myopathic changes on electromyogram, and muscle fibre necrosis on biopsy are

well-known accompaniments. Chronic myopathy is more common than the acute form. It is a slow process that evolves over weeks or months, associated with painless weakness and atrophy of proximal muscles of the extremities. Muscle cramps may occur, CPK may be mildly elevated, but myoglobinuria does not occur. Formation of acetaldehyde adducts within the muscle in the sarcolemmal or subsarcolemmal regions, in response to acute or chronic exposure of alcohol may be a possible mechanism in alcoholic myopathy, though the significance of these adducts still remain unclear (44). Cessation of drinking, supportive care, and nutritional supplements including thiamine offer relief.

Pellagra

'Pelle agra' (rough skin) is considered typical of pellagra, which can be absent when the cases are called atypical. Pellagra is infrequently seen in developed countries. Though it predominantly involves alcoholic patients, it can also occur where malnutrition prevails. It is caused by nicotinic acid deficiency resulting in skin, gastrointestinal, and mental abnormalities, eventually causing death, described as the 'four Ds'—dermatitis, diarrhoea, dementia, and death. Cognitive defects include memory impairment, delusions, hallucinations, dementia, delirium with hypertonus, and startle myoclonus.

Niacin is involved in the synthesis of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are involved in the formation of

high-energy substrates. Tryptophan is involved in the formation of serotonin to nicotinamide, which is influenced by dietary tryptophan and niacin. If tryptophan synthesis is heavily diverted to serotonin production, a niacin deficiency can occur. Deficits in serotonin synthesis and abnormalities of serotonergic activity affect cognition (45). Since kynurenic acid is a tryptophan metabolite, its reduced synthesis and release, cause altered cognition (46), by potentiating glutamate activity at the NMDA receptor, and cholinergic activity at the nicotinic receptor. In physiological doses of niacin, there is often a dramatic response of the disease.

Tobacco–alcohol amblyopia

Tobacco–alcohol amblyopia (TAA) is a rare disorder, better described as a nutritional optic neuropathy, characterized by progressive, bilateral visual deterioration. Middle-aged and elderly men are most prone. Excessive alcohol consumption and malnutrition tend to increase the severity and frequency of the condition, which is probably related to the toxic effects of an unidentified constituent (probably cyanide) of tobacco. The primary insult is to the mitochondria, which disrupts the process of oxidative phosphorylation resulting in axonal loss, preferentially in the fast-firing, parvocellular neurons within the papillomacular bundle. Characteristic pathology includes papillomacular bundle damage, central or caecocentral scotoma, and reduction of colour vision in a patient who abuses tobacco and alcohol. While the optic nerve appears normal, peripapillary dilated vessels and haemorrhages have been described (47, 48). Perimetry often shows central scotomas, but pathological studies have failed to establish the primary lesion in the optic nerve, retina, chiasm, or even the

optic tracts. MRI reveals normal optic nerve images. Treatment warrants cessation of smoking and therapy with hydroxycobalamin.

Ethanol's effects on the fetus

By crossing the placental barrier, alcohol causes damage to the fetal brain. Apart from fetal alcohol syndrome (see Chapter 38), a triad of CNS dysfunction, intrauterine growth deficiency, and characteristic facial dysmorphism, alcohol is also known to cause alcohol-related neurodevelopmental disorder. While there is general consensus that alcohol causes teratogenicity, a threshold of safety remains controversial. Autopsy findings include microcephaly, abnormalities in cortical thickness, corpus callosum, cerebellar vermis, and reduced cerebral white matter volume. Proposed mechanisms include excessive activation of the glycogen synthase kinase 3β that regulates fetal neurogenesis (49), blockade at glutamate NMDA receptors, CNS ischaemia, vasospasm, and CNS ischaemia (50), among others.

Ethanol as a neuroprotectant

Drinking light to moderate amounts of alcohol may decrease the risk of coronary artery disease and ischaemic cerebrovascular disease. The protective effects remained after correcting for sociodemographic and other clinical characteristics (51). Benefit has been found for spirits, red and white wine, and beer. Conversely, heavy drinking is linked to an increased risk of intracerebral haemorrhage and ischaemic infarcts, by contributing to alcohol-induced hypertension, impaired haemostasis, decreased levels of

circulating clotting factors, excessive fibrinolysis, disseminated intravascular coagulation, cardiac arrhythmias, and cardiomyopathy. In the age group 45–50 years, where no cause for stroke was found, 50% of these cases were associated with chronic ethanolism (52).

Screening

The Alcohol Use Disorders Identification Test (AUDIT) helps in the early identification of abuse and harmful alcohol use. The three scales measure alcohol consumption, dependence, and harm. Short Index of Problems (SIP) is designed to assess five drinking related problem areas—physical, intrapersonal, social responsibility, interpersonal, and impulse control. The Depression, Anxiety, and Stress (DASS)-21 can be used to measure depression, anxiety, and stress, each assessed by a seven-item subscale, as good as the original 42-item version of the DASS.

Laboratory tests

In addition to a good screening and assessment of alcohol use and abuse, blood alcohol level, and physical examination, other laboratory tests may be useful. In chronic ethanolism, macrocytosis precedes well before anaemia appears (53, 54). Alcohol-related liver disease is strongly suggested by the ratio of serum aspartate aminotransferase compared with alanine aminotransferase greater than two (55). A better tool to identify chronic ethanolism is serum carbohydrate-deficient transferrin with a strong sensitivity and specificity (56). Thiamine deficiency can be most reliably detected by measurement of erythrocyte thiamine transketolase (ETKA)

before and after the addition of thiamine pyrophosphate (TPP). A low ETKA, along with more than 25% stimulation, establishes the diagnosis of thiamine deficiency (57). A serum thiamine or TPP level in serum or whole blood can also be measured by chromatography.

Conclusion

The deleterious effect of alcohol on the nervous system and psyche is diffuse, and very pervasive. Associated with disability and early mortality, alcohol use mental disorders are frequently co-morbid with other psychiatric disorders, and play an aetiological role in other mental diseases. Although alcohol is associated with a broad spectrum of neurological and mental disorders, only recently stroke has been recognized as a sequela. The chronic misuse of alcohol often leads to lifelong impairment of CNS function resulting in unparalleled familial, social, and fiscal costs. Education, prevention, early detection, and intervention are of paramount importance, with obvious benefits to individual, family, community, and work place.

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Chapter 37
Infectious disease

Andriy V. Samokhvalov, Paul A. Shuper, and Jürgen Rehm

Introduction

Since ancient times, alcohol consumption has been associated with increased susceptibility to infectious diseases. In the past decades growing evidence allowed for describing this association on epidemiological and pathobiological levels, and the causal role of alcohol, especially heavy drinking (HD), in increased susceptibility to infectious diseases was established. This causal relationship has been shown to be mediated by a number of psychosocial and biological factors.

Psychosocial factors

HD and/or alcohol use disorders (AUDs) negatively affect social, work, and family obligations that in turn may result in lowering of socio-economic status of the drinkers with an increase of risk for financial losses and changes in lifestyle—living in overcrowded habitats, and having suboptimal nutrition and healthcare. These factors are of importance for acquisition and course of many infectious diseases, such as tuberculosis (1, 2). Frequent alcohol inebriations are also associated with a number of behavioural consequences such as unprotected sex which leads to a significantly higher risk of acquisition of sexually transmitted diseases, such as human immunodeficiency virus (HIV) (3, 4). Furthermore, irregular food intake and medication

adherence, disrupted sleeping pattern, etc., can lead to weakened defence mechanisms, increased susceptibility, and more severe course of existing infectious diseases (2, 5–7).

Biological factors

Alcohol consumption results in significant immunosuppression, typically proportional to the amount of alcohol consumed (7–9). HD and AUDs also impact general health in several other ways, one of the most important of which is malnutrition—as heavy drinkers and people with AUDs tend to have lower socio-economic status and in many cases low budgets, most of which may be spent for purchasing alcohol rather than food. Also, when choosing their food, these individuals tend to prefer less expensive and ready-to-eat products over more expensive nutritionally-rich foods. In many cases they eat sporadically and inconsistently, and most of their caloric intake comes from ethanol. In addition to inadequate food intake, alcohol consumption has been shown to significantly interfere with food digestion, absorption, and metabolism. Alcohol depletes glycogen storage, which is the major source of body glucose necessary for normal functioning of most organs between meals. Also, intensive metabolism of alcohol leads to the depletion of certain
vitamins such as B_1 and B_{12}, both of which are crucial for cell proliferation in all tissues, and are particularly important for the cells of immune system.

Thus, effects of inadequate nutrition and metabolic changes significantly weaken the body's ability to regenerate tissues and provide them with adequate amounts of energy necessary

for securing proper functioning of immune system. In addition, alcohol has been shown to act directly on almost every single component of the immune system, suppressing it either directly or indirectly via distorting its regulation (8, 9).

The immune system is divided into two parts, innate and acquired, which act synergistically and serve the same function—the elimination of foreign pathogens. The innate immune system consists of several components that provide non-specific passive and active defences against microorganisms. Passive defences include natural physical barriers such as the epithelium of the skin and the mucosal layer of gastrointestinal, respiratory, and genitourinary tracts. They also include chemical barriers such as highly acidic gastric content that can destroy most of the microorganisms coming with food, and the acidic pH of urine that together with unobstructed urine flow make the reverse spread of microorganisms in genitourinary tract nearly impossible. Active defences are represented by active elimination of pathogens by a variety of mechanical (e.g. coughing, propulsive movements of cilia of respiratory tract, etc.), cellular (e.g. action of tissue macrophages, neutrophils, etc.), and chemical (e.g. lysozyme, interferons, etc.) mechanisms.

Acquired immunity provides antigen-specific responses to foreign substances, mainly proteins. These responses are based on coordinated actions of several types of cells of the immune system, including lymphocytes, leucocytes, macrophages, neutrophils, etc. Acting together these cells allow for efficient recognition of foreign antigens and own infected cells as well as for further cellular (facilitated phagocytosis, natural killer cells) or humoral (production of antibodies) response to them.

In cases of infection, both arms of the immune system always act simultaneously and synergistically resulting in the process called inflammation. Complex interactions between the cells of the immune system are carried out by multiple chemicals such as cytokines and interleukins produced by one kind of cells in order to modulate activity of others—to attract them to the site of inflammation, to initiate production of antibodies, to increase proliferation of certain type of cells, to change blood flow and vascular permeability in the area of inflammation, and to increase the rate of diapedesis of neutrophils.

It has been shown that alcohol consumption interferes with both innate and acquired immune defences (Figure 37.1) and disrupts their synergistic interactions (8, 9). Decreased rate of tissue regeneration increases vulnerability of natural barriers, and together with malnutrition, leads to impaired wound healing. Alcohol consumption changes include alterations of peristalsis, suppressed coughing reflex, changes in urine pH and flow, and interference with many other mechanisms associated with the elimination of microorganisms, leading to higher susceptibility to gastric ulcers, pneumonia, urinary (including sexually-transmitted), and gastrointestinal tract infections. Malnutrition and chronic liver damage lead to decreased production of complement system proteins, and thus, impaired innate immune system responses. In addition, alcohol has been shown to suppress activity of tissue macrophages and neutrophils (i.e. the cellular component of innate immune system and the main source of antigens for acquired immune system cells). Thus, alcohol not only impedes phagocytosis of microorganisms but also hampers the creation of immunological memory and incapacitates future responses to specific microorganisms. In addition to

this, alcohol suppresses proliferation of several types of immunocompetent cells and production of certain cytokines and interleukins that are important for proper coordination of immune responses, rendering them less effective.

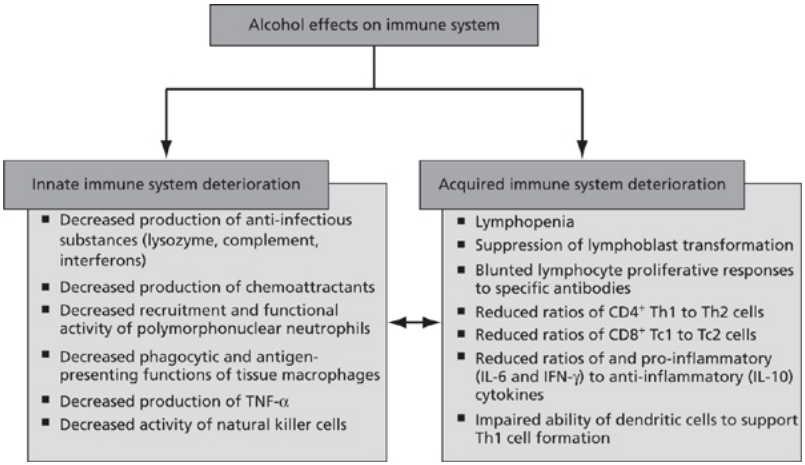

Figure 37.1 Major effects of alcohol consumption on immune system.

Adapted from Rehm J, Anderson P, Kanteres F, Parry CD, Samokhvalov AV, and Patra J, *Alcohol, social development and infectious disease*, Centre for Addiction and Mental Health, Toronto, Canada, Copyright © 2009, with permission from the author.

Socio-biological consequences of alcohol consumption on infectious disease susceptibility

Pneumonia

Pneumonia is one of the most prevalent infectious diseases worldwide, with annual incidence varying from 1% to 12%, according to different estimates (10). Alcohol consumption is classically considered to be one of the major contributors to this pathological condition. Increased susceptibility of drinkers to pneumonia can be described on several levels starting with malnutrition and poor living conditions, and ending with specific biological factors significantly increasing the risk of development of pneumonia. One of the biological factors specific to pneumonia is diminished oropharyngeal tone that, in combination with vomiting which is typical for heavy drinkers, significantly increases the risk of aspiration of stomach contents. Also, decreased bronchoalveolar lavage due to suppression of the coughing reflex and decreased cilia motility in combination with decreased alveolar macrophages' activity impairs timely elimination of foreign bodies from the respiratory system and presentation of antigens to immunocompetent cells (8). Chronic liver damage and malnutrition further weaken immune responses by decreased production of bactericidal substances such as lysozyme, complement, interferons, etc. (8, 9). Among other effects of alcohol on the immune system shown in experimental studies is the suppression of chemoattractant molecules production, and hence, decreased recruitment of polymorphonuclear leucocytes as well as reduced functional activity and impaired response to chemotactic signals (9). Alcohol-related suppression of granulopoietic cytokine

production and impairment of the granulopoietic progenitor cell response to the cytokine stimulation lead to inhibition of bone marrow granulopoietic function, and hence to diminished number and immaturity of immunocompetent cells. Alcohol has been shown to cause lymphopenia, suppression of lymphoblast transformation, and
blunted lymphocyte proliferative responses to specific antibodies (9), as well as diminished number of CD4+ T lymphocytes and their capacity to produce interferon-γ and impaired ability to develop specific antibodies following new antigen challenges.

All these factors increase the risk of development of pneumonia in drinkers proportionally to amounts of alcohol consumed on daily basis; a recent meta-analysis has shown that the risk of community-acquired pneumonia (the vast majority of pneumonia cases are community acquired) increased linearly with increasing alcohol consumption. Individuals consuming 24 g, 60 g, and 120 g of alcohol daily had relative risks (RRs) of 1.12 (95% confidence interval (CI): 1.02–1.23), 1.33 (95% CI: 1.06–1.67), and 1.76 (95% CI: 1.13–2.77), respectively, relative to non-drinkers. The RR of the onset of community-acquired pneumonia in drinkers is 1.06 (95% CI: 1.01–1.11) per each additional standard drink of 12 g pure alcohol per day (7). Studies of hospital-acquired pneumonia showed similar results.

Tuberculosis

Pulmonary tuberculosis (TB) is a particular case of pneumonia. It is caused by *Mycobacterium tuberculosis*, the specific features of which make this case stand out from the

rest of pneumonias. Specificity of *Mycobacterium tuberculosis* is determined by its resistance to multiple external factors and ability to remain contagious for years without the host. Also, being an intracellular pathogen, it can remain dormant for years in a host's body after initial infection and can be reactivated when a host's immune status decreases. This feature of this microorganism leads to very high prevalence of infection in most populations with active disease outbreaks in either immunocom-promised or weakened individuals, or historically, in times of natural disasters or social crises. Sequelae of alcohol consumption incorporate both social and biological components classically associated with TB manifestations. Alcohol has been associated with TB for a long time (1, 2). The most recent estimates show strong and consistent association with a risk ratio of 2.94 (95% CI: 1.89–4.59) (2). Recently the existing evidence on the association between alcohol consumption and the risk of TB has been systematized and summarized yielding two plausible pathways enabling this association. First, alcohol-related immunosuppression can increase susceptibility to infection as well as conversion to active TB in infected individuals (8). Second, alcohol consumption tends to put drinkers in social environments which facilitate the spread of TB infection (1). Also, there is enough evidence to conclude that heavy drinkers are less likely to adhere to TB treatment regimens and to seek medical assistance, even in cases of significant health deterioration.

HIV/AIDS

HIV is a significant global health problem. In 2009, there were an estimated 33.3 million people living with HIV

worldwide, with 2.6 million people infected with HIV in that year alone (11). Acquired immune deficiency syndrome (AIDS), the fatal condition caused by HIV, was responsible for 1.8 million deaths in 2009, and to date, more than 30 million people worldwide have died from AIDS (12). The consumption of alcohol has been closely investigated within the context of this ongoing HIV epidemic, and evidence suggests that through both behavioural and biological pathways, alcohol may play a role in the acquisition and transmission of HIV, as well as in the worsening of the HIV disease and progression to AIDS (6, 13).

HIV acquisition and transmission

The vast majority of HIV infections result from sexual activity between HIV-infected and non-infected individuals (14). The consumption of alcohol may increase the likelihood of
unprotected sex and subsequent HIV seroconversion by having a direct disinhibitory effect on behaviour, or by constricting cognitive capabilities such that within an alcohol-influenced sexual decision-making paradigm, only risk-impelling cues (e.g. sexual arousal) are attended to while risk-inhibiting cues (e.g. risk of HIV infection) are ignored. Meta-analytic studies of investigations involving alcohol manipulations and assessments of sexual risk behaviour intentions have suggested a clear dose–response effect of alcohol on intentions to engage in unprotected sex without condoms, demonstrating a 5.0% (95% CI: 2.8–7.1%) increased likelihood of engaging in unprotected sex for an increase in blood alcohol concentration of 0.1 mg/ml (4).

This link between alcohol and unprotected sex has also been shown to extend to the acquisition of sexually transmitted infections (STIs), including HIV, with support deriving from key systematic reviews and meta-analyses. Specifically, Cook et al. (15) reported associations between alcohol consumption and STIs, and these associations appeared to be held regardless of drinking patterns or gender. With respect to HIV, Fisher et al. (16) found a 57% (95% CI: 1.42–1.72) increased risk of being HIV-positive among drinkers compared to non-drinkers. Similarly, Baliunas et al. (3), who performed a meta-analysis based on prospective studies, demonstrated a 77% (95% CI: 1.43–2.19) increased likelihood of acquiring HIV among drinkers (versus non-drinkers), an 87% (95% CI: 1.39–2.50) increased likelihood among those consuming alcohol prior to sex (versus those not consuming alcohol in sexual contexts), and over twice the likelihood (2.20, 95% CI: 1.29–3.74) of HIV acquisition among binge drinkers (versus non-binge drinkers). Alcohol consumption may also contribute to the transmission of HIV, with meta-analytic findings demonstrating that among HIV-positive populations, drinkers, problematic drinkers, and those who used alcohol in sexual contexts were 63% (95% CI: 1.39–1.91), 69% (95% CI: 1.45–1.97), and 98% (95% CI: 1.63–2.39) more likely to engage in unprotected sex compared to non-drinkers, problematic drinkers, and alcohol non-users in sexual contexts, respectively (17).

While the immunosuppressant effects of alcohol described still play a certain role in HIV acquisition in cases of exposure to the virus, other alcohol-attributable biological factors are more important. For example, among those infected with HIV, the consumption of alcohol may lead to an

increase in HIV viral replication (13), which in turn can significantly impact the likelihood of transmitting HIV to non-infected others (18). Alcohol may also lead to an increase in the shedding of HIV in the genital tract, with recent research demonstrating a greater than twofold increase (odds ratio (OR) = 2.29, 95% CI: 1.18–14.43) in vaginal HIV shedding among women on antiretroviral therapy (ART) who were moderate to heavy drinkers (19). These findings suggest that the degree of HIV infectivity among those living with HIV may be influenced in part by their level of alcohol use.

HIV disease progression

ART has been key to improving and maintaining physical health, reducing HIV viral load, and reducing morbidity and mortality among those living with HIV. However, near-perfect adherence over time (i.e. >90–95%) is required to attain the maximal benefits of ART and suboptimally adhering to one's regimen can result in the development of resistance to ART, poor treatment outcomes, and mortality. Alcohol consumption may impact the cognitive processes necessary to maintain adequate adherence, particularly when ART regimens are complex. Furthermore, even possessing the belief that ART medications should not be taken while consuming alcohol may cause drinkers to fail to adhere. In these regards, clear links between alcohol consumption and non-adherence to ART have been demonstrated (20, 21). For example, a recent meta-analysis demonstrated that drinkers were 50–60% as likely to be adherent as non-drinkers (OR = 0.55, 95% CI: 0.49–0.61), and this effect was especially amplified for problem drinkers, who were 47% less likely to be adherent

as non-problem or non-drinkers (OR = 0.47. 95% CI: 0.41–0.55) (21). These meta-analytic results have been further supported by evidence of an alcohol-adherence dose–response relationship, demonstrating not only that among HIV-positive individuals on ART, missed doses tend to be highest among binge drinkers compared to non-binge drinkers and non-drinkers, but also that missed doses tend to occur with highest frequency on drinking days, followed by post-drinking days, and then non-drinking days (22). Similar results have been shown by Parsons et al. who found that non-adherence was approximately nine times more likely to occur (OR = 8.78, 95% CI: 7.17–10.77) on days in which alcohol was consumed (23). In direct correspondence with these findings, the consumption of alcohol has been shown to be significantly associated with time to ART treatment failure as well as subsequent survival (24). Specifically, daily drinking among non-hazardous and hazardous drinkers has been shown to decrease the time to ART treatment failure by 33% and 72%, respectively. Furthermore, among non-hazardous and hazardous drinkers who consume alcohol daily, survival has been shown to be reduced by 15% and 40%, respectively, representing a reduction of 3.3 life years for non-hazardous drinkers and 6.4 years for hazardous drinkers (24). Alcohol thus appears to be a significant factor that underlies ART non-adherence, treatment failure, and mortality among HIV-infected individuals.

Summary

Alcohol consumption impacts on a variety of biological and social factors including general health, immune system functioning, socio-economic status, and behaviour of a

drinker that, in turn, lead to increased exposure to infectious agents, increased susceptibility to acquiring infectious diseases, and a number of complications slowing down recovery or promoting disease progression. The most recent epidemiological evidence demonstrates significantly higher incidence and prevalence rates of the most common forms of infectious diseases in drinkers compared to abstainers, but especially high for HD and AUDs. Further implementation of alcohol policy interventions, effective treatment of AUDs, and promotion of light drinking or abstinence should significantly decrease incidence, prevalence, and burden of infectious diseases.

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Chapter 38
Alcohol and pregnancy: fetal alcohol spectrum disorders and the fetal alcohol syndrome

Kenneth R. Warren and Margaret M. Murray

Introduction

Alcohol is a teratogen. It is included among a list of specific agents and factors that interfere with prenatal development. But because alcohol is so widely accepted and used in so many cultures, it is more than just a teratogen—it is the most prominent behavioural teratogen in the world. In the case of alcohol consumption by a pregnant woman, a broad range of physical and central nervous system (CNS) effects can result in facial dysmorphology, growth deficiencies, and cognitive and behavioural deficits in the developing fetus, most of which persist throughout the life of the affected individual.

The teratagenic effects of alcohol were not established until the second half of the twentieth century. A paediatrician, Paul Lemoine (France, 1967) (1), and two paediatric dysmorphologists, Kenneth Lyons Jones and David Smith (United States, 1973) (2), independently documented the pattern of deficits resulting from heavy prenatal alcohol exposure. Alcohol was attributed because the children in both settings had common patterns of deficits and it was observed that all of the birth mothers had been diagnosed with alcohol use disorders. It was Smith who decided to label the condition described in these children ‘fetal alcohol syndrome’ (FAS)

because he believed that such a name would serve as its own prevention message (3).

Today, alcohol is recognized as one of the leading preventable causes of birth defects and developmental disorders (4, 5). It is now established that there are a range of effects on the developing fetus and that the severity of these effects are the result of timing and amount of alcohol exposure, as well as genetic vulnerabilities, environmental factors such as nutrition, and epigenetic changes (6–8). In addition to FAS, which is seen as the most severe outcome of maternal alcohol drinking, there is a developing lexicon of terms that describes the range of effects under the umbrella fetal alcohol spectrum disorders (FASD). This lexicon currently includes the terms fetal alcohol effects (FAE), alcohol-related birth defects (ARBD), alcohol-related neurodevelopmental disorders (ARND), and partial fetal alcohol syndrome (pFAS) (9, 10).

Definitions

Fetal alcohol spectrum disorders

This term originated from a working group in the United States made up of several federal government agencies, private advocacy organizations, scientific and clinical experts, and concerned members of the general public (11):

Fetal alcohol spectrum disorders (FASD) is an umbrella term describing the range of effects that can occur in an individual whose mother drank alcohol during pregnancy. These effects may include physical, behavioral, and/or learning disabilities

with possible lifelong implications. The term FASD is not intended for use as a clinical diagnosis.

Fetal alcohol syndrome

There are three defining characteristics of FAS, and all must be present for a diagnosis:

1 a specific pattern of facial features (Figure 38.1)

2 prenatal and or postnatal growth deficiency

3 evidence of CNS dysfunction, usually conforming to a characteristic pattern.

The cardinal or discriminating features include short palpebral fissures (eye opening), an elongated and hypoplastic philtrum (groove between nose and upper lip), and a thin upper vermillion lip border or hypoplastic 'cupid's bow'. Associated features include a low nasal bridge, epicanthal folds (skin folds covering inner corner of the eye), minor ear anomalies, and micrognathia (abnormal smallness of the jaws). Finally, there may be the presence of microencephaly (a small head circumference) which is not considered a facial feature but is a CNS dysfunction. Figure 38.2 shows a child at age five diagnosed with FAS.

Prenatal and/or postnatal growth deficiencies include weight less than the tenth percentile and length or height less than the tenth percentile.

CNS dysfunctions can include any of the following (not all must be present for a diagnosis):

♦ head circumference less than tenth percentile

♦ memory problems

♦ attachment concerns

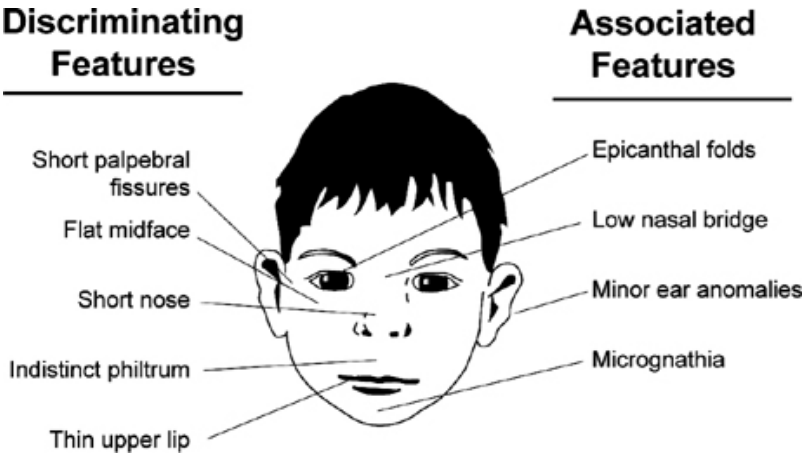

Figure 38.1 The face of fetal alcohol syndrome.

U.S. National Institute on Alcohol Abuse and Alcoholism, used with permission.

Figure 38.2 A five-year-old child with fetal alcohol syndrome.

Photograph used with permission.

♦ impaired motor skills

♦ neurosensory hearing loss

♦ learning disabilities (language and mathematics)

♦ impaired visual/spatial skills

♦ intellectual impairment

♦ delayed development

♦ attention deficit disorder (as many as 70% of children with FASD are mistakenly diagnosed with attention deficit hyperactivity disorder. For a complete discussion of discrimination between the two see Coles (12))

♦ hyperactivity

♦ problems with reasoning and judgement

♦ inability to appreciate consequences of actions.

In 1996, the Institute of Medicine (IOM) of the US National Academy of Sciences recommended two categories—FAS with a history of maternal alcohol exposure and FAS without a history of maternal alcohol exposure (13). They also recommended a third category called partial FAS (pFAS), which includes those individuals with signs and symptoms attributable to significant prenatal alcohol exposure but who would not receive a diagnosis of FAS.

While the facial characteristics of FAS are important, the most significant effects for quality of life of the affected individual and family are on the CNS dysfunctions. Research over the past 40 years has demonstrated that alcohol interrupts development at all stages from neurogenesis to myelination. In fact, the facial characteristics manifested correlate with brain development at each stage making it important to view FAS as a disorder of the brain, not one of facial characteristics (14).

Alcohol-related birth defects and alcohol-related neurodevelopmental disorders

Prenatal alcohol exposure can result in characteristics that do not meet all of the diagnostic criteria for FAS, but cause problems for the affected individual. The IOM recommended two additional categories of FASD that describe problems in children without the facial characteristics. Alcohol-related birth defects include other alcohol-induced abnormalities of the face, eyes, ears, heart, brain, kidneys, and limbs (13).

Alcohol-related neurodevelopmental disorders include problems in behaviour, cognitive function, language, attention, attachment, memory, and fine motor skills that are a result of maternal drinking (15).

There are currently four different diagnostic schemes based on the principles outlined by the IOM that have been published to aid clinicians in the diagnosis of FAS, pFAS, and ARND. These include:

♦ Revised Institute of Medicine Criteria (16)

♦ US Department of Health and Human Services Task Force on FAS (13)

♦ Canadian guidelines (17)

♦ 4-digit code (18).

Diagnosis of ARND presents unique problems if an accurate history of maternal alcohol use cannot be obtained, which is often the case. Research focused on the development of a

valid and reliable neurobehavioural profile of heavy prenatal alcohol exposure is ongoing and critical to increase identification of and intervention with affected individuals (19).

Intervention strategies for FASD

Pharmacological interventions

Pharmacologic and nutritional treatments include agents that may offer protective benefits to the foetus by blocking the teratogenic effects of the alcohol and are given to the mother during pregnancy. Some examples of drugs under study are N-methyl D-aspartate receptor antagonists such as MK-801, agmatine, eliprodil, and memantine; and neuroprotective peptides such as NAPVSIPQ (NAP) and SALLRSIPA (SAL).

Another important focus is on agents that improve CNS dysfunction which may be useful both during pregnancy as well as when given to the affected individual after birth. These include antioxidants, vitamins A and C, and the nutritional supplement choline (20).

Behavioural interventions

Behavioural interventions have been developed that target both the primary deficits occurring in individuals with FASD, as well as the ancillary problems that need addressing in order to improve the lives of those affected. These interventions include educational and cognitive interventions, parenting interventions, adaptive skills training, and case management (21).

Incidence and prevalence of FAS and FASD

There are limits to what is known about the prevalence of FASD. Prevalence studies of FAS have followed three approaches—surveillance and record review systems, clinic-based studies, and active case ascertainment. The methodological strengths and weaknesses of all three strategies
have been reviewed by May and colleagues (22), and it is generally agreed that active case ascertainment, especially where in-school screening and diagnosis are used, yields the most accurate estimates. In fact, studies done this way predict the ratio of FAS to pFAS cases based on general measures of women's alcohol consumption (22).

The IOM prevalence estimate for FAS in the United States in 1996—which did not rely on active case ascertainment—was 0.5–2/1,000 live births. Table 34.1 shows results based on a study of FAS in first grade students, typically aged six to seven, using active case ascertainment where much higher estimates in a mid-Western city in the United States, 6–11/1,000 live births, were obtained in a predominantly white, middle-class population (22). Active case ascertainment was used by investigators in a study conducted in the Lazio region of Italy where a rate of 4–9/1,000 live births was found in a predominantly middle socio-economic population (23), which far exceeds estimates of 0.97/1,000 that were reported for the Western world based on an examination of clinic-based studies (24). The highest rates of FAS have been recorded in South Africa, where two active case ascertainment studies estimated up to 67 cases per 1,000 live births in all socioeconomic levels in white, black, and mixed ancestry

populations (25, 26). Table 38.1 also reports the prevalence of PFAS found in these active case ascertainment studies.

A World Health Organization systematic review of the FASD prevalence literature (27) demonstrates the difficulty in establishing either country by country or global prevalence estimates of FASD. The review examined all available international literature and found incidence/prevalence data on FASD in 77 studies from 21 countries. Unfortunately, most of these were conducted in limited geographic areas within each country, were based on clinic samples or record reviews, and did not use active case ascertainment methods. Serious methodological limitations were noted (varying diagnostic criteria, surveillance methods, and methods of case selection) which likely account for the large differences between countries that were reported.

Table 38.1 Prevalence of FAS/pFAS in various countries based on active case ascertainment studies

Location	Population	Socio-economic status (SES)	FAS (FAS + pFAS) rate per 1,000 births
United States, mid-western medium-size city (22)	75% white; 25% American Indian, African American, and Asian	Middle SES with full range (low to upper)	6–11 (14–25)
Italy, Lazio region (23)	Predominantly white	Middle SES	4–9 (27–55)
South Africa, Western Cape (25)	85% mixed ancestry, 15% European white	Low-middle SES White: middle-upper SES	51–67 (68–90)
South Africa, Northern Cape (26)	64% mixed ancestry 36% native black	Low and middle SES	67 (75–119)

Data from May PA et al., Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies, *Developmental Disabilities Research Reviews*, Volume 15, Issue 3, pp. 176–92, Copyright ©2009; May PA et al., Epidemiology of FASD in a province in Italy: Prevalence and characteristics of children in a random sample of schools, *Alcoholism: Clinical and Experimental Research*, Volume **30**, Issue 9, pages 1562–1575, September 2006, Copyright © 2006; Abel EL, An update on the incidence of FAS: FAS is not an equal opportunity birth defect, *Neurotoxicology and Teratology*, Volume **17**, Issue 4, pp. 437–443, Copyright ©1995 and May et al., The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. *Drug and Alcohol Dependence*, Volume **88**, Issues 2–3, pp. 259–271, Copyright © 2007.

Maternal risk factors for FASD and the need for effective prevention strategies

One of the most compelling aspects of FASD is the fact that it is preventable. Strategies to prevent alcohol use in pregnancy need to take into consideration that the prevalence of drinking by women of child-bearing age is on the rise in many parts of the world and most pregnancies are not planned (28). In addition, drinking early in the gestational period, before the woman even knows she is pregnant, can present special risks for the developing embryo (29).

It is not yet known how specific timing, frequency, and quantity of alcohol use throughout the gestational period affects the specific features of FAS, ARBD, and ARND in humans, although animal models are continually making this clearer (30). A number of maternal risk factors have been identified in the literature in addition to timing, frequency,

and quantity of drinking. These include maternal age, number of pregnancies, number of full-term pregnancies, mother's body size, nutrition, alcohol metabolism, religious and spirituality factors, socio-economic status, mental health, other substance use, and social relationships (31).

There are prevention interventions under development, but more research based on the IOM model of prevention strategies—universal, selected, and indicated—is needed (12). At present, screening for alcohol use and delivering brief interventions to women of child-bearing age in primary care, family medicine, and obstetrics and gynaecology clinics have been shown to be effective (32, 33), as well as similar approaches in community settings that include counselling on contraceptive use for women who choose to continue drinking (34, 35). One study found reductions in alcohol use by post-partum women in family medicine clinics after receiving a brief intervention (36). This population is important because the risk for severity of alcohol symptoms in the exposed child increase with each pregnancy (37).

Other problems resulting from alcohol use in pregnancy

Drinking during pregnancy can be associated with additional adverse outcomes (38, 39). Those noted in the literature include spontaneous abortion, stillbirth, preterm birth, sudden infant death syndrome, low birth weight, and the child being small for gestational age.

Implications for research and policy

The science underlying the teratogenic effects of alcohol is clear, and because of this, recommendations for alcohol use during pregnancy should always advise against any use from the point of conception throughout the pregnancy. While there is a growing awareness around the world of the harms alcohol can cause to a developing fetus (5), there is still false information and misunderstandings in public perception and even physician attitudes that continue to raise barriers to effective FASD prevention. Policy-makers need to be aware of medical and public health attitudes and practices in their regions and work to ensure that scientific knowledge is disseminated, and sound, efficacious prevention strategies are in place.

Research, especially studies that employ new technologies in brain imaging, continues to increase understanding of the aetiology of FASD, improve techniques for diagnosis, and develop effective treatments and prevention interventions. One of the most exciting areas is a three-dimensional camera system and image analysis (40) that can aid both clinicians and researchers in identifying and tracking the sometimes subtle facial abnormalities associated with FAS and pFAS. This technology is compatible with telemedicine, and would allow those children who do not live in areas where there is a clinician capable of diagnosing FASD the opportunity for an accurate diagnosis.

Because it is not always possible to determine maternal drinking levels and patterns, it is important to find reliable biomarkers of alcohol use (and ensuing damage) during the

prenatal period. This would allow early case recognition and intervention.

Finally, there is a continued need for good epidemiology, based on the most accurate methods, that will establish true incidence and prevalence of FAS by country and globally, calling attention to the need for policies to both help affected children and families receive appropriate support and prevent further cases.

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Part VIII
Therapeutic aspects: current approaches

Chapter 39
Screening of high-risk drinkers

Amy O'Donnell and Eileen Kaner

Background

Excessive drinking is a significant public health problem and the third greatest risk to health and well-being in developed countries (1). However, there is a recognized continuum of both alcohol consumption and harm (2, 3). Epidemiological data have shown that the majority of alcohol-related problems that occur in a population are not due to the most problematic drinkers—generally individuals with alcohol dependence—but to a much larger group of hazardous and harmful drinkers (4). Hazardous drinking is consumption at a level, or in such a pattern, that increases an individual's risk of physical or psychological consequences (5), whilst harmful drinking is defined by the presence of these consequences (6). However, hazardous and harmful drinkers may not be aware of the risk or harm that they are experiencing due to alcohol, and they will often be presenting to generalist health settings, where time is limited, for a range of other health problems. Consequently, the screening of high-risk drinking generally needs to be short and acceptable in form to both practitioners and potential recipients who may have a range of drinking patterns.

Overview of available screening tests

Screening is a process by which practitioners are able to estimate the probability of occurrence of a specific disorder, such as an alcohol use disorder. Screening is not the same as diagnostic testing, which establishes the actual presence of a disorder. Rather, screening is often used to indicate if early-stage risk or harm is present, and acts as a precursor to preventive intervention to avoid the development of more serious future problems (7). There is a wide range of alcohol screening tests and approaches available to practitioners, including blood tests, urine toxicology screens, self-report measures, structured interviews, and educated guessing based on clinical experience. These tests vary in their degree of accuracy, intrusiveness, and acceptability to practitioners and patients.

Biomedical markers of alcohol abuse

Clinicians are often most familiar with laboratory tests in which elevated values are associated with chronic excessive alcohol intake. Biomedical markers of alcohol abuse include mean corpuscular volume, gamma-glutamyl transferase (GGT), carbohydrate deficient transferrin (CDT), and the rate of alanine aminotransferase to asparatate aminotransferase. However, although such tests may detect organ damage or malfunction, they generally only identify those patients with long-term use in whom secondary symptoms have already occurred. In addition, certain laboratory tests can pick up pathologies unrelated to alcohol (such as liver disease due to obesity) and they can be affected by several medications (8). Further, urine, blood, and breath

tests are all relatively unreliable indicators of different levels of alcohol use, particularly early-stage problems, since alcohol is metabolized quickly and is unlikely to be detected in body fluids. Indeed, biomedical markers tend to perform significantly better in clinical populations, for example, patients with liver disease, and are therefore not recommended in community settings where high sensitivity is required (9). As a result, biomedical markers have a relatively limited role to play in the detection of hazardous and harmful drinking in public health settings. However, there is some support for their use as a supplementary screening measure (10), or for monitoring following intervention (11).

Questionnaire-based screening tools

As an alternative to the biomedical markers just described, educated guessing based on clinical experience may identify some users, but this approach is heavily dependent on the practitioner's attitudes and experience. Structured interviewing, although arguably a more consistent approach, is both time-intensive to deliver and requires a level of training and monitoring that is impractical in most clinical settings. Therefore, the most effective method for detecting high-risk drinkers is often via a validated, standardized questionnaire-based screening tool, generally designed to be administered face-to-face, patient-to-provider. Importantly, their standardization permits uniformity in administration and scoring across interviewers with diverse experience, training, and treatment philosophies. In addition, questionnaire-based screening is less costly than laboratory analysis and is far less intrusive and more acceptable to patients. Crucially, in medical practice, standardized questionnaires have been

found to have a greater sensitivity and specificity than biomedical markers.

One of the oldest and most popular screening tools, CAGE is a straightforward, international screening test for identifying patients who are experiencing alcohol abuse (regarded to be drinking that leads to problems but not necessarily dependence; it may be less helpful at identifying pre-symptomatic, hazardous drinking). CAGE is a mnemonic that cues four items covering a 'past year' timeframe. (**C**utting down, **A**nnoyance by criticism, **G**uilty feeling, and **E**ye-openers) (12). The CAGE questionnaire is best used as part of a general clinical history taking and should not be preceded by any questions about alcohol intake because its sensitivity is dramatically enhanced by an open-ended introduction. Two 'yes' responses is considered clinically significant (sensitivity of 93%, specificity of 76% for the identification of problem drinking); compared with GGT liver function test which detect only a third of patients having more than 16 standard drinks per day.

The Alcohol Use Disorders Identification Test (AUDIT) was the first screening tool designed specifically to detect hazardous and harmful drinking in both primary and secondary care. Developed by the World Health Organization (WHO) (13), AUDIT has ten questions that consider drinking frequency and intensity (binge drinking), together with experience of alcohol-related problems and dependence (Table 39.1). At a score of eight or more out of a possible 40, its ability to detect genuine excessive drinkers (sensitivity), and to exclude false cases (specificity), is 92% and 94%, respectively. Thus, AUDIT is a highly accurate tool which has been validated in a large number of countries with

consistently strong psychometric performance. It is now regarded as the 'gold standard' screening tool to detect hazardous and harmful drinking in primary care patients.

Nevertheless, at ten items, AUDIT may be considered to be too lengthy for use in regular screening activity. Further, in primary care, approximately four out of every five patients tend to screen negative for hazardous and harmful drinking. Thus, practitioners need a more time-effective detection method and so several shorter versions of AUDIT have been developed, including:

Table 39.1 Alcohol Users Disorders Identification Test (AUDIT)

Questions	Scoring system					Your score
	0	1	2	3	4	
How often do you have a drink that contains alcohol?	Never	Monthly or less	2–4 times per month	2–3 times per week	4+ times per week	
How many standard alcoholic drinks do you have on a typical day when you are drinking?	1–2	3–4	5–6	7–9	10+	
How often do you have 6 or more standard drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often in the last year have you found you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often in the last year have you failed to do what was expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often in the last year have	Never	Less than	Monthly	Weekly	Daily or almost	

you needed an alcoholic drink in the morning to get you going?		monthly			daily
How often in the last year have you had a feeling of guilt or regret after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often in the last year have you not been able to remember what happened when drinking the night before?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Have you or someone else been injured as a result of your drinking?	No	–	Yes, but not in the last year	–	Yes, during the last year
Has a relative/friend/doctor/health worker been concerned about your drinking or advised you to cut down?	No	–	Yes, but not in the last year	–	Yes, during the last year

Reproduced from John B. Saunders et al., Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II, *Addiction*, Volume **88**, Issue 6, pp. 791–804, Copyright © 1993 John Wiley & Sons, Inc., DOI: 10.1111/j.1360-0443.1993.tb02093.x.

♦ AUDIT-C—the first three (consumption) items of the full AUDIT. A score of 5+ indicates hazardous or harmful drinking.

♦ AUDIT-PC—the first two (consumption) questions of AUDIT, plus items four, five, and ten which focus on alcohol-related problems and possible dependence. A score of 5+ indicates hazardous or harmful drinking.

♦ Fast Alcohol Screening Test (FAST)—a two-stage screening procedure based on four of the original AUDIT items. Item three is asked first and classifies over half of respondents as either non-hazardous or hazardous drinkers. Only those not classified at the first stage go on to the second stage, consisting of AUDIT items five, eight, and ten. A response other than ‘never’ to any of these three items classifies the respondent as a hazardous drinker.

♦ Single Alcohol Screening Questionnaire (SASQ)—'When was the last time you had more than "x" drinks in one day?' (where x = five for men and four for women (US values), eight for men and six for women (UK values)). Possible responses are: never; over 12 months; three-to-12 months; within three months: the last response suggests hazardous or harmful drinking.

These short instruments are quicker to administer than AUDIT, but are generally less accurate than the longer tool, and do not all clearly differentiate between hazardous, harmful, and dependent drinking. Nevertheless, a recent review reported that these shorter tools have relatively good psychometric properties, with AUDIT-C in particular nearly as accurate as the full version (14). Thus, a pragmatic approach for practitioners may be to use AUDIT-C as a pre-screening tool to quickly filter out negative cases; administering the remaining seven AUDIT questions to the smaller pool of cases to provide an accurate and differential assessment of alcohol-related risk or harm.

Other available screening tests include the Michigan Alcohol Screening Test (MAST), which contains 22 yes-or-no questions, with six positive responses indicating a drinking problem. A key identified disadvantage of the MAST test is its length and the time required to score in a busy clinical setting. However, shortened versions are available, such as the Short Michigan Alcohol Screening Test (SMAST), with no substantial variation in reliability compared with the full MAST (15). In addition, there are also tests developed for particular population groups, such as T-ACE (**T**olerance, **A**nnoyed, **C**ut-down and **E**ye-opener) and TWEAK

(**T**olerance, **W**orried, **E**ye-opener, **A**mnesia and **K**(c)ut-down); both designed for use with pregnant women.

Screening in different population groups and settings

For practitioners selecting an appropriate screening instrument it is vital to choose a test that will both accurately detect alcohol problems and be practical to deliver (16). Screening implementation can be affected by the age, ethnicity, and gender of the target population; the means of administration ('pen and paper' versus interview or computer-based forms of inquiry); and the level of training required for test delivery. In addition, some self-report screening questionnaires are more effective at detecting recent or lower level risk drinking whilst others are more appropriate for screening longer-term chronic alcohol abuse or dependence. Two reviews have confirmed that AUDIT is most suitable at screening less severe alcohol problems such as hazardous and harmful drinking (17, 18), whereas CAGE is recommended as the optimum screening tool for lifetime and current abuse or dependence (17). However, there are a limited number of studies which make direct comparison between multiple instruments.

A further debate concerns the relative merits of two different approaches to screening—universal screening, aimed at all patients attending a setting, and targeted screening, aimed at groups of patients with a higher likely risk of drinking. Some research has shown that targeted screening is preferred by both practitioners and patients for reasons of efficiency and salience respectively. However, universal screening, if practicable, has the obvious advantage that high-risk drinkers

are less likely to be missed. The relative (cost) effectiveness and acceptability of universal versus targeted screening are the focus of ongoing research. However, in certain contexts, there is
evidence that well-publicized and strongly enforced screening programmes can serve as a deterrent to high-risk drinking and reduce alcohol-related harm. A review of the effect of a random alcohol screening programme (random breath testing) in reducing motor vehicle crash injuries, found it was followed by a period of reduced injuries and fatalities in Australia and the United States (19). Hence, wider community-based alcohol screening programmes may be a positive public health approach.

A substantial evidence-base is available to inform the selection of appropriate screening tools—at least 25 reviews have been published, including 20 focusing on self-report questionnaire tools (14, 15, 17, 18, 20–35); and a further six on biomedical markers (8–11, 36, 37). This section explores the available evidence on their use in different population groups and settings.

Language and culture

First, screening tools need to be culturally appropriate for their target population. Although a key review reported little variation in performance by ethnic group for AUDIT, this was for the English language version only (32). Other studies have highlighted the problem of translating questionnaires into different languages or cultural contexts. Aertgeerts et al. (20) found that the subjectiveness of CAGE questions was affected by the difference in meanings of words translated in various

languages (in this case, Malay, Tamil, and Chinese). Further, there were identified impacts of certain cultural factors on subjects' responses, for example, the influence of severe religious taboos against consuming alcohol in Malaysia (20).

Screening women for high-risk drinking

Gender can also affect the performance of screening tools and in particular, evidence suggests a need for gender-appropriate cut-off points. Reinert and Allen reported that AUDIT is less sensitive for women at the standard cut-off score of eight, suggesting a lower cut-off of five as more appropriate (32). In addition, there are differences in tool performance between women from different ethnic backgrounds. Bradley et al. found that test sensitivity may be affected by ethnicity of population, with CAGE and AUDIT generally more sensitive for alcohol abuse in black female populations and TWEAK more effective than other tools in white populations (25).

In addition, a number of studies have focused specifically on the accuracy of screening in pregnancy. Although many women reduce or cease their alcohol consumption once they are aware they are pregnant, prior drinking may have already had a harmful effect on the fetus, meaning questions about a woman's current quantity and frequency of alcohol use may not show her true risk for problems. Further, women may be reluctant to report current alcohol consumption due to feelings of guilt or embarrassment. Hence a number of tools have been specifically designed for use in this population group, such as TWEAK and T-ACE, which evidence suggests are more sensitive than other tools in the prenatal population, alongside AUDIT-C (25, 26).

Age

The majority of screening tools have been developed with an adult population and therefore may be less effective in younger people. Some evidence supports the use of AUDIT in adolescent populations, albeit using a lower cut-off point of two-to-three (27, 32). In college-age students however, the evidence is more ambiguous. CAGE appears to perform relatively poorly in college-age students (28), and Berner et al. also found weak evidence to support the diagnostic accuracy of AUDIT for detecting at-risk drinking in student populations (18). Thus, a youth specific screening tool may be preferable (32), for example, CRAFFT (**C**ar, **R**elax, **A**lone, **F**orget, **F**riends,
Trouble), a relatively brief, simple, and sensitive screener to identify problematic alcohol use among adolescents and young adults (38), and the Adolescent Drinking Inventory (ADI) (39).

There is also a need to focus on the other end of the age spectrum. Older populations are more vulnerable to the effects of alcohol due to reduced body mass, co-morbid conditions, and interaction with medication. However, most research in older populations has been conducted in the United States, mainly in veteran groups, and so may not be generalizable elsewhere (31). Nevertheless, there is strong evidence to support the accuracy of AUDIT in elderly populations, including elderly psychiatric patients, albeit at a reduced cut-off point (18). Shortened versions of AUDIT also appear effective in older age-groups. One review suggested that AUDIT-C was as good, if not better, than AUDIT at detecting hazardous and harmful drinking in elderly

populations, with AUDIT-5 potentially more useful in elderly psychiatric patients (31). MAST and its variations were also robust screening tools in older alcohol abusers but, since the full MAST is time-consuming to deliver, CAGE was suggested as a more practical alternative (31).

Screening in busy health care settings

In many respects, primary care is an ideal context for screening high-risk drinkers due to its high contact-exposure to the population (40), and the frequency with which such drinkers present (41). However, lack of training, an unsupportive policy environment, and time pressures have all been identified as barriers to screening in this setting (23). Moreover, it has been reported that methodological standards are inconsistently adhered to in primary care (17). A number of reviews report that AUDIT is the most accurate screening tool for primary care (17, 18, 28), however, due to time pressures, shortened versions may be more practical. Indeed, a recent meta-analysis indicates a comparable performance between AUDIT-C and AUDIT, although some individual studies found a superiority of AUDIT overall (14).

A high proportion of admissions to emergency departments (EDs) are also related to alcohol use (16). In EDs, alcohol problems tend to be acute rather than chronic (17), with alcohol often still present in the bloodstream (33). However, there are also barriers to screening in this often fast-moving and time-pressured environment. Accordingly, the accuracy of AUDIT in such settings has been questioned (18), with a recent review concluding that FAST was the optimum tool for accurately identifying alcohol problems in ED (30). However,

a universal screening approach with FAST may prove impractical; therefore the use of targeted tools, such as the Paddington Alcohol Test, has been suggested (30).

Conclusion

A number of screening tests are available to practitioners wishing to screen for high-risk drinking. A wide range of evidence indicates that the most effective and efficient screening method is the use of validated, questionnaire-based tools, although a number of patient and setting factors need to be considered when selecting the most appropriate test. Overall, a consistently good performance is reported for AUDIT; however, its shorter versions may need to be adopted for practical reasons. Finally, there appears to be a need for more research on age and culturally appropriate screening tools.

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Chapter 40
Brief intervention: does it work?

Eileen Kaner and Amy O'Donnell

Background

Due to the large aggregate number of health and social problems experienced by hazardous and harmful drinkers, the greatest impact in reducing alcohol problems at a population level is made by focusing on this group rather than the smaller group of dependent drinkers; this is known as the preventive paradox (1). The paradox comes from the fact that whilst dependent drinkers individually experience the most alcohol-related damage compared to other types of drinkers, society incurs more damage and financial cost from a larger group whose members each experience less severe problems—at least for much of their drinking life. Moreover, empirical evidence shows that the preventive paradox is most pronounced in populations where heavy episodic drinking (commonly known as binge drinking) is a common component of hazardous or harmful drinking (2, 3). Binge drinkers may or may not drink on a regular basis. However, this high-intensity pattern of drinking leads to intoxication, impaired behavioural control, and the experience of acute alcohol problems.

Thus there is a clear need for an effective preventive intervention to help reduce excessive drinking in a large sector of society and covering a range of drinking patterns. In public health terms, the focus is on a secondary preventive

approach which aims to detect alcohol problems at an early stage, when they are most amenable to adjustment, and then intervene to promote positive behaviour change (4). Given the size of the group requiring attention it is necessary to have an intervention that is feasible to deliver in community-based settings by generalist practitioners. Moreover, since many potential recipients of brief intervention will most often not be aware of their alcohol-related risk or harm, the intervention needs to be acceptable and practically relevant to them.

Brief alcohol intervention refers to the use of structured, talk-based advice or counselling which is aimed at reducing drinking behaviour. Most often, brief intervention aims to reduce drinking to lower risk levels rather than achieve abstinence from alcohol (although in some patients abstinence may be preferred). Brief intervention can also be accompanied by additional components such as information leaflets, drinking diaries, web-based resources, and booster sessions to reinforce the initial brief intervention activity. The majority of brief intervention work has been opportunistically delivered in primary care. In this setting, patients present for a wide range of reasons and not usually (or at least consciously) for alcohol-related care. Hence most brief intervention recipients tend not to be seeking help for alcohol problems. However, brief intervention has also sometimes been used to describe shorter forms of therapy within a specialist care context and in drinkers who are aware they have an alcohol problem; this is sometimes called brief treatment (5). Nevertheless, it is important to point out that brief intervention is not merely traditional (psychiatric or psychological) treatment carried out in a short time-scale; it has a specific theoretical under-pinning and practical structure.

Theoretical basis of brief alcohol intervention

Brief intervention is grounded in social cognitive theory from the field of psychology which is concerned with understanding, predicting, and changing human behaviour. Social cognitive theory itself draws upon the broader concept of social learning (6). This social perspective on behaviour takes the view that all activity results from a dynamic and reciprocal interaction between an individual, his or her actions, and the physical and social environment. Each individual is regarded as having cognitive (thinking) and affective (feeling) attributes that affect how they respond to the external world and are reinforced by it. Moreover, all individuals have the capacity to observe and learn from the behaviour of other people around them or situations they have previously encountered.

Consequently, drinking behaviour is influenced not only by an individual's attitudes towards alcohol, their knowledge about its risks, and perceptions of its reinforcing effects, but also by the attitudes of family members and friends towards drinking, and the patterns of use within relevant groups. Thus, brief intervention focuses on both personal and contextual factors. Important components include drawing out individuals' beliefs and attitudes about drinking, their self-efficacy or sense of personal confidence about changing their drinking, and a view about how their drinking sits in relation to other people's drinking behaviour (normative comparison). All these factors influence an individual's motivation for and ability to change their drinking behaviour and improve their health and well-being.

Brief intervention structure

Brief intervention has two broad modalities (7): simple structured advice in the form of personalized feedback following screening and practical steps on how to reduce drinking behaviour and/or avoid its adverse consequences and extended brief intervention which generally involves counselling techniques, most often motivational interviewing. Both forms of brief intervention share the common aim of changing drinking behaviour to promote health but they vary in the precise means by which this is achieved.

Brief interventions have been delivered either in a single appointment or a series of related sessions which can last between five and 60 minutes. Whilst brief interventions for non-treatment-seeking populations tend not to exceed five sessions in total, those aimed at more problematic drinkers can involve more sessions and include a wider variety of counselling techniques (including cognitive behavioural therapy, motivational enhancement therapy, and motivational interviewing). More recently, brief interventions have been delivered increasingly via the use of computers or the Internet. The latter electronic forms of brief intervention may be helpful to individuals who tend not to present to services, including young people or those in the working population (8). Although there is variability in brief intervention activity, its content should always be based on the FRAMES structure (9):

♦ Feedback—provide feedback on the individual's risk from their drinking.

♦ Responsibility—be clear that the individual is responsible for change.

♦ Advice—provide advice on risk reduction or give explicit direction to change.

♦ Menu—provide a variety of options or strategies for behaviour change.

♦ Empathy—deliver advice or counselling using empathy and avoid judgement.

♦ Self-efficacy—encourage optimism about the scope for behaviour change.

The evidence base

There is a large and robust evidence base supporting the effectiveness of brief alcohol intervention at reducing alcohol-related problems across a range of population groups. To date, over 40 systematic reviews have been published; many including meta-analysis of controlled trial outcomes. In health settings, eight systematic reviews have focused on primary care (10–17), three on emergency care (18–20), two on general hospital settings (21, 22), and two on obstetric or antenatal care (23, 24). In addition, five reviews have covered a wide range of different health settings (25–29). Two reviews have also included social care (30, 31) and two have extended their scope to educational and/or community settings (32, 33).

Beyond health services, nine reviews have focused on high-risk drinkers in schools or colleges (34–42) and nine

reviews considered electronic forms of brief intervention generally delivered via computerized feedback or accessed via the Internet (35–37, 40, 43–47). Finally, four reviews focused on motivational interviewing delivered in a wide array of settings (48–51) and one focused on psychosocial intervention directed at younger drinkers (33). These broad ranging reviews could include substances other than alcohol and input other than brief intervention. Nevertheless, brief alcohol intervention featured significantly in reported outcomes.

Across this wide body of work, it has consistently been reported that brief alcohol intervention is effective at reducing risky drinking in a wide range of settings (31). In particular, brief intervention has been found to reduce drinking quantity, frequency, or intensity (14). Other positive outcomes include a reduction in alcohol-related problems (14), mortality (28), and reduced health-care utilization (27). The evidence on beneficial effects of brief alcohol intervention is particularly strong in primary care settings where 29 controlled trials have accumulated over a 25-year period (14). Brief intervention outcomes in emergency care, general hospital settings, and obstetric or antenatal care have been more equivocal with both positive and null findings. A key issue is that brief alcohol intervention seems to be most impactful in non-treatment-seeking populations compared to treatment-seeking patients (29, 31). In addition, directly delivered, individually-focused brief intervention generally produces positive effects in terms compared to indirect delivery. Electronic forms of brief intervention, whilst beneficial compared to no intervention controls, rarely produce superior outcomes in comparison to other active interventions (36).

Motivational interviewing is a common component of brief intervention and the typical form of intervention directed towards younger drinkers (35). Motivational interviewing consistently produces positive reductions in alcohol consumption when compared to assessment-only controls (35). However, it rarely produces superior effects compared to other active treatments (35). Moreover, psychosocial intervention (which encompasses both brief intervention and motivational interviewing) has been found to be effective at reducing alcohol consumption in young people in a wide range of settings but it is not enhanced by the addition of family focused input (33). Indeed, across the field of brief intervention research, the evidence does not generally indicate an additional benefit of longer or more intensive brief intervention over shorter, less intensive input (14). One exception was a review of motivational interviewing, but it was not clear how many alcohol-specific trials contributed to the meta-analysis of 19 trials (out of 72 identified overall) (50). Nevertheless, length, complexity, and intensity of the input by practitioners do not seem to be essential to brief intervention effects. Moreover, two reviews have reported consistent positive changes in drinking outcomes reported for control groups in brief intervention trials (26, 30). Consequently, it has been suggested that screening or assessment reactivity may be important elements of positive alcohol-related behaviour change. Indeed, two well-designed randomized controlled trials have confirmed this effect (52, 53).

Implementation issues

The majority of research on implementing brief alcohol interventions has occurred in primary care. This setting is where most of the evidence on the health benefits of brief intervention has accumulated. Moreover, there are many opportunities for brief intervention delivery in primary care since patients are routinely asked about alcohol during new patient registrations, general health checks, and specific disease clinics (e.g. hypertension, diabetes). However, despite considerable efforts over the years to persuade practitioners to adopt brief interventions in practice, most have yet to do so.

There is a large international literature on barriers to brief alcohol intervention (54–59) and these include:

♦ a lack of time among busy health care professionals

♦ a lack of appropriate training in this topic area

♦ a lack of suitable screening and intervention materials

♦ too little support from government health policies

♦ a lack of incentivization or reimbursement from government health schemes

♦ a belief that patients will not take advice to change drinking behaviour

♦ a fear amongst practitioners of offending patients by discussing alcohol.

Some of these obstacles are relatively straightforward to overcome, such as translating and disseminating the evidence base supporting brief intervention effectiveness to public health practitioners (60). National guidance such as that produced in England has supported this process (7). Some of the anxiety about discussing alcohol issues can also be allayed by a number of research studies which have indicated that patients feel that alcohol-related issues are a legitimate concern for practitioners (61–64). However, the most difficult obstacles to brief intervention delivery are related to a lack of time and lack of reimbursement for this work. Thus there is a need to encourage national and local policy-makers to prioritize alcohol issues, find ways of embedding this work in busy practice, and identify relevant means to incentivize brief intervention delivery (65).

Conclusion

The process of helping individuals become aware of their alcohol-related risk or harm may be beneficial in itself. However, good screening practice requires follow through with an evidence-supported intervention. Indirect feedback is rarely enough to achieve robust behaviour change. Thus, directly delivered intervention and a personalized content seem to be key ingredients of positive brief intervention outcomes, whether they are delivered via simple structured advice or brief counselling approaches. Nevertheless, in population groups that rarely present to services, it may be helpful to consider the use of technology to augment brief intervention work due to the low cost, high reach, and moderate health benefits.

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Chapter 41
Drug therapy: reviewing the evidence

Michael Soyka

Background

The basic principle for treating withdrawal from alcohol is adequate sedation and seizure prophylaxis. Second-choice drugs—which can also be given in combination—primarily include substances to prevent blood pressure spikes, e.g. atenolol or clonidine. For a long time, disulfiram was the only drug used for relapse prevention, although evidence for its efficacy is relatively limited (1–3). Disulfiram blocks the enzyme acetaldehyde dehydrogenase, so that acetaldehyde accumulates when alcohol is consumed. The almost inevitable intolerability reactions are supposed to prevent the person from drinking alcohol again. Meanwhile, a few new substances are available that have a somewhat better evidence base than disulfiram and do not make use of 'punishment' strategies (Table 41.1).

Acamprosate

Although acamprosate has been studied intensively for about two decades, its exact mechanism of effect remains unclear. Acamprosate is known for certain not to have classical psychotropic or sedating effects.

Many randomized studies have been performed on acamprosate. A recent Cochrane analysis analysed 24

randomized clinical studies with a total of 6,045 patients (4). As in almost all studies on relapse prevention in alcohol dependence, the overall results were heterogeneous—the abstinence rate of 42% found in the one-year German study (5) was almost twice as high as that in the placebo group, whereas the other studies did not find such differences in effect (4).

The Cochrane analysis (4) confirmed the findings of earlier meta-analyses regarding the efficiency of acamprosate and found a number-needed-to-treat of eight. The relative risk of ever drinking again was 0.84 with acamprosate compared with placebo.

Opiate antagonists

Opiate antagonists of the naltrexone type are able to block endogenous opioids and thus reduce or even nullify the euphoric effect of alcohol (6). In animal models they decrease alcohol consumption in alcohol-dependent animals (2).

Naltrexone

Naltrexone is available as an oral formulation and was approved in the United States in 1994 for the treatment of alcohol dependence. The initial approval was based on two very small placebo-controlled studies in US veterans with alcoholism (7) that showed naltrexone to be effective. Meanwhile, more than 50 randomized clinical studies have been performed with naltrexone (8–17). Many but not all of the studies have proven naltrexone's efficacy. The results of a German placebo-controlled double-blind study were negative

(12). However, by far the largest study, the so-called COMBINE study, found that naltrexone reduces relapse risk, particularly in heavy drinkers, and also increases the duration of the abstinent periods (16).

Table 41.1 Anticraving substances in alcohol dependence

Substance	Mode of action	Evidence base	Comment
Acamprosate	Via glutamatergic and perhaps glycine receptors	+++ Proven by Cochrane analysis	Relatively poor bioavailability, favourable side effect profile No interactions with alcohol Approved drug
Naltrexone	Opioid receptor antagonist (mu receptor)	+++ Proven by Cochrane analysis	1 × 50 mg tablet/day sufficient Nausea common, No interactions with alcohol Approved drug
Depot naltrexone	Opioid receptor antagonist	++	Better compliance than oral form Regulatory approval being strived for
Nalmefene	Mu-opioid receptor antagonist Kappa partial agonist	++ Fewer studies than for naltrexone	Better tolerability? Regulatory approval being strived for
Baclofen	GABA receptor agonist	(+) Only a few studies available	More studies necessary
Topiramate	Blockade of glycin receptors or AMPA receptors Increased GABAergic neurotransmission Modulation of calcium channels	+ Relatively few studies	Problematic side effects profile 'Off patent' Regulatory approval is not an objective
Gabapentin	Inhibition of glutamate receptors Blockade of central L-type calcium channels	Some clinical studies (+)	Studied also in combination with flumazenil
Quetiapine	5-HT1A, 5-HT2A, D1, D2, H1, α1, α2 receptor	(+) Only some data available	Most likely of use in co-morbid patients with schizophrenia or bipolar disorder

AMPA, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid; GABA, gamma-aminobutyric acid; 5-HT, 5-hydroxytryptamine (serotonin).

Overall, the studies and meta-analyses come to the conclusion that naltrexone reduces the relapse rate in alcohol dependence (2). A recent, comprehensive Cochrane analysis on the efficacy of opioid antagonists in alcohol dependence (7) found that naltrexone reduced the relative risk of consuming alcohol again to 91% (non-significant), while the risk of returning to heavy drinking was significantly reduced.

Again, results and abstinence rates differ considerably, which is probably due to the heterogeneity of the patient groups and the different recruitment and treatment settings. Only a few studies have compared acamprosate and naltrexone (17, 18). An interesting approach is the search for individual genetic factors that could explain response to acamprosate or naltrexone. Oslin et al. (19) found a functional polymorphism in the mu-opioid receptor gene that corresponded with the therapeutic response to naltrexone. Patients heterozygous for the mu-opioid receptor ASP40 allele (ASP40–ASN40) benefited from naltrexone more than homozygote patients (ASP40–ASP40). An analysis of the COMBINE study data reached the same conclusion (20), whereas another retrospective analysis was unable to find an association between response to naltrexone and this genetic polymorphism (21).

It is difficult to assess on the basis of clinical characteristics and typologies which patients are more likely to benefit from treatment with acamprosate or naltrexone. A recent post hoc analysis of data from the COMBINE study—which incidentally was unable to demonstrate efficacy for acamprosate—found that particularly heavy drinkers benefited from treatment with acamprosate while, contradictory to the original hypothesis, acamprosate was less

effective than placebo in patients who had already had longer periods of abstinence before treatment (22). In contrast, naltrexone improved sustained abstinence in very heavy drinkers. Overall, these analyses did not provide reliable clinical results.

Depot naltrexone

Compliance with drug treatment is known to often be worse in alcohol-dependent patients than in other patients. Depot naltrexone is thus an interesting treatment form that was approved in the United States in 2006 (23–26). Three different depot preparations are available. Studies have shown that plasma naltrexone levels are highest three days after the injection and remain at a high level for a further 18 days (26).

So far, four controlled, randomized studies (23–26) have evaluated the efficacy and safety of depot naltrexone. The first (23) included only 20 patients, 15 of whom received depot naltrexone. In the four-week follow-up phase, patients treated with naltrexone consumed less alcohol than those given placebo. A similar effect was observed in another pilot study in 30 patients (27). In a larger, three-month study in 315 patients, the time of first alcohol consumption was later and the rate of sustained abstinence higher with depot naltrexone (25). Naltrexone showed better results than placebo in the usual drinking parameters, without reaching statistical significance. The largest study so far, a six-month study in 624 patients (26), found that alcohol consumption was significantly reduced in patients treated with a high dose of depot naltrexone (380 mg) compared with those treated with placebo; consumption in the group treated with 190 mg did

not differ significantly from that in the placebo group. An open study with depot naltrexone showed good tolerability (28).

Nalmefene

Nalmefene is another oral opioid antagonist that is used clinically in several countries but is still being studied intensively. The chemical structure of nalmefene is similar to that of naltrexone. Nalmefene has a high bioavailability (29–31, overview in (32)). Nalmefene is a selective opioid receptor antagonist at the Mu- and Delta and partial agonist at the KAPPA-receptor.

Several controlled studies have been conducted with nalmefene. Mason et al. (33) evaluated 10 mg and 40 mg in a pilot study and found that only the higher dose was effective. In a later study in 105 patients (34), 20 mg and 80 mg were found to be effective compared with placebo. In contrast, a multicentre study in 270 patients with doses of 25 mg to 40 mg failed to show efficacy for nalmefene (35). At least the clinical studies are being evaluated in preparation for regulatory submission (review in (32)).

Baclofen

The selective gamma-aminobutyric acid (GABA)-B receptor agonist baclofen has been studied as a potential anticraving substance (36). It achieved a certain resonance among the general public after an alcohol-dependent physician reported about how he ‘healed’ himself with baclofen (37). The drug

itself has been used for neurological illnesses (dose range 15–80 mg).

In preclinical studies, baclofen suppressed alcohol-mediated dopamine release in the nucleus accumbens (38, 39) and reduced alcohol intake in rats (40–42). It may have favourable effects on alcohol-withdrawal syndrome (43), although the data are unclear (44, 45). Only a few clinical studies have been conducted with baclofen (46–50), An Italian research group evaluated relapse prevention in two placebo-controlled studies on 39 and 84 patients (48, 49), which showed clear efficacy. Results were better with higher doses (49). On the other hand, the results of a recently published study were negative (50).

Topiramate

Antiepileptic drugs such as carbamazepine and topiramate have been used for a long time to treat alcohol withdrawal syndrome (51), although they are drugs of second choice (2). After a few preclinical studies with topiramate (52–55), it was used clinically in the United States in doses of 150–300 mg to treat alcohol dependence. An initial, 12-week study in 150 patients showed a reduction in the amount of alcohol consumed and an increase in the number of abstinence days (56). A 14-week study also showed efficacy versus placebo (57).

Other studies compared topiramate with disulfiram (58) or naltrexone (59–61). Topiramate proved to be less effective than disulfiram at preventing relapse but reduced craving more than naltrexone. Of particular interest is an open study

(62) with comparatively low doses of topiramate (up to 75 mg/day) that found a pronounced improvement in psychopathology (depressivity, anxiety, etc.) in comparison to patients who received psychotherapy alone. Patients also relapsed less frequently. An open study versus naltrexone found that topiramate reduced craving and increased abstinence (61). A meta-analysis (63) concluded that two of three placebo-controlled studies found topiramate to be effective.

Gabapentin

Gabapentin, another antiepileptic, was studied as an anticraving substance and showed efficacy in a short, placebo-controlled study (64). In the so-called prometa protocol, gabapentin was studied in combination with the benzodiazepine-antagonist flumazenil in the treatment of dependence on alcohol (and psychostimulants) (65).

Quetiapine

The neuroleptic quetiapine was proposed as a possible anticraving substance (66). A clinical effect was discussed as being most likely via an improvement of psychopathological symptoms such as anxiety, sleep, or mood. So far, the evidence for quetiapine comes mainly from a few retrospective data analyses or naturalistic studies (67). An initial, 12-week, placebo-controlled study in 94
patients (67) found higher abstinence rates with quetiapine (400 mg/day). However, the result was only significant in a subgroup of alcohol-dependent patients (so-called type B alcohol-dependent patients). A case series of 28

alcohol-dependent patients with co-morbid bipolar disorder (68) found that quetiapine reduced alcohol consumption and craving, improved psychopathology, and was well tolerated. A small, open study has been performed in schizophrenia patients with co-morbid substance use disorders (69).

Conclusion

Biologically-oriented addiction research has yet to find a 'magic bullet' to improve the prognosis of alcohol-dependent patients or to reduce their risk of relapse. However, the understanding of the neurobiological background of alcohol dependence is so far advanced that it may be possible to develop more targeted drugs in the future.

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Part IX
Alcohol policy

Chapter 42
The private sector and public policy: can they be reconciled?

Paul Miller and Marjana Martinic

The private sector and the public good

The field of alcohol policy has witnessed a long and often heated debate around the respective roles of the public and private sectors when it comes to reducing alcohol-related harm. There is a presumption by some that the aims and priorities of the two are irreconcilable (1–4). Governments are expected to address issues relevant to society; they are expected to resolve them through decision-making that is driven by accountability to the public and by what is in the public good. These decisions lead to action that includes regulation and legislation. The private sector, on the other hand, is presumed to be driven by profit-seeking, with accountability limited to its shareholders. In order to defend its profitability and its 'licence to operate', the private sector is expected to inevitably oppose any public policy positions that threaten its existence.

A world in black and white is convenient, but reality usually dwells in the grey area in between. Public policy is often driven by expediency and a need to demonstrate action, not necessarily by altruism. Governments can be as motivated by profit-seeking as private enterprise—in a number of countries they hold a monopoly over the production and retail of commodities and are also driven by profit, not always with

the public's best interest in mind. The Chinese government, for example, is the world's largest retailer of tobacco; governments in Scandinavian countries, Canada, and parts of the United States are in the business of selling alcohol through retail monopolies; and the Russian government is a major producer of distilled spirits, particularly vodka. The argument is often made that since profit from government-owned enterprise flows directly into public coffers, the end justifies the means. However, it has been pointed out that government-owned industries can also behave much like their private sector counterparts in striving to maximize profit (5, 6).

Conversely, while the private sector is, by definition, largely driven by the bottom line, its profits are often channelled into philanthropic endeavours. This may be done directly by a company or through foundations, charities, and other organizations whose purpose is removed from profit-making. The pharmaceutical industry, for example, gave birth to the Novartis Foundation for Sustainable Development, a not-for-profit organization with a corporate social responsibility (CSR) agenda, whose activities are aimed at improving quality of life through health projects in developing countries (7). In the alcohol sector, Diageo, the world's largest spirits producer, supports efforts around water conservation, life skills development, and disaster relief through the Diageo Foundation whose efforts are aimed at building sustainability, and not related to Diageo's core alcohol business (8). Some might argue that such charitable endeavours have value
for industry—they can enhance reputation or may represent tax benefits. However, the means through which this end goal is achieved are undeniably in the public good.

We argue here that the interests of the public and private sectors can, indeed, be reconciled and that synergy between them is desirable and can be used to reduce societal harm. While there are sensitivities and criticisms around the use of particular terminology, whether 'working together', 'cooperation', or 'partnership' (2), the fact remains that there are areas in which public policy and private sector interests can be complementary as long as roles and responsibilities are clearly circumscribed and boundaries for engagement defined.

What is the case for industry involvement?

Across industries, including among producers of alcoholic drinks, the past several decades have witnessed increased emphasis on CSR (9–17). There is also growing accountability, not only to shareholders, but to society as a whole. With greater public awareness of environmental, health, and social issues, coupled with increased access to information and scrutiny of industry practices, it is recognized that responsible corporate behaviour is 'enlightened self-interest' and necessary for long-term profitability, even survival (18–20). Four justifications have been offered for CSR: moral obligation, sustainability, licence to operate, and reputation (21).

When it comes to alcohol, it should be acknowledged that the prevention of harm is a shared objective, common to alcohol producers, governments, non-governmental organizations, and other stakeholders. There is an ethical imperative for action. Furthermore, a responsible industry recognizes that the harmful use of its products is not in its best interest and is inevitably damaging to its reputation and long-term gains.

The long-term sustainability of businesses depends on their ability to interact with society in a positive way, which, in the alcohol context, includes having a stake in reducing alcohol-related harm.

It is becoming increasingly acknowledged that industry members, or 'economic operators', may have a valuable (and legitimate) contribution to make to the social agenda, be it around alcohol-related harm or other issues (16). This view is evident in the United Nations' Global Compact that defines itself as a 'strategic policy initiative for businesses that are committed to aligning their operations and strategies with ten universally accepted principles in the areas of human rights, labour, environment and anti-corruption' (22). This initiative recognizes the need for private sector engagement and the role business can play.

Similarly, a legitimate space has been created for industry members in contributing to prevention of alcohol-related harm. The establishment of the European Union Alcohol and Health Forum by the European Commission's Directorate General Health and Consumers (DG SANCO), for example, has created a platform that brings together stakeholders from the private and public sectors, and from civil society, in an effort to encourage 'debate, compare approaches and act to tackle alcohol related harm' (23).

Most recently, the World Health Assembly adopted a Global Strategy to reduce the harmful use of alcohol (24), which, while clearly placing responsibility for implementation with governments of member states, acknowledges the need for broader and pragmatic engagement with a wide range of stakeholders, including with 'economic operators':

The diversity of alcohol-related problems and measures necessary to reduce alcohol-related harm points to the need for comprehensive action across numerous sectors. Policies to reduce the harmful use of alcohol must reach beyond the health sector, and appropriately engage such sectors as development, transport, justice, social welfare, fiscal policy, trade, agriculture, consumer policy, education and employment, as well as civil society and economic operators (24).

How can industry contribute?

Public policy measures are generally based on regulation and legislation. With regard to alcohol, these include taxation and pricing, restrictions on the availability of alcohol and where it can be purchased, when, and by whom (25, 26). They also include measures such as setting appropriate blood alcohol concentration (BAC) limits for drinking and driving and legal age limits for the consumption and purchase of alcoholic drinks. It is the role of government to enact and also enforce these regulations and laws. While the views of industry members may diverge from those of governments on where appropriate thresholds for some of these measures should be set, there is general agreement that access to alcohol should not be unfettered; that, like other commodities, alcohol is subject to taxation; that special measures are needed to keep young people safe; and that drinking and driving is a serious social and public health problem (27). The divisive issue is not whether regulations are needed, but to what degree; different approaches are required in different countries, depending on the maturity of alcohol policies and the context around alcohol (25, 27, 28).

With this in mind, it needs to be acknowledged that industry members can make a significant contribution to reducing alcohol-related harm in a number of areas. Some correspond directly to what the World Health Organization Strategy describes as their core competencies as 'developers, producers, distributors, marketers and sellers' of alcoholic drinks (24), while in others, there is indirect benefit from putting industry's resources and expertise to work. There are also areas in which industry actually may be better placed to engage than government.

Social, economic, and environmental

The most obvious contribution to society by any industry is economic. This is no different for producers of alcoholic drinks, who represent a sizeable source of government revenue through taxation in most countries. In the United Kingdom, for example, tax on alcoholic drinks alone represented 2.1% of total government revenue during the fiscal year 2010–2011 (29, 30). There is also a wider, albeit indirect contribution. The alcohol industry, broadly, provides employment and generates income throughout the 'value chain', from the farmers who grow the raw materials used as ingredients, to those who make beer, wine, and spirits, to the retailers, waiters, and bartenders who sell and serve them (31–36). This economic contribution has an impact on social development and can help alleviate poverty and improve living conditions, especially in less affluent communities that are engaged in the production of raw materials or working in manufacturing plants. At the same time, some have challenged this notion, arguing that any social or economic

gains will be offset by negative impact on public health, social order, and workplace productivity (37, 38).

Producers of alcoholic drinks are also engaged in initiatives that are beneficial to the environment. Water, along with agricultural products, is an essential ingredient for brewing, distilling, and fermentation. Therefore, the preservation of clean and reliable sources of drinking water is an important objective. Where such sources are not readily available, they are often established locally by alcohol producers and have a broader impact. For the brewer Molson Coors, water conservation is an important part of the company's commitment to environmental stewardship. The target for the initiative 'Every Drink, Every Ripple' is a 15% reduction in the company's water usage by 2012 (39). Diageo's 'Water of Life' programme includes reduction of water waste and pollution at the company's African operations. At the same time, this initiative extends access to clean water to the local population (40).

Further environmental improvements have been made by other producers, such as Anheuser-Busch InBev's (ABI) initiative to reduce energy use (41) or Asahi's commitment to the reduction
of carbon dioxide emissions (42). There is also support for new standards and innovations in packaging to reduce the carbon footprint of the production and trade of alcohol (43). Alternate packaging for wine and distilled spirits already exists and is being used by some producers (44), as are lightweight bottles, particularly in the wine industry (45).

Technical expertise

Commercial producers have an interest in upholding government standards around the purity of drinks and in helping ensure that others do the same. Their technical expertise can help to develop standards around the purity, integrity, and quality of drinks. Where standards do not exist, they can be established through cooperation between government and industry at a technical level. Safeguarding product integrity and safety is not only beneficial to industry members, but also protects consumers (46, 47). This is of particular relevance in countries where a significant proportion of the alcohol consumed is not commercially produced.

Legal producers can play an important role in helping government to ensure quality standards. There are numerous examples of joint action in this area. In Uganda, a joint initiative between the government and Nile Breweries to produce a sorghum beer that is of high quality and yet affordable enough so that it can compete with products that are not commercially produced (27, 48) has helped raise quality standards. The programme has also been successful in stimulating local agriculture through sorghum production. A similar initiative is the production of Senator Keg beer in Kenya, which is priced comparably to non-commercial alcohol, but produced according to quality standards and with clean and safe equipment and packaging, which reduces the potential for health harm (47).

Producers also work closely with authorities to address the production of counterfeit and illicit products, which often involves organized crime (49). Efforts include quality testing

of illicitly produced and counterfeit drinks suspected to contain contaminants (47). While the motivation for industry in engaging in these areas may not be altruistic, eliminating potentially harmful products from the marketplace is not only in their best interest, but also has advantages for the public in terms of health and social outcomes.

One key objective for any industry producing consumer goods is to generate and sell innovative products. The alcoholic drink industry is no exception. While some products have come under intense public scrutiny and criticism, particularly for their potential appeal to young people, others need not be controversial. There is, for example, an opportunity to stimulate consumer demand for lower-strength alcoholic drinks. Lower-alcohol beers, for example, are already on the market, as are ready-to-drink mixed drinks, whose alcohol content is also lower. The production of low-alcohol wines remains a technical challenge. Drinks with lower alcohol content are viewed by some as a useful public health tool for reducing alcohol-related harm (50, 51).

Marketing and promotion

The marketing of alcoholic drinks is another area where a strong case can be made for synergy between industry and the public sector. Government regulation and industry self-regulation of marketing are not always at odds. In reality, most countries where self-regulation is in place have a system of co-regulation under which government and industry jointly establish the rules for industry activities, industry administers them, but government reserves the right to intervene where needed (32, 52). According to the US Federal Trade

Commission, a 'well-constructed self-regulatory regime has advantages over government regulation. It conserves limited government resources and is more prompt and flexible than government regulation' (53). The Scottish
Government Alcohol Industry Partnership (SGAIP), for example, is a joint initiative between industry and government that has addressed a number of areas, including sports sponsorship, through its *Sponsorship Guidelines*, which are currently undergoing independent review (54, 55).

Support for public policies

Industry members have an important role to play in respecting and supporting public policies and government efforts to enforce them, complementing the work of the public sector. Initiatives around the legal purchase age for alcoholic drinks offer another useful example of what can be done when the private and public sectors work together. At points of sale, industry has established initiatives to check age identification and refuse service to minors. Where government-issued identification is not mandatory, proof of age schemes, often supported by industry, have been put into place in order to facilitate compliance with purchase age laws by both consumers and retailers (56). One such example is the UK's 'Challenge 25' scheme, which was developed by the Retail of Alcohol Standards Group and rolled out in member retail outlets across the UK (57, 58). The programme has recently received additional support in Scotland through the development of a joint initiative between the Scottish Beer and Pub Association and Members of Scottish Parliament that makes it mandatory in all licensed premises through the Scotland Alcohol Act 2010 (59). Other similar initiatives

include partnerships between industry members and law enforcement to ensure compliance with legal age limits, for example, through the use of undercover police in retail outlets. An example of such an initiative is the Century Council's 'Cops in Shops' programme in the United States (60).

Similar engagement by industry is also seen in support of public policies aimed at drinking and driving. Industry support for mandated BAC limits and penalties for infractions is widespread. In countries where government resources may be limited, industry members have put their support behind rigorous enforcement through breath testing and random sobriety checkpoints. In Brazil, Bolivia, and Uruguay, for example, the drinks company Anheuser-Busch InBev (ABI) provides breathalysers and other resources to law enforcement (61). Since the distribution of alcoholic drinks relies largely on road transportation, drivers of distribution fleets also represent a useful target for efforts aimed at reducing drinking and driving and related harm. Producer companies have extensive codes and rules that apply to drinking and driving among their employees and contractors—Heineken's Cool@Work initiative (62) and Pernod Ricard's Road Safety Charter (63), developed in cooperation with government, are examples of such initiatives.

Information, awareness, and education

An important area for government engagement is the provision of accurate and balanced information aimed at guiding and educating the public (64). When it comes to

alcoholic drinks, governments engage in a range of initiatives: defining the size of a standard drink or unit (65); issuing guidelines on ‘safe’ or ‘low-risk’ drinking; using mass media campaigns and health warning labels to raise awareness about responsible drinking and potential for harm; and offering education programmes, particularly aimed at young people.

This is an area in which industry members can also play an important role and contribute to efforts by governments and to public policy measures. Producers have a role in providing information about ingredients, alcohol content (usually expressed as alcohol by volume), provenance, as well as sell-by dates or dates of production. This information allows the consumer to make a choice about a particular drink. While the impact of providing this information on consumer choice is not fully understood, there is some indication that the facts are helpful (66).
The provision of such information is required by law in some countries, but in others it is provided voluntarily.

Industry members can also play a useful role in raising awareness about drinking guidelines, alcohol content, and standard drink size on packaging or labels on their products (67). While such information is required in some countries, in others its inclusion is a voluntary effort by producers. In the United Kingdom, for example, units per serving in a glass or container, advice about drinking during pregnancy (through a pictogram or written statement), ‘know your limits’ advice, as well as reference to the UK ‘sensible drinking’ guidelines are found on containers of beer, wine, and spirits (68). The Drinkaware Trust, a UK charity dedicated to prevention around alcohol-related harm, includes representation from industry, government, and public health and research working

together to disseminate information about drinking, including about official guidelines, and to engage in prevention campaigns (69). Voluntary provision of information by industry members or organizations they support is also found in other countries. In many cases, company policies require that the same provision of information apply across the European Union or even globally. In addition to packaging, points of sale are also appropriate and useful channels for reminding consumers about standard measures, official guidelines, and recommendations.

While producers provide factual information, they also engage in initiatives to provide specific 'directional' information intended to reduce the risk for harm by targeting potential consumers at increased risk, or by addressing risky behaviours and contexts. The voluntary inclusion of pictogram warnings about drinking during pregnancy is one such example that has been applied by some producers (67), notably the distiller Pernod Ricard and the brewer SABMiller, whose messaging also includes pictograms about underage drinking, drinking whilst pregnant, and drink-driving (23).

Reducing harm

Various other areas for intervention also lend themselves to industry efforts, which are intended to complement and strengthen public policy measures. For example, public policy measures around drinking and driving are strengthened by a number of industry-supported schemes that range from mass media campaigns and responsibility messages, to safe alternative transportation and 'dial-a-cab' initiatives (25, 67, 70, 71).

Broader efforts to make the general drinking environment safer can be paired with drink-drive initiatives that have an impact on the entire community. For example, in Colombia, industry members have formed a partnership with local government, police, taxi companies, retailers, and server associations to create 'safe zones' (Zonas de Rumba Segura) in city centres and entertainment districts where alcohol is sold and served. This initiative also includes supporting the local community in improving infrastructure, improving the design of venues, and providing better security and lighting (72).

The training of servers in responsible practice is another key area where industry initiatives are complementary to public policy measures. While regulations exist around the sale and service of alcohol, industry initiatives have been used to educate servers and encourage them to enforce these laws. Not serving minors and being mindful of intoxicated patrons are two key areas, as is attention to drinking and driving. Partnerships around responsible service exist in many countries and involve producers, retailers, as well as local communities, governments, law enforcement, and others (25). The 'Best Bar None' initiative in the United Kingdom, supported by the UK Home Office, is a responsibility scheme for licensed premises that recognizes good practice (73).

Initiatives to support drinking and purchase age legislation are complemented by a variety of other intervention efforts in which the private sector can play a role. Producer companies have engaged in a range of initiatives aimed at educating young people about alcohol, encouraging them to abstain from drinking if they are underage, and attempting to instil responsible behaviour for those above the legally mandated

age threshold. In particular, heavy drinking by young people is an issue of considerable concern (74, 75). Various intervention efforts have been implemented by producers, whether as individual companies or through trade associations and social aspects organizations set up specifically for this purpose. Included among them are social marketing efforts, aimed at shaping attitudes and behaviours around drinking.

Research

Finally, good practice, be it in public policy or other areas, relies on the availability of a solid evidence base. This is also an area in which industry members can play a useful role, for example, by making production and sales data available to the public. Such data are accessible through industry-funded organizations like the International Center for Alcohol Policies (76). Aside from figures on commercial drink production and sales, industry members may have access to information about the non-commercial and illicit markets in many countries and initiatives are underway to collect available data (77) that can significantly contribute to the body of knowledge and also aid in the development of interventions and public policy approaches.

Conclusions

As this chapter has attempted to illustrate, not only can the private sector and public policy be reconciled, but active cooperation can be desirable and should be encouraged. As long as the responsibilities and remits of individual stakeholders are clear and firmly delineated, there is no

reason why industry action should not be in support of public sector initiatives.

It may be time to shift attention from discussions about assumptions about the motivation of one side or the others. Good intentions alone, whether they come from the public sector or from industry, are insufficient. What counts is what works, approaches that can yield tangible outcomes and demonstrable impact. Motivations may be of limited importance as long as the outcomes are beneficial to the public good. It may be time to accept that although industry action may be motivated by the bottom line, the outcomes of its actions can still be in the public good. We cannot expect corporations to be altruistic, or at least not fully so, but we can expect them to be responsible. When responsibility and self-interest can be harnessed for the public good and reconciled with the aims of public policy, everyone wins. Short-run gain is in nobody's interest, but long-term partnerships have a proven track record and have made an impact, at the very least, at a local level.

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Chapter 43
Impact of alcohol on poverty and the need for appropriate policy

Aneel Karnani

Introduction

Despite the tremendous economic growth around the world in the last 30 years, the number of people living in poverty, defined as those living on less than US$2 per day, has remained constant at about 2.5 billion. Regional trends over the same period are even more distressing. The number of those living in poverty has increased since 1981 in every region of the world except East Asia. When China is excluded, the number of people in poverty in the rest of the world increased from 1.6 billion in 1981 to 2.1 billion in 2005 (most recent available data). In a world where many spend US$3 on a cup of coffee, it is unacceptable that so many people live on less than this per day. Approximately 1.2 billion people in the world suffer from hunger and malnutrition; at the same time, about 1.2 billion people suffer from obesity. The arid desert of poverty is surrounded by an ocean of affluence, and even opulence—that is the injustice that is morally reprehensible. Widespread poverty is an economic, social, political, and moral problem. Eradicating poverty is an urgent challenge (1).

Alcohol exacerbates poverty

Poverty and alcohol create a vicious circle. Research by the Chronic Poverty Research Center has found a strong two-way relationship between alcohol dependence and chronic poverty. Alcohol abuse can be a cause of poverty (2). It is also a consequence of, and exacerbates, the negative impact of poverty. Alcohol consumption is a financial drain for the poor; money spent on alcohol could have been spent on more basic human needs such as food, shelter, health care, and education. The reported share of household income spent on alcohol and tobacco by the poor is high in many countries, ranging from 1% in Nicaragua to 6% in Indonesia (3). The poor in India spend about 3% of their household income on alcohol and tobacco (4). Unfortunately, these estimates based on self-reported surveys significantly underestimate the actual expenditures on alcohol due to several reasons. An in-depth field study in Sri Lanka found that 'money spent on alcohol by poor families and communities is underestimated to a remarkable degree […] A large part of alcohol expenditure is unseen' (5). People often intentionally or unintentionally under-report expenditures on alcohol. A hidden channel of alcohol expenditure is the subsidization of others' drinking. When one person deliberately or unwittingly pays for someone else's alcohol, most often neither person reports the expense in surveys. The poor spend a surprisingly high fraction of their income on festivals and celebrations. In a survey of the poor in Udaipur, India, the median household spent 10% of its budget on festivals (3). A significant fraction of this expenditure is on alcohol.

The average consumption numbers, while already high, hide a frightening picture. Since many people do not drink alcohol, the averages understate the impact on the families of the people who do. Families with frequent-drinking husbands in Delhi spent 24% of family income on alcohol, compared to 2% in other families. A survey among the urban poor in Sri Lanka found that 30% of families used alcohol and those who did spent more than 30% of their income on it (6). The average numbers understate the true consumption level since it is often only the man in the household who engages in this consumption. Over 10% of male respondents in the Sri Lanka study reported spending as much as (or more than) their regular income on alcohol. Sadly, those in greatest poverty spend a larger fraction of their income on alcohol than those better off than them.

The addictive substances of alcohol and tobacco often enter the lives of those in poverty as analgesics from extreme labour. In addition, those in poverty often encounter stressors including hunger, pollution, overcrowding, and violence that may lead them to act in ways that may alleviate suffering in the short term, but hinder economic prosperity in the long term. Alcohol might serve as an escape mechanism from these difficult circumstances. While such behaviour might be understandable, that does not reduce its negative consequences. A 27-year-old man in Chembe, Malawi, reported ‘I used up all the money I received as salary on beers. Whenever I try to recall on what happened I feel sorry for myself because the following month I starved very much because I had nothing to feed the family’ (7).

Aside from the direct financial cost, alcohol abuse imposes other economic and social costs such as reduced work

performance, lowered wages, decreased eligibility for loans, increased medical expenses, health problems, and accidents. A study in Uganda found a strong association between alcohol consumption and domestic violence, with 57% of women reporting recent domestic violence saying that their partner had consumed alcohol (8). 'Domestic violence and gender-based violence was almost taken for granted in nearly all settings as an automatic consequence of alcohol use. Deprivation of the needs of children due to the father's heavy alcohol use was regarded simply as a misfortune of the children concerned' (5). A study in India found an association between use of tobacco and alcohol, and impoverishment through borrowing and distress selling of assets due to costs of hospitalization (9).

A poor person who drinks is much more likely to suffer damaging health consequences than an affluent person drinking an equivalent amount; this could be due to the effect on nutrition, transmission of tuberculosis, and even the incidence of liver diseases (7). In the other direction, a few days' illness or decreased income due to alcohol-related problems has a much greater impact on a family that is already desperately poor. There is much evidence showing alcohol abuse exacerbates poverty (10).

'Voices of the Poor'

It is useful to confirm the linkage between alcohol and poverty by listening to those in poverty directly. In a survey of the poor in Uganda, 56% of the respondents said alcohol consumption was a cause of poverty, and 24% said it was a response to poverty (11). In an unprecedented effort to

understand poverty from the perspective of the poor themselves, the World Bank project 'Voices of the Poor' interviewed more than 60,000 women and men in poverty from 60 countries (12). Many people 'mention a syndrome of poverty–money spent on alcohol or other drugs, male drunkenness and domestic violence'. In Africa, the poor mention alcoholism more frequently than other drug abuse. In Ak Kiya village in the Kyrgyz Republic a woman says, 'There are a lot of people in this village who drink vodka in the morning, and then go and do something bad, commit crime'. Many discussion groups from all regions in the study report problems of physical abuse
of women when husbands come home drunk. Group discussions in Kuphera, Malawi, showed a causal linkage from beer-drinking to promiscuity, subsequent diseases, and then death.

Freedom of choice

The alcohol industry has become increasingly consolidated with a few large companies—such as Anheuser-Busch InBev, SABMiller, Heineken, Carlsberg, Diageo, and Pernod Ricard—becoming dominant and promoting their products globally. The wealthier countries in the world, which account for much of the alcohol consumption, are becoming saturated markets. Consequently, the multinational alcohol companies are increasingly targeting low- and middle-income countries with large populations, such as India, China, Brazil, South Africa, Nigeria, and Uganda, to achieve their growth objectives.

The neoliberal economics perspective assumes that people are well-informed and rational actors who make best choices in their own self-interest. Building on this perspective, proponents of market-based solutions to poverty assume that those in poverty are fully capable and willing participants in free-market economies. In the first paragraph of his best-selling book *The Fortune at the Bottom of the Pyramid: Eradicating Poverty through Profits*, business guru C.K. Prahalad urges readers to recognize the poor as 'value-conscious consumers' (13). The 'bottom of the pyramid' (BOP) proposition argues that multinational companies can grow profitably—indeed, make a fortune—by targeting the poor in emerging markets and simultaneously reduce poverty.

The Economist approvingly cites SABMiller, which has succeeded in several African countries with Eagle, a cheap beer made from locally grown sorghum (rather than imported malt) (14). SABMiller is able to price the beer at a level below that of mainstream clear beers in Uganda, Zambia, and Zimbabwe, partly because it has obtained a reduction in excise duties from the governments involved. Andre Parker, managing director for the company's Africa and Asia divisions, says, 'The brand is reliant on the excise break, so we are working with the governments to lower the excise rate so that the retail price is below that of clear beer. The margin, though, is at least as good as our other brands' (15). Eagle beer is profitable for SABMiller and a practical example consistent with the BOP proposition, but it is probably detrimental to the overall welfare of its consumers. Activist consumer organizations advocate higher (not lower) taxes on alcohol to support public education and rehabilitation programmes (10). Even if unwittingly, the BOP proposition

provides cover for companies that exploit the vulnerabilities of the poor.

Those in poverty, of course, have the right to drink, and even to abuse, alcohol; but it is not in their self-interest to do so, at least not at the levels typically consumed. Companies have the right to profit from the sale of alcohol. Radical free-market ideology argues that firms should maximize profits subject to obeying the laws, and that firms do not have any corporate social responsibility (CSR) (16). This assumes that the consumers are well informed and rational. In reality, those in poverty are often ill informed, poorly educated, and in many cases illiterate

Mounting evidence suggests that just being poor hinders an individual's ability to make good decisions. Dozens of psychological studies find that, compared to their wealthier counterparts, the poor often feel more powerless, depressed, and anxious, and believe that they have less control, mastery, and choice (17, 18). 'Perhaps at some level this avoidance is emotionally wise', argue Banerjee and Duflo; 'Thinking about the economic problems of life must make it harder to avoid confronting the sheer inadequacy of the standard of living' (3). Similarly, almost 100 years ago George Orwell observed in his book *Down and Out in Paris and London* that poverty 'annihilates the future'.

These concerns about vulnerable consumers are even greater when children and youth are affected. In addition to the price children pay for parental abuse of alcohol, young people themselves are being targeted by the alcohol industry. Free market ideology cannot be applied wholesale in the context of alcohol sales to the poor. When there is a divergence between

private profits and public welfare, markets should not be left free and some intervention is warranted. When the profit maximizing behaviour of firms results in negative consequences to public welfare, constraints need to be imposed; this is not such a radical idea—governments often impose constraints on free markets to protect vulnerable consumers in various ways, such as regulations related to labelling disclosure, truth and fairness in advertising, and marketing to minors.

Regulation

In all high-income countries governments impose various regulations on the alcohol industry, such as 'sin taxes' and restrictions on advertising and sales to minors. In contrast, low-income countries tend to have more lax regulations and weak enforcement. As an extreme example, in Uganda there is no regulation at all concerning the advertising and marketing of alcohol; there are no restrictions on sponsorships of sports or youth events. The age limit for purchasing and/or consumption of alcohol is set at 18 years; however, there is extremely limited enforcement of this. There are no restrictions on the consumption of alcohol on public transport, in parks or streets, or at sports and leisure events. It is not coincidental that Uganda has the dubious distinction of having the highest recorded average annual consumption in the world of 19.47 litres of pure alcohol per adult (aged 15 years and above) (19). In addition, there is unrecorded consumption from home and illicit production, estimated at 10.7 litres of pure alcohol per adult, per year. By comparison, the total average annual consumption level in the United States is 8.51 litres per adult. The Uganda Participatory

Poverty Assessment Project in 2002 highlighted excessive alcohol consumption as one of the key drivers and maintainers of poverty, especially in the rural countryside, and identified alcoholism as the number one priority factor for downward mobility of households (20).

In many developing countries, regulatory constraints on the alcohol industry are sometimes missing; even when they do exist they are poorly enforced, especially in the context of marketing alcohol to the poor (21). For example, in Malaysia, bottles of *samsu* (the generic name for cheap spirits) advertise claims that it is 'good for health, it can cure rheumatism, body aches, low blood pressure, and indigestion'. Labels also claim 'it is good for the elderly and for mothers who are lactating' (22). Even multinational corporations are involved in these claims; DOM Benedictine, which contains 40% alcohol, claims health-giving and medicinal properties and Guinness Stout suggests it is good for male fertility and virility. Alcoholic drinks are easily available in Malaysian coffee shops and sundry shops without a liquor licence. Forty-five per cent of Malaysian youths under age 18 consume alcohol regularly (22). In an ironic twist on the single-use packaging advocated by the BOP proposition, *samsu* is available in small bottles of about 150 millilitres (5.1 ounces) and 'sold for as little as $0.40–0.80 […] It is obvious that these potent drinks are packaged to especially appeal to the poor' (22).

Unfortunately, many governments, especially in low-income countries, are highly dependent on revenues from alcohol taxes and thus have an incentive to not impose appropriate restrictions on the marketing and sale of alcohol (2). Nepal gains 6% of total government revenues from alcohol. In India, tax on alcohol generates an estimated equivalent of US$5

billion annually, with some states relying on alcohol for as much as 33% of revenues. In India, alcohol is thought to generate the equivalent of about US$5 billion in 'black money' in the form of bribes, protection payments, and profits from illicit alcohol, allowing the industry to gain significant leverage (2).

Most large alcohol companies claim to practise CSR, as can be seen on their websites. Many companies are members of organizations whose goal is to promote and encourage CSR, such as Business in the Community, The International Business Leaders Forum, Business for Social Responsibility, and the United Nations Global Compact. The alcohol industry has also established its own specialized trade associations, such as International Center for Alcoholic Policies, The Amsterdam Group (Europe), The Century Council (United States), and The Portman Group (United Kingdom). These organizations have multiple functions, with the most pertinent being to reduce the abuse of alcohol and to lobby governments. The alcohol industry argues in favour of voluntary constraints, including self-regulation and CSR, rather than government regulation. It is necessary to examine the actions of the alcohol firms in depth to determine whether this is genuine CSR, or a public relations ploy—derisively referred to as 'greenwash'—to delay or pre-empt government regulation. Research suggests that in the case of the alcohol industry, 'public claims to social responsibility do not seem to be borne out in practice', and that CSR provides insufficient controls and that such voluntary approaches must be backed by statutory regulation (23).

The United Kingdom House of Commons Health Select Committee recently examined the practices of some British

alcohol producers and communications agencies to determine whether the industry's system of self-regulation and codes of conduct are effective (24). The committee looked at four themes that are banned by the industry's self-regulated advertising codes of conduct: (i) targeting and appealing to young people, (ii) attitudes to drunkenness and potency, (iii) association with social success, and (iv) sexual attractiveness. The committee found that the codes of conduct are systematically violated in all of these areas. The committee recommended that regulation of advertising practices for alcohol should be independent of the alcohol and advertising industries. The need for regulation of the alcohol industry is even greater in developing countries than in the United Kingdom.

Aside from government, activist movements also play a role in protecting the consumer. Alcoholics Anonymous is a fellowship of men and women who share their experiences and help each other to solve their common problem with alcoholism. Those in poverty in emerging economies usually do not have access to such rehabilitation programmes. In 1991, Heileman Brewery in the United States introduced PowerMaster, a malt liquor with a high alcohol content, targeted at the African American community. Community leaders began a campaign that resulted in the product being withdrawn from the market within a few months. Such social mechanisms for consumer protection are often very weak in developing countries and even more so with regard to the poor.

Case study: Carlsberg in Malawi

In May 2009, the national Swedish broadcasting corporation Radio Sweden aired an in-depth documentary on the alcohol industry in Malawi (25). Malawi is one of the poorest countries in the world; more than half the population lives on less than US$2 per day. Nelson Zakeyu, the founder and head of Drug Fight Malawi which is dedicated to fighting alcohol problems, says that alcohol has an important impact on the three main social problems in Malawi: poverty, the HIV epidemic, and the maltreatment of women. In the documentary, reporters interviewed several women who recounted stories in which women and children fall victim—domestic violence, child neglect, and malnourishment—to men's alcohol addictions. Carlsberg, the multinational Danish beer company, which introduced itself to Malawi about 40 years ago as an aid project, now controls 97% of the bottled beer market. The logic for a brewery being an aid project is questionable. Carlsberg is certainly not aiding Malawi today.

The alcohol policy in Malawi is very liberal; the prices of beer and liquor are low; alcohol is available almost everywhere, and to anyone, at any time of the day. The reporters for Radio Sweden were struck by the extent of poverty and alcohol addiction in the capital city of Lilongwe. Yet, the marketing director of Carlsberg in Malawi claims that there are no addiction problems in Malawi. Dag Endahl, an official with the Norwegian aid organization FORUT that specializes in alcohol problems in developing countries disagrees, saying that 'Carlsberg ought to take a walk outside the office and talk to people' (25). The marketing director of

Carlsberg also claims that the company applies the same restrictions on advertising in Malawi as it does in Europe. The documentary reports facts to the contrary; the company's marketing tactics in Malawi are inconsistent with Carlsberg's corporate code. For example, the code prohibits advertisements from implying that drinking the brand is linked to wealth or professional success. However, Carlsberg Malawi published a full-page advertisement showing students celebrating their graduation, which is an obvious sign of success in a country where over the half population is illiterate. The code also prohibits placing emphasis on the alcoholic strength of the beer, as well as to avoid implying it is to be preferred because of its high alcohol content. In 2008, Carlsberg Malawi launched a new, stronger beer with the advertisement 'Drink Elephant beer when you want a beer with more alcohol than in other beers! A real Elephant person is someone who is strong and full of character'. The code says that advertisements should not show or encourage excessive or irresponsible drinking. Carlsberg Malawi sells a slightly cheaper beer for the local market called Kuche Kuche, which means 'drink until dawn' in the local language, Chichewa (26).

The major global alcohol companies finance the Washington-based lobbying organization International Center for Alcohol Policies (ICAP). ICAP is active in many African countries, lobbying to limit state regulation of the alcohol industry and promoting policies that encourage 'responsible drinking'. However, research shows that educational approaches are not that effective. Experts on alcohol policies and social activists argue that higher taxes and restrictions on the availability of alcohol are the most effective ways to reduce the negative impacts of alcohol. Endahl claims that

ICAP advocates policies that do not take into account the effects of alcohol on public health, violence against women, HIV, and poverty; 'They [ICAP] are extremely keen to avoid regulations of the market through increased taxes, a change of opening hours and age limits, etc.' (25).

Conclusion

The alcohol industry should be regulated to reduce demand and control supply (27). Policies to reduce demand include counselling and support for people with alcohol dependency problems and public education campaigns to raise awareness. Restrictions on marketing and advertising of alcohol reduce demand. Alcohol consumption is normally price sensitive and taxes on alcohol drive up prices and reduce consumption. Supply of alcohol can be controlled by imposing a minimum drinking age, restricting outlets where alcohol can be purchased and consumed, and restricting times when outlets are open. Wealthier consumers tend to be more responsive to education campaigns while their poorer counterparts are more sensitive to price changes. Given the nexus between alcohol and poverty, it is critical that governments regulate the alcohol industry appropriately to protect the poor.

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Chapter 44
Control of alcohol availability: historical and current policies and their effects

Esa Österberg

Introduction

There are many alcohol control strategies and measures used for social policy or public health-oriented interventions. These include regulating alcohol availability, modifying drinking contexts, drink driving countermeasures, restrictions on alcohol marketing, alcohol education and persuasion, and treatment and early interventions (1). Alcohol availability regulations are usually divided on the one hand into those affecting the physical availability of alcohol and on the other into those affecting economic availability of alcohol. Taxing of alcoholic drinks is the most common measure used in restricting the economic availability of alcohol. Taxing alcoholic drinks and other control measures on economic availability are dealt with in detail in Chapter 45, 'Taxation and price control'.

On a very general level, physical availability of alcohol refers to the ease or convenience of consumers obtaining alcohol. Sometimes the physical availability of alcohol has been converted to economic availability by speaking of the effective or full price of alcoholic drinks (2, 3). Effective or full price of alcohol then includes both the listed retail price of alcoholic drinks that the customer pays for the drinks and the costs in money and time, time converted to money, to

reach the retail selling place and also a cost figure for other inconveniences caused to a customer by alcohol control measures when he or she is acquiring alcohol. In this chapter there will be no attempts to convert restrictions on physical alcohol availability into money terms.

Special regulations on physical availability of alcohol often reflect concerns about social policy, public order and safety, and individual or public health. These regulations include the monopolization or licensing of on- and off-premise retail sales of alcoholic drinks as well as general or special limits of opening hours and days of alcohol retail sales. Physical availability also includes the placement and location of retail outlets selling alcoholic drinks, special off-premise sales practices—for instance, sales over the counter or self-service sales as well as special on-premise sales practices—and rules like the maximum ethyl alcohol amount in drinks to be served to customers at one time or the necessary clothing of the customers to be served in restaurants. Availability regulations can furthermore dictate who can purchase or receive alcoholic drinks on-or off-premise. Usually, these regulations concern legal age limits for selling, buying, possessing, or consuming alcoholic drinks and for selling alcoholic drinks to intoxicated persons. There may also be rules of rationing alcohol sales which are specified according to age and sex or even denying the sales of alcoholic drinks on the bases of religion, race, or ethnical group (4).

The main conclusion of the 1975 World Health Organization (WHO) report *Alcohol Control Policies in Public Health Perspective*, by Bruun and colleagues, is that ‘changes in the overall consumption of alcoholic beverages have a bearing on the health of the people in any society.

Alcohol control measures can be used to limit consumption: thus, control of alcohol availability becomes a public health issue' (5, pp. 12–13). In other words, social order or public health-motivated restrictions on the availability of alcoholic drinks are based on the knowledge or assumption that easier access to alcohol increases its consumption in a population and leads to increased alcohol-related harms, and that the tighter the availability of alcohol is in a society, the smaller the alcohol consumption level and related harms.

The reasons for regulating alcohol consumption are not just to maintain social order or to improve public health. As Mäkelä and Viikari have pointed out, the state has four basic interests with regard to alcoholic drinks: a fiscal interest, an economic development interest, an interest in maintaining public order and safety, and an interest in maintaining reproduction and general health of the population (6). It is important to note that even in countries where alcohol control has been or still is mostly motivated by social order or public health considerations, other motives have also affected and affect the level and forms of prevailing alcohol control. The actors behind these other motives may set limits to how strict alcohol control measures can be. Furthermore, as time passes there may be changes in political or economic power structures which set new limits and lead either to stricter or more liberal alcohol control measures and alcohol availability.

This chapter will first take a general look at historical developments and trends in measures controlling the physical availability of alcohol. In this context it also gives more concrete examples of the wide variety of alcohol control measures practised in different countries in different times.

The next step is to review the scientific evidence of the effects of limiting the physical availability of alcohol. Finally the findings will be summarized.

Historical background and trends

In the late nineteenth and early twentieth centuries, acquiring fiscal resources to the state played an important role in many industrialized Western countries (3). This of course affected the decisions regarding the level of alcohol taxes but it was also at least partly the reason behind the decisions to restrict and forbid home distilling in order to concentrate spirits production to factories. One motive for favouring factory production over home distilling was that factory production is more efficient with regard to the use of raw materials (7). The basic motive, however, was that it is much easier to collect alcohol tax revenues and to control the production of a few factories than lots of small home producers. In earlier centuries, one important motive to temporarily restrict, and at times prohibit, home distilling, was to save grain to avoid famines during crop failures.

In Sweden in the 1770s, one way to regulate distilling was to monopolize it and concentrate it in special state-owned distilleries (8). Sweden is also the country where the system of local municipal monopolies, first for on-premise retail sales but later also for off-premise retail sales, was initiated—in the town of Falun, although this practice later became known as the Gothenburg system (9).

Restricting alcohol availability physically through law goes back in history for much longer periods than the examples

given from Sweden indicate. For instance, Babor and colleagues give as an example the Code of Hammurabi dating from 3,800 years ago, which included three articles governing the behaviour of tavern-keepers and their customers in Mesopotamia (1). The code of Hammurabi is important because it reminds us that alcohol has been with us for a long time and that alcohol use, trade, and manufacture have been controlled almost from the beginning of its consumption, by informal social norms and even with laws and other formal orders. Also, in ancient Egypt and Greece, local authorities controlled alcohol production, distribution, and consumption (1).

Britons have been drinking mostly ale since the Bronze Age. The eighteenth century saw a huge growth in the number of drinking establishments in the United Kingdom, primarily due to the introduction of gin which was brought to England by the Dutch. The English Beer Act of 1830 introduced beer houses, though permission to sell beer or cider did not extend to the sale of spirits (10). In the United Kingdom, restrictions were placed on the opening hours of licensed premises from the middle of the nineteenth century. The sale of beers, wines, or spirits required a local licence for the premises. Further provisions regulated gaming, drunkenness, prostitution, and undesirable conduct on licensed premises. These developments culminated in 1914 when opening hours of public houses in England were restricted to 12 noon to 2.30 p.m. and 6.30 p.m. to 9.30 p.m. Scotland and Northern Ireland's licensing laws have long been more flexible. In later decades these opening-time regulations have been relaxed, and following the 2003 Licensing Act in the United Kingdom, shops and supermarkets are allowed to sell alcohol at any time they choose to open (11).

In the first half of the twentieth century total prohibition on alcoholic drinks was used in many Western countries, mostly in North America and in the Nordic countries (1). In the state of Mississippi, United States, prohibition was officially ended only in 1966, and beer was prohibited in Iceland from 1915 to 1989. Nowadays, total bans on alcohol production and sales are uncommon and the prevailing prohibition laws on alcoholic drinks are found mostly in Muslim countries. Alcoholic drinks have also been prohibited in some Indian states. Moreover, partial bans on alcohol sales are still sometimes practised in Western developed countries during days of elections or political unrest or locally in heated sport events. Even today, measures affecting the physical availability of alcoholic drinks also include bans of retail sales in certain places like football or ice-hockey stadiums or in opera or film theatres. Total prohibition can also be found in designated land areas like in some American Indian reservations in the Unites States (4).

The repeal of prohibition acts between the world wars gave birth, in many countries, to state-run alcohol monopolies, mostly on wholesale and off-premise retail sale but also for alcohol production, especially in the Nordic countries. In Finland, the comprehensive state alcohol monopoly even included setting both off- and on-premise retail prices of alcoholic drinks. One motive to establish retail alcohol monopolies was to eliminate or restrict the possibilities to make private profit by retailing alcoholic drinks. Another motive for off-premise alcohol retail monopolies is that they are also tools for affecting physical availability of alcoholic drinks by restricting the number and density of outlets, the days and hours of trade, or limiting alcohol sales on an individual basis such as minimum alcohol-purchasing age.

These control measures do not presuppose alcohol monopolies but it is much easier for the state authorities to control or direct state-owned alcohol monopolies than a few large, or many small, private alcohol enterprises. According to WHO's *Global status report on alcohol and health*, published in 2011, government-controlled alcohol monopolies exist in 30 of the 147 member states reporting on alcohol availability policies (12).

Another common measure to restrict alcohol availability is through government-sanctioned licensing systems. Producers, distributors, and sellers of alcohol may be required to obtain licences for the sale of alcohol, the availability of which may be restricted, particularly in the retail sector. There may, for instance, be regulations establishing limits on the number of outlets per local population. The licences may also include rules which further restrict the physical availability of alcohol. The location of outlets selling alcoholic drinks may be regulated, i.e. no outlets near schools, nursery schools, churches, or along motorways, and licences for retailing alcoholic drinks may not be granted to outlets located in certain places like hospitals, petrol stations, or work-place canteens and kiosks. According to the earlier mentioned WHO report, as many as 93 member states have licensing practices in the absence of alcohol monopoly, whereas only one member
state has a monopoly but no licensing on alcohol production or sales. Roughly one-third of the WHO member states have banned sales of alcoholic drinks at petrol stations for off-premise consumption (12).

In some countries, alcohol sale is forbidden in vending machines. In many countries, any person involved with

alcoholic drinks at the retail level has to be specifically trained. Also, in many countries, regulating alcohol availability also includes dram shop liability laws, social host liability, and bans on public drinking. In the Spitzbergen, Norway, alcohol rationing is still practised.

Most countries prescribe a legal minimum age for purchasing or consuming alcoholic drinks. The legal age may differ according to the strength of the alcoholic drink, i.e. distilled spirits, wine, and beer, or according to whether a drink is purchased for on- or off-premise consumption. Of the 147 WHO member states reporting on alcohol availability policies only 17 had no age restrictions for on-premise consumption and just over 20 had no age limits for off-premise consumption of beer, wine, and distilled spirits. On-premise and off-premise restrictions tended to cluster at age 18. Age restrictions are as low as 15 years in Angola and as high as 25 years in Nepal (12). In the United States the age limit is 21 years for all alcoholic drink categories.

In some countries, the sale of alcoholic beverages to intoxicated persons is forbidden. There have also been stipulations about how much alcohol a customer can buy during one visit to an off-premises outlet. In Belgium, the Vandervelde law from 1919 stipulated a minimum purchase limit of two litres of distilled spirits until 1983 whereas in Finland prior to 1985 a customer could not buy more than two litres of vodka in one visit to the monopoly store. There have also been stipulations of the content of alcohol packages to be retailed. In some countries alcohol may not be sold on credit; men and women may not be allowed to be served alcohol together in the same establishment; or alcoholic beverages may only be served with meals. There have also been rules

forbidding dancing in restaurants in connection with selling alcohol (13).

The effects of controlling physical availability of alcohol

Not all of the alcohol control interventions mentioned so far have been properly evaluated, partly because the interventions have taken place in countries not especially interested in their exact effects and partly because of the difficulties in evaluating their effects. One more problem is that in some cases the interventions have been evaluated, but the research evidence goes so far back in history that it may not be relevant for current alcohol policy discussions. This is the case, for instance, with regard to the effects of prohibition laws between the world wars or to individual rationing of alcoholic beverages during the Bratt system in Sweden, which was discontinued in 1955 (13, 14).

Total or partial prohibition

Although prohibition is never completely effective in eliminating alcohol availability, evaluations of the prohibition periods in North America and the Nordic countries show that total bans on alcohol production and sales can reduce total alcohol consumption and alcohol-related harms (1). In India, prohibition is in force in a number of states and research indicates that overall alcohol consumption decreased substantially when prohibition was introduced (15, see also 4). Also, the data collected by WHO shows that in the Moslem countries where prohibition laws are in force at the moment, such as Afghanistan, Iran, Pakistan, Saudi Arabia,

Somalia, and Sudan, total alcohol consumption is very low, if any (12).

However, where there is substantial demand for alcohol, illegal operators will partly satisfy the demand and illegal markets may produce considerable violence as well as other undesired consequences (1, 4). Because demand exists for alcoholic beverages in the Western developed countries, and because most citizens in these democratic states do not accept this kind of restriction of their personal freedom as consumers, total prohibition is not a politically viable option, even if the potential for reducing alcohol problems does exist.

Partial elimination of alcohol retail monopoly

Partial elimination of off-premise alcohol retail monopolies is a measure where physical alcohol availability has abruptly increased dramatically. These kinds of incidents have been studied in many countries. In the Nordic countries, studies have dealt with the introduction of retail sales of the so-called medium beer, beer with an alcohol content as high as 4.7% by volume, into ordinary grocery stores. In Finland, where the sale of medium beer in ordinary grocery stores was allowed from 1969, total alcohol consumption increased in that year by 46%, completely due to the rise in consumption of medium beer (16, 17). In Sweden, similar availability change in 1965 allowed the sale of medium beer in ordinary grocery stores but then in 1977 this policy was discontinued by banning the sale of medium beer in grocery stores. During the time period medium beer was available in grocery stores, total alcohol consumption was about 15% higher than before 1965 and after 1977 (18). In more recent years, the availability of

beer has also been decreased in Norway by discontinuing the sale of strong beer in grocery stores in 1993 (19).

The sale of wine, an increasingly popular beverage in non-wine-growing countries, has also been shown to be sensitive to increases of retail availability. When retail monopolies on wine have been eliminated both wine consumption and total alcohol consumption have increased. This kind of evidence comes mainly from the United States, Canada, and New Zealand (20–22). Consequently, the research evidence is quite strong that off-premise monopoly systems limit alcohol consumption and alcohol-related harms, and that partial elimination of government off-premise monopolies increases total alcohol consumption. In addition to a greater number of outlets for off-premise sale, privatization of alcohol sale has usually resulted in longer available hours for purchase and other kinds of increases in alcohol availability as might be expected when control measures are reduced.

Opening days, business hours, and number of outlets

Control of opening days and business hours for alcohol outlets has been a common regulatory measure (1, 11, 19). Most of the studies of changes in hours of sale or opening days have demonstrated increased drinking or rate of harmful effects with increased number of sales hours and days, and decreased drinking with elimination of some days of sale (11). A review including 48 studies from eight countries and across four decades found that in a clear majority of these studies changes in hours of sale affected at least one outcome measure (1). In Sweden, Norström and Skog found nearly a

4% increase in total alcohol consumption in 2001 when government alcohol monopoly stores were again opened on Saturdays (23). Restrictions on hours of sale appear to affect both heavier and lighter drinkers (17).

Curbs on number of alcohol outlets and their location have been implemented in various countries. Early studies of alcohol outlet density suggested that this factor had little effect on alcohol consumption. However, more recent studies utilizing multivariate econometric technique, including pooled cross-series analysis approaches, have demonstrated that geographical density does have an effect on alcohol sale (1).

Minimum drinking age

Minimum drinking age is a measure that bans a specific age group from purchasing alcoholic beverages, or makes it illegal to sell alcoholic beverages to underage customers, or at least makes it
more difficult for adolescents and youngsters to acquire alcoholic beverages. Changes in drinking laws in countries such as Australia, Canada, and United States have led to a number of studies on the effects of minimum legal age limits. Studies, especially in the United States but also in other countries, have consistently shown that a lowered age limit produces greater alcohol-involved traffic crashes for the age groups affected by the change, while increased age limits reduced the rate of such crashes (1, 24, 25). A review of 132 studies published between 1960 and 1999 found very strong evidence that changes in minimum drinking age laws can have substantial effects on drinking among young people and

alcohol-related harms (11). The effects were stable over follow-up times ranging from seven months to nine years. The full benefits of higher drinking age were only realized if the law was properly enforced. Even moderate increases in enforcement can reduce sales to minors, especially when combined with media and other community activities. The most effective means of enforcement is on sellers, who have a vested interest in selling alcoholic beverages (11).

Synthesizing the efficiency of different measures

Babor and his colleagues have developed a relatively simple method to synthesize the result of the efficiency of measures affecting the physical availability of alcohol. They provide ratings which reflect the consensus views of the authors and are designed to serve as a guide for those who would like to evaluate the strengths and weaknesses of different policy measures. Their table of the ratings on policy-relevant strategies and intervention is organized according to three major criteria: evidence of effectiveness, breadth of research support, and extent of cross testing across diverse countries and cultures. The scale of the ratings in each criteria area goes from zero to three pluses. The result of this enterprise is that ban on sales of alcoholic beverages, minimum legal purchase age, rationing the retail sales of alcoholic beverages, government monopoly of alcohol retail sales, restrictions on hours and days of alcohol sales, and restrictions on density of alcohol outlets all get at least two pluses out of a maximum three pluses on each rating area (1).

There is the additional question of the impact of alcohol availability measures on heavy or problematic alcohol

consumers. As already mentioned in earlier sections, there are also the so-called 'alcohol strike studies' which show that among heavy or problem drinkers reductions in public disturbances, crimes of violence, and alcohol-related hospital admissions have often been much more marked than the decrease in overall alcohol consumption (26). It is, therefore, reasonable to conclude that a variety of ecological measures will influence the behaviour of heavy or problematic drinkers as well as moderate alcohol consumers. In one form or another, this finding is repeatedly confirmed (1).

Summary and discussion

Generally speaking, studies have found that when alcohol is less available, less convenient to purchase, or less accessible, alcohol consumption and alcohol-related harms decrease. As these research findings are confirmed for more than one country, one can conclude that such findings are not culturally unique even if their effects are not exactly the same in all countries.

We are not expecting that wine in countries where it is mostly used as an ordinary drink with meals has the same price elasticity value than wine in countries where it is mostly consumed as luxury commodity. Similarly, the effects of restrictions on physical availability of alcohol will differ in countries where alcoholic beverages are put to different uses, e.g. where they are mostly used as beverages with meals, as intoxicants, as thirst quenchers, or as means of recreation and enjoyment.

Furthermore, the effectiveness or ineffectiveness of any measure affecting physical availability of alcohol is related to many interactive factors, such as public support and compliance. Without sufficient popular support, enforcement and maintenance of any restriction is handicapped, meaning that restrictions may be circumvented.

Within each jurisdiction there are parallel and competing processes in the alcohol policy arena because different interest groups attempt to influence the outcome of regulating alcohol availability. There are many players in the policy debates and alcohol policy is always a product of competing interests, values, and ideologies. An appreciation of the roles, motives, and power of various players in the alcohol policy arena can heighten the understanding of the alcohol situation and help to realize effective evidence bases for alcohol control measures for better social policy, more secure environments, and better public health.

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Chapter 45
Taxation and price control

Michael Livingston

Introduction

Along with measures designed to reduce the availability of alcohol, taxation has been the most common policy approach used by governments to control alcohol consumption and its attendant health and social problems (1). This has provided the means for extensive studies of its impact on alcohol consumption and related harm in a variety of societal settings. This chapter will review this literature, broadly summarizing the relationships between alcohol prices, alcohol consumption, and alcohol problems. This will include a summary of the variation in pricing effects observed in the literature, specific discussion of the impact of alcohol prices on particular subgroups of the population, and an examination of the direct relationships between alcohol pricing/taxation and rates of alcohol-related problems.

History and practice of alcohol pricing controls

There is a well-established relationship between population-level alcohol consumption and rates of alcohol-related problems experienced in a society (1). Thus, alcohol control policies are often primarily aimed at reducing overall consumption. In this context, basic economic theory underpins the use of taxation as a means of reducing alcohol-related harm. Increases in alcohol taxes increase

prices, which in turn reduce demand, resulting in lower levels of consumption and therefore reduced rates of health and social harm.

The taxation of alcohol has a long history, with excise taxes first levied on distilled spirits in 1643 in the United Kingdom (2, p. 41) and on beer in colonial America in 1644 (3, p. 201). Historically, the aim of alcohol taxation was often revenue generation for government rather than public health. This was particularly true in the United States, where excise on distilled spirits generated around one-sixth of all government revenue in the 1880s, rising to nearly 40% at the turn of the century (4, p. 16). However, excise was also used by governments to try to reduce problems from alcohol. For example, the British parliament introduced a special tax on gin in 1729 in an attempt to deal with the 'gin craze' and increasing levels of drunkenness (5, p. 37).

Because alcohol taxes are not linked to income or wealth, the use of alcohol taxes to improve public health has often been criticized as a regressive measure. However, the accuracy of this criticism is unclear. In the United States, alcohol taxes do fall more heavily on poor than rich households, although this inequality is smaller if viewed in the long term (6). Contrastingly, studies in five African countries (7), the United Kingdom (8, p. 64), New Zealand (9), and in Russia (10) found no evidence that alcohol taxes disproportionately impact disadvantaged people. Even in situations where alcohol taxes are regressive, Schmidt et al. have argued (11) that their positive effects on health would likely reduce the socio-economic inequalities in alcohol-related harm that currently exist.

The price of alcohol is affected by more than taxation rates; it is also driven by factors including the cost of production, levels of demand, and other market conditions. However, the predominant policy intervention available to governments to manipulate the price of alcohol is to levy taxes on its production or sale, and tax changes are largely passed on to consumers (12). Thus, studies in the field have generally used tax and price measures interchangeably, reflecting the general relationship between the two.

The effects of price on consumption

For tax increases to be effective as alcohol policies, they need to sufficiently affect how much alcohol people drink. The degree to which alcohol consumption is affected by price is known as 'price elasticity'. Elasticity is measured as the relative change in consumption of a product given a price change. For example, a price elasticity of −1 implies that a 10% increase in price would lead to a 10% reduction in consumption, while an elasticity of −0.5 implies consumption would fall by 5%. The consumption of a product that was completely inelastic (i.e. elasticity = 0) would be unaffected by price changes.

Three meta-analyses examining the elasticity of alcohol have been undertaken in recent years (13–15). These reviews have compiled and systematically weighted the estimates of elasticity from more than 100 studies from over 25 countries. Across the two meta-analyses that reviewed total alcohol consumption (13, 15), elasticity was estimated at approximately −0.5. In other words, a price increase of 10% results, on average, in a reduction in per capita alcohol

consumption of 5%. Across the three meta-analyses, there was evidence that different beverages responded differently to price changes, with consumption of wine and spirits (median elasticities between −0.7 and −0.8) affected more by price changes than consumption of beer (median elasticity between −0.4 and −0.5). The results of studies published since these meta-analyses are broadly in line with these elasticities (e.g. 16, 17).

These meta-analyses summarize a broad literature including studies that exploit natural price variation over time and/or space and those that focus specifically on price changes driven by government intervention. While the general elasticity literature provides good evidence as to how consumers might respond to alcohol price changes, it is worth reviewing in particular studies assessing the impact of actual tax policy changes.

The impact of pricing policy changes

Distinct changes to alcohol taxes provide the best evidence of how consumers respond to price, by removing the range of other factors that may interfere with more gradual price effects. One of the earliest evaluated policy changes is the raising of alcohol taxes during World War I in Denmark. The price of spirits increased more than tenfold between 1917 and 1918, while beer prices increased by 60%. In response, there was an overall reduction in alcohol consumption of 75%, with spirits sales collapsing. Beer sales increased slightly as a result of the tax changes despite an increase in price, as beer became the most affordable alcoholic beverage (18).

Kendell examined the effect of an increase in the price of alcohol using survey data from regular drinkers in Scotland either side of an alcohol excise rise (19). Alcohol consumption among this group fell by nearly 20% after the tax increase, although some of this decline was driven by simultaneous deterioration in general economic conditions. In Australia's Northern Territory, a levy of five cents per standard drink (10 g of alcohol) was placed on all alcoholic beverages above 3% alcohol by volume in 1992. This levy produced modest price increases across the entire market, proportionally affecting cheap cask wine the most. An evaluation of the programme showed that per capita consumption dropped by more than 20% following its introduction (although
consumption was already trending downwards) (20). More recent reductions in alcohol taxes in Finland have demonstrated that price works in both directions, with a reduction of one-third in alcohol excise rates leading to an increase in per capita consumption of 10% (21). Cook (4) used state data from the United States across a 30-year period to examine how changes in tax rates affected consumption, finding that increases in excise taxes significantly reduced consumption, with an overall elasticity of −0.34.

Other recent changes to alcohol taxes have focused on particular beverages. For example, the tax on distilled spirits in Switzerland was reduced sharply in 1999, with studies based on survey data finding significant increases in spirits consumption (22). Similar reductions in spirits taxes implemented in Denmark in 2003 were expected to increase alcohol consumption in Denmark and in Southern Sweden (where substantial cross-border trade with Denmark takes place). However, both official statistics and survey data

showed no impact of the tax change, with consumption declining gradually (23). There was some evidence from the recorded consumption data that spirits sales increased in Denmark between 2002 and 2004, but this was offset by reductions in beer and wine consumption (23). Studies from Australia and Germany following alcopops tax increases produced similar results—alcopops sales declined sharply, but this was offset by increases in other beverages, resulting in only small reductions in overall consumption (24, 25). These beverage-specific policies raise the obvious issue of how consumers change the specific types of alcohol they consume in response to price changes, which will be discussed in detail later in this chapter.

Variation in price elasticity

While the discussed meta-analyses show that alcohol consumption generally declines with price increases (and increases when prices go down), the medians discussed earlier hide substantial variations in effect size. Wagenaar and Gallet (13, 15) both demonstrate that this variation is in part methodological, with studies based on individual reports of alcohol consumption generally finding smaller price effects than those based on aggregate sales data. More substantively, Fogarty (14) found that the beverage-specific differences in elasticity estimates were entirely explained by the relative contribution of beverages to total alcohol consumption. In other words, in a society where wine is the dominant beverage, price will have less effect on wine consumption than on other beverages. It is worth noting that this effect can be seen within a single country—Babor et al. (1, p. 113) highlight substantial variations in elasticity estimates for

Sweden as the drinking culture shifted from predominantly spirits drinking to beer drinking and then to a more mixed beverage distribution, with elasticities shifting along with consumption patterns.

Further, the place of alcohol in the broader culture is likely to affect the ways in which consumers respond to price changes. Room et al. (26) lay out a model of alcohol consumption incorporating the social, cultural, and policy factors that interact with price policies. This work was attempting to explain the lack of impact of reductions in the Danish spirits tax (discussed in the section 'The impact of pricing policy changes'), pointing to the widespread availability of alcohol, high consumption, and cultural place of alcohol in Denmark as factors that may have mitigated the effects of price. Many of these factors have not been well studied, but it is clear that the effectiveness of tax policies is not uniform. For example, Fogarty finds that elasticity is less in countries with higher alcohol consumption (14). A handful of studies have examined the interaction between pricing and other alcohol policies. Trolldal and Ponicki (27) found that alcohol was significantly less price elastic in states with strict alcohol controls than in states wither fewer restrictions. Similarly, US studies show that the effect of price on youth consumption was higher before the minimum age of purchase was raised to 21 (e.g. (28)).

Given the significant variation in price elasticities identified and the dominance of developed countries in the research literature, it is important to consider the effects of alcohol price in developing countries. Studies undertaken in developing countries generally find price effects similar to those discussed earlier. Studies from Kenya (29), India (30),

Mexico (31), China (32), Taiwan (33), and Tanzania (34) find that alcohol consumption is responsive to price changes, with elasticities between −0.3 and −1.1. A multi-country study (35) compared the price elasticity of alcohol across 43 countries, with the median of the 24 developed countries (−0.44) similar to the median of the 19 developing countries (−0.57).

In summary, while there is variation between countries and over time, there is robust evidence that price affects alcohol consumption. On average, a 10% increase in alcohol price leads to a reduction of around 5% in per capita consumption, although this varies depending on socio-economic, cultural, and policy-related factors. The effect of price is not limited to developed economies, with substantial price elasticities found in studies from the developing world.

Beverage-specific pricing policies and substitution

A number of recent tax policy changes have focused on particular types of alcohol rather than on the whole spectrum of alcoholic beverages, making the issue of beverage substitution a critical one. If consumers respond to a tax increase in a particular beverage category by reducing their consumption of that beverage but making up the difference via other types of alcohol then full substitution will have taken place, and tax policies aimed at single beverage categories will have no impact on overall alcohol consumption. However, while studies typically find some substitution in response to price changes in particular beverages, there is no evidence that alcoholic beverages are completely substitutable. Econometric studies (35–37) have found that partial, but not complete, substitution takes place.

Studies of recent increases to alcopops taxes also find significant, but not complete, substitution (24, 25). Similarly the sharp increases in spirits taxes in Denmark in 1917 increased the consumption of beer slightly, while reducing overall alcohol consumption (18).

Other researchers have broadened the analysis in this area by incorporating more complex meanings of substitution. Gruenewald et al. (37) demonstrated that price changes lead to substitution between beverage types but also between different quality products within beverage categories. Their work suggests that price changes at the cheapest end of the price spectrum impact consumption much more than those at the most expensive end. The effects of price can also influence where consumers buy alcohol. Huang (38) demonstrated that price effects on alcohol consumption in the United Kingdom are much higher for cheaper off-premise alcohol than for more expensive on-premise, with consumers partly substituting off-premise beer for on-premise to deal with price increases. In the most sophisticated analysis of substitution yet undertaken, Meier et al. (39) analysed on- and off-premise consumption of four beverage types, broken into high- and low-price categories. They modelled own-price and cross-price effects for moderate, heavy, and hazardous drinkers, finding a complex web of substitutions between price points, purchase locations, and beverage types. This study highlights the complexity of the effects of price changes on consumption even when the focus is solely on commercially sold beverage alcohol.

A further issue to consider is the potential impact of price changes on the consumption of unrecorded alcohol (e.g. smuggled, home-produced). Due to the difficulty in

estimating unrecorded consumption, there has been only limited research in this field. In Russia, recent analyses have suggested that overall vodka consumption is unaffected by price changes to licit vodka, with consumers substituting to home-stilled or smuggled vodka to make up the difference (40). Studies from Africa that have incorporated locally brewed beer have found that increases in imported
beer prices lead to significant substitution to the locally made alternative (34). These non-market sources of alcohol may be more problematic than commercially available products, meaning that the impact of tax policies in countries with significant untaxed alcohol supply should be carefully monitored to prevent unintended harmful outcomes.

Discounting and minimum pricing

The substitution between higher- and lower-priced beverages discussed previously (37, 39) points to the particular importance of prices of cheap alcohol. Recognizing this, a number of jurisdictions have implemented minimum prices for alcoholic beverages, although often at levels too low to have any major impact on the market (41). There have been no real evaluations of the impact of minimum pricing, although the modelling described earlier in 'Beverage-specific pricing policies and substitution' (39) suggests that setting a minimum price has the potential to greatly reduce the harm from alcohol, without overly impacting moderate drinkers. Studies have demonstrated that discounting in on-premise settings (e.g. happy hours) results in heavier drinking (42), while a recent study suggests that discounts on bulk-buying in off-premise settings increase purchasing (43). Purshouse et al. (16) also estimated the

impact of banning off-premise discounts, estimating a 2.8% reduction in per capita consumption and an annual reduction of 35,200 hospital admissions and 1,140 deaths.

Price effects on subgroups of drinkers

While the research summarized in earlier sections has clearly established that population-level alcohol consumption is responsive to price changes, the effectiveness of tax and pricing policies in reducing harms is contingent on their impacts on risky drinkers. If changes in per capita consumption in response to price changes are driven solely by moderate drinkers, then price changes will have limited impact on alcohol problems. Thus, the heterogeneity of price effects across different subpopulations has increasingly become a research concern (39). While there has been less work examining this issue than there has been at a whole of population level, researchers have paid particular attention to the effectiveness of tax to reduce the consumption of two subgroups: youth and heavy drinkers.

Youth

Young people may be expected to be the most price responsive given their limited resources, with disposable income identified as a key driver of youth heavy drinking (44). A review of the literature (45) found clear and consistent evidence that increased alcohol prices reduced overall alcohol consumption and episodic heavy drinking amongst high school students. Gallet (15) combined 13 studies of price elasticity among young drinkers, finding a median elasticity of −0.39, a slightly smaller effect than found for adult

drinkers (−0.56). Some studies have produced contrasting findings to the body of the literature, particularly amongst college drinkers (46). Recent studies of tax policy changes have produced mixed findings. The cut to the spirits tax in Switzerland had the most impact on the drinking of young people (22), while the similar tax cuts in Finland were shown to mostly affect older drinkers, with surveys detecting no change in youth consumption (21).

Heavy drinkers

The meta-analysis by Wagenaar et al. (13) specifically examined elasticity estimates for heavy drinkers. Across ten studies (many of them focusing on youth), they found a small but significant price effect. More recently, Meier et al. (39) found that heavy drinkers are affected by price, but proportionally less than moderate or light drinkers, largely due to their propensity for substitution. In Scotland, Kendell et al. (19) found that tax increases reduced the consumption of heavy drinkers at least as much as that of moderate drinkers. In Australia, substantial reductions in self-reported heavy drinking followed the introduction of a levy of five cents per standard drink, although this levy coincided with substantial investment in a range of other prevention programmes (20). In Switzerland, Gmel et al. (47) used a rigorous methodological approach, finding that a spirits price decrease substantially increased the consumption of heavy drinkers, although this effect diminished over time. While the studies discussed here provide some support that heavy drinkers are price responsive, clearer and more robust evidence is available from studies examining the impact of price on harms from heavy drinking such as liver cirrhosis,

which are presented in more detail in the section 'The effect of price on alcohol-related harm'.

The effect of price on alcohol-related harm

While the direct impacts of price on alcohol-related harm have not been studied as systematically as the effects on consumption, there is a substantial body of research examining how price relates to a range of negative health and social outcomes. This literature has been the subject of a meta-analysis (48), summarizing the broad effects of price on specific categories of alcohol-related harm. This analysis found significant relationships between alcohol price and a series of harms: alcohol-related morbidity/mortality, violence, traffic accidents, risky sexual behaviour, drug use, and crime. Particularly strong effects were identified for morbidity and mortality (studies here were largely focusing on cirrhosis and other chronic conditions) and for traffic accidents/ drink-driving.

Evaluations of the 'Living with Alcohol' programme in the Northern Territory (described in 'The impact of pricing policy changes') highlight significant reductions in both acute and chronic harms from alcohol following the imposition of a small levy on alcoholic beverages (20, 49). Similarly, two studies used time-series methods to look at the impact of changes to alcohol taxes in Alaska and Florida, United States, with both finding substantial reductions in mortality following tax increases (50, 51). As with many previous studies (e.g. (18, 52)), these studies examined chronic conditions, with their findings clearly demonstrating that the heaviest drinkers in society are price responsive. Studies of

the recent decrease in Finnish alcohol taxes have also shown that price impacts on chronic heavy drinking, with sharp increases in hospitalizations and mortality identified (53). Acute harms are also affected by price changes, particularly traffic accidents (e.g. (54)). The literature provides a robust and consistent picture—increases (decreases) in alcohol taxes lead to decreases (increases) in a range of alcohol-related problems, affecting both chronic disease and acute problems.

Conclusions

This chapter has summarized a substantial body of research that clearly and consistently demonstrates the effectiveness of alcohol taxation as a public health policy. Studies show that consumers respond to price increases by reducing their consumption and to reductions in price by drinking more. Many critics of alcohol taxation suggest that it fails to affect problematic drinkers. This is not supported by the literature, with studies showing that both young people and heavy drinkers respond to price changes. Indeed, the impact of price on chronic alcohol-related harm like liver cirrhosis clearly demonstrates that the heaviest drinkers in society are price responsive. Further, a range of acute harms related to alcohol (e.g. crime, traffic accidents) have also been shown to respond to price, implying that alcohol taxes have the potential to reduce alcohol-related harm across the board. The failure of many governments concerned with alcohol-related harm to act on alcohol taxes is undoubtedly connected to their lack of public appeal (e.g. (55)) and implacable industry opposition (56). However, the evidence summarized here clearly demonstrates the potential for alcohol taxes to reduce the substantial health and social burden of alcohol, making

taxation a critical component of any evidence-based approach to reducing alcohol-related harm.

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Chapter 46
Alcohol control measures and traffic safety

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Introduction

A small number of influential epidemiological studies established the increased motor vehicle collision (MVC) risk that occurred with driving after drinking, and were very important in galvanizing action to address impaired driving (1–3). A co-author of one of these reports recently recalled interviewing a taxi driver in the late 1940s who reported killing people on three separate occasions while driving drunk (Popham, personal communication). By the late 1960s, jurisdictions monitoring alcohol levels among fatally injured drivers found that as many as two-thirds of them had been drinking prior to their collisions (4). Today, rates of drink-driving deaths in most countries are substantially lower, and efforts to prevent drink-driving and resulting collisions, injuries, and deaths are considered among the most important public health successes of the past century (5, 6). The foundations for this success include the extensive research conducted on the determinants of drink-driving and on potential countermeasures, a willingness on the part of policy-makers to act on evidence of effective countermeasure approaches, and the ongoing motivation provided by community-based organizations such as Mothers Against Drunk Driving.

In this chapter, we review the impact of alcohol control measures on traffic safety. We begin by summarizing evidence on the effects of deterrence and remedial initiatives. Although not commonly considered alcohol control measures, they act at least in part by affecting the psychological and social availability of alcohol (7) and are widely considered to be key factors in recent reductions in drink-driving deaths. We then examine research on the link between alcohol control measures and traffic safety more directly, including a consideration of the role these measures may have played in reductions in drink-driving deaths over the past few decades and their potential for influencing drink-driving rates in the future.

Drink-driving initiatives and traffic safety

Development of reliable technology for measurement of alcohol in the body and the ability to link it to impairment and increased collision risk provided the basis for a revolution in the deterrence of drink-driving (8–12). Norway was the first country to introduce a law making it an offence to drive with a blood alcohol concentration (BAC) over a specified limit, which was set at 0.05% (13) and similar laws were soon adopted by other Scandinavian countries. These laws were unique in making driving at a specific BAC level by itself an offence, and are known as per se laws.

Interest in the use of per se laws as a means to address the drink-driving problem grew in other jurisdictions. Great Britain introduced a per se law (the Road Safety Act) in 1967 with a legal limit of 0.08%. According to Ross (14), the results were initially very strong, with a substantial reduction

in rates of alcohol-related collisions, but subsequently collision rates appeared to return to close to pre-law levels. Nevertheless, the initial impact of these laws was impressive and other countries introduced them in the following decades. The introduction of per se laws in other European countries, Canada, the United States, Australia, Japan, and elsewhere have had a sustained impact on rates of drink-driving and resulting casualties (8, 15–18). A key factor influencing the success of these laws is the extent to which they influence the perceived likelihood of being caught if inappropriate drinking and driving occurs (9, 11, 12).

Subsequently, many jurisdictions that originally set legal limits at higher levels (e.g. 0.08% or higher) have since reduced the legal BAC limit. The justifications for lowering legal limits include evidence that significant impairment of driving-related skills begins at very low BACs, collision risks are significantly elevated at BACs of 0.05% or perhaps lower, and that introduction and lowering legal limits can reduce drink-driving collision, injury, and death rates in the population (8, 19–21). Lowered legal limits have generally resulted in lower collision, injury, and fatality rates in many countries (8, 22–25).

In some jurisdictions, young drivers, new drivers, and convicted drink-drivers have been identified as at particular risk for collision involvement and have been subject to reduced legal limits or prohibition of driving after any alcohol is consumed (8, 26–29). These targeted BAC restrictions appear to be effective in reducing drink-driving among affected groups, including young and new drivers and those already convicted of a drink-driving offence (8, 17, 26, 28, 30–32).

Other deterrence-based initiatives have been shown to reduce drink-driving fatality rates. Administrative licence suspensions (ALSs), where a driver's licence is removed by the licensing authority, typically for a short period of time (several days to several months), at the time a drink-driving charge is laid or when a driver is apprehended with a BAC above a specific level, were first introduced in the United States as a way to promote consistency of licensing action against impaired driving offenders and to improve the deterrent benefits of these actions (13). Evaluations of ALS laws have shown that they can reduce rates of self-reported drink-driving and traffic fatality rates (18, 33–36). The use of spot-check, sobriety check point or 'blitz' programmes represents one effort to maintain high levels of perceived likelihood of apprehension (12, 14), and research confirms the ability of spot-check programmes combining public education and high visibility enforcement to achieve reductions in collision rates, at least during the time when these activities are occurring (17). In Australia and many parts of Europe, random breath testing (RBT) has been introduced where police are able to request breath samples from drivers with no prior suspicion of impaired driving. Under these conditions, many more drivers can be tested and presumably this would increase perceptions of the likelihood of being caught in the driving population (37). Evaluations of RBT show that it can reduce rates of drink-driving and alcohol-related collisions substantially, particularly when it is combined with high-visibility enforcement efforts (25, 37).

Individuals who drive impaired or who are charged with drink-driving offences have rates of alcohol problems that are substantially higher than in the general population (38–41). Rehabilitation or remedial programmes for drink-driving

offenders, typically involving alcohol education or brief interventions and occasionally requirements for extended treatment, have been introduced in many jurisdictions. These programmes have important benefits for participants ranging from improved traffic safety outcomes, reductions in drinking and drug use, and health benefits including reduced mortality rates (42–47). Other measures that aim to change drink-driving behaviour, particularly ignition interlock programmes, show promise for improving traffic safety (10, 48).

Alcohol control measures and drink-driving

Over the years, extensive research has shown that alcohol impairs behavioural and cognitive skills involved in driving, and epidemiological studies show an exponential relationship between BAC reached after drinking and the likelihood of collision involvement (3, 49, 50). It is now also clear that population rates of alcohol consumption and availability are important determinants of drink-driving rates, but that has not always been the case. In an early review of the literature on the relationships among alcohol availability and consumption, on one hand, and drink-driving measures on the other, Popham, Schmidt, and de Lint concluded that while there was convincing evidence of strong relationships between population consumption and various health measures including cirrhosis mortality rates, drink-driving measures seemed to be an outlier (51).

Subsequently, Mann and Anglin (7) were able to conclude that a link between per capita consumption and alcohol-related collision rates had been demonstrated. However, they noted that not all studies had found this relationship. They suggested that these studies were characterized by smaller sample sizes and inability to control for important covariates; when more methodologically rigorous studies were examined, a relationship of per capita consumption with drink-driving was observed.

Since then, several studies have confirmed an important relationship between per capita consumption and traffic safety measures. Several studies have examined Canadian data using time series analyses. Skog (52) examined the association of per capita consumption of alcohol with total MVC deaths in Canada from 1950 to 1998. He found a significant relationship for male MVC deaths, with a one-litre increase in per capita consumption associated with an increase of 3.61 in the male MVC mortality rate (per 100,000 population). Asbridge et al. (15) examined the effects of alcohol consumption level, along with the introduction of Canada's per se law and the level of citizen activism, on the numbers of drink-drivers and non-drink-drivers killed in Ontario between 1962 and 1996. They observed a significant association of per capita consumption of alcohol with drink-driver fatalities, but not with non-drink-driver fatalities. Asbridge et al. (15) found that an increase of one litre in per capita consumption of alcohol was associated with an increase in drink-driver fatality rate of between 8% and 14%, depending on the other variables included in the equation. Mann et al. (53) examined the impact of consumption of alcohol in the form of beer,

wine, or spirits on the drink-driver fatality rate in the same period (1962–1996). They found significant relationships of beer consumption, but not spirits or wine consumption, on the drink-driver fatality rate. They observed that a one-litre increase in per capita consumption in the form of beer resulted in an increase of 23% in the drink-driver fatality rate.

Research conducted in other countries confirms these observations. Mann, Smart, and Anglin (54) observed that changes in per capita consumption of alcohol in American states between 1982 and 1990 were significantly and positively associated with changes in both total traffic fatality rates and alcohol-related traffic fatality rates. Skog (55) examined the association of per capita consumption of alcohol with drink-driving fatality rates in 14 European countries. He observed a significant association of per capita consumption of alcohol with male MVC fatality rates for central and southern European, but not northern European, countries. Gruenewald and Ponicki (56) examined the impact of sales of beer, wine, and spirits on single-vehicle night-time (SVN) fatal collisions in 38 states with cross-section time series analyses. They found a significant impact of beer sales, and less so of spirits and wine sales, on fatal collision rates. Zlatoper (57) conducted a multivariate analysis of determinants of MVC fatalities across US states. He found that alcohol
consumption was directly and significantly associated with MVC fatality rates. Noland (58) evaluated the impact of a variety of factors, including per capita consumption of alcohol, on traffic fatality rates in the 50 American states over a 14-year period. Interestingly, he found no evidence for a safety impact of road infrastructure improvements, but instead

that decreasing per capita consumption of alcohol was a major determinant of declining traffic fatality rates.

It can be concluded that as alcohol consumption and alcohol availability increase in populations, rates of drink-driving and associated collisions, injuries, and deaths will tend to increase as well, with the converse also being true (7, 59, 60). Thus, anything that might be expected to increase alcohol consumption rates will be expected to increase drink-driving rates and problems, and anything that might be expected to decrease alcohol consumption rates will be expected to decrease drink-driving rates and problems. Alcohol availability, including economic, physical, legal, and social aspects of availability, has been shown to be the strongest determinant of alcohol consumption rates in populations, and thus can be predicted to be a strong determinant of drink-driving rates as well. These observations form the cornerstones of alcohol availability approaches to addressing the drink-driving problem.

Price, taxes, and rates of drink-driving

Research has provided a substantial amount of support for an important impact of alcohol availability on drink-driving rates. Evidence on economic availability has been most consistent. A substantial amount of research demonstrates that the price of alcohol, or the amount of tax charged, is a significant determinant of alcohol consumption and alcohol problems (61–65). As seen in the section ‘Population consumption levels and drink-driving measures’, research demonstrates that average consumption of alcohol is significantly associated with MVC fatalities, and in particular

those related to alcohol. A smaller body of research has assessed the impact of alcohol price on MVCs and associated fatalities.

Adrian, Ferguson, and Her (66) reported multiple regression analyses of factors affecting MVC fatality rates in Ontario, Canada. In time series analyses, controlling for potential confounders such as income and proportion of young males in the population, they found a significant negative relationship between price of alcohol and the rate of alcohol-related MVCs, and also between the price of alcohol and the rate of alcohol-related criminal traffic offences, such that as price increased, collisions and offences decreased. Chaloupka, Saffer, and Grossman (67) utilized cross-section time series analyses to examine the impact of several alcohol-related factors, including alcohol price, on night-time driver fatality and alcohol-related driver fatality rates in US states. The price of alcohol was represented in their analyses by the excise tax rates on beer. They observed significant negative relationships between price of alcohol and fatality rates.

Physical availability and drink-driving

Physical availability, through hours of sale and accessibility or density of outlets, has been studied as a determinant of drink-driving rates. Its effects have been less consistently seen, but nevertheless on balance the evidence supports an important effect. Some studies have not seen large or significant effects of changes in the physical availability of alcohol. For example, Vingilis et al. (68, 69) examined the effects of an extension of the closing hour from 1 am to 2 am of on-premise alcohol sales in the province of Ontario,

Canada. They did not find a specific increase in drink-driving collisions or fatalities in Ontario in comparison to control data from the state of Michigan in the United States. Similarly, in the province of Alberta, Canada when alcohol sales were privatized, which resulted in increased numbers of outlets and hours of sale, Trolldal (70) found no
effects on rates of drink-driving collisions and fatalities. However, in both instances, around the time these changes were made other initiatives were being introduced which would be expected to affect drink-driving rates and thus may have obscured any availability effects on drink-driving measures, and also significant effects of these measures on other indicators of alcohol-related problems were seen (assaults in Ontario and suicide mortality rates in Alberta; 68, 69, 71).

Other investigators have examined effects of outlet density on rates of drink-driving problems and some have found no significant effects of numbers of outlets on drink-driving measures. Gruenewald and Ponicki (56) examined the impact of beverage-specific alcohol sales and numbers of outlets on rates of SVN fatal crashes in 38 US states over a 12-year period. They found a strong relationship of SVN fatality rates to beer sales, but no effect of outlets. Kelleher et al. (72) examined the association between alcohol availability measures, including number of outlets, and motor vehicle fatality rates for male drivers aged 15–24 years in 75 US counties. They found no significant relationships between any availability measure and fatality rates. Meliker et al. (73) conducted a cross-sectional analysis to examine the impact of alcohol outlets on alcohol-related MVCs in southeastern Michigan. They observed no significant relationships between alcohol outlets and alcohol-related MVCs. Lapham et al. (74)

assessed the effects of a change in the number of alcohol outlets on alcohol-related MVCs in the US state of New Mexico. They found that closing drive-up liquor windows in the state had no significant impact that could be discernible from an ongoing downward trend in collisions.

However, a larger number of studies have found that number of alcohol outlets does exert a significant impact on drink-driving collisions. Scribner, MacKinnon, and Dwyer (75) assessed the effects of various forms of on-premise and off-premise outlets on property damage and injury alcohol-related MVCs using data from 72 cities from within Los Angeles County. They observed that both on-premise and off-premise outlets significantly affected alcohol-related injury collisions, while alcohol-related property damage collisions were significantly related to on-premise outlets. Gruenewald et al. (76) examined the impact of on-premise alcohol availability to self-reported driving after drinking and single-vehicle night-time collision (SVNC) rates. They observed no relationship between numbers of outlets and self-reported driving after drinking, but a significant relationship between numbers of outlets and SVNC rates. Gruenewald et al. (77) assessed the impact of on-premise drinking places and beverage-specific sales on drink-driving in data from Perth, Australia. They observed that outlets selling larger amounts of beer and spirits produced significantly larger numbers of drink-drivers. Gruenewald, Johnson, and Treno (78) conducted a multilevel analysis to examine the degree to which the physical availability of alcohol is related to self-reported drinking patterns, preferred drinking location, driving after drinking, and driving while intoxicated. The results indicated that outlet density and preferred location jointly contribute to driving after drinking.

LaScala, Johnson, and Gruenewald (79) examined the impact of alcohol outlets on pedestrian injury collisions. They observed greater bar density was associated with a higher rate of alcohol-involved pedestrian injury collisions.

Treno, Grube, and Martin (80) assessed the impact of alcohol outlet density on survey-reported drink-driving, and riding with a drink-driver, in California. They found a significant positive relationship between outlet density, including both on- and off-premise establishments, and rates of both drink-driving and riding with a drink-driver. Escobedo and Ortiz (81) assessed the impact of liquor outlet density on alcohol-related MVCs and alcohol-related MVC fatalities in New Mexico. They observed a significant positive relationship between liquor outlet densities and MVCs and MVC fatalities. They observed that moving from the first tertile to the third tertile of outlet density increased MVCs by 50% and alcohol-related MVC fatalities by 100%.

Further confirmation of the impact of alcohol availability and accessibility measures on collisions was provided by Cohen, Mason, and Scribner (82). These investigators examined the relationships among alcohol control policies and practices, including regulations related to alcohol accessibility, licensure of outlets, disciplinary actions, and alcohol-related MVC fatality rates in 107 American cities. They observed a significant negative relationship between numbers of alcohol regulations and fatalities. Cities that had nine or fewer of the 20 regulations considered had a fatality rate 1.46 times higher than cities with 15 or more of the 20 regulations.

Legal availability and drink-driving

While the number of opportunities internationally to evaluate the effects of changes in the legal availability of alcohol have been limited, because occasions when alcohol has become legally available or unavailable to specific jurisdictions or groups have been few, nevertheless some very important opportunities for examining legal availability changes have occurred over the years. In North America, the legal drinking age for alcohol was first reduced, and then increased, in most states and provinces between the late 1960s and the 1990s. In some cases the reductions in legal drinking age were from 21 to 18 years (although in some jurisdictions a smaller change was introduced). Subsequent increases in legal drinking age included a similar range (as large as from 18 to 21 years; 60). The adverse effects of the reductions in drinking age on traffic safety measures were soon observed (83). While other adverse effects were also seen (41), the increased rate of drink-driving problems was a major factor in decisions to increase drinking ages again in American states and some Canadian provinces (60). Individual analyses and reviews of this experience provide strong evidence for the impact of the increased legal drinking age, with important reductions in drink-driving rates and associated deaths being seen (60, 84, 85).

Have alcohol control measures contributed to declines in drink-driving fatalities?

The factors most commonly identified as contributing to reductions in drink-driving deaths in recent decades have been deterrence-based and rehabilitative countermeasures

(53). These measures work in part by influencing the drinking behaviour of populations and individuals through affecting psychological and social availability of alcohol. Alcohol control measures more generally may also have a very large impact on traffic safety measures. A clear example where an alcohol control measure was implemented for traffic safety purposes was the increased legal drinking age in the United States and parts of Canada. Another example where traffic safety concerns played a major role in an alcohol control initiative was in Ontario, where the provincial government decided against privatizing the provincial alcohol retailing system, in part because of the projected impact on drink-driving rates (53). Finally, it is also very clear that changes in per capita consumption rates have affected drink-driving rates. Given that over the past few decades reductions in per capita consumption rates were observed in many parts of the world, these reductions have likely contributed to reduced drink-driver death rates (15, 59).

However, with important exceptions as already noted, it has been rare that alcohol control measures have been proposed specifically to reduce drink-driving rates. In view of the substantial impact of alcohol control measures on traffic safety, this omission may overlook what is a very powerful means to reduce traffic safety problems. It is now abundantly clear that physical, legal, and social availability of alcohol exert a strong impact on traffic safety measures, and should be considered among effective policy tools for reducing drink-driving injuries and deaths.

Concluding comments

Since recognition of the magnitude of the impact of alcohol on traffic safety, much information has accumulated on effective measures to prevent those problems. Implementation of that knowledge has prevented many deaths, and recent efforts to quantify that impact suggest how large it has been. In Ontario, Canada alone, implementation of drink-driving countermeasures, including the federal per se law, increased legal drinking age, administrative licence suspensions, mandatory remedial programmes, and maintaining public control over alcohol retailing (in the face of privatization efforts) were estimated to have prevented more than 4,800 deaths and 178,000 injuries between 1970 and 2006, with estimated cost savings in the province ranging between $8.5 and $77.9 billion dollars (53).

Nevertheless, drink-driving remains a leading cause of alcohol-related deaths. Additional progress in reducing those deaths will likely come from several sources, including social evolution, improved countermeasures, and learning from international experience (86). However, opportunities for reducing drink-driving deaths with new deterrence or remedial initiatives may be limited. We have seen that alcohol control policies can have a substantial effect on traffic safety measures, but in the past have rarely been employed for these purposes specifically, with some important exceptions. Perhaps now alcohol control policies may receive more attention as important means to improve traffic safety.

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Chapter 47
Public information and education campaigns

Claire Wilkinson

Introduction

The price and availability of alcohol, as well as laws around drink driving, are well-known avenues for the regulation of alcohol. There are, however, other strategies which may be an important part of preventing alcohol-related harms. While not normally described as alcohol controls, because they do not control alcohol use directly, these strategies nevertheless are directed at reducing alcohol-related harm. Knowing more about these less obvious measures, how they complement one another, and their comparative effectiveness increases the range of actions possible in reducing harm from alcohol.

Strategies aimed at preventing alcohol-related harms are commonly grouped together on the basis of similar characteristics, or underlying theoretical approaches to reducing harm. This chapter reviews a number of such strategies which are commonly grouped together as *public information* and *education campaigns*. Other groups of strategies include placing restrictions on the amount or content of advertising (1) and regulating the context and environment in which alcohol is drunk (2–4). For those seeking further discussion, Babor et al. (5) is an influential book written by a prominent group of researchers which provides the most recent and comprehensive review of alcohol control policies.

The chapter concludes that while public information and education campaigns may increase knowledge and awareness of alcohol-related harms, there is not strong evidence that, on their own, they can reduce alcohol use or alcohol-related harms.

Public information and education campaigns

A common approach taken by governments to prevent alcohol-related harms is to provide public information about the risks and harms associated with alcohol consumption. The reasoning behind this kind of approach is that people will refrain from behaviour that is potentially harmful if they know and understand the risks involved. The strategies focus on the public communication of messages about drinking. They are most frequently evaluated in terms of awareness and recall of messages rather than in terms of actual drinking or risk behaviours. Four of these types of strategies are reviewed here: (i) population drinking guidelines, (ii) alcohol beverage warning labels, (iii) public education and social marketing campaigns, and (iv) school-based prevention programmes.

Population drinking guidelines

One strategy aimed at providing information about alcohol-related harms is the production and dissemination of official drinking guidelines. Guidelines are based on comprehensive reviews of
the epidemiological evidence on the health effects of alcohol. Guidelines are often expressed in terms of the number of standard drinks one should not exceed in order to reduce alcohol-related harm. In a few countries, labels on alcohol

beverage containers state the number of standard drinks they contain; in some countries guideline levels are also printed on labels. Guidelines may be disseminated more widely through public education campaigns (printing pamphlets and booklets, for example) or through information and advice available at primary health care settings. There is generally significant population support for information on alcohol guidelines being provided. For example, in an Australian population sample, 85% of the sample supported or strongly supported including recommendations of daily guidelines for low-risk drinking on alcohol beverage containers (6). Guidelines may be an important component of reducing alcohol-related harm, because they synthesize complex research evidence into straightforward messages about drinking and harm. This information can then be used as the basis on which to inform public education and information campaigns.

Evaluation research on alcohol guidelines measures the awareness of guidelines amongst general population samples. Generally, these studies find the public have limited awareness of guidelines and of guideline drinking limits. For example, a recent study of the Australian general population (7) found less than 5% of Australians could accurately estimate official guideline levels. The study found estimates were better for long-term low-risk drinking guidelines than those for short-term harms. A substantial minority (ranging between 30% and 50% depending on which gender was being asked to estimate which guidelines) responded that they did not know low-risk drinking limits, and could not provide estimates. Awareness of guideline limits may increase, though, when accompanied by a public education effort. In Denmark, the National Board of Health funded an education campaign of the limits using TV ads, mail outs, and posters,

beginning in 1990. Awareness of sensible drinking limits increased over a ten-year evaluation period, during which time the campaign continued, to 47% for women and 67% for men (8). Thus, although many people in the population are not aware of low-risk drinking levels, there is some evidence that, when publicized, guidelines can inform people's understanding of low-risk drinking levels.

There is some evidence that guidelines do affect the public's knowledge about safe drinking limits. The study by Livingston (7) examined estimates of low-risk drinking levels over two large national surveys during a period in which the Australian official drinking guideline estimates were revised: long-term low-risk drinking limits decreased for males but limits for females remained the same. Livingston found males gave a lower estimate for long-term low-risk guidelines in 2010 than in 2007. Females also gave a lower estimate in 2010 but the reduction was not as substantial as that for males. Given that the long-term low-risk drinking guidelines changed for males and not females, the differential degree of change in population estimates was interpreted as partial support for the influence of guidelines on the public's understanding of risky drinking levels. Like this study, the majority of research has generally focused on the awareness of guidelines, there is no research evidence that drinking guidelines actually affect drinking behaviour or reduce alcohol-related harm (9).

Alcohol beverage warning labels

Another strategy to raise awareness of alcohol-related harms is to put information about such harms on alcohol containers

and packaging. A recent Australian policy paper on alcohol warning labels identified at least 18 countries or territories where alcohol warning labels are mandated (10). The message and the format of labels varies between countries, although messages warning of the health risks of drinking while pregnant seem to be particularly common. Warnings are generally
short and small and most often appear on the labels on the back of containers; they may be text or pictogram.

Research into the effect of warning labels concentrates on the US experience where a label has been required on alcohol products since 1989. The label warns of the risks of drinking and driving, operating machinery, drinking while pregnant, and other general health risks. The most comprehensive and recent review of the evidence was conducted by Stockwell (11). The majority of the evidence reviewed comes from a series of studies using US national population surveys, with Ontario, Canada, where no labels were introduced, as the control site. The review found that when alcohol warning labels were introduced, awareness of the health messages contained on alcohol labels increased. Among the messages appearing on the label, there was greatest recall of the message to not consume alcohol while pregnant because of the risk of birth defects. Those who had seen alcohol warning labels were also more likely to have conversations about alcohol-related harms. There were no effects of the introduction of the label on alcohol consumption. However, it is important to keep in mind that these results were found with the US label, which is small and hard to read, often appearing vertically in very small font on the back label of alcohol containers. Unfortunately, there is no evaluation literature with other types of alcohol labels—including larger

pictorial ones—although the evidence from tobacco research suggests labels which were attention-getting, which occupy a considerable portion of the package surface, and involve rotating, rather than fixed messages would be more likely to be effective (12).

One advantage of alcohol beverage warning labels as a means of disseminating information about alcohol is that, in principle, those who drink more frequently are most likely to see the information. Awareness of label messages has been found to be highest amongst heavy drinkers, as well as other high-risks groups of adolescents and pregnant women. For example, in the United States, 43% of survey respondents reported having seen the warning labels compared to 73% of heavy drinkers and 61% of 18–29 year olds (13).

The alcohol industry in many countries has voluntarily introduced labels advising caution or moderation. This is often seen as a pre-emptive move designed to avoid mandatory warning labels. Many alcohol companies in Australia, for example, plan to introduce voluntary labels on products which will say 'Get the Facts' at an industry-funded webpage. Such an approach avoids information about alcohol-related harm being communicated at the point of consumption and purchase and requires people to actively choose to seek further information, and then to get only the information that the industry decides to include on their website.

Warning labels are relatively well supported by the public (12, 14, 15), often more so than other alcohol controls. While questions remain over whether warning labels increase knowledge and awareness of alcohol problems, alcohol

warning labels are also advocated for from a consumer protection and right to know principle. In comparison with other consumer products with known harms (e.g. poisons, cigarettes), labelling requirements on alcohol products in many countries have been negligible or non-existent.

While there is no evidence warning labels will reduce alcohol-related harms on their own, they may be a significant part of a broader approach to reducing alcohol-related harm. Furthermore, part of their effectiveness is related to their visibility; current warnings are often small, hard to read, and do not stand out from other information on the label. Making labels larger and clearer (12, p. 433) makes it more likely they will have an effect in raising awareness of harms. Furthermore, since one study suggested that there was no further increases in awareness, recognition, or recall of the single US warning label message after 3.5 years (16), rotating warning messages may help reduce message fatigue or habituation.

Public education and social marketing campaigns

Another approach to providing information on the potential risks and harms of alcohol consumption to the general population is to use the mass media, such as TV, radio, billboards, newspapers, and magazines. When these campaigns adopt advertising principles and techniques they are known as social marketing campaigns (17). Unlike other public information initiatives such as drinking guidelines and warning labels, social marketing campaigns focus more on persuasion than on presenting straightforward factual information. A recent example is the Australian government's

national binge drinking campaign which used the key tagline message 'Don't turn a night out into a nightmare' (18).

There is little evaluation literature on social media and public information campaigns. A review by Wakefield and colleagues (19) identified four review articles which included mass media campaigns targeting alcohol use, although one review included no studies of mass media campaigns only. The authors concluded there was little evidence of effects of mass media campaigns in reducing alcohol use, although those targeting drink driving may have had greater success. The authors pointed out that the wide availability and marketing of alcohol, as well as positive social norms about alcohol use, were all forces competing with mass media campaigns to influence the public's alcohol use. The authors highlighted that because many social marketing campaigns go beyond public information campaigns and include community and school programmes, identifying the effectiveness of mass media campaigns in isolation is challenging.

In some cases, the alcohol industry has included social messages on their products. Messages are often ambiguous in strategy or promote the product further. For example, ads for Absolut Vodka provide the message 'Enjoy with Absolut Responsibility'. There is little research on industry initiatives, and what there is suggests that industry-funded initiatives can lead to positive views about alcohol and the alcohol industry (20, p. 2237).

School-based prevention programmes

Perhaps because adolescence is a time when many young people, particularly in Western societies, first begin to use

alcohol, there are many school-based education programmes about alcohol use and other drugs. School-based prevention programmes use a prevention curriculum developed for and delivered to school students with the aims of delaying the age of first alcohol use, minimizing alcohol use, or minimizing harms related to alcohol use (5). School-based prevention programmes are broadly grouped into two types: those which target developing psychological and social skills and those which aim to increase awareness of harms related to alcohol use. Over the last three decades, programmes have increasingly been about developing social skills, for instance, in refusing an offer of alcohol, rather than purely informational (5).

While there is a large evaluation literature on school-based programmes, there is little evidence that they are effective at preventing alcohol-related harm (5). One recent Cochrane review (21) of randomized control trials found some evidence of effects. The review found 53 randomized control studies of school-based prevention programmes, the majority of which (n = 41) evaluated programmes delivered in the United States. Students were aged between five and 18 at the time the programmes begun. The programmes were all universal, meaning they were delivered to all students in a year level, or school, rather than only to those who were identified as high risk. The majority of the programmes were generic, that is, they targeted a range of risky behaviours including, but not limited to, alcohol use. The remainder of the programmes focused solely on alcohol use. The outcome measures reported in the review were alcohol consumption, rather than indirect

measures of awareness or knowledge of alcohol-related harms, although these were often included in individual studies.

While many school-based programmes showed no effects on drinking behaviour, the authors concluded that some generic school-based programmes can be effective at reducing risky drinking. The authors point out that generic programmes have the additional benefit of potentially impacting on other risky behaviours beyond alcohol use (such as antisocial behaviour). Why generic programmes may be more effective than alcohol-specific programmes was not elaborated on.

The content of the school prevention programmes was not reported in individual studies in adequate detail for the authors to make claims about effective programme content, although programmes which focused on psychosocial and skill development, rather than those that concentrated on purely creating awareness, may be more likely to be effective. The authors summarize: 'It is not clear why some prevention interventions seem to work in some studies but not in others, so further investigation of the specific content of prevention programmes, and the context of their delivery, is warranted, so that clear recommendations regarding the transfer of particular prevention interventions to new settings can be made' (21, p. 14). Further research could work towards identifying specific content or implementation context for delivering effective programmes.

The significant findings of the study are, however, modest. For example, from the 39 studies of generic school-based prevention programmes, 14 found significant reductions in alcohol use, while 24 found non-significant differences

between intervention and control groups, and one found a negative effect of the intervention programme. Babor et al. (5) point out that many school-based programmes which are found to be effective go beyond the classroom in providing education; they often include programmes working within communities, and with parents and families, and thus whether school-based only programmes are effective is not always clear. The review by Foxcroft (21), however, was limited only to interventions occurring in schools, and thus provides better evidence on the potential effectiveness of school-based programmes. There is thus some evidence that school-based programmes can be effective, although many programmes are not. In particular, programmes which provide development of generic social skills have the best evidence for effectiveness.

Conclusion

Public information and education strategies are based on the principle that people will drink less if they are given information or persuaded to do so. While there is very little evidence that these strategies affect drinking behaviour, they can influence public awareness and knowledge of alcohol-related harms. The impacts are likely to be increased with greater efforts at dissemination and presentation. The strategies may contribute to preventing alcohol-related harm indirectly by increasing support for alcohol control policies (22), changing social norms about the place of alcohol in society, and providing information to consumers about harms associated with alcohol. Future research could examine the effects of alcohol warning labels beyond the US experience, and examine the content of effective school-based prevention

curriculums and characteristics of public information and dissemination campaigns which have shown positive effects.

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Chapter 48
Towards a global alcohol policy: current directions

Harry Burns

Why pursue a global policy on alcohol?

The factors which drive alcohol consumption in any society are complex and often poorly understood. What is clear, however, is that the problems caused to most countries through inappropriate alcohol consumption are significant. Any government which attempts to introduce measures to control or influence the supply or affect the demand for alcoholic beverages in its population will usually face opposition from the public and, usually, it will also have to deal with well-orchestrated attempts from the alcohol industry to prevent implementation of any controls on its activities.

The range of policy options open to a government intent on reducing societal harm from alcohol is considerable and the measures it chooses need to be both effective and acceptable to the population. These measures will usually consist of a mix of education, treatment programmes, and alcohol control and harm-reduction strategies (1). The World Health Organization (WHO) states that:

A national alcohol policy will be made up of a set of individual policies, strategies, and implementing actions. There are also a variety of other policies which impinge on alcohol-related problems, increasing or reducing them, but

which are neither normally described as alcohol policies nor normally included within an overall alcohol policy, since the policies are not adopted or implemented with the minimization of alcohol problems as a primary aim' (2).

Alcohol policy, therefore, can be seen as a complex arrangement of interventions which affect many sectors of society. If governments are to have confidence take difficult decisions, they need to be reassured that the policies they choose have an evidence base and have been implemented successfully elsewhere. There is, therefore, an important role for a globally agreed set of policy recommendations. There is a role for a global partnership for sharing experience and learning across countries. Perhaps the most important reason for globally agreed policies on alcohol is the momentum for alcohol control that can be created as countries across the world are seen to move in step. That is perhaps the greatest reassurance which politicians can have when adopting potentially unpopular policies.

This chapter will consider some of the many and complex factors which have shaped alcohol policy in different parts of the world, how international consensus on alcohol policy is evolving, and it will also touch on prospects for further concerted action on alcohol.

The factors causing divergence in alcohol policy

The policy approaches adopted by different countries when tackling alcohol problems are influenced by social, cultural, geographical, and economic factors (3).

Social and cultural influences on alcohol policy

For many, if not most, countries throughout the world, alcohol plays a significant role in the social affairs of the majority of the population. For most drinkers, alcohol does not create problems and most societies would consider complete prohibition of alcohol consumption to be an unreasonable intrusion on personal choice. However, in countries experiencing the adverse consequences of irresponsible and excessive drinking—and that means most countries—policies to control consumption are more acceptable. The nature and intrusiveness of alcohol policy, therefore, will depend on the pattern of consumption of the particular society as well as the degree of damage which alcohol is causing to the population.

For several countries, the most significant social influence on alcohol consumption is religious in nature. Several Islamic countries have complete or partial bans on alcohol use. WHO reports that a total ban on alcohol use exists in Afghanistan, Brunei Darussalam, the Islamic Republic of Iran, Maldives, Mauritania, Pakistan, Saudi Arabia, Somalia, and Sudan. Four other countries report partial bans—Bangladesh, Comoros, India (in five states), and Qatar (4).

The importance of geography

The geographical situation of countries is an important consideration in public attitude to alcohol. Countries which produce the raw materials for different forms of alcohol will have employment and economic reasons for protecting use of locally produced alcohol. Europe is a clear example of the

importance of geography influencing consumption. The southern countries, with extensive grape cultivation and wine production, have different patterns of consumption from northern Europe where grain cultivation is more important and, as a result, beer and spirits industries have, historically, been more prevalent.

Geography and, in particular, climate, also appear to be predictive, to a degree, of social attitudes to alcohol. Sunnier, southern European countries experience different consumption pattern to the colder, darker, wetter northern countries. Consequently, the different drinking habits seen across Europe tend to be reflected in the different attitudes to policy in place in north and south.

Economic considerations

There are a considerable number of studies examining the economic impact of alcohol consumption on society. Typically, these studies attempt to demonstrate the costs to governments and individuals. Rehm and colleagues (5) examined costs attributable to alcohol consumption in four high-income countries and two middle-income countries. These costs ranged from 1.3% to 3.3% of gross domestic product. In economically difficult times, such costs are considerable and will influence public support for controls on alcohol. How strongly that support is expressed will depend on the type of control policy which is proposed.

The economic importance of alcohol has already been mentioned in the context of income to farmers and the alcohol producers. Globalization of trade and the creation of large collaborative economic entities such as the European Union

(EU) are other major influences on consumption and consumer attitudes. Opening of markets and abolition of trade barriers have been powerful drivers towards the liberalization of economic controls over the sale of alcohol. The Single European Market aligned with growing consumerism was associated with significant changes in the alcohol regulation policies of many countries (6). Often, governments respond to these economic drivers by loosening alcohol controls, particularly on its import and export and the break-up of wholesale monopolies. Laws which support freedom to trade give the alcohol industry considerable influence over policies aimed at controlling consumption of their products.

The different drivers of consumption make the task faced by government complex, and hence unified policy approaches across countries have been difficult to develop.

Patterns of policy implementation

There are a few policy areas from which most of the attempts to control consumption are formed. However, there is wide variability in how they are applied in different countries.

Restrictions on availability

In the past, control of alcohol consumption has often meant prohibition of sale or consumption of alcohol. However, most societies will include people who rarely drink or who drink in moderation, as well as those who drink to excess and harm their health. Policies based on prohibition are, therefore, seen as infringing people's rights to consume alcohol in moderation, a habit which some might argue to have health

benefits. In most Western countries, policies are now aimed at reducing the misuse of alcohol, not its use. There is evidence that this harm reduction approach is at least as effective as more draconian approaches to control of alcohol consumption (7).

Most member states of WHO report restrictions on availability of alcohol on the basis of age. This is seen as a highly effective way of reducing harm (8). In most countries, the age at which alcohol can be purchased is 18 but ranges from 15 (Angola) to 25 (Nepal). A small number of member states report no age limits for the sale of alcohol (4).

Around 65% of countries have laws to control the production or sale of alcohol through a licensing arrangement. This type of intervention seems effective in reducing consumption (8). Some prohibit sale of alcohol in petrol stations and some restrict the sale of alcohol to government outlets. Some countries limit the density of alcohol outlets although such policies seem uncommon (4).

Control by pricing

There is clear evidence that, as the price of alcohol rises, consumption falls (7). The WHO *Global Status Report on Alcohol and Health 2011* (4) contains calculations of the amount of tax levied on one litre of pure alcohol in 74 countries. The average percentage of cost levied as tax was 17.3% but it varied from 0.3% in Kyrgyzstan to 44.9% in Norway. Scotland is currently considering introducing a requirement to charge a minimum price for alcoholic beverages depending on the number of units of alcohol contained in each bottle. Price is thus directly related to the

alcohol content of the drink. Low-alcohol drinks would cost less than cheaply sold high-alcohol drinks. Few countries regulate promotion of alcohol sales at below cost pricing. This marketing strategy sees retailers, usually supermarkets, sell alcohol often on a 'two for the price of one' basis in order to increase footfall in stores.

Alcohol and driving

Blood alcohol concentration (BAC) is the percentage of alcohol by volume in the bloodstream. Driving ability begins to be impaired at a BAC of 0.04% (9). Enforcing maximum BACs for drivers with breath testing can reduce alcohol-related accidents by approximately 20%, and are highly cost-effective (10–12). Also, many countries set lower permissible BACs for young drivers in an effort to reduce crashes in a particularly vulnerable group (13).

In a survey of maximum permissible BAC in 133 countries, the highest allowed level for drivers in most countries is either 0.05% (in 52 countries) or 0.08% (in 46 countries). Fourteen countries allow no permissible BAC for drivers, whereas 24 countries set no limits. Only 18 countries set a lower limit of alcohol for young and new drivers. Of these, eight countries (Australia, Croatia, Fiji, Germany, Palau, Slovenia, the former Yugoslav Republic of Macedonia, and the United Republic of Tanzania) have zero tolerance policies, which prohibit young drivers from having any detectable alcohol in their blood. Austria permits only 0.01% BAC for young drivers. Bulgaria, Greece, Latvia, Lithuania, the Netherlands, and the United States set the maximum BAC

at 0.02%. New Zealand and Spain allow 0.03% for young and new drivers while Canada sets the limit at 0.04% (4).

Some countries have a policy of random screening of drivers. In Australia any driver stopped for whatever reason, is given a breath test. In the United States, on the other hand, breath tests are administered only if the use of alcohol is suspected after the driver has been stopped for another reason. There is evidence to suggest that random breath tests on drivers have a deterrent effect on drinking and driving and a consequent reduction in accidents.

Advertising and sponsorship

A wide range of measures are in place in different countries to control efforts by the alcohol industry to market their products. Many countries rely on the industry to regulate its advertising and marketing efforts. In Europe, the European Forum on Responsible Drinking is an alliance of European alcohol companies which seeks to promote responsible drinking among consumers as well as encouraging industry to adopt responsible advertising standards.

Many countries have partial or complete bans on advertising. The French alcohol and tobacco law bans the advertising in cinemas or on television of all alcoholic beverages containing more than 1.2% alcohol by volume. There are stringent regulations banning sponsorship of sporting events by alcohol producers. The content of advertisements is also controlled to prevent young people being specifically targeted and health warnings are included on advertisements. WHO has reviewed marketing controls in a number of countries in surveys carried out in 2002 and 2008. They found an increase in the number

and extent of advertising and sponsorship restrictions in a number of countries.

Although countries differ in the pattern of alcohol consumption and the societal influences which drive it, there are a number of common themes which have emerged in their policy responses to alcohol.

Attempts to create an international consensus through research

As governments have responded to the challenge of inappropriate alcohol consumption by developing public policy, the research community has been working in parallel to develop an evidence base for such policies. The research effort effectively began with the publication in 1975 of *Alcohol Control Policies in Public Health Perspective* (14). This book was a collaboration of researchers from several countries brought together by the European office of WHO. One of the principal and most controversial conclusions of this work was to recommend that efforts should be made to control the average level of consumption of alcohol across the whole population rather than simply tackling consumption of problem drinkers. It also highlighted the important leadership role of governments and international agencies in the development of effective alcohol control policies.

WHO continued to support the efforts of the group responsible for developing its 1975 report. The International Study of Alcohol Control Experiences (ISACE) published in 1981 set out to establish the epidemiology of alcohol consumption in Europe and North America. ISACE studied

trends in consumption and how policies to control consumption were affecting those trends (15–17). The project focused on activity in alcohol control in seven countries: Finland, the Netherlands, Poland, Switzerland, Ireland, Canada, and the United States. It found that consumption patterns varied between the studied countries and estimated the prevalence of problems arising
from consumption of alcohol. The study reached interesting conclusions about the policy effectiveness. Basically, it suggested that governments had not realized the importance of prevention and were still focused on managing problem drinkers rather than on influencing average levels of consumption across the population. Further international collaborations have studied the involvement of community organizations in managing problem drinking (18, 19) and the development of new health care strategies for the management of alcohol dependence (20).

In 1994, a review of the evidence on policy effectiveness in a number of areas was commissioned, again by WHO. *Alcohol Policy and the Public Good* (21) considered evidence on the effectiveness of taxation, environmental control measures, alcohol and driving controls, as well as education in schools, community action programmes, and treatment interventions.

The review offered two major conclusions:

♦ Public health measures of proven effectiveness are available to influence the consequences of alcohol use.

♦ Policy-makers should design policies to influence per capita alcohol consumption across the whole population while also targeting problem drinkers and their behaviours.

A number of studies have been published more recently which have examined the role of the alcohol industry in changing patterns of consumption.

Jernigan (22) concluded that globalization and deregulation of markets had allowed the alcohol industry to influence the pattern of alcohol supply and consumption in developing countries. Indigenous low-alcohol drinks were often replaced by higher-alcohol international brands. International trade agreements were found to impede efforts to control alcohol consumption by restricting supply. Trade agreements, by their nature, seek to make commodities freely available to consumers while alcohol control policies will seek to impose control on availability (23). The report concluded that public health issues were rarely considered in constructing trade agreements.

Studies of alcohol consumption patterns, its consequences, and evidence of effective control policies have been instrumental in supporting policy development over the past three decades. Babor (1) reviewed these studies and identified the key themes emerging from the literature. They were:

1 Alcohol policies that limit access discourage driving under the influence, and lowering the legal purchasing age is likely to be effective in reducing harm.

2 Health care systems have a major impact on alcoholism treatment and health outcomes.

3 Individual approaches to prevention are less effective than population-based approaches.

4 Public policy on alcohol is rarely dictated by scientific evidence, despite major advances in the understanding of drinking patterns, alcohol-related problems, and policy interventions.

5 There seems to be a fundamental incompatibility between the economic and political values of free trade, which encourages open access to alcohol on the one hand, and public health values on the other hand.

Babor suggested that alcohol policies are based on a combination of four factors: political expediency, commercial interests, common sense, and public safety. He expressed the view that scientific research is perhaps the most important, but least influential, factor in minimizing or preventing alcohol-related problems. This opinion is perhaps too negative in its view of the significance of research. An understanding of the epidemiology of alcohol-related harm together with the descriptive studies of the impact of different interventions aimed at controlling that harm has arguably driven governments to enact appropriate policies. What is clear is that international collaboration in research was key to the production of effective policy.

Attempts to create an international consensus on policy

The role of WHO

In concert with the development of an international research and evidence base on effects of alcohol use, a number of attempts have been made to establish the policy basis for concerted action on alcohol across international borders. Just

as it was instrumental in supporting the research effort, WHO has been at the heart of these efforts and the European region of WHO has been particularly prominent in efforts to gain a consensus across European states. Several WHO strategies have been published in the past decades but WHO has been more active in this area since the early 1990s.

Its documents acknowledge the importance of alcohol as a substantial threat to the health of both individuals and wider society. They recommend the strategies most likely to mitigate alcohol-related harm. The problem seems to be achieving widespread adoption of those strategies.

Health for All

Health for All was launched in 1979 by WHO in collaboration with its member states. It would be no exaggeration to say that Health for All has been one of the most influential programmes ever introduced by WHO. It offered a vision of health and well-being for people around the world (24) and it continues to influence international public health ambition. It became the basis for WHO's primary health care strategy to promote health, human dignity, and enhanced quality of life.

It was not primarily a document about alcohol. It had a much wider scope. It identified a number of health challenges facing the world over the succeeding decades and sought to encourage equity in health by recommending ways of tackling them. In 1998, perhaps recognizing that progress had been less rapid than hoped for, the European Region of WHO produced a new strategy for Europe in a document entitled *Health21: an introduction to the health for all policy*

framework for the WHO European Region (25). This Declaration identified 21 targets for the twenty-first century. Target 12 of this declaration is aimed at reducing harm from alcohol, drugs, and tobacco. It urged that: 'by the year 2015, the adverse health effects from the consumption of addictive substances such as tobacco, alcohol and psychoactive drugs should have been significantly reduced in all member states'.

Health21 encouraged member states to embrace the principles and recommendations of the European Charter on Alcohol and the European Alcohol Action Plan.

European Charter on Alcohol

In 1995, a meeting of experts, convened by WHO in Paris, considered the ethical principles and goals that countries might use to develop comprehensive alcohol policies and programmes for protecting the health and well-being of all citizens (26). These principles included statements on the rights of individuals and families to protection from the harmful effects of alcohol and its societal consequences. This was published as the European Charter on Alcohol. The Charter details ten strategies for alcohol action. Strategies ranged from encouraging better education of the population and training of professionals to legislative and economic actions aimed at restricting access to alcohol and managing behavioural consequences of consumption. For each of these strategies, countries were asked to consider the nature of the alcohol-related problems they faced and so determine which actions would prove to be most applicable and effective given the local situation.

European Alcohol Action Plan

An important step in encouraging action on alcohol in European countries was the European Alcohol Action Plan (EAAP). This plan was launched in 1992 and has been updated subsequently
(27). The 1992 plan identified alcohol-related harm as a particular problem for Europe, which it identified as having the highest alcohol production, export trade, and consumption in the world.

The aim of the 1992 plan was to '… help Member States prevent the health risks and social consequences arising from alcohol use. To achieve this, two things are needed: a reduction in overall alcohol consumption and measures to combat high-risk behavior'. In setting this as its aim, it was reflecting the emerging consensus on the most effective strategies. It set out a bold statement of intent:

Reducing the harm that can be done by alcohol is one of the greatest public health challenges facing the European Region of WHO. Ways of taking up this challenge are well known. What is needed now is to exercise political will, to mobilize civil society and carry out systematic programmes in every Member State. The European Alcohol Action Plan, by outlining effective actions which will result in clearly identified outcomes, creates a European movement to reduce the harm that can be done by alcohol and to promote health and wellbeing across the Region (28).

The EAAP during the period 1992–1999 was to encourage member states of the European region of WHO to develop and implement policies aimed at achieving a significant

reduction in consumption of alcohol and a consequent reduction in health damage. The Plan suggested an action plan which involved consideration of areas such as public policy, health promotion, primary health care, support systems, and international cooperation. The WHO Regional Office also provided a support network to assist in implementation of the plan in each member state.

The EAAP was updated in 2000 (28). The 2000 version detailed action to be adopted during the 2000–2005 period. It also reported a study carried out in 1998 of how countries had implemented the recommendations of the 1992 plan. Based on questionnaire responses from 33 countries spread over Europe, the main findings were that over half of the countries had a national alcohol action plan and a coordinating body responsible for its implementation. Young people and drink drivers were the main target groups of programmes.

The most effective strategies were rigorous rules concerning the marketing of alcohol, tax increases directed at prevention, and, in some countries, stricter drink driving regulations. Intensive marketing by alcohol and hospitality industries seemed to be preventing effective implementation of harm reduction strategies.

Of those countries where data were available at the time of the review, 11 had seen a decrease in per capita consumption and three (Italy, Poland, and Spain) had achieved the European target of a 25%-reduction, but 11 countries had experienced an increase in consumption since 1992. UK consumption remained steady during this period.

The updated plan argued that there is no single policy that could or should be applied across all European states, and therefore emphasis was placed on the actions most likely to reduce the harm caused by alcohol in particular countries depending on the nature of the alcohol-related problems they faced. The overall objectives of the 2000–2005 EAAP were:

♦ Generate greater awareness of, provide education in, and build up support for public health policies that address the task of preventing the harm that can be done by alcohol.

♦ Reduce the risk of alcohol-related problems that may occur in a variety of settings such as the home, workplace, community, or drinking environment.

♦ Reduce both the breadth and depth of alcohol-related harm such as fatalities, accidents, violence, child abuse and neglect, and family crises.

♦ Provide accessible and effective treatment for people with hazardous and harmful alcohol consumption and those with alcohol dependence.

♦ Provide greater protection from the pressures to drink for children, young people, and those who choose not to drink alcohol.

Declaration on Young People and Alcohol

Adopted by EU countries in 2001, the Declaration on Young People and Alcohol aims to protect children and young people from the pressures to drink and reduce the harm caused directly or indirectly by alcohol (29).

The Declaration reaffirms the five principles of the European Charter on Alcohol. In addition, the Declaration sets a number of targets that it recommended should be achieved in member states by 2006. It advocates promotion of a mix of alcohol policy measures in the four broad areas of protection, education, supporting healthy drinking environments, and harm reduction. It establishes four broad processes necessary to implement the strategies and achieve the targets. These involve partnerships with young people aimed at developing a comprehensive approach to protection from the effects of alcohol while harnessing political commitment to the creation of supportive environments which allow sensible use of alcohol. The importance of international cooperation in supporting the development of policies to prevent harm to young people is again reaffirmed.

Other policy organizations

WHO has been the key advocate for international consistency in alcohol policy. However, a number of non-governmental organizations (NGOs) have emerged over the years to support the development of new solutions to the problems caused by alcohol. One of the best known is the Global Alcohol Policy Alliance (GAPA). This organization developed from a meeting of alcohol experts and activists held in 2001 in the United States. This meeting identified an urgent need to understand and monitor the marketing strategies undertaken by the global alcohol industry in its attempts to increase sales of its products. The tactics used by the industry to circumvent attempts at health promotion policies was recognized as an area for study. The experts felt that, with a sharing of scientific knowledge and expertise, they could become a

resource in helping governments formulate strategies to counter the health and social problems created by alcohol consumption. Its mission statement is 'to reduce alcohol-related harm worldwide by promoting science-based policies independent of commercial interests' (30).

Member organizations are involved in advocacy and research, as well as in the provision of information and training on alcohol issues, and the provision of services for people whose lives are affected by alcohol-related problems.

Eurocare is a member of GAPA and of the European Public Health Alliance (EPHA). It participates in the European Commission's Health Policy Forum and is a founding member of the European Alcohol and Health Forum. Its stated goal is to raise awareness among European national and regional decision-makers of the harms caused by alcohol and to ensure that these harms are taken into consideration in all relevant EU policy discussions. It also acts to promote the development and implementation of evidence-based policies aimed at effectively preventing and reducing this burden. It comprises almost 50 organizations in 21 countries in Europe, together with some supranational organizations. An important principle for Eurocare is that it does not accept funding from the alcohol industry or any of its associated organizations. Since its formation, Eurocare has carried out a number of studies and published reports on a range of topics on alcohol policy in the EU.

Other bodies associated with GAPA include an equivalent organization in India, the Institute of Alcohol Studies in the UK, and institutions in the United States including the American Medical Association.

These organizations, like WHO, have emerged and operate in response to the challenge of alcohol around the world. They are part of a consensus on the harms experienced by individuals and society at large as a result of inappropriate use of alcohol.

Concerted action on alcohol—is it feasible?

Inappropriate use of alcohol undoubtedly damages health, economic performance, and disrupts families and wider society. There is a broad consensus in the research community as to the effectiveness of policies likely to control alcohol misuse. Internationally, most countries have, at least, some policies in place. Alcohol causes problems, there is evidence as to what can be done about it and there is some acceptance in countries as to the need to act. By moving in step on policy development, governments could enhance public acceptance of alcohol control policies and generate momentum in tackling alcohol-related harm. WHO has provided consistent and important leadership in development of alcohol policy for more than 30 years. It continues to do so and such leadership is essential.

In September 2011, The *European action plan to reduce the harmful use of alcohol 2012–2020* was agreed at the WHO Regional Committee meeting in Baku, Azerbaijan. It follows the structure of previous WHO documents by providing an overview of the current problems in Europe due to alcohol and the policy options likely to reduce them. It points out that alcohol probably accounts for a difference of six years in life expectancy when comparing western and eastern European men aged 20–64 in 2002. It provides commentary on the

harms caused to people other than the drinker, whether through violence and injury in the domestic or public situation.

The action plan goes on to emphasize the policies which have the strongest evidence base. It points to the efficacy of taxation, restrictions on outlet density, on hours of sale, and minimum purchase age. It recommends lower blood alcohol levels for driving and random breath testing; and brief counselling programmes and treatment for alcohol use disorder.

Finally, it calls for leadership in tackling alcohol-related harm.

While Europe can take some satisfaction from the work carried out in research and policy development by international agencies and individual countries, the action plan points out that every country will benefit from reviewing, adjusting, and strengthening their strategies. The *European action plan to reduce the harmful use of alcohol 2012–2020* calls on European society to work together to implement the five main objectives of the plan which build on previous European plans, and support the WHO global strategy on alcohol to raise awareness burdens of alcohol misuse and the action required to deal with it.

This plan represents an opportunity for the international community to support a highly evidenced-based set of recommendations. For 30 years, countries have been counting the cost of alcohol-related harm. WHO and a range of NGOs have advocated a variety of remedies. There has been steady refinement of the science and the effective interventions are

broadly agreed. Governments should recognize that, by working together and with WHO, they will find it easier to implement policies which, though perhaps unpopular, will be effective in minimizing the consequences of inappropriate alcohol consumption. The *European action plan to reduce the harmful use of alcohol 2012–2020* offers a real opportunity for concerted global action.

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