Edited by Andreas Marneros
and Frederick Goodwin

Bipolar Disorders

Mixed States, Rapid Cycling and Atypical Forms

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Mixed States, Rapid-Cycling, and Atypical Forms

Bipolar disorder manifests itself in a variety of forms. It can coexist with other psychiatric conditions, and treatment efficacy can depend on the type of bipolar state. This book covers the full range of mixed states, rapid-cycling, and transient forms of bipolar disorder, from atypical and agitated depression to schizoaffective mixed states. The most recent ICD and DSM categories are covered, and the authors also look at the biology and genetics of bipolar disorder, along with issues relating to age (children and the elderly), comorbidity, choice of drug treatment, and investigational strategies.

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Mixed States, Rapid-Cycling, and Atypical Forms

Edited by

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Preface

Bipolar disorders have a long history. Mania and melancholia are the oldest terms and descriptions within psychiatry, having been created in Homeric times by the Greeks, and conceptualized by Hippocrates and his school 2500 years ago. Aretaeus of Cappadocia put melancholia and mania together, because he recognized both psychopathological states as parts of the same disease, thereby giving birth to the bipolar disorders. His formulation stressed that, while mania has various phenomenological manifestations, nevertheless all of these forms belong to the same disease. Some of these special forms of bipolar disorder that are of major clinical and research relevance are the topic of this book.

Even though the three groups of bipolar disorders – mixed states, rapid-cycling, and atypical bipolar disorder – were well known by the nineteenth century, interest accelerated after the psychopharmacological revolution in the middle of the twentieth century. Thus the importance of defining rapid cycling was made clear by the observation that the response to lithium treatment was poorer in patients experiencing four or more episodes per year. The "rediscovery" of mixed states, which were conceptualized by Emil Kraepelin and Wilhelm Weygandt at the end of the nineteenth century, was also associated with problems concerning treatment with antidepressants and mood stabilizers. It has been half a century since the start of the pharmacological revolution. Its consequences across all fields of psychiatry have been enormous: biological research and genetics, treatment and prophylaxis, clinical and prognostic research, and psychopathological and diagnostic approaches. Furthermore, the way our culture views mental illness has been profoundly influenced by this revolution, and the lives of our patients are much better for it.

This book synthesizes valuable knowledge from the past, integrates it with new insights from the modern era, and looks to the future of mixed states, rapid-cycling, and atypical bipolar disorders. The editors would like to thank all contributors and supporters, especially Lilly Germany, for supporting this edition.

1

Bipolar disorders beyond major depression and euphoric mania

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Introduction: knowledge from the past, goals for the future

The last five decades have brought essential changes and developments in psychiatry. One of the most important reasons for these developments is certainly the psychopharmacological revolution. The discovery of antipsychotics, antidepressants, mood stabilizers, and other psychotropic substances has had an enormous impact, not only on many fields of research, treatment, social life, and social politics, but also on ideological aspects and attitudes. Concerning psychiatric research, the psychopharmacological revolution has been an important and sustained stimulus not only for the development of neuroscience, genetics, and pharmacology, but also for psychiatric methodology, the development of new diagnostic concepts, and new research on treatment, prognosis, and rehabilitation. One indirect but fundamental development was the rediscovery and rebirth of old diagnostic, nosological, and phenomenological concepts. For example, new pharmacological experiences led to the rediscovery of the relevance of the unipolar–bipolar dichotomy. The concepts examined by Falret (1854), Baillarger (1854), Kleist (1929, 1953), Neele (1949), Leonhard (1957), and others were confirmed in the new psychopharmacological era, including the nosological refinements made by Jules Angst (1966), Carlo Perris (1966), Winokur and Clayton (1967), and others. But soon the enthusiasm for the new psychopharmacology gave way to an increasing awareness of some limitations. Within broadly defined diagnostic groups like schizophrenia, depression, and bipolar disorder, many patients proved to be non-responders or partial responders. The identification of such non-responder groups and their careful investigation showed some special or atypical features, like coexistence of manic and depressive symptoms or schizophrenic and mood symptoms (depressive and manic), as well as rapid changes of mood states or rapid onset of episodes. As a result, the

old concepts of mixed states, schizoaffective disorders, rapid cycling, cyclothymia, atypical depression, and others underwent a rebirth (Goodwin and Jamison, 1990; Marneros, 1999, 2001; Marneros and Angst, 2000; Angst and Marneros, 2001). But some of the rediscovered psychopathological states – although very well described – are still *terra incognita* and a source of confusion for many psychiatrists. Thus, more educational efforts are needed. This book summarizes our current knowledge on these atypical forms, and makes suggestions for much needed additional research.

Mixed states

The ancient times

The early descriptions and roots of mixed states are very closely connected with the history and development of concepts regarding bipolar disorders. These concepts have their roots in the work and theories of the Greek physicians of the classical period, especially of the school of Hippocrates and, later, of the school of Aretaeus of Cappadocia (Marneros and Angst, 2000; Angst and Marneros, 2001; Marneros, 2001).

Hippocrates based his work partially on the views of Pythagoras and his scholar Alcmeon and partially on the views of Empedocles. Like Alcmeon, Hippocrates (Fig. 1.1) thought that the origin of mental diseases lay in the disturbed interaction of body fluids with the brain. Affective pathological states, as well as psychotic states, are the results of illnesses or disturbances of brain functions. He wrote in *About the Sacred Disease*:

Εἰδέναι δέ χρή τούς ἀνθρώπους ὅτι ἐξ οὐδενός ἡμῖν αἱ ἡδοναί γίνονται καί εὐφροσύναι καί γέλωτες καί παιδιαί ἡ ἐντεῦθεν, καί λῦπαι καί ἀνίαι καί δυσφροσύναι καί κλαυθμοί. καί τούτῳ φρονέομεν μάλιστα καί βλέπομεν καί ἀκούομεν καί διαγιγνώσκομεν τά τε αἰσχρά καί καλά καί κακά καί ἀγαθά καί ἡδέα καί ἀηδέα, τά μέν νόμῳ διακρίνοντες, τά δέ τῷ συμφέροντι αἰσθανόμενοι, τῷ δέ καί τάς ἡδονάς καί τάς ἀηδίας τοῖσι καιροῖσι διαγιγνώσκοντες οὐ ταῦτα ἀρέσκει ἡμῖν. τῷ δέ αὐτῷ τούτῳ καί μαινόμεθα καί παραφρονέομεν, καί δείματα καί φόβοι παρίστανται ἡμῖν, τά μέν νύκτωρ, τά δέ καί μεθ ἡμέρην, καί ἀγρυπνίαι καί πλάνοι ἄκαιροι, καί φροντίδες οὐχ ἱκνεύμεναι, καί ἀγνωσίαι τῶν καθεστώτων καί ἀηθίαι. καί ταῦτα πά σχωμεν ἀπό τοῦ ἐγκεφάλου πάντα, ὅταν οὗτος μή ὑγιαίνη ...
People ought to know that the brain is the sole origin of pleasure and joy, laughter and jests, sadness and worry, as well as dysphoria and crying. Through the brain we can think, see, hear and differentiate between feeling ashamed, good, bad, happy ... Through the brain we become insane, enraged, we develop anxiety and fear, which can come in the night or during the day, we suffer from sleeplessness, we make mistakes and have unfounded worries, we lose the ability to recognize reality, we become apathetic and we cannot participate in social life. We suffer all those things mentioned

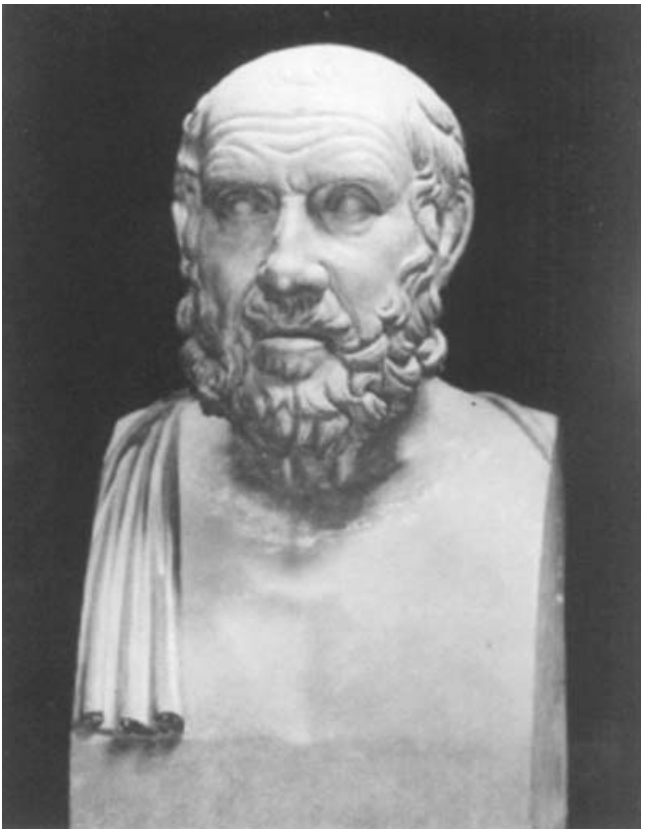


Fig. 1.1 Hippocrates (460–370 BC).

above through the brain when it is ill (Hippocrates, 1897: translation of original Greek and German quotations by Andreas Marneros).

Hippocrates also formulated the first classification of mental disorders, namely into melancholia, mania, and paranoia. He also described, together with the so-called Hippocratic physicians, organic and toxic deliria, postpartum psychoses, phobias, personality disorders, and temperaments. They also coined the term "hysteria." The ancient classifications and descriptions of mental disorders provided by Hippocrates and the Hippocratic school present a basis for broader definitions and concepts than the modern ones do. Some authors claimed that the concepts of mania and melancholia as described by Hippocrates (and also by Aretaeus and other Greek physicians) were different from the modern concepts. But this is not correct. The clinical concepts of melancholia and mania were broader than modern concepts – but not different. They included (according to modern criteria): melancholia or mania, mixed states, schizoaffective disorders,

Fig. 1.2 Aretaeus of Cappadocia (AD 81–138).

some types of schizophrenia, and some types of acute organic psychoses and atypical psychoses (Marneros, 1999; Marneros and Angst, 2000; Angst and Marneros, 2001). The similarities but also the differences between the ancient concepts and the modern ones, as well as the involvement of mixed states in these descriptions, can be illustrated by directly quoting the texts written at that time:

Hippocrates assumed long-lasting anxiety, fear (phobos) and moodiness (dysthymia) as basic characteristics of melancholia. He wrote: *"Ην φόβος καί δυσθυμίη πολύν χρόνον διατελέει, μελαγχολικόν τό τοιοῦτον." If anxiety (phobos) and moodiness (dysthymia) are present for a longer period, that is melancholia.*

Aretaeus of Cappadocia, one of the most famous Greek physicians, lived in Alexandria in the first century AD (Fig. 1.2). His dates of birth and death are not exactly known (some authors say he lived from around AD 40 to 90, others from AD 50 to 130), but he was a prominent representative of the Eclectics (Marneros

and Angst, 2000) who described a polymorphism of symptoms in melancholia as follows:

Τεκμήρια μέν οὖν οὐκ ἄσημα· ἢ γάρ ἥσυχοι, ἢ στυγνοί, κατηφέες, νωθροί ἔασι· ἔτι δέ καί ὀργηλοί προσγίγνονται ἀλόγως, οὐ τινί ἐπ᾽ αἴτιη δύσθυμοι, ἄγρυπνοι, ἐκ τῶν ὕπνων ἐκθορυβούμενοι.
The symptoms [of melancholia] are not unclear: [the melancholics] are either quiet or dysphoric, sad or apathetic. Additionally, they could be angry without reason and suddenly awake in panic (van Kappadokien, 1847).

Also, he described a phenomenological polymorphism of mania in Chapter 6 of his first book *On the Causes and Symptoms of Chronic Diseases* as follows:

Καί οἷσι μέν ἡδονή ἡ μανίη, γελῶσι, παίζουσι, ὀρχεύονται νυκτός καί ἡμέρης, καί ἐς ἀγορήν ἀμφαδόν καί ἐστεμμένοι κοτέ, ὅκως ἐξ ἀγωνίης νικηφόροι, ἐξίασι. ἄλυπος τοῖσι πέλας ἡ ἰδέη. Μετεξέτεροι δέ ὑπό ὀργῆς ἐκμαίνονται … ἰδέαι δέ μύριαι. Τοῖσι μέν γε εὐφύεσι τε καί εὐμαθέσι ἀστρονομίη ἀδίδακτος, φιλοσοφίη αὐτομάτη, ποίησις δῆθεν ἀπό μουσέων.
Some patients with mania are cheerful – they laugh, play, dance day and night, and stroll through the market, sometimes with a garland on their head, as if they had won a game: these patients do not worry their relatives. But others fly into a rage … The manifestations of mania are countless. Some manics, who are intelligent and well educated, deal with astronomy, although they never studied it, with philosophy, but autodidactically, they consider poetry a gift of muses (van Kappadokien, 1847).

The problem of the polymorphism of mania is also reflected in the writings of the Roman physician Caelius Aurelianus trying to describe the etymology of the word "mania". In his book *On Acute Diseases*. (Chapter 5), Caelius Aurelianus, a member of the Methodist school and student of the Soranus of Ephesos, gave at least six possible etymologies of the word "mania." The fact that he was able to do so demonstrated the many meanings of the term. He wrote:

The school of Empedocles holds that one form of madness consists of a purification of the soul, and the other of an impairment of the reason resulting from a bodily disease or indisposition. It is this latter form that we shall now consider. The Greeks call it *mania* because it produces great mental anguish (Greek *ania*); or because there is an excessive relaxing of the soul or mind, the Greek word for "relaxed" or "loose" being *manos*; or because the disease defiles the patient, the Greek word "to defile" being *lymaenein*; or because it makes the patient desirous of being alone and in solitude, the Greek word "to be bereft" and "to seek solitude" being *monusthae*; or because the disease holds the body tenaciously and is not easily shaken off, the Greek word for "persistence" being *monia*; or because it makes the patient tough and enduring, Greek *hypomeneticos*" (Caelius Aurelianus, translated by Drabkin, 1950).

The first descriptor of manic-depressive illness as one entity – one disease with two opposite symptomatological constellations – was Aretaeus of Cappadocia (Marneros, 1999, 2001; Angst and Marneros, 2001; Marneros and Angst, 2000). His descriptions of the boundless developments of melancholia into mania led to the thinking that there is not only a "switch" but also a "mixture" of symptoms. In his books: *On the Aetiology and Symptomatology of Chronic Diseases* and *The Treatment of Chronic Diseases*, he wrote: "*Δοκέει τέ δέ μοι μανίης γε ἔμμεναι ἀρχή καί μέρος ἡ μελαγχολίη*": "I think that melancholia is the beginning and a part of mania" and: "*οἱ δέ μαίνονται, αὐξῃ τῆς νούσου μᾶλλον, ἡ ἀλλαγῇ πάθεος*": "The development of mania is really a worsening of the disease [melancholia], rather than a change into another disease." And some sentences later: "*Ην δε ἐξ ἀθυμίης ἄλλοτε καί ἄλλοτε διάχυσις γένηται, ἡδονή προσγίγνεται ἐπί τοῖσι πλείστοισι· οἱ δέ μαίνονται*": "In most of them [melancholics], the sadness became better after various lengths of time and changed into happiness; the patients then develop a mania."

Ideas similar to those of Hippocrates and Aretaeus of Cappadocia were also presented by many other classical Greek and Roman physicians, such as Asclepiades (who established Greek medicine in Rome), Aurelius Cornelius Celsus (who translated the most important Greek medical authors into Latin), Soranus of Ephesos and his scholar Caelius Aurelianus (who extensively recorded the views of his teacher on phrenitis, mania, and melancholia), and later Galenus of Pergamos. All of these physicians focused their interest on mental disorders, especially melancholia and mania (Alexander and Selesnick, 1966; Fischer-Homberger, 1968).

From Heinroth to the psychopharmacological revolution

As Koukopoulos and Koukopoulos (1999) pointed out, the nosologists of the eighteenth century, such as Lorry, Boissier de Sauvages, and William Cullen, have already classified among the melancholias such forms as melancholia moria, melancholia saltans, melancholia errabunda, melancholia silvestris, melancholia furens, and melancholia enthusiastica, which are in fact "mixed". But the scientific description really began in the 19th century (Marneros, 2001).

Perhaps the first psychiatrist to systematically describe mixed states was the German professor of psychiatry Johann Christian August Heinroth (1773–1843). He was the first professor of "Mental Medicine" at *a German university (Leipzig)*. In his textbook *Disorders of Mental Life* (1818) he classified mental disorders into three voluminous categories:

The first category comprised the exaltations (hyperthymias). The second category embraced the depressions (asthenias), and the third category, the mixed states of exaltation and weakness (hypo-asthenias) (Heinroth used the

Table 1.1 Mixture of exaltation and depression according to Heinroth, 1818

Hyper-asthenias
First group: mixed mood disorders (*animi morbi complicati*)
1. *Ecstasis melancholica*
2. *Melancholia moria*
3. *Melancholica furens*
4. *Melancholia mixta catholica*
Second group: mixed mental disorders (*morbi mentis mixti*)
1. *Paranoia anoa*
2. *Paranoia anomala*
3. *Paranoia anomala maniaca*
4. *Paranoia anomala catholica*
Third group: mixed volition disorders (*morbi voluntatis mixti, athymia*)
1. *Panphobia, melancholia hypochondriaca*
2. *Athymia melancholica*
3. *Athymia paranoica*
4. *Athymia melancholico-maniaca*

German word "Mischung", which can be translated as "mixture"). This last category of mixed states was divided into mixed mood disorders (*animi morbi complicati*), mixed mental disorders (*morbi mentis mixti*), and mixed volition disorders (*morbi voluntatis mixti*), as shown in Table 1.1. It is evident that mainly in the categories "mixed mood disorders" and "mixed volition disorders," mixed affective and schizoaffective disorders according to modern definitions are involved.

In addition to the above-mentioned mixed states, Heinroth described the pure forms of exaltation (hyperthymias), including *melancholia erotica* and *melancholia metamorphosis*. *Melancholia saltans*, however, is defined by Heinroth as a form of mania (Fig. 1.3).

The French psychiatrist Joseph Guislain described in his book *Treatise on Phrenopathias or New System of Mental Disorders* (1838) a category of mixed states named "joints of diseases." To this category, he allocated "grumpy depression," "grumpy exaltation," and "depression with exaltation and foolishness," which also included "depression with anxiety." The first type, especially, features long episodes and an unfavorable prognosis (Guislain, 1838).

But the real author of what we today call mixed states is Emil Kraepelin (Fig. 1.4). He distilled, conceptualized, and categorized previous knowledge regarding mixed

Fig. 1.3 Johann Christian August Heinroth (1773–1843).

Fig. 1.4 Emil Kraepelin (*c.* 1900).

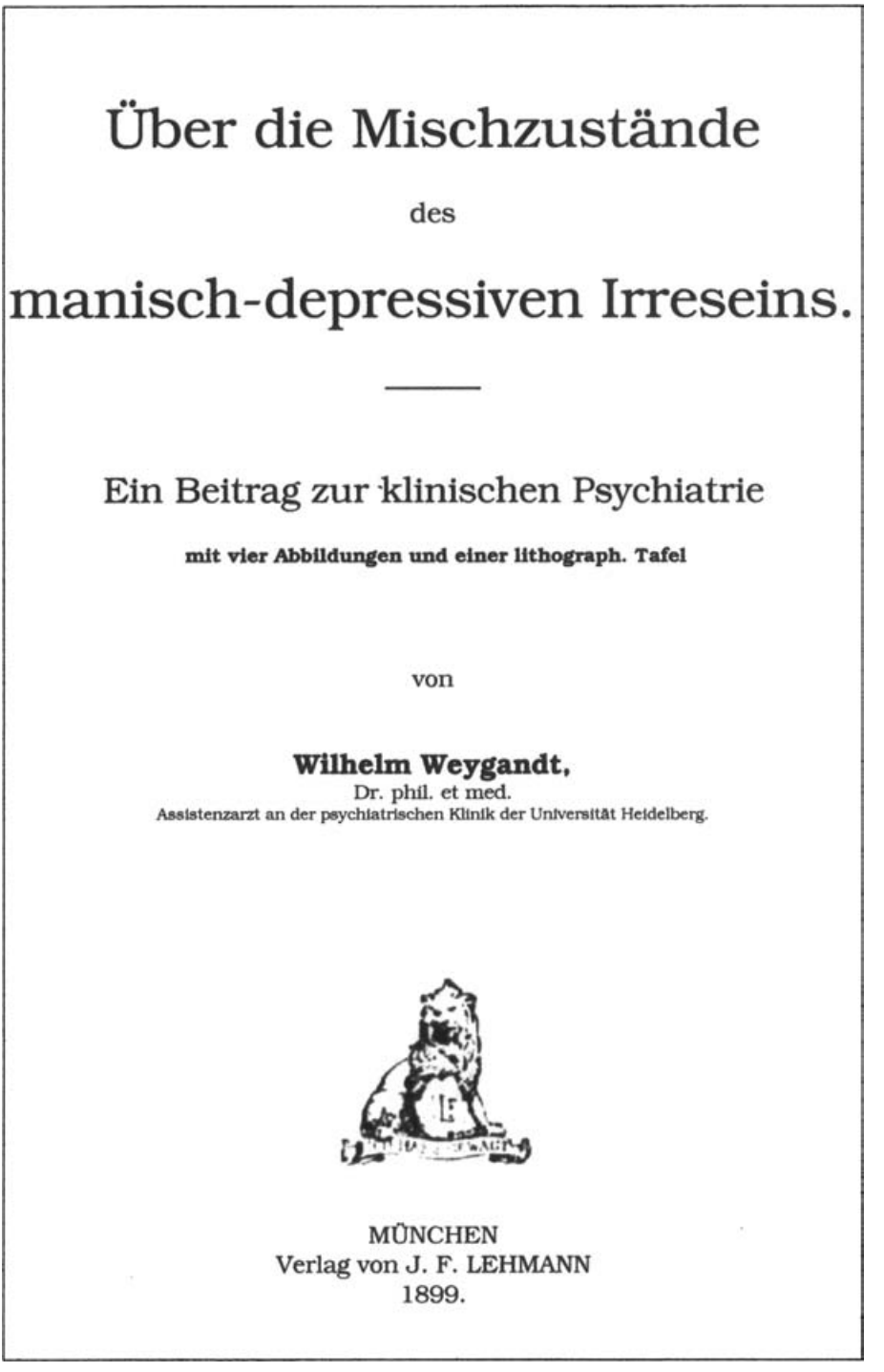
Table 1.2 The development of Kraepelin's concept of "mixed states"

1893	1899	1904	1913
1. "Manic stupor" (*manischer Stupor*)	1. "Manic state with inhibition" (*manische Zustände mit Hemmung*) 2. "Depressive states with excitation" (*depressive Zustände mit Erregung*)	1. "Furious mania" (*zornige Manie*) 2. "Depressive excitation" (*depressive Hemmung*) 3. "Unproductive mania with thought poverty" (*unproduktive gedankenarme Manie*) 4. "Manic stupor" (*manischer Stupor*) 5. "Depression with flight of ideas" (*Depression mit Ideenflucht*) 6. "Manic inhibition" (*manische Hemmung*)	1. "Depressive or anxious mania" (*depressive oder ängstliche Manie*) 2. "Excited depression" (*erregte Depression*) 3. "Mania with thought poverty" (*ideenarme Manie*) 4. "Manic stupor" (*manischer Stupor*) 5. "Depression with flight of ideas" (*ideenflüchtige Depression*) 6. "Inhibited mania" (*gehemmte Manie*)

states, as well as other mental disorders. Kraepelin used the term *Mischzustände* (mixed states) or *Mischformen* (mixed forms) for the first time in the fifth edition of his textbook (1896, p. 634), although, already in 1893, he had described the "manic stupor" (1 year after Kraepelin's description of manic stupor, Dehio referred to it during the 1894 meeting of "South-western German Alienists"). He practically completed their theoretical conceptualization in the sixth edition (1899, pp. 394–399), although their final categorization and nomenclature came with the eighth edition in 1913 (Table 1.2).

In the same year that Kraepelin's sixth edition (1899) was published, Wilhelm Weygandt (pupil and colleague of Kraepelin in Heidelberg) published the first book on mixed states in psychiatric literature: *Über die Mischzustände des manisch-depressiven Irreseins* (*On the Mixed States of Manic-Depressive Insanity*; see Fig. 1.5).

Since Weygandt referred to the sixth edition of Kraepelin's handbook as a source, it can be assumed that Kraepelin's handbook was published earlier in the year or that Weygandt was familiar with his teacher's manuscript. Kraepelin did



Über die Mischzustände

des

manisch-depressiven Irreseins.

Ein Beitrag zur klinischen Psychiatrie

mit vier Abbildungen und einer lithograph. Tafel

von

Wilhelm Weygandt,
Dr. phil. et med.
Assistenzarzt an der psychiatrischen Klinik der Universität Heidelberg.

MÜNCHEN
Verlag von J. F. LEHMANN
1899.

Fig. 1.5 The first book in psychiatric literature on mixed states (Weygandt, 1899).

Fig. 1.6 Wilhelm Weygandt (1870–1939).

not use the term "mixed states" per se in 1893; rather he noted that "the cases are mixed" (pp. 366–7). But even before the first use of the term "mixed states" in 1896, Kraepelin described "manic stupor" (1893, pp. 366–7), later characterized by him as the most convincing type of mixed state (1899, p. 396). In the final description of mixed states (eighth edition of the handbook in 1913, pp. 1284–303), Kraepelin defined six types (Table 1.2).

Although Kraepelin, as the one who clarified and systematized previous observations, is undoubtedly the definer of the concept, the work of Wilhelm Weygandt (Fig. 1.6) makes it difficult to distinguish the respective roles of the two men with regard to the development of the final concept. It is, however, beyond any doubt that the clarification of former views, the systematic descriptions, and theoretical formulations are the work of Kraepelin. Mixed states belonged to the core of Kraepelin's "manic-depressive insanity" (Koukopoulos and Koukopoulos, 1999; Marneros, 1999; Marneros and Angst, 2000; Angst and Marneros, 2001). However,

it can be assumed that the final clinical description, the categorization, and the systematic gathering of data on the topic is the common work of both men.

In his slim, 63-page monograph *Über die Mischzustände des manisch-depressiven Irreseins* (1899), Weygandt gives a very plastic description of mixed states in a style very similar to that of Kraepelin. A year before the publication of his monograph, Weygandt presented his findings during the 29th meeting of the South-western German Alienists, held in Heidelberg on 27 November 1898. Weygandt's contribution was cited pedantically, including the exact time of the session (from "1.15 p.m. to 3.45 p.m."); perhaps a sign that it was the first oral presentation on the subject of mixed states during a scientific conference. In his presentation (published a year later, in 1899), Weygandt spoke about many possible types of mixed states, three of which ("manic stupor," "agitated depression," and "unproductive mania") he considered the most important (Weygandt, 1899). Weygandt wrote in his book:

> It is very common, both in the manic and in the depressive episodes of manic-depressive or circular insanity, for there to be not only periods of time which are mostly without symptoms, but also, often, hours or days when the symptoms switch to the opposite pole. So, during a manic episode, **euphoria** can suddenly change into a **deeply depressive** mood, while the other symptoms of exaltation, such as hyperkinesia and hyperactivity, distractibility and excitability, logorrhea, and flight of ideas, persist; or after a month-long **depression**, suddenly a smile can be observed on the face of the patient and the depressive mood can change for hours or days into a high or manic mood, but without any change in psychomotor behavior, in the inhibition or, sometimes, in the severe stupor. Less common, but actually frequent enough if observation is careful, is a temporary change in psychomotor behavior while the affective aspects of the psychosis continue without any change; the patients remain euphoric, but the manic **excitability** changes into a **psychomotor inhibition**. Instead of tireless hyperactivity, the patients stay in bed, show slowness of movement and little or no mutism. In patients with the phenomenological picture of depression with stupor, one can sometimes observe a change to mild excitability, agitation and an urge to speak lasting for hours or days, while the depressive mood continues.
>
> Additionally, we have to consider one more pair of opposite symptoms, because this is the only way that we can touch all the relevant points in their totality. Similar to the euphoric mood and the psychomotor excitability for mania are also morbid changes in the domain of thinking, the **flight of ideas**.
>
> . . .
>
> In depressive episodes, instead of flight of ideas, one sees **thought inhibition**.
> These states, very well known, but because of their short duration, usually less noted, are a mix of manic and depressive episodes of circular insanity (Weygandt, 1899, pp. 1–2).

Weygandt concluded:

> The co-existence of the main symptoms of both typical episodes of manic-depressive insanity, mostly only of short duration, is extraordinarily frequent: in some cases, the mixed states

can occupy the entire episode or at least the greater part of its duration. Usually, it is the later episodes that have the tendency to change to long-lasting mixed states. The course is in many aspects somewhat more chronic than that of the pure manic or depressive episodes, but in other ways, the prognosis regarding the recovery of the episode is exactly the same (Weygandt, 1899, p. 63).

Weygandt explained the manifestation of mixed states as follows:

It is relevant to consider that the two symptom lines, i.e. euphoric mood, psychomotor excitability and flight of ideas, on the one hand, and depressive mood, psychomotor inhibition and thought inhibition, on the other hand, are not stable. But the disorders are characterized by instability in the domain of mood, psychomobility and thought, and this is a characteristic of the whole circular or manic-depressive insanity (Weygandt, 1899, p. 5).

The mixture of the three opposite pairs of symptoms mentioned above could give rise – according to Weygandt – to the six possible types of mixed states previously mentioned but occasionally, and only for a short period, perhaps more than six. Three of the six types are most relevant: "We are forced by reasons of practical psychiatry, because we are opposed to speculation, to distinguish and describe only three groups of mixed states as the most relevant; they are the most frequent and have the longest duration ... **manic stupor** ... **agitated depression** ... and **unproductive mania** ..."(Weygandt, 1899, p. 20). He used the remaining two-thirds of his book to describe only these three types of mixed states, not the other three possible types, which he mentioned but did not name (pp. 20–36). In 1913, Kraepelin gave extensive descriptions of all six types of mixed states (Table 1.2).

According to Koukopoulos and Koukopoulos (1999), Weygandt was the first to introduce the term "agitated depression" (*agitierte Depression*) in his book, although in fact the syndrome had been described by Frank Richarz (*melancholia agitans*) more than 40 years earlier (1858). Weygandt himself quoted Richarz's paper in his book (pp. 41, 42). Koukopoulos and Koukopoulos' paper contains a very interesting discussion on the origin and diagnostic placement of agitated depression. The authors argue that agitated depression is in fact a form of mixed state, as Kraepelin and Weygandt assumed. According to the opinion of Akiskal and Pinto (2000), the term "hyperthymic depression" can more closely be associated with mixed states than the term "agitated depression."

Kraepelin thought that the first three types of mixed states ("depressive or anxious mania," "excited or agitated depression," and "mania with thought poverty") were based on the three fundamental symptoms of mania, namely flight of ideas, euphoria, and hyperactivity (Fig. 1.7). A depressive or anxious mania can arise if two of the three basic symptoms of mania, namely flight of ideas and hyperactivity, are present, but euphoria is replaced by depressive mood. If,

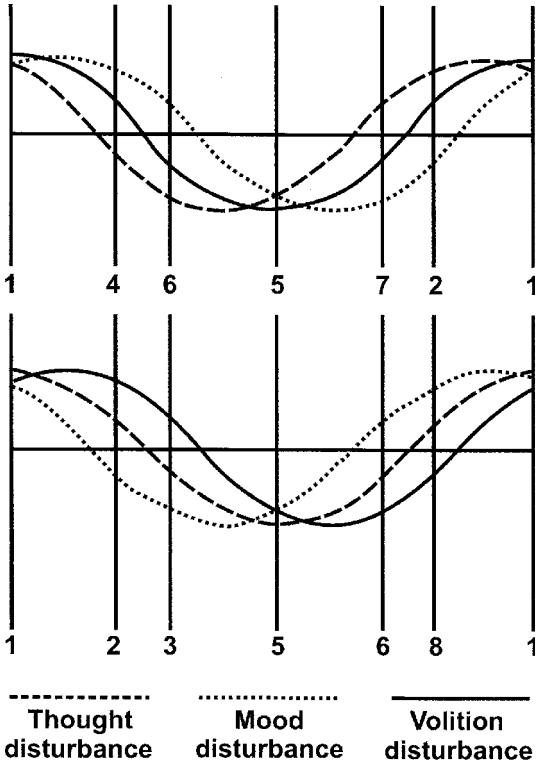


Fig. 1.7 The modus of manifestation of mixed states of manic-depressive insanity (according to Kraepelin, 1913).

additionally, the symptom flight of ideas changes to inhibition of thought, only the hyperactivity remains as a manic symptom and, thus, "excited" or "agitated depression" can arise. Mania with thought poverty occurs if poverty of thought is associated with the manic symptom euphoria and perhaps also hyperactivity.

The basis of the next three types of mixed states – according to Kraepelin – is the fundamental symptomatology of depression, namely "inhibition of thought," "depressive mood," and "weakness of volition." "Manic stupor" (which for Weygandt is the most important type of mixed state and for Kraepelin the most convincing) arises when depressive mood is replaced by "euphoria," but depressive thoughts and lack of will or abulia persist. "Depression with flight of ideas" comes into being when the poverty of thoughts is replaced by flight of ideas, while the two other basic symptoms of depression (depressive mood and abulia) continue. If, in addition to flight of ideas, depressive mood changes to euphoria, "inhibited mania" arises. Kraepelin separated inhibited mania from manic stupor because flight of ideas is absent in manic stupor, but present in inhibited mania.

Kraepelin distinguished two groups of mixed states: (1) *transitional forms*, a stage in between, when depression changes to mania and vice versa; and (2) *autonomic forms*, a disorder on its own. Between these two groups relevant differences exist. The autonomic group is characterized by Kraepelin as the most unfavorable form of manic-depressive insanity. The course is longer, with a tendency to chronicity, and the individual episodes are longer than in other types of manic-depressive insanity (Kraepelin, 1899, 1904, 1913; Weygandt, 1899) – findings that were confirmed 100 years later. Also confirmed by some modern studies are the findings of Kraepelin and Weygandt:

(1) Females are more frequently represented in groups of mixed states.
(2) Using broad definitions, more than two-thirds of patients with manic-depressive illness have a mixed state (usually a transitional form) at least once. Even when using narrow definitions, approximately 20% of them experience mixed states (as many modern authors have also found, for example, see Winokur *et al.*, 1969; Himmelhoch *et al.*, 1976a, b; Akiskal and Puzantian, 1979; Goodwin and Jamison, 1990; Marneros *et al.*, 1991a, b, 1996a, b; Akiskal, 1992; Himmelhoch, 1992; McElroy *et al.*, 1995, 1997; Swann *et al.*, 1995, 1997; Akiskal and Pinto, 2000)

But even during the period after Kraepelin, in which the relevance of mixed states faded in scientific literature, many influential psychiatrists, such as Johannes Lange (1928) in Germany and Campbell (1953) in the English-speaking countries, continued to emphasize the relevance of mixed states.

J. D. Campbell, in his book *Manic-Depressive Disease: Clinical and Psychiatric Significance*, which was published exactly at the beginning of the psychopharmacological revolution, but before its consequences, namely in 1953, emphasized the conceptual significance of mixed states in a way very similar to Kraepelin and Weygandt:

> The mixed type of manic-depressive psychosis epitomizes the entire cyclothymic process, in that it contains the symptoms characteristic of the various phases. Whether it is a sustained reaction or represents a phase of metamorphosis between the major forms, the mixed type emphasizes the underlying similarities between the depressive and hypomanic, the fact that the manic and depressive reactions may be superimposed, and that the same individual possesses the potentialities for either form.

The renaissance of mixed states

The renaissance of mixed states began in the USA at the end of the 1970s and the beginning of the 1980s as a consequence of the pharmacological revolution in psychiatry, especially through the contributions of Winokur *et al.* (1969), Kotin and Goodwin (1972), Himmelhoch *et al.* (1976a, b), Akiskal *et al.* (1979), Akiskal

(1981, 1992, 1997), Secunda *et al.* (1987), Goodwin and Jamison (1990), Himmelhoch (1992), McElroy *et al.* (1992, 1995, 1997, 2000), Swann *et al.* (1995), and Akiskal and Pinto (2000). The cooperation between the groups of Akiskal and Cassano led to the Memphis–San Diego–Pisa study on mixed states (Dell'Osso *et al.*, 1991). The work of Cassano *et al.* (1992) as well as that of the Perugi group in Pisa (end of 1997), Koukopoulos and Koukopoulos (1999), Koukopoulos *et al.* (1992, 1995) in Italy, and Bourgeois and colleagues in France (1995) supported this renaissance.

An interesting enrichment was introduced by Hagop Akiskal (Akiskal, 1981, 1992; Akiskal and Mallya, 1987; Akiskal and Pinto, 2000). He suggested a mixing of manic or depressive symptoms with cyclothymic, hyperthymic, or depressive temperament. The seed of this idea can be found in Griesinger (1845, p. 205), adapted later by Kraepelin (1913). The mixing of symptoms and temperament can give rise, in Akiskal's view, to three different types of mixed states:

(1) Type B-I: "depressive temperament + psychosis"
(2) Type B-II: "cyclothymic temperament + depression"
(3) Type B-III: "hyperthymic temperament + depression"

The Pisa–Memphis collaborative study (Dell'Osso *et al.*, 1991) on the temperament and course of mood disorders of over 200 classical B-I manic-depressive patients suggests that B-I mixed states are typically psychotic, often mood-incongruent, and seem to arise from a depressive temperament. The clinical picture is in conformity with Kraepelin's classic description of a mixed state where depression and mania coexist more or less syndromally. Its distinctive features derive from the simultaneous occurrence of numerous signs and symptoms of the two syndromes: crying, euphoria, racing thoughts, grandiosity, hypersexuality, suicidal ideation, irritability and anger, psychomotor agitation, severe insomnia, persecutory delusions, auditory hallucinations, and confusion (Akiskal and Puzantian, 1979). Alcohol abuse, a not infrequently associated finding, can be a contributory cause or a complication. B-I mixed states thus overlap with schizoaffective conditions (Marneros and Tsuang, 1986) and with what in francophone psychiatry is labelled as *bouffées délirantes*.

B-II mixed states are typically non-psychotic and consist of cyclothymic intrusions into a retarded depression (Akiskal, 1981). That is, the unstable cyclothymic background (Akiskal *et al.*, 1979) serves to change the clinical phenomenology of the depression. Thus, depressed mood, hyperphagia, hypersomnia, fatigue, and low self-esteem can be mixed with racing thoughts – which may manifest in spurts of creativity, such as writing verses – jocularity, angry outbursts, tension, restlessness, impulsive hypersexuality, other evidence of uninhibited behavior, gambling, or dramatic suicide attempts. Abuse of stimulants (including caffeine) and of sedatives–hypnotics (including alcohol), either as sensation-seeking or attempts

at self-treatment, are common comorbid conditions. These cases are then mistaken for borderline personality disorder, as shown by the University of Tennessee research on over 200 probands studied to date (Akiskal and Pinto, 2000).

B-III mixed states are increasingly seen following the overzealous treatment of retarded, seemingly unipolar depressions arising from a stable hyperthymic temperamental background without hypomanic episodes. As reported by Akiskal and Mallya (1987), based on a series of 25 cases, the end results of multiple antidepressant trials in these patients could manifest as follows: unrelenting dysphoria and irascibility; agitation against a background of retardation; extreme fatigue with racing thoughts; panic and insomnia; suicidal obsessions and impulses; unendurable sexual excitement; histrionic countenance, yet genuine expressions of intense suffering. Here, too, abuse of stimulants and alcohol is commonly observed. These patients are often misdiagnosed as being agitated depressives when symptoms are severe, or neurotic depressives when they are moderate in intensity. It is here, according to Akiskal, that lithium "augmentation" works best. (Lithium alone might work as well.) This highly refractory group of patients, whose temperament is seriously compromised by the protracted "depression," presents a major therapeutic challenge (Akiskal, 1992).

Another aspect of the evolution of the concept of mixed states is their extension into the group of *schizoaffective disorders*. Marneros *et al.* have described the frequency, clinical characteristics, and prognostic value of "schizoaffective mixed episodes" (Marneros, 1989; Marneros *et al.*, 1986, 1988a–c, 1989a–c, 1991a, b, 1996a, b, 2000). It seems that mixed states in schizoaffective disorders are not rare: 33% of bipolar schizoaffective patients in the Cologne study had at least one schizomanic–depressive mixed episode during an average duration of illness of 25 years (Marneros *et al.*, 1991a, b, 1996a, b). Unfortunately, however, no other systematic investigations on this topic have been carried out with the exception of the Halle Bipolarity Longitudinal Study (HABILOS), the preliminary findings of which we present in this book.

The HABILOS showed that 32.2% of patients with bipolar schizoaffective disorder have at least one mixed episode showing no significant difference from the frequency of the pure bipolar affective disorder (Fig. 1.8). Additionally, the study shows that schizoaffective mixed states are apparently the most severe type of bipolar disorders in general (see Chapter 8).

It can be concluded that mixed states are well established. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn (DSM-III) (American Psychiatric Association, 1980), DSM-III-R (American Psychiatric Association, 1987), and DSM-IV (American Psychiatric Association, 1994), as well as *Tenth Revision of the International Classification of Diseases* (ICD: World Health Organization, 1991) include definitions and diagnostic criteria. The modern definitions of

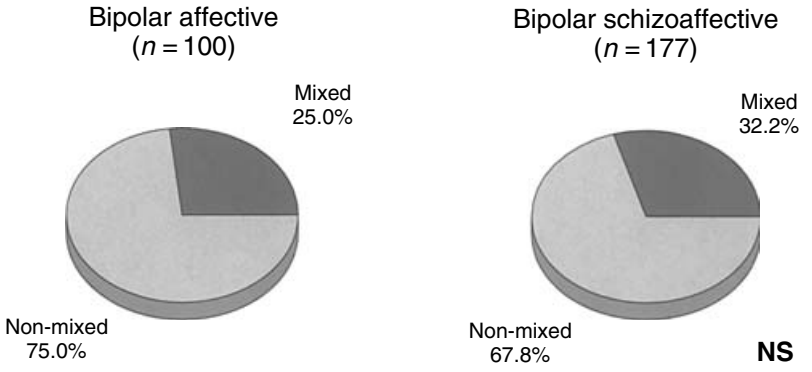


Fig. 1.8 Frequency of patients with mixed course in the Halle Bipolarity Longitudinal Study (HABILOS). NS, not significant.

mixed states are similar to those of Kraepelin and Weygandt, who distinguished between narrow (coexistence of the full symptomatology of a manic and a depressive episode) and broad definitions ("cardinal" depressive symptoms in manic episodes, and vice versa). The modern definitions can be divided into three groups:

(1) Broad definitions: the presence of single depressive symptoms within a manic episode is considered sufficient for diagnosis of a mixed episode.
(2) Narrow or strict definitions: only the coincidence of the full symptomatology of a manic and a depressive episode allows for the diagnosis of a mixed episode. This category corresponds to the diagnostic criteria of ICD-10 (Table 1.3) and DSM-IV (Table 1.4).
(3) Moderate definitions: according to moderate definitions, the coincidence of the full syndromes of mania and melancholia is not necessary. However, the presence of either the depressive or manic syndrome is not sufficient. These definitions demand prominent depressive symptoms within a manic syndrome, or vice versa. The Cincinnati, Pisa, and Vienna criteria belong to this category (Berner *et al.*, 1983; McElroy *et al.*, 1992; Perugi *et al.*, 1997).

McElroy *et al.* (2000) pointed out that numerous modern phenomenological studies, including factor-analytic studies, have confirmed the occurrence of depressive symptoms in mania, and have provided support for the hypothesis that mixed mania (mania with depressive features) may be distinct from pure or euphoric mania (mania without depressive features). Moreover, these studies suggest that systems used to define mixed states should be broad and dimensional, as well as categorical, rather than overly narrow. As Goodwin and Jamison (1990) wrote, "in general, it is best to consider the depressive spectrum and the manic spectrum as independent and capable of interacting in a variety of combinations

Table 1.3 Demographics of rapid cycling (RC) versus non-rapid (NRC) bipolar disorder (BP-II) (according to Kilzieh and Akiskal, 1999)

	n		Age		% Female		% BP-II		
Study	RC	NRC	RC	NRC	RC	NRC	RC	NRC	% RC
Dunner and Fieve (1974)	33	215	29	30	71	47	40	36	13
Koukopoulos *et al.* (1980)	87	347			70	57	82	43	20
Cowdry *et al.* (1983)	24	19	45	41	83	53*			56
Nurnberger *et al.* (1988)	29	29			86	53*	41	28	15
Wehr and Goodwin (1979)	51	19	30	27	92	44*	47	47	
Coryell *et al.* (1992)	45	198	26	25	71	50*	36	18*	18
Lish *et al.* (1993)	45	44	39	82	64*				
Maj *et al.* (1994)	37	74	43.3	37.7*	65	51.4	40.5	24.3	13.6
Bauer *et al.* (1994)	120	119	39.3	37.8	70	50.4	45	37.8	

*$P \leq 0.05$.

Table 1.4 Schizoaffective disorders (F25) according to *Tenth Revision of the International Classification of Diseases* (ICD-10: World Health Organization, 1991)

G1. The disorder meets the criteria for one of the affective disorders (F30, F31, F32) of moderate or severe degree, as specified for each category

G2. Symptoms from at least one of the groups listed below must be clearly present for most of the time during a period of at least 2 weeks (these groups are almost the same as for schizophrenia F20.0–F20.3)

G3. Criteria G1 and G2 above must be met within the same episode of the disorder, and concurrently for at least part of the episode. Symptoms from both G1 and G2 must be prominent in the clinical picture

G4. Most commonly used exclusion clause. The disorder is not attributable to organic mental disorder (in the sense of F00–F09) or to psychoactive substance-related intoxication, dependence, or withdrawal (F10–F19)

and permutations." For clinical purposes, therefore, we use a bidimensional categorical system for classifying the cross-sectional affective state of our patients with bipolar disorder (McElroy and Weller, 1997). Patients can have various combinations of various degrees (none, mild, moderate, severe) of manic and depressive symptoms, thereby allowing for more accurate diagnosis and, hence, more appropriate treatment.

Frequency

There are no systematic epidemiological studies on mixed states. The estimation of their frequency is mainly based on studies of psychiatric inpatients and, to a lesser extent, outpatients. Going back to Kraepelin, it has always been clear that their frequency is dependent on the definition applied. Thus, Kraepelin (1899), as well as Weygandt (1899), estimated that by applying broad definitions, their frequency is very high: approximately 60%. Applying a narrow definition, which requires the full symptomatology of melancholia and of mania, reduces the frequency to about 20%. Thus, contemporary reviews of the prevalence rates of mixed states in patients with bipolar disorder report a range between 5 and 70% (Goodwin and Jamison, 1990; McElroy *et al.*, 2000). With a median of about 43% (Goodwin and Jamison, 1990), exactly the same percentage was found in the Cologne study (Marneros *et al.*, 1991a, b). Further, the Cologne study observed bipolar patients over 25 years and noted that only 1% of the patients consistently had mixed states (Marneros *et al.*, 1991a, b). It seems that the frequency of mixed states is related to the duration of the illness, and the predominance of manic or depressive phases. Thus, the longer the duration of the illness, the greater the possibility of mixed states. Additionally, the HABILOS showed with regard to the ratio of manic to depressive episodes that the more manic the course, the greater the possibility of mixed states (see Chapter 9). The frequency of mixed states has been reported to be higher among females; although this finding is controversial (Marneros *et al.*, 1991a, b; McElroy *et al.*, 1992, 1995; Akiskal *et al.*, 1998; Arnold *et al.*, 2000). Some studies suggested that mixed states are not uncommon in childhood and adolescence (Geller and Luby, 1997; McElroy *et al.*, 1997) (see Chapter 10).

Phenomenology

The classical work of Kraepelin (1899, 1913, 1921) and of Weygandt (1899) provided a rich and fascinating description of mixed states. Modern studies confirm the observations of the classical literature that depressive symptoms are common in mania and hypomania (Kotin and Goodwin, 1972), and vice versa: manic features can also occur in depression (Himmelhoch, 1979; Koukopoulos *et al.*, 1992, 1995, 2000; Bauer *et al.*, 1994; Perugi, *et al.*, 1997; Akiskal *et al.*, 1998; Cassidy *et al.*, 1998a, b; Dilsaver *et al.*, 1999; see Chapter 7). Contemporary data-based studies provide support for conceptualized mixed states broadly and dimensionally, as well as categorically (McElroy *et al.*, 2000). However, one has to be aware that the broader the definition, the greater its shortcomings.

In addition to a mixture of manic and depressive symptoms, mixed states are also frequently characterized by anxiety, suicidal tendencies, and catatonic and psychotic symptoms (Kraepelin, 1899, 1913; Weygandt, 1899; McElroy *et al.*, 2000;

Krüger *et al.*, 2003). In the classical descriptions of Kraepelin and Weygandt, as well as the modern studies, such as Winokur *et al.* (1969), Post *et al.* (1989), Cassidy *et al.* (1998a, b); Dilsaver *et al.* (1999), and Marneros *et al.* (see Chapter 9), anxiety symptoms are not uncommon in mixed states. Anxiety symptoms appear to correlate with depressive symptomatology (Kraepelin, 1899, 1913; Post *et al.*, 1989; Cassidy *et al.*, 1998a, b; Dilsaver *et al.*, 1999; see Chapter 9). Although suicidal symptoms during mixed episodes clearly occur, their reported frequency varies considerably – between 55% (Dilsaver *et al.*, 1994) and 14% (Marneros *et al.*, 1991a, b). Nevertheless, all available data show a considerably greater frequency of suicidal symptoms in mixed states than in pure mania (Dilsaver *et al.*, 1994: 55% versus 2%, Strakowski *et al.* (1996): 26% versus 7%, Marneros *et al.*, 2004: 14% versus 0% for pure manic disorder, and for schizoaffective mixed episodes 22% versus 1% pure schizomanic episodes). It should be noted that the investigations of Marneros *et al.* (1991a), in contrast to the other studies noted above, have the advantage of being longitudinal, considering all episodes during a period of more than 25 years. As noted by Kraepelin, psychotic symptoms are not uncommon in mixed states. Nevertheless, the occurrence of psychotic symptoms, especially mood-incongruent symptoms, gives rise to the question of differential diagnosis – mixed bipolar episode or schizoaffective? Although DSM-IV and ICD-10 define schizoaffective bipolar mixed episode, there is limited research on the topic (Marneros, 1986–2004). Findings on schizoaffective mixed states are presented in Chapter 8 of this book.

Catatonic symptoms can also occur in mixed states. Krüger *et al.* (2003) assert that, in spite of the assumption that catatonic symptoms are associated with good prognosis in psychotic or affective disorders, the opposite is true in the case of mixed states: catatonic symptoms in mixed bipolar states are associated with greater severity and poor prognosis.

Onset, course, and outcome

Studies on the onset, course, and outcome of mixed states are somewhat inconsistent. One of the problems in the literature are the terms "patients with mixed mania" or "patients with mixed states." Perhaps the correct formulation is "patients who have at least one mixed episode during their course." That is, as noted above, patients having mixed states usually also have pure depressive and pure manic episodes during their course, and in some cases, also schizodepressive and schizomanic episodes. Perhaps it would be helpful if mixed states were defined according to the predominance of mixed symptomatology over pure manic or schizoaffective symptomatology (Marneros *et al.*, 1991a, b; see Chapter 9).

The relationship between mixed states and age at onset is of interest. Some studies have reported that patients with mixed states have a younger age at

onset (Nunn, 1979; Post *et al.*, 1989). Marneros *et al.* (Chapter 9) also found this relationship, but noted that it only applied to schizoaffective mixed episodes. On the other hand, some have found no differences in age at onset in patients with or without mixed states (Marneros *et al.*, 1991a, b; Perugi *et al.*, 1997; see Chapter 9), while one study actually found that patients with mixed states had an older age at onset (Strakowski *et al.*, 1996). McElroy *et al.* (1997) found that adolescent manics were more likely to be mixed than adult manics.

The duration of a mixed episode, as initially described by Kraepelin and by Weygandt, is longer and more complicated than pure manic or depressive episodes – an observation replicated by some modern investigations (Keller *et al.*, 1986; Dell'Osso *et al.*, 1991; Marneros *et al.*, 1991a), but not all: Calabrese and Delucchi (1990), for example, found mixed episodes to be shorter, while Winokur *et al.* (1969) found them to be equal in length. In the Cologne study (Marneros *et al.*, 1991a), mixed episodes were longer than other episodes, but, 12 years later, the same team found no differences between mixed manic and pure manic episodes. The authors note that the difference might be explained by the fact that the population of the initial Cologne study had been treated only very rarely with anticonvulsants like valproate or carbamazepine, but the population of the later study quite frequently received anticonvulsant therapies (valproate, lamotrigine, carbamazepine). However this later study found that schizoaffective manic episodes were significantly longer than any other kind of episode (see Chapter 9).

The initial observations of Kraepelin (1899), and Weygandt (1899), that the outcome of patients with mixed states is much more unfavorable, was replicated in the Cologne study (Marneros *et al.*, 1986–1991) and in the later HABILOS study, as well as being noted in many contemporary studies (Himmelhoch *et al.*, 1976b; Keller *et al.*, 1986; Prien *et al.*, 1988; Cohen *et al.*, 1988; Tohen *et al.*, 1990; McElroy *et al.*, 1995; Perugi, *et al.*, 1997). However, not all studies agree. Thus, Winokur *et al.* (1969) and Keck *et al.* (1998) reported no difference in outcome between patients with mixed versus patients with pure mania.

Comorbidity

The comorbidity of mixed states with other psychiatric conditions is receiving increasing attention (McElroy *et al.*, 2000), but the findings are controversial (Brieger and Marneros, 1999; see Chapter 12). Thus, one report noted higher rates of comorbid substance abuse in patients with mixed states (Himmelhoch *et al.*, 1976a, b), but others did not find such an association (McElroy *et al.*, 1995). However, the latter study did note a higher rate of comorbid obsessive-compulsive disorders (McElroy *et al.*, 1995) (see Chapter 12).

Family history

Few systematic data on the family history of patients with mixed states exist. Perugi *et al.* (1997) did not report any differences in family history between patients with mixed and patients with pure manic states.

Treatment

Although the data regarding treatment of mixed states are also controversial, there is a reasonable amount of data suggesting that lithium may be less effective in the short- and possibly long-term treatment of mixed states than pure mania (Goodwin and Jamison, 1990; McElroy *et al.*, 2000). Valproate, lamotrigine, and possibly atypical antipsychotics, especially clozapine and olanzapine, may be more effective than lithium for patients with mixed episodes. However, the data are based on studies using different definitions of mixed states, so we need further comparative studies. Also, some studies suggest that antidepressant agents may exacerbate mixed states (Koukopoulos *et al.*, 2000, McElroy *et al.*, 2000; see Chapter 3).

Future perspectives on mixed states

As Perugi and Akiskal have pointed out (see Chapter 2), mixed state does not represent a mere superimposition of affective symptoms of opposite polarity, but a complex process of temperamental, affective, and other components – mixed states might be considered the most eloquent expression of a neurophysiological dysregulation.

Today, more than 100 years after the publication of the first book on mixed states by Wilhelm Weygandt in 1899, our understanding of the condition has increased, but there are still uncertainties and gaps. What we need is much more research on the topic. What are the major issues in designing such research?

- First of all, we need a single consensus, which takes into account the advantages and disadvantages of broader definitions versus more narrow definitions.
- How do we operationalize and assess the boundaries drawn by Kraepelin between "transitional forms" (which should represent a stage in between when depression changes to mania and vice versa) and "autonomous forms" (which should mean mixed disorder on its own)?
- Once a consensus definition is established, we should be able to clarify some of the following points:
  - What is the gender distribution?
  - How stable are mixed states over the course of illness?
  - Are the mixed states a challenge of the bipolar I versus bipolar II dichotomy (a question raised by Vieta *et al.* in Chapter 4 of this book)?

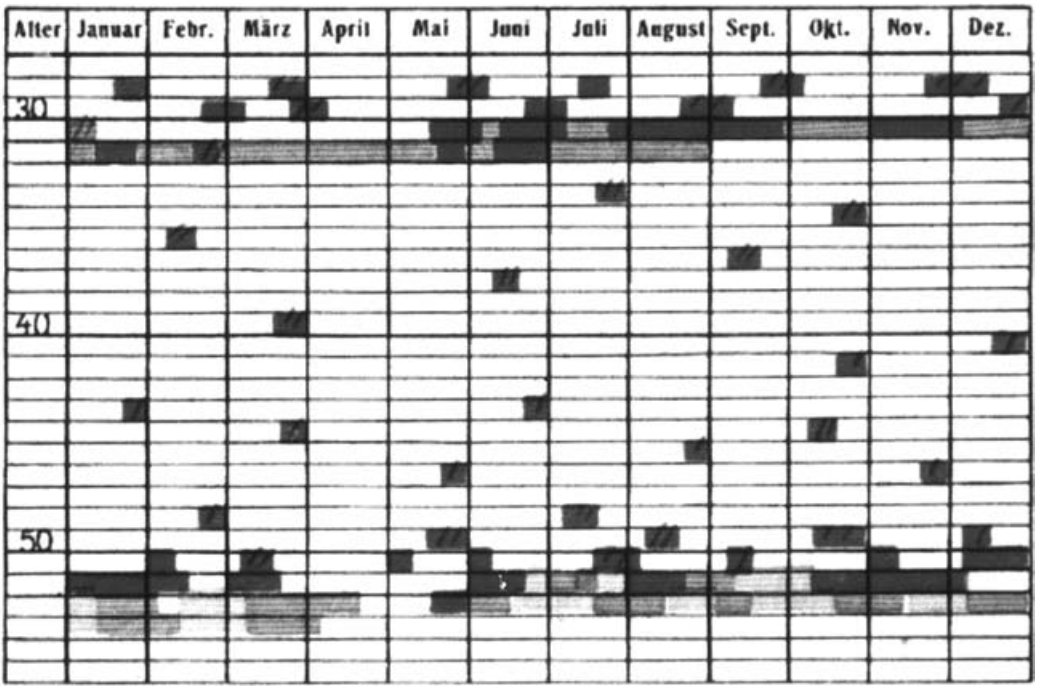


Fig. 1.9 Periodic mania with development in *folie circulaire* (*periodische Manie mit Ausgang in circuläres Irresein*: Kraepelin, 1913).

Rapid cycling

The term "rapid cycling" is a modern one. However, the phenomenon of frequent, or very frequent, recurrence of manic-depressive and mixed episodes was very well known early in the evolution of scientific psychiatry. Emil Kraepelin was perhaps the first who systematically described the phenomenon of rapid cycling (1899, 1913).

Of course, Kraepelin never used the term "rapid cycling" (Figs. 1.9–1.11). In one of the earliest uses of the method of retrospective and prospective chart review, Kraepelin documented the frequency and duration of episodes in life charts; he described patients with more than four episodes per year, those with many more than four episodes, patients with very short symptom-free intervals, and those with no free intervals at all (Kraepelin, 1913). However, in the following decades, essentially nothing more was done.

The term "rapid cycling," as well as the increasing interest in this phenomenon, also grew out of the psychopharmacological revolution. Dunner and Fieve first coined the term "rapid cycling" in 1974, in what Calabrese *et al.* called a "landmark paper" (Calabrese *et al.*, 2000), which summarized longitudinal data designed to evaluate clinical factors associated with lithium prophylaxis failure. But the

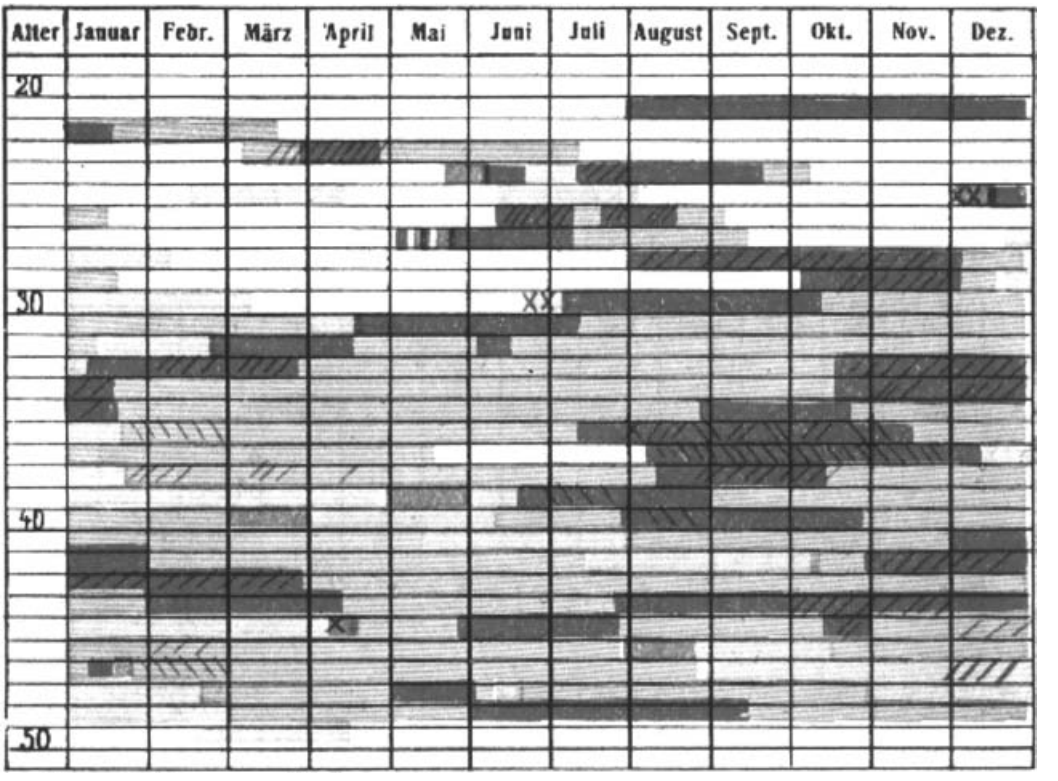


Fig. 1.10 Irregular almost lifelong *folie circulaire* (*unregelmäßiges, fast das ganze Leben ausfüllendes zirkuläres Irresein*: Kraepelin, 1913).

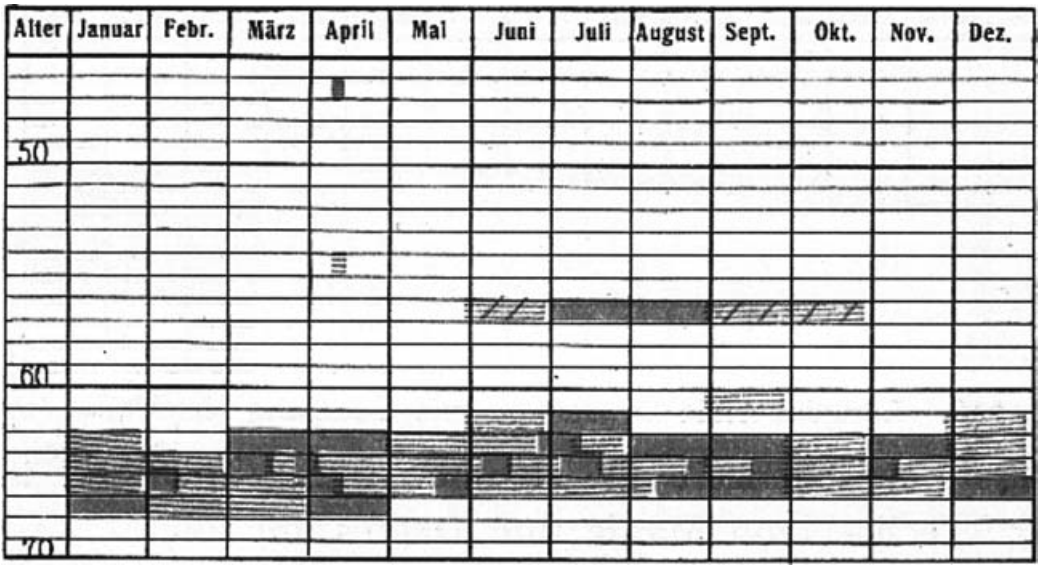


Fig. 1.11 *Folie circulaire* with beginning psychotic attacks (*zirkuläres Irresein mit einleitenden deliranten Anfällen*: Kraepelin, 1913).

boundaries between "rapid cycling" (having at least four episodes in a year) and "not rapid cycling" (having fewer than four episodes per year) are in fact arbitrary, although Dunner and Fieve found that most lithium non-responders belonged to the group of more than four episodes.

The subsequent work of Wehr and Goodwin (1979) replicated and extended the rapid-cycling findings of Dunner and Fieve, and additionally proposed that antidepressant agents could contribute to the manifestation of rapid cycling. This finding was also later replicated (Calabrese *et al.*, 1991, 1993; see Chapter 3). Calabrese *et al.* (2000) pointed out:

> The DSM-IV definition of rapid cycling describes it as a course modifier and is predicated for the most part on the Dunner and Fieve conceptualization of the phenomenon:
> (1) Four or more episodes of depression, mania, or hypomania in the previous 12 months.
> (2) Patients need not have an intervening euthymic interval for a mania and a depression to be counted as two episodes.
> (3) Numbers of episodes were tabulated, rather than numbers of cycles; for example, two cycles in which manic episodes are biphasically coupled with depressions followed by euthymic intervals would count as four episodes and satisfy criteria for rapid cycling.
> (4) Episodes are demarcated by a switch to a mood state of opposite polarity or by a period of relative remission lasting 2 months (DSM-IV, American Psychiatric Association, 1994). Therefore, consecutive episodes with the same polarity must be separated by a period of relative remission lasting 2 months.

DSM-IV included rapid cycling as a specifier of longitudinal course, but not as a specific mood disorder subtype (American Psychiatric Association, 1994). ICD-10 (World Health Organization, 1991) did not include any specifier or subgroup "rapid cycling." According to DSM-IV, the specifier "with rapid cycling" can be applied to bipolar I disorder or bipolar II disorder.

The essential feature of a rapid-cycling bipolar disorder is the occurrence of four or more mood episodes during the previous 12 months. These episodes can occur in any combination and order. The episodes must meet both the duration and symptom criteria for a major depressive, manic, mixed, or hypomanic episode and must be demarcated by either a period of full remission or by a switch to an episode of the opposite polarity. Manic, hypomanic, and mixed episodes are counted as being on the same pole (e.g., a manic episode immediately followed by a mixed episode counts as only one episode = when considering the specifier "with rapid cycling"). Except for the fact that they occur more frequently, the episodes that occur in a rapid-cycling pattern are no different from those that occur in a non-rapid-cycling pattern. Mood episodes that count toward defining a rapid-cycling pattern exclude those episodes directly caused by a substance (e.g., cocaine, corticosteroids) or a general medical condition (American Psychiatric Association, 1994).

Prolonged single episodes accompanied by intermittent fluctuations within the mood state (i.e., cycling above or below baseline due to changes in medication doses or levels) are counted as one episode. For example, patients who have one long period of mania followed by a short period of hypomania due to the transient use of neuroleptics or benzodiazepines, followed by a return to mania, are counted as having only one episode (Calabrese *et al.*, 2000). DSM-IV applies "rapid cycling" only to bipolar I and bipolar II disorders in recognition of the reality that rapid cycling of unipolar depression is extremely rare, and when it does occur, the family history is usually positive for bipolar disorder (Tay and Dunner, 1992; Kilzieh and Akiskal, 1999).

As noted above, the cut-off of four episodes per year has been criticized for being arbitrary. The key question, still unanswered, is whether cycle length distributes more or less evenly across a spectrum, or if there is a true bimodal distribution into two concrete (as opposed to arbitrary) subgroups – namely, rapid-cycling and non-rapid-cycling (Goodwin and Jamison, 1990; Coryell *et al.*, 1992). Another problem regarding the definition of rapid cycling relates to the nature and duration of the interepisodic period, which varies widely among studies. Studies differ regarding its duration and level of symptoms (Kilzieh and Akiskal, 1999): some require partial or full remission for at least 2 months or a switch to an episode of opposite polarity, other researchers have set the duration of remission as low as 4 weeks, while still others require a period of euthymia as long as the proximate episodes. The prevalence of rapid cycling in bipolar populations is also indeterminate because most of the data come from studies mostly done at tertiary centers with a high proportion of difficult-to-treat patients (Kilzieh and Akiskal, 1999). No community-based studies have been conducted, and the true prevalence of rapid cycling in an unselected bipolar patient population remains unknown (Kilzieh and Akiskal, 1999). Another problem related to the estimation of the prevalence of rapid cycling is its longitudinal instability; that is, it often occurs intermittently during the course of illness (Coryell *et al.*, 1992).

Studies on the prevalence of rapid cycling in a clinical bipolar population range from 24.2% (Tondo *et al.*, 1998) down to 13.6% (Maj *et al.*, 1994), with others in between: Coryell *et al.* (1992) 18.5%, Dunner and Fieve (1974) 20%, and Koukopoulos *et al.* (1980) 19%. A prevalence of rapid cycling with "approximately 5–15% of people with bipolar disorders seen in mood disorder clinics" is cited. Higher prevalence rates than those noted above were reported by Cowdry *et al.* (1983) from the US National Institute of Mental Health (56%), but this probably reflects the specialization of this major research center.

The gender difference – on average, more than 70% of rapid cyclers are females – is the most extensively replicated finding in rapid cycling (Table 1.3).

The meta-analysis of Tondo *et al.* (1998) showed that, although the majority of rapid-cycling cases (72%) are women, rapid cycling occurred in less than 30% of the total female bipolar population.

Another explanation delivered by the finding of Coryell *et al.* (1992) may derive from the assumption that a greater cyclicity seems to be frequently associated with females.

Age at onset

According to the findings of Fujiwara *et al.* (1998), age at onset (for rapid-cycling patients) can be divided into early (onset at an age of 25 years and younger) and later onset (onset at an age of 26 years or older). These data suggest that early- and late-onset bipolar disorders are distinct illness subtypes with different courses and responses to treatment (Calabrese *et al.*, 2000). The Japanese authors concluded that patients with an earlier onset tend to have rapid cycling at an early stage and a good response to carbamazepine. Those with later onsets tended to have relatively long latency until the appearance of rapid cycling and a good response to lithium.

Rapid cycling, as well as mixed states in childhood and adolescence, has not been investigated systematically, but some reports have shown that the prevalence of these states in childhood and adolescence is not rare (Calabrese *et al.*, 2000; see Chapter 10).

Family studies and genetics

Most of the studies of the families of patients with rapid-cycling bipolar disorder show no difference between rapid- and non-rapid-cycling patients. That is, rapid cycling is not more frequent in families of patients with rapid cyclers (Nurnberger *et al.*, 1988; Coryell *et al.*, 1992; Lish *et al.*, 1993; Maj *et al.*, 1994). Although the studies mentioned appear to argue convincingly against any inheritance of rapid cycling in general, the less common form of early-onset rapid cycling may be family-related (Calabrese *et al.*, 2000). Studies reporting on genetic abnormalities (more or less anecdotal) are rare and should be replicated (Kilzieh and Akiskal, 1999; Calabrese *et al.*, 2000).

Biological data

Also uncertain are other biological correlations of rapid cycling, as described in the present book by Grunze and Walden (Chapter 14).

Comorbidity

The issue of comorbidity as it relates to rapid cycling is complex. Calabrese *et al.* (2000) reviewed the extensive literature on thyroid dysfunction in patients with bipolar rapid cycling, noting that while many studies do report an association between rapid cycling and reduced thyroid function, not every study confirmed it. Alcohol and drug abuse is another comorbid disorder that is frequently associated with the acceleration of remanifestations and rehospitalizations, but there is no

systematic research regarding association with rapid cycling (Brieger and Marneros, 1999; Calabrese *et al.*, 2000; see Chapter 12). Finally, a few reports, essentially anecdotal, suggest an association between rapid cycling and neuropsychological deficits (Calabrese *et al.*, 2000; see Chapter 12).

Longitudinal prognosis

The impact of rapid cycling on longitudinal prognosis is also uncertain. While Coryell *et al.* (1992) and Wu and Dunner (1993) do not find an association between rapid cycling and a worsening of long-term prognosis, Okuma (1993) did. These differences may reflect sampling. That is, among patients for whom rapid cycling is transient and intermittent, one might not expect a negative effect or prognosis.

Treatment

The treatment of rapid cycling is discussed extensively by Calabrese *et al.* (2000), as well as by Elhaj and Calabrese (see Chapter 3).

Bipolar schizoaffective mixed states

Schizoaffective disorders present as unipolar or bipolar forms in a way similar to mood disorders (Marneros *et al.*, 1989a–c; 1990a–c; 2000), as is reflected in both DSM-IV and ICD-10 (American Psychiatric Association, 1994; World Health Organization, 1993). However, there are differences between DSM-IV and ICD-10. While DSM-IV defines two subtypes based on longitudinal course, namely bipolar and depressive, ICD-10 defines three types (manic, depressive, and mixed) based on the most recent episode, rather than longitudinal course (World Health Organization, 1993). These differences present a difficulty for cross-national research.

Tables 1.4 and 1.5 illustrate how differently ICD-10 and DSM-IV handle the definition of schizoaffective disorder.

While the main problem with the definition of ICD-10 concerns the longitudinal issue, the problem with DSM-IV concerns both – cross-sectional and longitudinal issues. The problem with the cross-sectional definition of DSM-IV concerns time criteria for criterion B (during the period of illness there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms). Obviously, that is an attempt of the DSM-IV to separate schizoaffective disorders from psychotic mood disorders. The DSM-IV definition of mood disorders is broad, including even those with mood-incongruent symptoms (even first-rank schizophrenic symptoms) as the mood disorders. But the chronological criterion is an arbitrary one (2 weeks of psychotic symptoms without mood disorders is schizoaffective; less than 2 weeks is a psychotic mood disorder). One

Table 1.5 Schizoaffective disorders (295.70) according to DSM-IV

A.	An uninterrupted period of illness during which, at some time, there is a major depressive episode, a manic episode, or a mixed episode concurrent with symptoms that meet criterion A for schizophrenia. Note: The major depressive episode must include criterion A1: depressed mood
B.	During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms
C.	Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness
D.	The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.
Specify type:	
Bipolar type:	If the disturbance includes a manic episode (or a mixed episode or a manic or a mixed episode and major depressive episodes)
Depressive type:	If the disturbance only includes major depressive episodes

problem with this is that the beginning of a psychotic episode can rarely be assessed exactly. Every clinician knows that there is usually a gap of many days, weeks, or months between the beginning of a psychotic episode and admission to a hospital. Reconstruction of the psychopathological picture, retrospectively, is fraught with difficulty. Given the likelihood that the psychotic period would be underestimated, many patients who are really schizoaffective could be diagnosed as schizophrenic or as having psychotic mood disorder.

Furthermore, the intensity of both concurrent syndromes can vary enormously during an episode – it seems arbitrary to give chronological priority to the psychotic symptoms over the mood component. It is curious that DSM-IV rejected Jasper's hierarchical diagnostic principle, which suggested a diagnostic superiority of schizophrenic symptoms over affective symptoms but, regarding the chronological criterion of the schizoaffective definition, obviously made an exception!

Considering what is now known about schizoaffective disorders (see overviews in Marneros and Tsuang, 1986, 1990; Marneros *et al.*, 1995), we suggest that the definition of schizoaffective disorders should contain two components: cross-sectional and longitudinal. The *cross-sectional* definition should be the definition of an episode, while the longitudinal definition should be that of a disease or disorder. The cross-sectional definition of a schizoaffective episode should be based on the simultaneous occurrence of symptoms of a schizophrenic and a mood episode, independent of the chronological manifestation. Thus, we agree

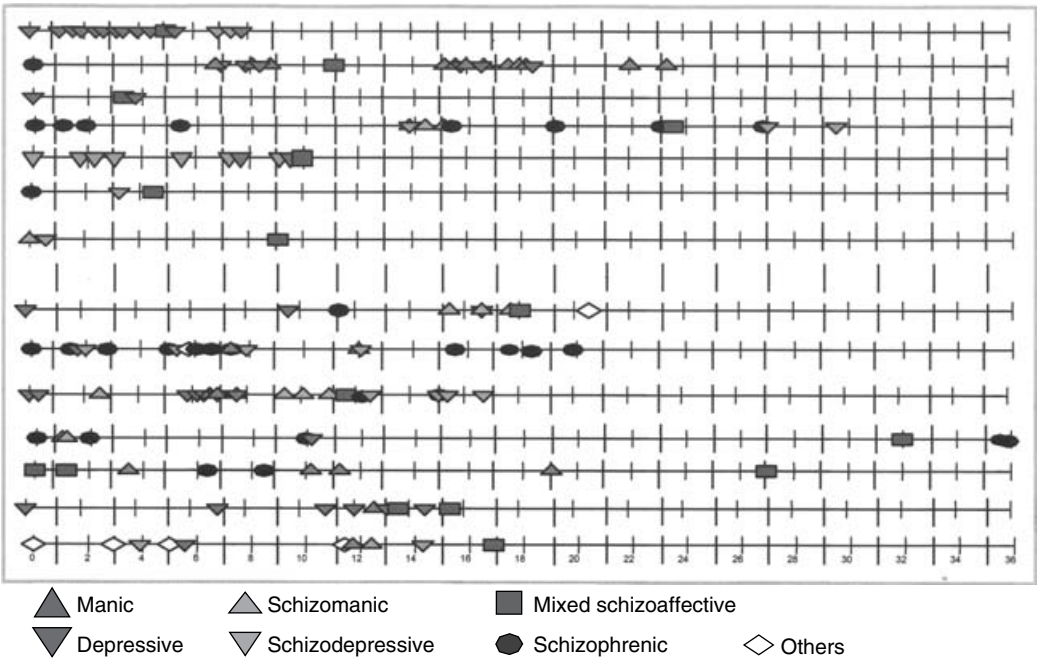


Fig. 1.12 Longitudinal course of patients with mixed schizo-manic-depressive episodes in the Halle Bipolarity Longitudinal Study (HABILOS).

with the definition of ICD-10, which yields three types of schizoaffective episodes: schizodepressive, schizomanic, and mixed.

The *longitudinal* definition of the schizoaffective disorder should consider the sequential occurrence of mood and schizophrenic episodes during the course. The longitudinal research demonstrates that the course of schizoaffective disorders can be very unstable because schizoaffective episodes, pure mood episodes, and pure schizophrenic episodes can each occur at different points in the patient's longitudinal course (Fig. 1.12). What are such disorders when viewed longitudinally? Are they to be considered mood disorders because of the pure mood episodes, or schizophrenic disorders because of some pure schizophrenic episodes, or schizoaffective disorders because of some schizoaffective episodes? Relevant to this question is the finding that there are no differences between patients who have only had schizoaffective episodes, and those in whom schizoaffective episodes occur along with pure mood and schizophrenic episodes. Thus, there are no differences between the "concurrent" and the "sequential" type of schizoaffective disorder (Marneros *et al.*, 1986, 1991a, b). Patients who change from pure mood episodes to pure schizophrenic episodes and vice versa do not differ from patients having schizoaffective episodes. In this sense, Marneros *et al.* suggest a longitudinal definition of schizoaffective disorders, including a concurrent and a sequential

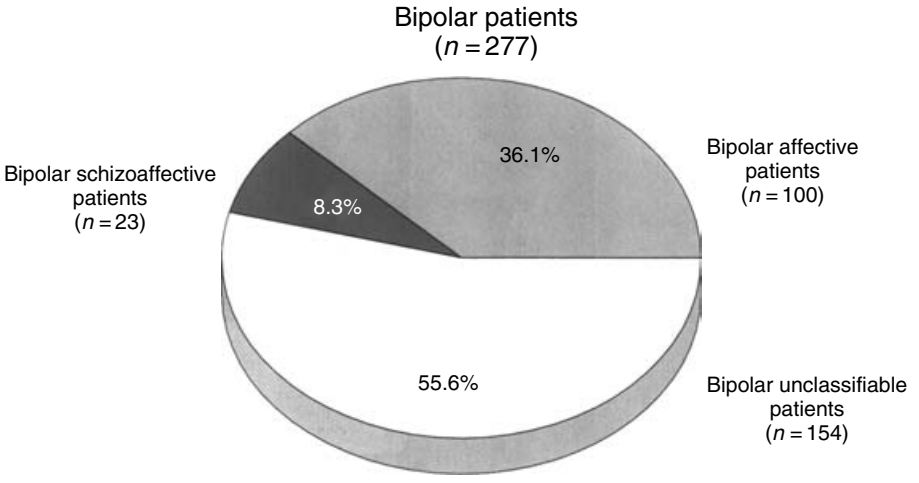


Fig. 1.13 *Tenth Revision of the International Classification of Diseases* (ICD-10) longitudinal classification of bipolar patients in the Halle Bipolarity Longitudinal Study (HABILOS).

type (Marneros *et al.*, 1986–2004): the concurrent type is characterized by the coincidence of schizophrenic and affective episodes, while the sequential type is characterized by the longitudinal change from schizophrenic to affective episodes and vice versa (Marneros *et al.*, 1986, 1988c, 1989a, 1991b, 2000; Marneros and Angst, 2000).

How essential it is to make a longitudinal diagnosis is illustrated by the HABILOS, in which the investigators tried to allocate disorders with manic symptomatology into pure mood disorders or schizoaffective disorders, according to DSM-IV, ICD-10, and to an empirical definition by the Marneros group (as defined above). Applying the ICD-10 definition, the findings illustrated in Figure 1.13 were produced. As shown, only 8.3% of the 277 patients could be allocated longitudinally as schizoaffective bipolar and 36.1% as affective bipolar, while the majority of patients (55.6%) could not be allocated longitudinally because of the occurrence of different types of episodes (schizophrenic, schizoaffective, affective) at different times.

However, if we use the empirical definition with its cross-sectional and sequential aspect, all patients can be allocated: 36.1%, as in the ICD-10 categorization, could be allocated as bipolar mood disorder, and 63.9% could be allocated as schizoaffective disorder (Fig. 1.14).

Recent research has confirmed earlier assumptions that schizoaffective disorders occupy a position between affective and schizophrenic disorders as regards relevant sociodemographic and premorbid features, as well as patterns of course, outcome, treatment response, and prophylaxis (Maj, 1985; Maj and Perris, 1985;

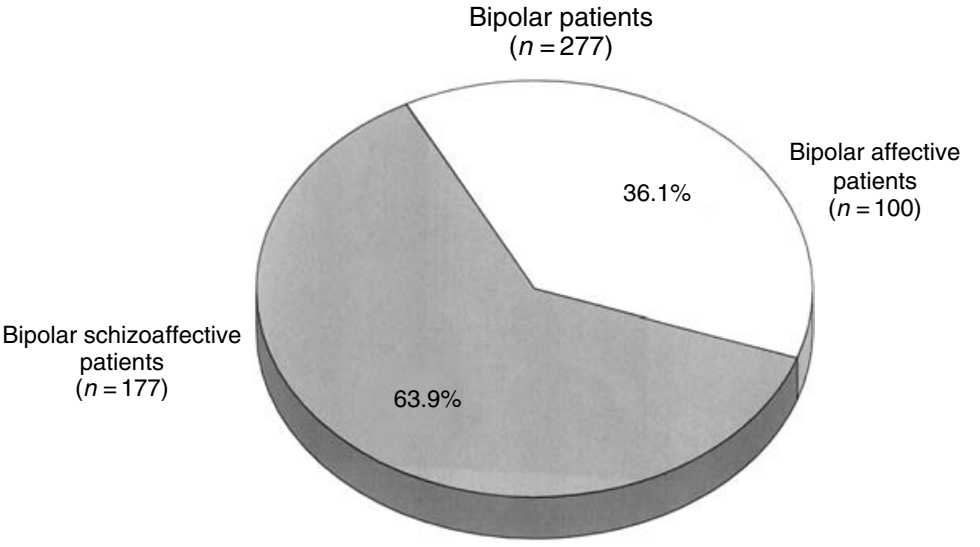


Fig. 1.14 Empirical longitudinal classification of bipolar patients in the Halle Bipolarity Longitudinal Study (HABILOS). Schizoaffective = occurence of schizoaffective episodes or sequentially schizophrenic and affective episodes.

Angst, 1986, 1989; Marneros *et al.*, 1988a–c, 1989a–c, 1991a, b; Deister *et al.*, 1990; see also various contributions in Marneros 1989; and in Marneros and Tsuang, 1986, 1990; as well as Marneros *et al.*, 1995).

It seems certain that schizoaffective disorders are not simply a type of schizophrenic disorder, although in some cases with schizo-dominance, the relationship to schizophrenia is clear. With respect to the relationship between schizoaffective and mood disorders, the similarities are more compelling than the differences (Marneros and Tsuang, 1986, 1990; Marneros *et al.*, 1995; Marneros, 1999).

Atypical depressions

The DSM-IV defines non-melancholic and non-catatonic major depressive episodes or dysthymic disorders as forms of "atypical depression" (full title: "criteria for atypical features specifier") when they fulfill the criteria shown in Table 1.6.

A look in the historical literature shows that the term "atypical depression" has many meanings (Angst *et al.*, 2002; Parker *et al.*, 2002). In 1959, West and Dally in London identified a group of patients with good response to monoamine oxidase inhibitors as having atypical depression "resembling anxiety hysteria with secondary depression," who had previous phobias and "hysterical conversions" and were less likely to have clinical features of "classical endogenous depression." The

Table 1.6 Criteria for atypical features specifiers (*Diagnostic and Statistical Manual of Mental Disorders:* DSM-IV)

A. Mood reactivity (i.e., mood brightens in response to actual or potential positive events)
B. Two (or more) of the following features:
1. significant weight gain or increase in appetite
2. hypersomnia
3. leaden paralysis (i.e., heavy, leaden feeling in arms or legs)
4. long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbances) that results in significant social or occupational impairment
C. Criteria are not met for "with melancholic features" or "with catatonic features" during the same period

definition of West and Dally differs from the later definition applied by the Columbia group (Quitkin *et al.*, 1978, 1993; Davidson *et al.*, 1982; Parker *et al.*, 2002). Angst *et al.* (2002) pointed out that a major impediment to the validity of atypical depression is the lack of consistency in the definitions employed by studies that have investigated the clinical significance of this depressive subtype. According to Parker *et al.* (2002), the current definition and modelling of the DSM-IV atypical features specifier for a major depressive episode and major depressive disorder appears problematic. As suggested by earlier descriptions of atypical depression, certain manifestations of anxiety may have primacy, and some clinical features associated with the DSM-IV model may be adaptive homeostatic responses, rather than pathological symptoms. The authors support the opinion of Davidson *et al.* (1982) that the relationship between anxiety and atypical depression requires further investigation. Substantial clinical research has also yielded indirect support for an association between atypical depression and the bipolar subtype of affective disorders, particularly subthreshold bipolar disorders and bipolar disorder II (Perugi *et al.*, 1998; Angst *et al.*, 2002; see Chapter 6). But, nevertheless, the results of recent research are controversial. While Angst *et al.* (2002) conclude that their findings from the Zurich study support the validity of the atypical depression subtype, considering it to be an important classifier, Parker *et al.* (2002) recommended a redefinition of atypical depression. Benazzi suggests in this book (see Chapter 6) a significant relationship between atypical depression and bipolar II disorder, which is consistent with the findings of Perugi *et al.* (1998) and Benazzi (1999a, b).

For a long time, agitated depression has been considered by some authors to be a type of mixed state (Koukopoulos and Koukopoulos, 1999; Akiskal and Pinto, 2000; Marneros, 2001). Kraepelin (1899, 1913) and Weygandt (1899) described

states of agitated depression as belonging to the mixed states. However, according to Kraepelin's concept of manic-depressive insanity, a distinction between bipolar or unipolar was not important. According to his concept, all affective disorders belong together, and the mixed states were for Kraepelin the strongest argument for such a unification (Kraepelin, 1899). But the rebirth of the unipolar–bipolar distinction in the mid-1960s again raised the question of the nature of agitated depression. For Koukopoulos *et al.*, the answer is clear: agitated depression is a bipolar disorder belonging to the mixed states (Koukopoulos and Koukopoulos, 1999; see Chapter 7). They concluded:

> Agitated depression should be considered a mixed affective state given its phenomenology and response to treatments. Antidepressants worsen the condition of these patients and, in many cases, induce agitation or psychosis in cases with otherwise simple depression. The authors propose new diagnostic criteria for agitated depression and introduce the term *minor agitated depression* for the cases with psychic agitation without motor agitation or psychotic symptoms. Three forms of agitated depression*(mixed depression)* are described:
> (1) psychotic agitated depression
> (2) agitated depression with psychomotor agitation and
> (3) minor agitated depression.
>
> All these forms may be induced or aggravated by antidepressants and improve with mood-stabilizing and antipsychotic treatments, as well as ECT.

Akiskal coined the term "hyperthymic depression" (Akiskal and Pinto, 2000), which is similar to Koukopoulos's "excited depression" (Koukopoulos *et al.*, 1992). According to Akiskal and Pinto (2000), hyperthymic depression is a subtype of bipolar disorder (bipolar IV). For this category, they proposed using patients with clinical depression that occurs later in life and that is superimposed on a lifelong hyperthymic temperament. They are typically males in their 50s whose life-long drive, ambition, high energy, confidence, and extroverted interpersonal skills helped them to advance in life, to achieve success in a variety of business domains and/or political life.

The major external validation of the bipolar status of depressions in association with hyperthymic temperament is familial bipolarity comparable to that of bipolar II patients (Cassano *et al.*, 1992).

The criteria of bipolar depressive mixed states according to Akiskal and Pinto are given in Table 1.7:

Recurrent brief depression, as described by Jules Angst (1988), recurrent brief hypomania (Angst, 1992), and recurrent brief anxiety (Angst and Wicki, 1992), share an ultrarapid-cycling pattern of mood symptoms according to the findings of Angst *et al.* (see Chapter 5). The authors point out that the example of recurrent brief depression demonstrates that severe measures of mood disorders should not

Table 1.7 Clinical picture of (bipolar) depressive mixed state

Meets minimum criteria for major depressive disorder plus three or more of the following:
• Unrelenting dysphoria, irritability, and instability
• Dramatic expressions of suffering
• Psychomotoric agitation against a background of retardation
• Intense sexual excitement
• Extreme fatigue with racing thoughts
• Free-floating anxiety, as well as panic attacks
• Suicidal obsessions and impulses

Modified from Akiskal and Mallya (1987).

be restricted to the number of symptoms, the duration of episodes, and the consequences, but should also include recurrence (i.e., course). The concept of recurrent brief depression and of combined mood disorders and their integration into psychiatric practice is, according to the authors, clinically relevant because it enables psychiatrists to identify a highly prevalent, severely impaired, and often suicidal subgroup of patients and also opens the way for new therapeutic research (see Chapter 5).

Polymorphic psychotic disorders as a possible atypical bipolar disorder

In ICD-10, the World Health Organization defined the category "acute and transient psychotic disorders" (F23). This category involves a broad group of disorders corresponding to national original concepts (Marneros and Pillmann, 2004). But the core group of this category – the polymorphic psychotic disorders – has a high concordance with the so-called cycloid psychoses (Pillmann *et al.* 2002; Marneros and Pillmann, 2004). The creator of the concept of cycloid disorders, Karl Kleist, was convinced that they present a kind of bipolar disorder (Kleist, 1929; Pillmann *et al.*, 2000; Marneros and Pillmann, 2004). In fact, there are some similarities between polymorphic psychotic disorders (also cycloid disorders) and the "typical" bipolar disorders, but there are also differences, as elaborated elsewhere in this book (see Chapter 9).

Family, premorbid, course – especially kind of episode – and outcome data support the assumption that the acute polymorphic psychoses are related to the affective spectrum. It seems that the acute polymorphic psychotic disorders could belong to a psychotic continuum between schizophrenia and affective disorder, in a way similar to the schizoaffective disorders, but at a different position and with a different relationship (Marneros and Pillmann, 2004).

Lessons from the past and options for the future

Obviously, bipolar disorders belong to a great family, including members with very strong family similarities, but also individual characteristics, separating them from other members and characterizing them in an unchangeable way. But the basic characteristics remain common for all members. This is not a new concept, but one that is 2000 years old, originated by the father of bipolar disorders – Aretaeus of Cappadocia. We agree with what Aretaeus wrote 2000 years ago: "*τρόποι εἴδεσί μεν μύριοι, γένει δέ μοῦνο εἷς*": "There are many different phenomenological types of the illness, but they all belong to one and the same family."

But, nevertheless, we still need definitions and concepts with compelling validity. As Sachs and Graves point out in this book (see Chapter 17),

> The psychiatric literature includes relatively few adequately powered and controlled double-blind clinical trials reporting results for bipolar disorders. The majority of these randomized clinical trials report results for treatment of acute mania in hospitalized bipolar I (BP-I) patients. The majority of bipolar patients are, however, not BP-I, and manic states are relatively infrequent. Why are there so few published controlled treatment studies dealing with common clinical problems like rapid cycling, mixed episodes, and atypical bipolar disorder? (see Chapter 17).

The authors give the answer:

> "The first consideration is the conceptual dissimilarity of the terms rapid cycling, mixed episodes, and atypical bipolar disorder. These terms correspond to three distinct organizational levels used in the DSM-IV mood disorder nosology and represent the concepts of course specifier, acute episode, and subtype of bipolar (American Psychiatric Association, 1994). Study designs for each require attention to sample selection, outcome measures and an analysis plan matched to the appropriate level in the organizational hierarchy of the DSM-IV mood disorder classification (see Chapter 17).

The purpose of this book is to establish the evidence that can enhance the validity of our definitions and nosological allocations, which in turn might be expected to enhance our clinical care and lead to more focused research questions.

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2

Emerging concepts of mixed states: a longitudinal perspective

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Mixed state (MS) refers to an affective condition in which depressive and manic symptoms are simultaneously present. It may manifest as a transitional condition, bridging one phase of the illness with another, or may exist as an independent clinical attack. In the latter case, along with mania and depression, MS represents a major phase of manic-depressive illness; however, it is often misdiagnosed because of its pleomorphic symptomatological presentation, as well as underdiagnosed because of inadequate diagnostic delimitation. There is no terminological uniformity in the literature, and there is a regrettable tendency to use terms such as "mixed state," "mixed mania," "depression during mania," and "dysphoric mania" interchangeably. In this chapter, we critically review the empirical literature on different definitions of MS, focusing on their clinical validity. In doing so, we devote special attention to the evolution of MS in the overall course of manic-depressive illness.

Definition of bipolar mixed states

In the original description of MS given by Kraepelin (1899) and by his pupil Weygandt (1899), one or more of the main psychopathological features of mania (mood, cognition, psychomotor activity) were replaced by one or more of the main features of depression, and vice versa. This approach led Kraepelin to postulate six putative subtypes: (1) depression with flight of ideas; (2) excited depression; (3) depressive-anxious mania; (4) unproductive mania; (5) inhibited mania; and (6) manic stupor. In addition, Kraepelin described some specific characteristics of MS, such as the tendency to become chronic and the frequent presence of psychotic features (Table 2.1).

More recently, Berner *et al.* (1983, 1993) provided operational criteria (Vienna research criteria) for MS based on the "dynamic" concept proposed by Janzarik (1959). "Dynamic" in this context indicates a dimension of psychic life, biologically

Table 2.1 Clinical features of mixed states

Opposite symptoms (in the domains of mood, thought, and psychomotility)
Psychotic symptoms (mimicking dementia praecox)
Course (periodicity, better prognosis than dementia praecox)
Personal and family history (manic-depressive illness)
Length of episode (more chronic than mania or depression) according to Kraepelin (1899) and Weygandt (1899)

Table 2.2 Vienna criteria for stable mixed state according to Berner *et al.* (1993)

A. Appearance of persisting changes in affectivity, emotional resonance, or drive following a period of habitual functioning:
1. Depressed, anxious, euphoric, expansive or hostile mood
2. Emotional resonance either lacking in or limited to depressive, manic, hostile, or anxious responses
3. Persistent presence of a drive state contradictory to the mood state and/or the emotional resonance
B. Biorhythmic disturbances:
1. Diurnal variations of affectivity, emotional resonance, or drive
2. Sleep disturbances (interrupted, prolonged, or shortened sleep or early awakening)

determined, deriving from an intimate mixture of the individual's drive and emotions. In an MS, the affective oscillations would be the result of dysregulation in this process, giving rise to perplexity, indecisiveness, perceptual disturbances, and a sense of external interference and depersonalization (Table 2.2). These characteristics are specific to bipolar MS and cannot be derived from the mere combination of depressive and manic symptomatology. The Vienna criteria thereby delineate a mixed affective subtype with sustained instability characterized by the "persistent presence of a drive state contradictory to the mood state and/or the emotional resonance" (Berner *et al.*, 1993, p. 164). This formulation emphasizes the emotional instability of the MS, a feature shared with rapid cycling.

Diagnostic and Statistical Manual of Mental Disorders, 3rd edn revised (DSM-III-R: American Psychiatric Association, 1987) basically defined MS as the sum of manic and major depressive symptoms co-occurring over 1 week or longer, either as the intermixing of the two opposite syndromes or their ultrarapid alternation every few days. DSM-IV (American Psychiatric Association, 1994) essentially retained the former pattern and, wisely, excluded the latter. There are several problems with the DSM-IV concept of MS. First, the criteria do not consider

cases in which expansive and depressive elements are combined without fully satisfying the criteria for one or the other type of episode. Second, DSM-IV stipulates an exclusion criterion that mixed symptomatology is "not due to the direct physiological effects of a substance or a general medical condition" (DSM-IV, p. 333). To evaluate if a mixed episode is a direct consequence of brain damage, substance abuse and/or toxicity may be rather difficult; moreover, these conditions are frequently reported in the personal history of patients with MS (Post and Kopanda, 1976; Himmelhoch, 1979).

Tenth Revision of the International Classification of Diseases (ICD-10: World Health Organization, 1992) gives a less strict definition, including, *en passant*, the possibility of MS consisting of major depression plus hypomania (rather than full-blown mania). But, like the DSM concept, it requires that "the diagnosis of mixed bipolar disorder should be made only if the two sets of symptoms are both prominent for the greater part of the current episode" (ICD-10, p. 119). In addition, ICD-10 requires at least one past affective episode for the diagnosis of MS, and therefore does not recognize that mixed symptomatology frequently represents the first expression of a bipolar mood disorder.

In the last part of the past century, most research on MS has been focused on manic states coexisting with some depressive features. These conditions are generally defined as "dysphoric mania" and variously considered as a subtype of mania (Murphy and Beigel, 1974), a more severe manic state (Post *et al.*, 1989), or a transitional state between mania and depression (Bunney *et al.*, 1972). In the same period, the agitated depressive forms of MS, originally delineated by Kraepelin (1899) and Weygandt (1899), and consisting of intrusions of psychomotor restlessness, hypersexuality, and racing thoughts into depression (Akiskal and Mallya, 1987; Koukopoulos *et al.*, 1992) have been relatively neglected. We will consider both forms of MS in this chapter. We will also consider the hypothesis that derives MSs from the intrusion of a temperament into an episode of opposite polarity (Akiskal, 1992), i.e., depressive temperament into mania (manic mixed state) and hyperthymic temperament into major depression (depressive mixed state).

Dysphoric mania

We will first describe clinical research on dysphoric mania. A large literature (Bauer *et al.*, 1994; McElroy *et al.*, 1995; Perugi *et al.*, 1997; Swann *et al.*, 1997; Akiskal *et al.*, 1998) is now available indicating that the DSM-IV threshold for syndromal depression during mania is too restrictive, and suggesting that few depressive symptoms would suffice in validating the clinical diagnosis of mixed mania. The McElroy *et al.* (1992) operationalization of mixed mania (Table 2.3)

Table 2.3 Cincinnati criteria for mixed mania according to McElroy *et al.* (1992)

A.	A full manic syndrome by DSM-IIIR criteria
B.	Simultaneous presence of at least three associated depressive symptoms
C.	Simultaneous presence is defined as manic and depressive symptoms occurring at the same time or alternating extremely rapidly, within minutes
D.	Manic and depressive symptoms are simultaneously present for at least 24 h

DSM-IIR, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn revised (American Psychiatric Association, 1987).

conforms to the concept of dysphoric mania, i.e., mania plus at least three non-manic depressive symptoms. Utilizing this definition, some distinctive features of mixed mania compared with pure mania have been found: greater prevalence in females, more past MS episodes, higher probability of an MS at onset, and higher rate of comorbidity with obsessive-compulsive disorder (McElroy *et al.*, 1995).

A similar definition of MS was used in the clinical Epidemiology of Mania (EPIMAN) study, which was conducted in four centers in France, involving over 100 patients (Akiskal *et al.*, 1998). Because patients were entered into the study on the basis of meeting full criteria for index manic episodes, the rates for strictly defined DSM-IV mixed states were low (6.7%). But using a cut-off of two or more depressive symptoms, 37% could be characterized as dysphoric manic. As expected, these patients scored more than 10 on the modified Hamilton-D (HAM-D) scale. Depressed mood and suicidal thoughts had the best predictive diagnostic value for mixed mania. An important finding of this study was that mixed manic patients, compared with those with pure mania, had a higher percentage of depressive temperamental traits. Such data argue that mixed mania can be defined categorically by two or more depressive symptoms, psychometrically on the basis of HAM-D > 10, or dimensionally on the basis of depressive (dysthymic) temperamental traits. The latter finding supports the hypothesis that MSs arise when an affective episode is superimposed on a temperament of opposite polarity (Akiskal, 1992). Data along these lines have also been reported in the Pisa–San Diego collaborative study (Perugi *et al.*, 1997, to be more fully discussed later in this chapter) and the Halle study (Brieger *et al.*, 2003).

The optimum number of depressive symptoms during mania in characterizing MS has varied in the literature. McElroy *et al.* (1992) proposed a cut-off of $\geqslant 3$, Akiskal *et al.* (1998) $\geqslant 2$, and Swann *et al.* (1997) $\geqslant 1$ depressive symptoms in the midst of mania for the diagnosis of MS. Defining this cut-off is not a mere nosological exercise, because even one depressive symptom during mania seems to predict low response to lithium and good response to divalproex (Swann *et al.*, 1997).

Table 2.4 Pisa–San Diego criteria for mixed state based on Perugi *et al.* (1997)

A. A state of sustained (at least 2 weeks) emotional instability and/or perplexity in which depressive and manic symptoms are simultaneously present in a fluctuating manner. Opposite extreme manifestations in at least two of the following five areas should be present at the same time:
   1. Mood (anxious–sad versus euphoric–irritable)
   2. Thought flow (slowing versus racing)
   3. Thought content (depressive versus expansive)
   4. Perceptual disturbance (depressive versus expansive)
   5. Motility (retardation versus acceleration)

B. At least two of the following:
   1. Labile or hypersyntonic, i.e., heightened emotional resonance
   2. Low threshold for anger–hostility, especially impulse dyscontrol
   3. Major shifts in sexual drive from habitual baseline
   4. Marked sleep disturbances
   5. Diurnal variations of at least one of the items listed under A

C. Adequate interpersonal relationships and affective responses in the premorbid and/or interepisodic phases

The mixed state so defined could, in addition, be characterized as "non-psychotic" or "psychotic" (in which case further specified as mood-congruent or-incongruent) by *Diagnostic and Statistical Manual*, 3rd edn revised (DSM-IIIR) criteria; "chronicity" refers to duration of at least 2 years; and "rapid-cycling" is to be used as a qualifier if the patient has had four or more episodes (of whatever type) per year.

Toward a broader definition of mixed mania

As discussed, in the contemporary literature, bipolar MSs have been defined on the basis of a combination of manic with depressive symptoms, varying primarily on the basis of the minimum number of depressive symptoms required. In a collaborative study between the Department of Psychiatry at the University of Pisa and the International Mood Center at the University of California San Diego (Perugi *et al.*, 1997), we developed a more specific set of MS criteria based on the concepts of Kraepelin and the Vienna school (Table 2.4). These criteria include psychotic and non-psychotic forms. Clinical, temperamental, and familial characteristics of 143 patients so defined were compared with those of a group of 118 patients who met DSM-IIIR criteria for mania. The major finding of this study was that MS as defined by DSM-III-R criteria identified only half of all mixed states (Fig. 2.1). This subgroup conforms to the concept of dysphoric mania, which is the prototype of MS in the current literature (Post *et al.*, 1989; McElroy *et al.*, 1992). Kraepelin (1899) had described this entity as depressive-anxious mania. Our data

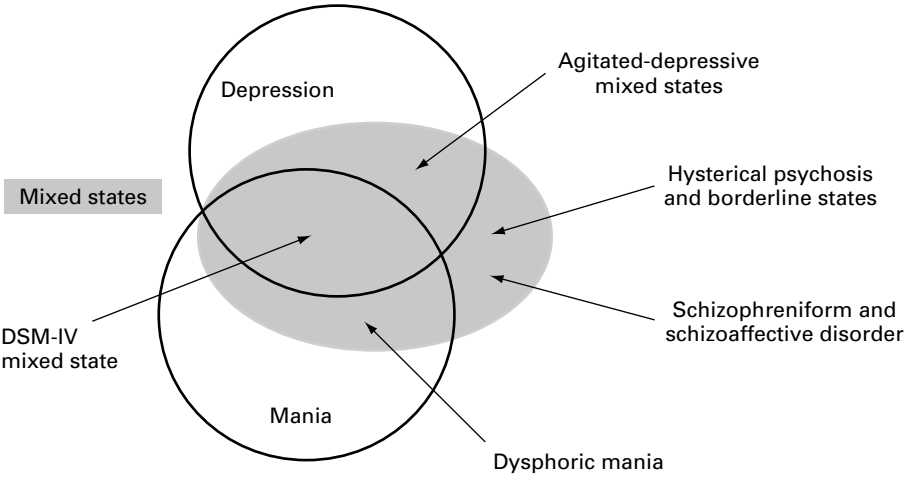

Fig. 2.1 The relationships of Kraepelinian, Vienna, and Pisa–San Diego mixed states (shaded area) to *Diagnostic and Statistical Manual*, 4th edn (DSM-IV) mixed state and related entities.

also document the existence of at least two other forms of MS. The first one (accounting for 26% of our patients) is best characterized as mania with fatigue and indecisiveness. The second mixed bipolar form (17% of our patients) is best described as agitated psychotic depression with pressure of speech and flight of ideas. These two mixed subgroups, which do not meet DSM-IIIR criteria for mixed bipolar episode, were well described by Kraepelin (1899) as, respectively, "inhibited-unproductive mania" and "excited depression with flight of ideas."

The results of the Pisa–San Diego collaborative study are in agreement with the suggestions made by McElroy *et al.* (1992) that an MS can exist with full syndromal mania and less than syndromal depression. In line with suggestions by Kraepelin (1899), Weygandt (1899), Akiskal and Mallya (1987), and Koukopoulos *et al.* (1992), we further delineated a mixed depressive state which consists of full syndromal depression and less than syndromal mania.

The descriptions that we adopted from Kraepelin (1899) and the Vienna school (Berner *et al.*, 1993) seem to be more inclusive than those proposed in DSM-IV and ICD-10 (Fig. 2.1). Indeed, utilizing these criteria we can redefine as MS a substantial proportion of manic and major depressive episodes according to DSM criteria. Some of the clinical pictures that could be defined as MS according to our criteria are probably covered under the non-affective psychoses and borderline personality disorder in DSM-IV and ICD-10. The validity of our broadly defined subtypes of bipolar MS is supported by the fact that their family history and course characteristics are essentially indistinguishable from those of the core dysphoric mixed-mania group (Perugi *et al.*, 1997). Moreover, our criteria appear useful in detecting an MS even as a first episode. In fact, although the most frequent polarity

Table 2.5 Differences between depressive mixed state and bipolar depression

Fewer number of episodes
Less cyclic course (no rapid cycling)
More likely to show mixed state at first episode
More previous mixed episodes
Longer duration of the current episode
Less interepisodic remission
More incongruent psychotic features
More agitation, irritable mood, pressured speech, and flight of ideas

Data from Perugi *et al.* (2001b).

of onset in our patient population was a depressive episode, MS represented the onset of mood disorder in more than 40% of MS index patients. In this respect, ICD-10 seems unduly restrictive in requesting at least one past affective episode.

Depressive mixed states

The depressive forms of MS are not included in the current official classificatory systems and, until recently, were largely neglected in the current literature. In order to characterize depression with mixed features, better we compared familial, demographic, clinical, and course characteristics of 32 patients with depressive MS according to Pisa criteria and those of 36 patients with major bipolar depression (Perugi *et al.*, 2001b). The two groups had close similarities in clinical and sociodemographic characteristics, including age, gender distribution, marital status, schooling, residence, age at onset, age of first treatment, age of first hospitalization, percentage of chronicity of the index episode, lifetime suicide attempts, and premorbid temperamental dispositions. First-degree family history for bipolar illness and other mental disorders was also similar, except that for major depression, which was significantly more common among the relatives of depressive MSs. These findings were in part foreshadowed in a previous Pisa study of MSs from the female unit at our institute (Dell'Osso *et al.*, 1991), where an excess of depressive familial background had been observed in the entire sample (that had not been divided into depressive and manic MS).

Depressive-MS patients can be distinguished from non-mixed bipolar depressives by the fact that they have fewer episodes of longer duration, and frequently begin their illness with a mixed episode (Table 2.5). Furthermore, as described by Keller *et al.* (1986), the prognosis of MSs in terms of interepisodic symptomatology is worse than in non-mixed depression. Concerning the symptomatological picture, incongruous psychotic features were more common in depressive MS compared to bipolar pure depressive patients. This observation is consistent

with the view that MS does not represent a mere superposition of affective symptoms of opposite polarity (Himmelhoch, 1979; Berner *et al.*, 1983; Akiskal and Mallya, 1987; Koukopoulos *et al.*, 1992; Perugi *et al.*, 1997; Akiskal *et al.*, 1998). Long-lasting affective instability emerges as the core phenomenological features; from this protracted instability seems to arise perplexity, psychotic experiences, and grossly disorganized behavior. This conclusion is further substantiated by the HAM-D symptomatological profile where MS patients report more cognitive disorders, agitation, and paranoid symptoms with less motor retardation, somatic symptoms, and sexual disturbances compared with bipolar pure depressives.

In agreement with previous clinical observations (Akiskal and Mallya, 1987; Koukopoulos *et al.*, 1992), the symptomatological profile of depressive MS is one of agitated, mostly psychotic depression with irritable mood, pressured speech, and flight of ideas. Akiskal and Mallya (1987) had reported that 25 patients referred for treatment-resistant depression displayed subacute or chronic MSs, apparently induced by tricyclic antidepressants; these mixed depressive states were characterized by dysphoria, severe agitation, refractory anxiety, unendurable sexual excitement, intractable insomnia, suicidal obsessions and impulses, and "histrionic" demeanor; they improved with antidepressant discontinuation and initiation of lithium or carbamazepine. Koukopoulos *et al.* (1992) found that 45 patients with bipolar disorder suffering from a "mixed depressive syndrome" who met DSM-IIIR criteria for major depression, but not for mania, deteriorated when treated with antidepressants, experiencing increased agitation, insomnia and, in some cases, suicidal impulses; these same patients responded to low-dose neuroleptics, lithium, anticonvulsants, and electroconvulsive therapy. Koukopoulos and Koukopoulos (1999) have subsequently written a scholarly review on the clinical rationale for the validity of the concept of agitated depression as an MS.

Bipolar II and unipolar depressive mixed states

The literature reviewed thus far pertains largely to mixed mania and agitated depression observed among hospitalized and/or psychotic patients. We will now consider depressive MS among outpatients with bipolar II and unipolar depression, which is even less studied. The high prevalence of hypomanic features in depressed bipolar II and unipolar outpatients has recently been reported by Benazzi (2000) and Benazzi and Akiskal (2001). The prevalence of full syndromal hypomania among 70 outpatients with major depression was low (2.8%), but three or more concurrent hypomanic symptoms were reported in 28.5% of the sample. About half (48.7%) of bipolar II patients had three or more concurrent hypomanic symptoms during major depression. Irritable mood, talkativeness, and

distractibility were significantly more common in bipolar II than in unipolar patients; racing thoughts were highly prevalent in both unipolar and bipolar II.

Among the (hypo)manic symptoms reported in depressive MS, flight of ideas, racing thoughts, and distractibility belong to the same dimension of psychic excitement. Increased mental activity (daydreaming, mental ruminations) has been reported as one of the fundamental features of bipolar II "depression" (Akiskal *et al.*, 1995; Perugi *et al.*, 1998). Other hypomanic symptoms such as euphoria and grandiosity, by definition, are too rare in depression to be utilized for the selection of patients with depressive MSs, whereas irritability and restlessness might be somewhat non-specific.

According to Akiskal and Benazzi (2003), unipolar depressives with depressive MS might be classified into the bipolar spectrum, and must be considered "pseudo-unipolar." The bipolar nature of these clinical pictures should, however, be further confirmed. No prospective longitudinal studies explored whether intraepisodic hypomanic symptoms during a depressive episode predict a diagnostic switch from unipolar depression to bipolar disorder. Clinical observations suggest that unipolar depressive MS may not adequately respond to antidepressants, and that the use of antidepressants for unipolar depressives with intraepisodic manic symptoms may be causative in treatment resistance or lead to cycling (Akiskal and Mallya, 1987; Koukopoulos *et al.*, 1992). Well-designed controlled trials with antidepressants versus mood stabilizers and/or other antimanic agents should be conducted comparing unipolar depressives with and without intraepisode excitatory symptoms.

Long-term aspects of mixed states

The literature on clinical and course characteristics of MS from Kraepelin through the last decade of the past century has been masterfully reviewed by McElroy *et al.* (1992). Alcohol abuse and neuropsychiatric conditions are common in MSs (Himmelhoch *et al.*, 1976). MS has been best characterized in female inpatients (Dell'Osso *et al.*, 1991; Perugi *et al.*, 1997; Akiskal *et al.*, 1998), often arising from a course of illness with more depressive than manic episodes and with a tendency to repeat over time (Perugi *et al.*, 2000). The available data further suggest that MS patients, in comparison with mania and bipolar depressives, more frequently begin their illness with a mixed episode and have fewer episodes of longer duration (Perugi *et al.*, 1997). The fact that MS is often the first episode in the course of the illness seems to indicate that it cannot be considered an end-stage or "malignant" *dénouement* of the illness. Moreover, MS and rapid cycling seem to be two independent manifestations of manic-depressive illness (Perugi *et al.*, 2000).

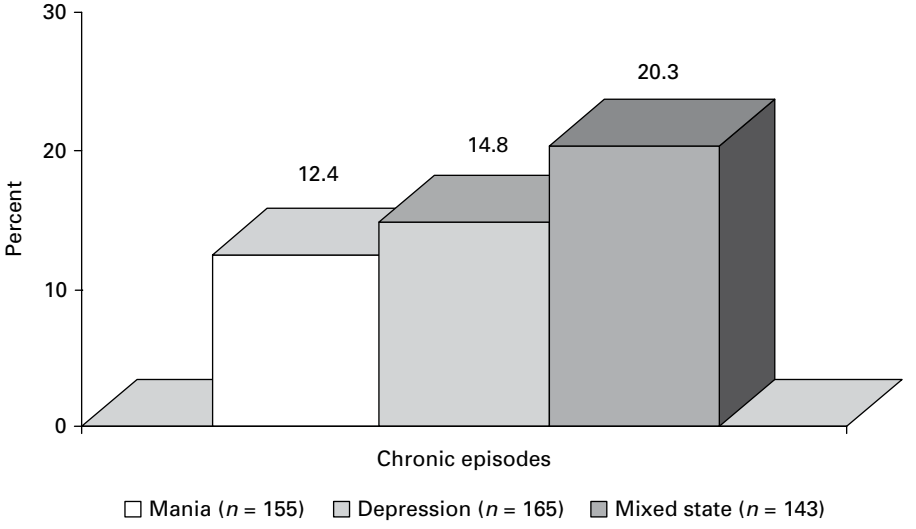

Fig. 2.2 Rates of chronic episodes (length < 2 years) in bipolar patients. Data from Perugi *et al.* (2000).

The rate of chronic episodes, defined as a duration of the current episode lasting more than 2 years, seems to be higher in MS than in mania and major depression (Perugi *et al.*, 2000; Fig. 2.2). Frequent chronic evolution was reported by Kraepelin (1899), in his original description, as a specific clinical feature of MS. Furthermore, as described by Keller *et al.* (1986) and Perugi *et al.* (2001b), the prognosis of MSs in terms of interepisodic symptomatology is worse than that of non-mixed episodes.

In considering the frequent coexistence of MS with long-lasting subaffective symptomatology, the role of temperamental disposition in the development of MS is a relevant factor (Akiskal, 1992). Affective temperaments, as conceived in the classical psychiatric literature (Kraepelin, 1899; Kretschmer, 1936) and more recently formulated (Akiskal *et al.*, 1979), refer to subaffective trait expressions that represent the earliest subclinical trait phenotypes of affective disorders, and which persist as the subthreshold interepisodic phase of these disorders. The identification of depressive, hyperthymic, cyclothymic, and irritable temperamental attributes has important implications not only for the classification of mood disorders, but also for their prevention, treatment, and prognosis.

We will now consider more fully the implications of the provocative hypothesis that derives MS from a temperament opposite to the polarity of the affective episode (Akiskal, 1992). Dell'Osso *et al.* (1991, 1993) have reported data in partial support of this hypothesis. In our study (Perugi *et al.*, 1997), mania seems to arise from a hyperthymic background; by contrast, MS seems to arise from a depressive or hyperthymic disposition and, more tentatively, when traits of the two

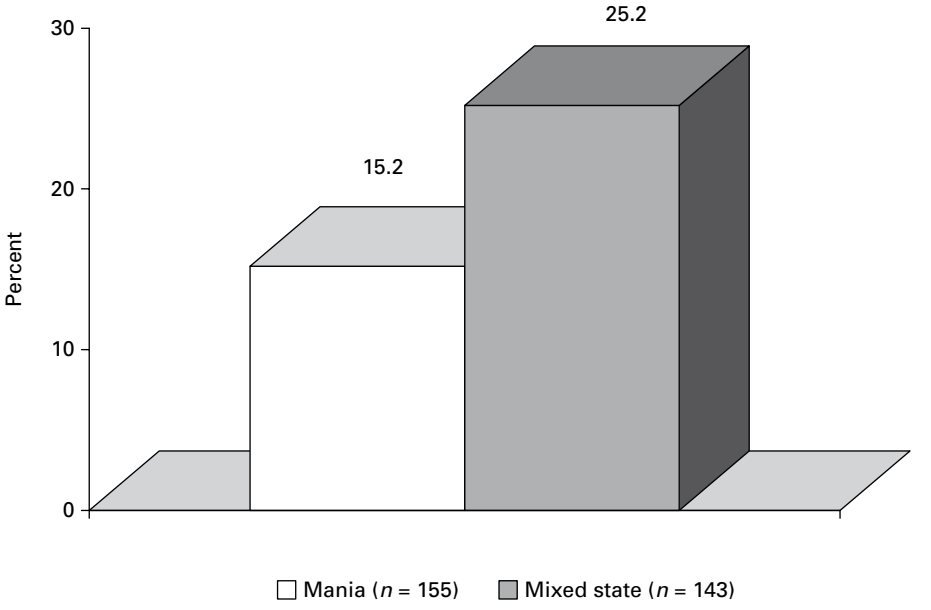

Fig. 2.3 Rates of mixed temperament (co-occurrence of at least three hyperthymic and three depressive temperamental traits) in patients with pure mania and mixed state. Data from Perugi *et al.* (1997).

temperaments coexist in a mixed-irritable form. Indeed, using a "mixed" threshold of temperamental traits – patients meeting the criteria of at least three or more of both types – we found that the MS group had a higher rate than the manic group of such "mixed temperamental" traits (Fig. 2.3).

The EPIMAN study (Akiskal *et al.*, 1998) validated the significantly higher rate of hyperthymic temperament in classic mania, in contrast with the significantly higher rate of depressive temperament in the mixed manic form; in addition, some mixed manic patients could be characterized as cyclothymic. The fact that these two temperaments have significantly higher female prevalence in the community (Placidi *et al.*, 1998) might explain the female preponderance of MS in clinical populations. The instability generated from the concomitance of cyclothymic traits on the one hand and mania on the other might explain the extreme affective turmoil of these patients.

The relationship between affective temperaments and subtypes of mania has been further investigated by Perugi *et al.* (2001c). In 155 patients with manic episode according to DSM-IIIR criteria, those characterized by "euphoric–grandiose," "paranoid–anxious," and "accelerated–sleepless" symptomatology were most likely to belong to the hyperthymic temperament; those with more "depressive" symptoms had the highest rate of depressive temperament, and "irritable-agitated" features were high on both temperaments. These findings are consistent with the

Table 2.6 Relationships between temperamental dispositions and affective episodes

Temperament	Depression	Mania
Hyperthymic	Agitated	Euphoric–paranoid
Depressive	Inhibited	Dysphoric–mixed
Cyclothymic	Atypical–anxious	Irritable–unstable–labile

Table 2.7 Relationships between temperamental dispositions and long-term complications of manic-depressive illness

Temperament	Bipolar II	Bipolar I
Hyperthymic	Rapid-cycling	Chronic mania
Depressive	Residual symptomatology	Chronic mixed state
Cyclothymic	Borderline features	Continuous cycling (deteriorative)

hypothesis that the presence of different affective temperaments influences the phenomenology of mania. Hyperthymic temperament seems to underlie the excited pole with euphoric–accelerated-paranoid phenomenology; by contrast, the depressive temperament seems to mute the expression of mania into a depressive–manic phenomenology. Finally, patients with a constellation of the traits of both temperaments seem to emerge as irritable–agitated manics with more severe symptomatology and treatment refusal.

The foregoing findings and considerations suggest the model reported in Table 2.6:

(1) The hyperthymic temperament underlying major depression produces agitated depressive MS and, combined with mania, gives rise to pure episode.
(2) The depressive temperament produces inhibited melancholic depression as well as mixed mania (which, of all mixed states, probably best deserves the designation of "dysphoric mania").
(3) The cyclothymic temperament underlies atypical depression or unstable–labile mixed state.

As regards the long-term complications of manic depressive illness (Table 2.7), we propose that the hyperthymic temperament is related to the development of rapid cycling in bipolar II and chronic mania in bipolar I, the depressive temperament to residual symptomatology and chronic mixed states, and the cyclothymic temperament to "borderline features" and/or to a deteriorating course of continuous cycling.

Conclusions

MS does not represent a mere superposition of affective symptoms of opposite polarity, but a complex 'process' of temperamental, affective, and other processes. Affective instability, fluctuation, lability, irritability, and diurnal variation – all sustained over a period of weeks – emerge as the core phenomenologic features of mixed bipolar states; perplexity, psychotic experiences, and grossly disorganized behavior seem to arise from this protracted instability. Such instability in turn appears to be the clinical expression of the neurophysiological dysregulation believed to underlie manic depression (Delay, 1961; Goodwin and Jamison, 1990). MS might be considered the most eloquent expression of this dysregulation. Hence the difficulties in clinical management and the high suicide potential (Strakowski *et al.*, 1996; Goldberg *et al.*, 1998).

The foregoing phenomenologic considerations, which suggest considerable broadening of the unstable terrain of mixed bipolar states beyond those of DSM-IV, have important clinical implications. Although DSM-IV disqualifies pharmacologic induction of mixed episodes from its definition of bipolar MSs, many clinical investigators (Post and Kopanda, 1976; Himmelhoch, 1979; Koukopoulos *et al.*, 1992) have commented on how antidepressants, alcohol, and stimulants could contribute to the genesis of MSs; regrettably, MSs in the setting of such contributing factors are currently excluded from the MS rubric in DSM-IV. The proper clinical recognition of depressive MSs would thus help in the cause of preventing these patients from taking such drugs (Cassano *et al.*, 1983; Akiskal, 1994; Koukopoulos and Koukopoulos, 1999). Hypothetically, temperamental dysregulation might underlie the exquisite sensitivity of these patients to such substances (Akiskal, 1994). Such trait factors as depressive and hyperthymic temperaments, when opposite to the polarity of superimposed affective episodes, might in turn underlie the affective instability of mixed bipolar states. Cyclothymic temperament appears to be more relevant to the labile instability of bipolar II.

The proper identification of a depressive MS has critical implications for clinical practice. These conditions might be confused with a number of other psychiatric disorders, including unipolar agitated depression, delusional depression, schizophrenia, borderline personality disorder, and organic mental disorder (Himmelhoch *et al.*, 1976; Secunda *et al.*, 1985; Koukopoulos *et al.*, 1992; Akiskal and Mallya, 1987). Therefore, it would be important to distinguish MSs from these conditions so that treatments (e.g., antidepressants) that might worsen their symptomatology would be avoided, and treatments that might be particularly effective (e.g., anticonvulsants, atypical antipsychotics, and electroconvulsive therapy) would not go underutilized.

Mixed states have re-emerged as a new focus of research in affective disorders, and future investigations from other centers will be important in extending the findings and conceptual advances described herein. Only one study (Cassidy *et al.*, 2001) has been published on the stability of MS over prospectively examined follow-up of interepisode duration of 6 months. Therefore, prospective studies will be particularly informative in future research on MS.

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3

Rapid-cycling bipolar disorder

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Introduction

Since the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edn (DSM-IV: American Psychiatric Association, 1994) recognized the existence of rapid cycling as a specific pattern of presentation, there has been increased interest in studying this treatment-refractory variant of bipolar disorder (Bauer *et al.*, 1994). Prior to recent years, only open naturalistic studies had been conducted on populations of patients with rapid-cycling bipolar disorder. More recent data have suggested that this variant of illness is not always refractory to conventional treatment (Baldessarini, *et al.*, 2000). In particular, the data suggest that the management of hypomania and mania accompanying this variant of illness is uncomplicated and that lithium is frequently quite effective in managing this phase of the illness (Dunner *et al.*, 1976). However, it is now recognized that it is the management of the depressed phase that poses the greatest challenge to our pharmacotherapeutic armamentarium (Calabrese *et al.*, 2001). The frequent recurrence of treatment-refractory depression is emerging as the greatest unmet need in the clinical management of patients with rapid-cycling bipolar disorder, and particularly those comorbid presentations with alcohol and drug abuse (Ketter and Calabrese, 2002). What follows is an update of the research conducted in the past 2 years that has aimed to clarify different aspects of rapid-cycling bipolar disorder, refine the tools of its diagnosis and management, and discover new pharmacotherapeutic interventions and strategies.

In a chapter of the "preceding book" (Marneros and Angst, 2000) *Bipolar Disorders. 100 Years After Manic-Depressive Insanity*, we gave an extensive overview of many aspects of rapid cycling (Calabrese *et al.*, 2000a). In this book, we cover the efforts and results made *after* the publication of the above-mentioned book. However, in order to complete the chapters, we will now give a summary of certain aspects of our previous paper, and then expand on this information by providing the new data.

Family genetics

In the above-mentioned paper (Calabrese *et al.*, 2000a), the following was reported concerning family history and genetics: family studies of rapid-cycling bipolar disorder show no difference in family loading for bipolar disorder as compared with non-rapid-cycling patients, nor does rapid cycling cluster in families of rapid cyclers. Nurnberg *et al.* (1988) first evaluated the inheritance of rapid cycling. Twenty-nine of 195 bipolar/episodic schizoaffective patients were judged to be rapid cyclers (15%). The age-corrected risk of major affective disorder was 23.5% in 179 relatives of rapid cyclers and 31% in 189 relatives of matched non-rapid cyclers, suggesting that rapid cycling is not genetic and does not aggregate within families. This result was replicated by Coryell *et al.* (1992) and Lish *et al.* (1993). Coryell *et al.* collected information through family history and family study methods for 268 relatives of 45 rapid cyclers and 1273 relatives of bipolar non-rapid cyclers. More extensive data were obtained for 111 relatives of rapid cyclers and 397 relatives of non-rapid cyclers who were also re-evaluated prospectively and at 6 years after their initial interview. Neither data set revealed evidence suggesting that rapid cycling had bred true in their cohort. Lish *et al.* (1993) used the Family History Research Diagnostic Criteria to interview 165 rapid cyclers, non-rapid cyclers, or individuals with recurrent unipolar depressive disorder about the psychiatric history of 812 adult first-degree relatives. Rapid cyclers were younger and more likely to be female than non-rapid cyclers, but the relatives of rapid cyclers did not differ significantly from those of non-rapid cyclers in the prevalence of bipolar disorder, unipolar disorder, rapid-cycling bipolar disorder, or substance abuse. However, there was a non-significant trend for the relatives of rapid-cycling bipolar patients to have more substance abuse than relatives of non-rapid-cycling patients. These three studies appear to argue convincingly against any specific inheritance of rapid cycling as a discrete course modifier. However, it remains a possibility that early-onset rapid cycling, as opposed to late-onset, might be discretely inherited.

Only very recently have genetic abnormalities begun to be examined in rapid cycling. One anecdotal report has noted the presence of the same chromosomal aberration, a pericentric inversion of chromosome 9, in a bipolar II father and daughter (McCandless *et al.*, 1998). The same group of investigators first demonstrated an association between ultradian rapid cycling and low activity of catechol-*O*-methyltransferase (COMT), and extended this finding to bipolar patients with either a current or a lifetime history of rapid cycling (Kirov *et al.*, 1998). They hypothesized that variation in the COMT gene modifies episode frequency. Concurrently, Veit *et al.* (1998) presented new data suggesting that COMT activity is subject to variability in humans, that this activity is associated with episode frequency, and that low activity is primarily due to a G–A transition at codon 158.

Psychiatric patients with psychiatric illness in velocardiofacial syndrome (a genetic condition caused by a microdeletion of chromosome 22q11, which includes the COMT gene) were studied. Of 8 patients studied, 100% were found to have $COMT^{met}$ polymorphism on the complementary chromosome 22. It was hypothesized that, since the blockade of catecholamine reuptake by tricyclic antidepressants and the blocking of breakdown by monoamine oxidase inhibitors have been associated with the induction of mania, homozygosity for $COMT158^{met}$ predisposes to rapid cycling, and possibly represents a risk factor in the use of antidepressants as well. This study examined the frequency of COMT 158^{met} in 60 rapid cyclers. Of the 60 ultrarapid cyclers enrolled, four had been genotyped at the time of this publication, and all four were homozygous for $COMT158^{met}$ (the low-activity allele), supporting the hypothesis that the presence of this allele may alter the course of bipolar disorder.

In addition to the above-mentioned data, attempts to explore any genetic correlation with susceptibility to rapid-cycling bipolar disorder have continued (Jones and Craddock, 2001; Cusin *et al.*, 2001). Some of the genes of particular interest include those encoding the serotonin transporter, monoamine oxidase A (MAOA) and COMT (Jones and Craddock, 2001). Cusin *et al.* (2001) reported results suggesting that the serotonin transporter gene-linked functional polymorphic region (5-HTTLPR) variants may confer susceptibility toward rapid-cycling mood disorders. They retrospectively studied a sample of inpatients affected by recurrent and rapid-cycling mood disorders. The serotonin transporter gene-linked functional polymorphic region (5-HTTLPR) and the (A218C) tryptophan hydroxylase (TPH) gene variant were determined using a polymerase chain reaction-based technique. For 5-HTTLPR polymorphism, they genotyped 435 inpatients affected by major depressive ($n = 153$), bipolar ($n = 213$), and rapid-cycling ($n = 69$) mood disorders and 456 controls. For TPH, they genotyped 399 inpatients (mood disorder, $n = 132$; bipolar, $n = 203$; rapid-cycling, $n = 64$) and 259 controls. Random regression model analysis was used to investigate the longitudinal time course of the illness. It was found that 5-HTTLPR and TPH polymorphisms were not associated with a mood-disorder time course. However, the researchers observed an excess of 5-HTTLPR* long alleles among rapid-cycling subjects compared with both controls ($P = 0.018$) and remitting mood disorders ($P = 0.006$). TPH frequencies did not differ between mood-disorder subtypes. Even though the results of this study were not definitive, the large sample of subjects lent it credibility. More studies are needed to duplicate or clarify these results.

Pathophysiology

Findings from neuroimaging studies continue to enrich our understanding of the pathophysiology of mood disorders generally and rapid-cycling bipolar disorder

particularly (more on this topic can be found in Chapter 14). Brain involvement is currently thought to include both cortical and subcortical areas (Benabarre *et al.*, 2001; Ketter *et al.*, 2001; Schreiner *et al.*, 2001). Ketter *et al.* (2001) studied the effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. Forty-three medication-free, treatment-resistant, predominantly rapid-cycling bipolar disorder patients and 43 age- and gender-matched healthy control subjects had cerebral glucose metabolism assessed using positron emission tomography and fluorine-18-deoxyglucose. The results indicated that, when compared to control subjects, depressed bipolar disorder patients had decreased global, absolute prefrontal, and anterior paralimbic cortical, and increased normalized subcortical (ventral striatum, thalamus, right amygdala) metabolism. Degree of depression correlated negatively with absolute prefrontal and paralimbic cortical, and positively with normalized anterior paralimbic subcortical metabolism. Increased normalized cerebelloposterior cortical metabolism was seen in all patient subgroups compared to control subjects, independent of mood state, disorder subtype, or cycle frequency. It was noted that, in bipolar depression, a pattern of prefrontal hypometabolism consistent with previous observations in primary unipolar and secondary depression was observed, suggesting that this is part of a common neural substrate for depression independent of etiology. In contrast, the presence of cerebelloposterior cortical normalized hypermetabolism seen in all bipolar subgroups (including euthymic) suggests a possible congenital or acquired trait abnormality. However, the degree to which these findings in treatment-resistant, predominantly rapid-cycling patients pertain to community samples remains to be established. More studies with larger sample size are needed to generalize these interesting findings.

The potential relationship between the rapid-cycling pattern of bipolar disorder and the circadian rhythm continues to draw attention. Schreiner *et al.* (2001) described (in a case report) the sleep and sleep–wake cycle of an 81-year-old patient with *de novo* ultrarapid-cycling bipolar disorder. Mood was self-rated daily over a period of 10 weeks. Additionally, polysomnographic and motor activity recordings were performed during a drug-free baseline period. The researchers noted that both depressive and hypomanic episodes had an average duration of about 30 h. They concluded that the affective cycle was thus independent from the sleep–wake cycle. When mood shifts occurred during night time, sleep was different in nights following depression than in nights following hypomania. Positron emission tomography revealed a moderate bilateral frontal hypermetabolism in the hypomanic phase and yielded normal findings for the depressive stage. In contrast to what is usually expected in ultrarapid-cycling bipolar disorder, this case demonstrated, according to the authors, an unusual sleep-unrelated cycle duration in the oldest reported patient so far. However, the generalizability of this case report's findings would still be limited.

On the other hand, Weske *et al.* (Weske *et al.*, 2001; Voderholzer *et al.*, 2002) reported the neurobiological findings in another patient with 48-h rapid-cycling bipolar affective disorder. Alternating reduction and prolongation of sleep duration during manic and depressive days were found, as well as differences in the amount of rapid-eye-movement sleep. Cortisol secretion was regularly increased during depressive days. Regarding thyroid-stimulating hormone (TSH) secretion, the circadian rhythm was absent on depressive days. However, the glucose metabolic rate, as measured by positron emission tomography, did not differ on manic and depressive days.

In an attempt to study any electrophysiological correlation with mood pattern, Kudo *et al.* (2001) conducted a comparative analysis of 13 patients with epilepsy. Ten of these patients had fluctuating mood disturbances, and eight had rapid cycling of mood episodes. The researchers reported that an epileptogenic zone in the frontal and temporal lobes seems to play an important role in the mood episodes of the majority of patients with epilepsy.

Epidemiology, phenomenology, and comorbidity

While most researchers continue to consider rapid-cycling bipolar disorder as a distinct and more challenging subtype of bipolar disorder in adults and children (Findling and Calabrese, 2000, Sachs *et al.*, 2000b, Calabrese *et al.*, 2001; Findling *et al.*, 2001, Ketter and Calabrese, 2002; American Psychiatric Association, 2002), a few still argue that in 20% it more likely represents a transient complication of the long-term course of bipolar disorder (Akiskal *et al.*, 2000).

On the other hand, the depressive phase continues to be the hallmark of this subtype and presents a challenge for the patient and the clinician (Calabrese *et al.*, 2001, 2002). Perugi *et al.* (2000) published the results of a systematic retrospective investigation of 320 patients with established bipolar I disorder. They examined the past course on the basis of polarity at onset (depressive, mixed, and manic), and found that depressive onsets were the most common, accounting for 50%, followed by mixed and manic onsets in about equal proportions. In general, the polarity of episodes over time reflected polarity at onset. Those with depressive onset had significantly higher levels of rapid cycling, as well as suicide attempts, but were significantly less likely to develop psychotic symptoms. Mixed onsets, too, had high rates of suicide attempts, but differed from depressive onsets in having significantly more chronicity yet negligible rates of rapid cycling at follow-up evaluation. Because cases with depressive onset had received significantly higher rates of psychopharmacologic treatment, the authors concluded that their data were compatible with the hypothesis that antidepressants may play a role in

Table 3.1 Current episode type and number of previous episodes

		Depresssive mania		Rapid cycling	
		No	Yes	No	Yes
Manic	≤11	71	41	94	02
	>11	24	21	22	16
	χ^2	1.3, $P = 0.25$		40, $P < 10^{-6}$	
Depressive	≤4	42	31	58	04
	>4	30	27	33	14
	χ^2	0.3, $P = 0.6$		8.9, $P < 0.003$	

the induction of rapid cycling. They suggested that their data support the existence of distinct longitudinal patterns within bipolar I disorder, which in turn appear to be correlated with the polarity at onset. In particular, rapid-cycling and mixed states emerge as distinct psychopathologic processes. These data further confirm the notion of rapid cycling as a distinct pattern of bipolar disorder.

Swann *et al.* (2000) indicated that, in their study of inpatients in parallel groups – double-blind comparison of lithium, divalproex, or placebo – there was a tendency for subjects with four or more previous depressive episodes to be women (25 of 57 were women versus 20 of 70 with three or fewer episodes, $\chi^2 = 3.2$, $P = 0.07$). They also reported a highly significant increase in the occurrence of rapid-cycling bipolar disorder in subjects with a history of more than eight manic episodes or four depressive ones (Table 3.1).

Reports on the prevalence of rapid cycling continue to show that significant proportions of patients with bipolar disorder suffer from a rapid-cycling course. Suppes *et al.* (2001) indicated that a prevalence rate higher than 24% is reported for rapid-cycling bipolar disorder when minimum duration criteria are dropped and patients with ultrafast rapid cycling are included. This notion of changing prevalence rates depending on the inclusion criteria of rapid cycling draws the attention back again to the potential need to revise the current nomenclatures and their definitions (Maj, 2001).

The phenomenology of rapid-cycling bipolar disorder in children has received much attention (Findling and Calabrese, 2000; Findling *et al.*, 2001; Chang and Ketter, 2001; Geller *et al.*, 2001; Schraufnagel *et al.*, 2001). Mostly, the findings indicated the high prevalence of rapid cycling in this population, as well as its poor prognosis.

Bringing attention to the high prevalence of rapid cycling among children with bipolar disorder, Findling *et al.* (2001) studied 90 youths between the ages of 5 and 17 years meeting full diagnostic symptom criteria for bipolar disorder I (BP-I). Researchers found that the clinical presentation of BP-I was similar in children and adolescents. BP-I was found to be a cyclic disorder characterized by high rates of rapid cycling (50%) with almost no interepisodic recovery. These data suggest that the presentation of juvenile BP-I is a cyclic and valid clinical condition with manifestations on a continuum with the later-onset forms of this illness.

Geller *et al.* (2001) reported the results of a study about 1-year recovery and relapse rates of children with a prepubertal and early adolescent bipolar disorder phenotype. Of 93 subjects seen at baseline, 89 were seen at year 1 (95.7% retention). The rate of recovery from mania was 37.1%, and the rate of relapse after recovery was 38.3%. No covariates were significantly associated with recovery or relapse. The low recovery and high relapse rates supported the study hypothesis of poor outcomes, which was made on the basis of similarity between the characteristics of the prepubertal and early adolescent bipolar disorder phenotype (long episode duration and high prevalence of mixed mania, psychosis, and rapid cycling) and those of severe bipolar disorder in adults.

Additionally, Schraufnagel *et al.* (2001) reported the results of a study on the patterns of affective illness presentation in children and adolescents, in relation to pubertal maturation and family history. One hundred children/adolescents with affective illness (72 boys and 28 girls; age range 2–20 years; mean age 10 years), who were consecutively referred to the Pediatric Behavioral Neurology Program, Children's Medical Center at Dallas, Texas, USA, were evaluated for the pattern and course of affective illness symptoms, family history, and pubertal stage. Seven patterns of affective illness were identified. In the 65 prepubertal children (Tanner stage 1), disorders with hypomanic/manic symptomatology were most common (47 / 65, 72%), followed by dysthymia with bipolar features (18 / 65, 28%), cyclothymia (11 / 65, 17%), hypomania (8 / 65, 12%), juvenile rapid-cycling bipolar disorder/ultradian cycling bipolar disorder (8 / 65, 12%), and mania (2 / 65, 3%). In contrast, the 26 fully pubertal adolescents (Tanner stages 3–5) had a predominance of patterns with only depressive symptomatology (16 / 26, 61%), followed by depression (12 / 26, 46%), along with juvenile rapid-cycling bipolar disorder/ ultradian cycling bipolar disorder (6 / 26, 23%), and dysthymia (4 / 26, 15%). Affective illness, alcoholism, and drug abuse were prominent in the family histories, regardless of the child's pattern of symptoms. Family histories of character disorder and Briquet's syndrome were also common, but thought disorder, suicide, and homicide were infrequent. This study supports the clinical observation that the presentation of affective illness changes with age: manic features predominate in younger children, whereas depressive symptomatology is more evident with

pubertal maturation. The results of these naturalistic studies warrant further controlled and longitudinal studies to provide more generalizable conclusions about the phenomenology of rapid-cycling bipolar disorder in children, and its management.

In Calabrese *et al.*'s paper (2000a) contained in the preceding book, we reported the following with regard to comorbidity: extensive literature exists on the presence of thyroid dysfunction in patients with bipolar rapid cycling. Some studies do (Cho *et al.*, 1979; Cowdry *et al.*, 1983; Bauer *et al.*, 1990; Kusalic, 1992; McKeon *et al.*, 1992) but most do not (Joffe *et al.*, 1988; Nurnberg *et al.*, 1988; Wehr *et al.*, 1988; Bartalena *et al.*, 1990; Coryell *et al.*, 1992; Shen, 1992; Cole *et al.*, 1993; Maj *et al.*, 1994; Oomen *et al.*, 1996; Post *et al.*, 1997) suggest that rapid cycling is associated with an underlying thyroid abnormality. Usually (Khouzam *et al.* 1991), the observed abnormality of thyroid dysfunction has been in the direction of decreased end-organ function. Herz (1964) first proposed that rhythmic disorders of mood might be caused by removal of the thyroid gland. Twenty-two recently thyroidectomized patients were examined for evidence of psychiatric complications in Frederiksberg Hospital, Copenhagen, Denmark. Ten exhibited postsurgical psychiatric symptoms in the absence of any family psychiatric history. The authors described this as the "endocrine psycho-syndrome" and specifically noted that eight patients exhibited temporary attacks of depression soon after the surgery.

Cho *et al.* (1979) first demonstrated that the prevalence of lithium-induced hypothyroidism was much higher in rapid cyclers (31%) than in non-rapid cyclers. This was replicated by Cowdry *et al.* (1983), who noted overt hypothyroidism in 50.7% of 24 rapid cyclers and in none of 19 non-rapid cyclers. Elevated TSH levels were present in 92% of the rapid cyclers and 32% of the non-rapid cyclers. Five years later, the same group (Wehr *et al.*, 1988) refuted their earlier finding that thyroid dysfunction was no more common in rapid cyclers than in non-rapid cyclers. Bauer *et al.* (1990) have carried out the most thorough examination of thyroid function, reporting a spectrum of thyroid abnormalities in rapid cycling. They have also begun a systematic examination of the potential mood-stabilizing properties of thyroid supplementation, when used in augmentation of conventional mood stabilizers. Of 30 patients with bipolar rapid cycling studied prospectively for the presence of thyroid failure, 23% had grade I hypothyroidism (decreased FTIs with overt signs and symptoms), 27% had grade II (normal FTI, elevated TSH, and a single sign/symptom), and 10% had grade III (everything is normal, but there is an augmented TSH response to thyroid-releasing hormone). A median and modal frequency of 24 episodes/year with a maximal frequency of two episodes per day suggests that episode counting was done with criteria inconsistent with the DSM-IV.

It is clear that there is an increase in the prevalence of alcohol and drug abuse in patients with bipolar disorder (Regier *et al.*, 1990). Whether rapid cyclers have an

increased prevalence of alcohol and drug abuse comorbidity compared to non-rapid cyclers has not been explored. Whether patients with bipolar disorder and comorbid alcohol or drug abuse/dependence have an increased prevalence of rapid cycling has likewise not been explored. However, preliminary data suggest that bipolar patients with comorbid alcohol and/or drug abuse/dependence cycle frequently, consistently experiencing twice as many lifetime hospitalizations (Keller *et al.*, 1986; Brady *et al.*, 1991; Sonne *et al.*, 1994; Haywood *et al.*, 1995).

Other manifestations of comorbidity in rapid cyclers have not yet been systematically studied. However, anecdotal reports have associated the onset of rapid cycling with neurologic events or states such as strokes (Berthier, 1992), subarachnoid hemorrhages (Blackwell, 1991), and profound mental retardation with periodic aggressive acting-out behavior (Glue, 1989; Lowry and Sovner, 1992).

After the publication of the above-mentioned book, Calabrese *et al.* (2001) reported that comorbidity with alcohol, cannabis, and/or cocaine abuse or dependence appeared to alter prognosis by increasing the prevalence of poor compliance, not by directly affecting the spectrum of activity of combined treatment with lithium and divalproex. In that study, Calabrese *et al.* evaluated the spectrum of efficacy of combined treatment with lithium and divalproex in a cohort of 84 patients with rapid-cycling BP-I or BP-II disorder comorbid with a current history of either abuse of or dependence on alcohol, cannabis, and/or cocaine. At the time of study entry, 86% of patients were using alcohol, 45% cannabis, and 40% cocaine. Of those using alcohol, 71% met DSM-IV criteria for dependence and 29% for abuse. Of those using cannabis, 24% met criteria for dependence, and 76% for abuse. Of those using cocaine, 65% met criteria for dependence and 35% for abuse. The profile of lifetime abuse/dependence was alcohol/cannabis/cocaine (42%), alcohol and cannabis (22%), alcohol alone (20%), alcohol and cocaine (12%), cannabis and cocaine (1%), cannabis alone (1%), and cocaine alone (1%). Physiologic dependence was present in 65% of those using alcohol, 8% of those using cannabis, and 57% of those using cocaine. These data suggest that the majority of alcohol and cocaine use, but not cannabis use, in rapid-cycling bipolar disorder is accompanied by physiologic dependence. A more detailed discussion of their outcome results will follow later in the chapter. Additionally, substance abuse has been linked to increasing the already high risk of suicide in rapid-cycling bipolar disorder (Nierenberg *et al.*, 2001; Sachs *et al.*, 2001).

Pharmacotherapy

Treatment recommendations

While the newly revised practice guidelines for the treatment of patients with bipolar disorder, published by the American Psychiatric Association in 2002,

recommended that the initial treatment for patients who experience rapid cycling should include lithium or valproate, lamotrigine has also been considered a first-choice option. It was also advised that for many patients, combinations of medications are required (American Psychiatric Association, 2002).

Most researchers and clinicians have come to realize that the depressive phase of bipolar disorder is probably more difficult to treat, especially in the rapid-cycling subtype (Ghaemi *et al.*, 2000; Möller and Grunze, 2000; Perugi *et al.*, 2000; Sachs *et al.*, 2000a; Calabrese *et al.*, 2001, 2002). Nevertheless, the use of antidepressants in treating the depressive phase of rapid-cycling bipolar disorder continues to draw significant controversy. While most have warned about the likelihood of antidepressants worsening the course of rapid-cycling bipolar disorder, and have strongly cautioned against using them alone (Ghaemi *et al.*, 2000, Perugi *et al.*, 2000; Sachs *et al.*, 2000a, 2000b; Calabrese *et al.*, 2001, American Psychiatric Association, 2002), others have warned that the decreased use of antidepressants might increase the risk of suicide (Möller and Grunze, 2000), and that antidepressant use along with a mood stabilizer constitutes a low risk for worsening rapid-cycling course (Amsterdam and Garcia-España, 2000; Sachs *et al.*, 2000a).

Amsterdam and Garcia-España (2000) reported results indicating that no episodes of drug-induced hypomania or rapid cycling were observed during 6 weeks of venlafaxine monotherapy for depression in women with BP-II and unipolar major depression. This study's limitations included that it was retrospective in nature and limited in patient number, that only BP-II women were included in this study, and it is possible that efficacy and the manic switch rate might have differed if BP-I women were included. However, it is noteworthy that the limitations of this study make it very difficult to formulate any generalizable conclusions about the use of antidepressants in treating rapid-cycling bipolar disorder.

A respective chart review of outpatients with affective disorders ($n = 85$, with both bipolar and unipolar disorders) was conducted over a 1-year period (Ghaemi *et al.*, 2000). The results indicated that bipolar disorder was found to be misdiagnosed as unipolar depression in 37% of patients who first saw a mental health professional after their first manic/hypomanic episode. Antidepressants were used earlier and more frequently than mood stabilizers, and 23% of this unselected sample experienced a new or worsening rapid-cycling course attributable to antidepressant use. These results suggest that bipolar disorder tends be misdiagnosed as unipolar major depressive disorder and that antidepressants seem to be associated with a worsened course of bipolar illness. While the results of this study are informative regarding the misdiagnosis of bipolar disorder and the eventual negative consequences on its course, longer, more controlled studies with larger sample size are still needed to clarify this long-lived controversy in the management of bipolar disorder, and especially the rapid-cycling course.

Lamotrigine

Lamotrigine utilization as a first option in the treatment of rapid-cycling bipolar disorder has gained more consensus (Sachs *et al.*, 2000b; American Psychiatric Association, 2002).

Calabrese *et al.* (2000b) reported on the first multicenter, double-blind, flexible-dose, placebo-controlled, parallel-group study to examine the safety and efficacy of lamotrigine for the long-term prophylaxis of mood episodes in patients with rapid-cycling bipolar disorder.

A total of 324 patients meeting DSM-IV criteria for rapid-cycling disorder entered the open-label phase, and 182 patients were eventually randomly assigned to the double-blind maintenance phase. For patients entering the open stabilization phase, the mean age was 38 years, the percentage of women was 59%, the percentage of BP-I subtype was 69%, and the percentage of patients receiving thyroid supplements for diagnosed hypothyroidism was 7%. At study entry, 57% of patients were depressed, 20% were hypomanic or manic, 18% were euthymic, and 5% had mixed states. The mean number of mood episodes in the 12 months prior to study entry was 6.3. The lifetime prevalence of psychosis was 27%, and the percentage of patients with prior suicide attempts was 36%. Prior lifetime exposure to psychotropics included lithium (68%), carbamazepine (27%), divalproex (57%), lamotrigine ($< 1\%$), antidepressants (82%), and antipsychotics (27%). Concomitant psychiatric medications at study entry included lithium (19%), carbamazepine (4%), divalproex (19%), antidepressants (30%), and antipsychotics (7%). Although the most commonly prescribed lifetime medications at the time of study entry were antidepressants, only 36% of patients reported having responded to them positively.

Lamotrigine was added to the patients' current psychotropic regimens and titrated to clinical effect during an open-label treatment phase. The treatment of stabilized patients with other psychotropics was tapered off and randomly assigned to lamotrigine or placebo monotherapy (in a 1:1 ratio) for 6 months after being stratified for BP-I or BP-II disorder.

Lamotrigine dose was titrated in the 6-week preliminary phase to a target dose of 200 mg/day. After week 5, lamotrigine dose increases were allowed in increments of 100 mg/week up to a maximum dose of 300 mg/day. In the randomized phase, the double-blind medication dosage was also flexible and varied from 100 to 500 mg/day. The average daily dose was 288 ± 94 mg.

Time to additional pharmacotherapy for emerging symptoms of a mood episode was the primary outcome measure. Secondary outcome measures included survival in the study, percentage of patients stable without relapse for 6 months, and changes in scores on the Global Assessment Scale (GAS) and the CGI-Severity of Illness (CGI-S) scale.

Kaplan–Meier methodology was used to analyze survival data, and median times to survival were calculated. Additionally, survival analyses were performed for each bipolar subtype. The percentage of patients stable without relapse for 6 months was analyzed using the Cochran–Mantel–Haenszel chi-squared test. Clinical efficacy scales (CGI-S, GAS) were evaluated using analysis of variance (ANOVA) at an $\alpha = 0.05$ level of significance using both observed and last-observation-carried-forward (LOCF) data.

Treatment groups during the randomized phase ($n = 182$) were similar with respect to age, sex, race, medical history, psychiatric history, prior treatments, response to treatments, and current psychiatric state. The majority of patients were classified as having BP-I disorder (71%). A comparison of BP-I and BP-II patients showed no differences on key parameters. Compared with BP-II patients, BP-I patients had a greater prevalence of suicide attempts (40% versus 28%) and average number of lifetime hospitalizations (2.3 versus 0.7).

Forty-nine placebo patients (56%) and 45 lamotrigine patients (50%) required additional pharmacotherapy for emerging symptoms of a mood episode. The difference between the two general treatment groups in time to additional pharmacotherapy did not achieve statistical significance. The median survival times were 18 weeks for lamotrigine and 12 weeks for placebo. When survival in study (any premature discontinuation, including for additional pharmacotherapy) was evaluated, the difference between the treatment groups was significant ($P = 0.04$). For survival in study, the median survival times were 14 weeks for lamotrigine and 8 weeks for placebo. Time to additional pharmacotherapy and survival in study did not yield significant differences between lamotrigine and placebo in patients with BP-I disorder. When time to additional pharmacotherapy was evaluated, a trend toward significance ($P = 0.07$) was found in the separation between placebo and lamotrigine. Median survival time without additional pharmacotherapy for the BP-II subtype was 17 weeks for lamotrigine and 7 weeks for placebo. The overall survival in study analysis yielded a significant separation between treatment groups ($P = 0.01$). Median overall survival was 15 weeks for lamotrigine and 4 weeks for placebo. The majority of those patients (80%) requiring additional pharmacotherapy were treated for depressive symptoms; 20% were treated for emerging manic, hypomanic, or mixed symptoms.

The percentage of patients who completed the 6-month randomized phase clinically stable on monotherapy without evidence of relapse into hypomania, mania, or depression was significantly greater in the lamotrigine group than in the placebo group. Of the 60 patients who were stable for 6 months of monotherapy, 37 of 90 (41%) were in the lamotrigine group compared with 23 of 87 (26%) in the placebo group ($P = 0.03$). The difference for lamotrigine versus placebo was not statistically significant for the BP-I subtype, but was significant (46% versus 18%,

respectively; $P = 0.04$) for the bipolar II subtype. The CGI-S and GAS were used to provide additional measures of clinical stability. For the overall study population and the BP-I subtype, there were no statistically significant differences between treatment groups in CGI-S change from baseline scores using the LOCF. For the BP-II subtype, trends toward statistically significant differences ($P < 0.10$) favoring the lamotrigine group were observed in CGI-S scores compared with the placebo group at weeks 6 and 12. No statistically significant differences favoring lamotrigine were observed between groups in GAS change from baseline scores in the general cohort of patients (LOCF). Significant differences favoring lamotrigine were noted at weeks 3, 6, and 12 in the BP-II subtype; however, no significant differences were noted at any time point for the BP-I subtype. There were no significant differences observed in the change from baseline LOCF analyses at any point for the 17-item Hamilton-D or the Mania Rating Scale.

The most common adverse events ($\geq 10\%$) observed during the open stabilization phase were headache, infection, influenza, nausea, dream abnormality, dizziness, and rash. In the randomized phase, 122 patients (67% lamotrigine; 68% placebo) experienced adverse events, and the most common adverse events were headache, nausea, infection, pain, and accidental injury. Lamotrigine-related rash occurred in 8% of patients during open stabilization and in no patients in the randomized phase. There were no serious rashes during either phase of the study, and no patients required hospitalization for a rash. From study entry to study point, there was no mean change in body weight for the lamotrigine group.

This study had several limitations. Because of the absence of monotherapy data relevant to this design, no statistical justification was used in determining sample size. The actual enrollment of fewer than 100 patients per treatment arm limited the power of the primary outcome analysis to approximately 47%. In contrast, the analysis of survival in study was retrospectively determined to have been powered at approximately 83%. Additionally, the design of this study did not permit an analysis of time to relapse into a full episode of depression, hypomania, or mania since patients were withdrawn at the first signs of relapse. In addition, this study enrolled a higher proportion of patients with BP-I disorder than is thought to occur in the rapid-cycling population.

It has been noted that lamotrigine was well tolerated during the current study. The type and frequency of adverse events after lamotrigine treatment were comparable to placebo.

In this study, lamotrigine demonstrated efficacy in the prevention of the recurrence of mood symptoms over a 6-month period. The results of this study suggest that lamotrigine may be a well-tolerated and effective mood stabilizer with prophylactic properties when used as monotherapy in some patients with rapid-cycling bipolar disorder. Lamotrigine may be an especially effective mood

stabilizer for patients diagnosed with BP-II disorder. Despite this study's previously mentioned limitations, it remains the first controlled study of its kind, especially with regard to the process of data analysis utilized, which is more generally suitable to prophylaxis studies.

Concurrently, Frye *et al.* (2000) reported a placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. The demographic profile of the study participants who were available for evaluation in all three treatment phases ($n = 31$) included 18 women and 13 men; 11 BP-I and 14 BP-II; 23 rapid-cycling and two non-rapid-cycling; and six unipolar patients.

The design initially employed a double-blind random assignment to parallel arms. This was followed by 6-week cross-over trials, in which patients eventually received all three medications as monotherapy (gabapentin, lamotrigine, or placebo). Between phases, a cross-over period of approximately 1 week was used. Patients were treated only with the study medications except for the following: four patients who continued receiving stable levothyroxine supplementation for corrected primary hypothyroidism; one patient who continued receiving diuretic therapy for essential hypertension; and two patients, who each continued receiving stable prior medications (i.e., triiodothyronine and clonazepam). The number of patients randomized to lamotrigine (L), gabapentin (G), and placebo (P) were as follows: PLG: 6; PGL: 5; LPG: 6; LGP: 6; GPL: 4; and GLP: 5. Lamotrigine was initially administered at a dose of 25 mg daily for the first week, and titrated up to 300–500 mg/day for the fifth through sixth weeks. Gabapentin was administered initially at a dose of 900 mg/day and was titrated to 4800 mg by the fifth through sixth weeks. After the three phases of the study were completed, the patients who had responded to a particular phase (I, II, or III) were offered the option of returning to that phase, still on a blinded basis, for response confirmation.

The primary outcome measure of overall improvement was the CGI scale that was modified for bipolar illness (CGI-BP). Supplementary ratings used in the evaluation and completion of the CGI response rating included prospective self- and observer-rated life charting, Hamilton-D, Young Mania Rating Scale (YMRS), the Spielberger State Anxiety Scale, and Brief Psychiatric Rating Scale (BPRS). CGI-BP change determinations were made by a consensus of blinded research physicians and clinicians, both in comparison with the previous phase of illness and the worst phase of documented illness. Previous treatment exposure and documented treatment failures, including therapeutic level with inadequate response, clinical intolerance, or affective relapse, were the following: for lithium, 28 (90%) of 31 patients experienced prior exposure and 28 (100%) of 28 patients experienced prior treatment failure; for valproic acid, 26 (79%) of 31 and 21 (81%) of 26; and for carbamazepine, 20 (58%) of 31 and 14 (70%) of 20, respectively.

Cochran's *Q*-statistic was used to compare the overall CGI response (i.e., considered a rating of either much or very much improved) for those patients who completed all three phases. Any significant Cochran's *Q* statistic was followed by a *post hoc* test. This test allowed pairwise comparisons of the proportion of responders in the medication phases to determine the location of a difference. The Fisher exact test was used for differential response rates based on gender status.

Clinical response

The mean daily doses at week 6 were 274 ± 128 mg for lamotrigine and 3987 ± 856 mg for gabapentin. There was no difference in lamotrigine and gabapentin doses between responders and non-responders. The response rates based on the overall CGI rating of much or very much improved were the following: lamotrigine, 52% (16 / 31); gabapentin, 26% (8 / 31), and placebo, 23% (7 / 31). *Post hoc Q* differences ($df = 1$, $n = 31$) were the following: lamotrigine versus gabapentin ($Q_{diff} = 5.33$, $P = 0.011$), lamotrigine versus placebo ($Q_{diff} = 4.76$, $P = 0.022$), and gabapentin versus placebo ($Q_{diff} = 0.08$, $P = 0.700$). The CGI response rates for manic and depressive components of the illness separately were similar to the overall response rate, but they only achieved trend levels of significance. The response rates for mania were the following: lamotrigine, 44% (11 / 25); gabapentin, 20% (5 / 25); and placebo, 32% (8 / 25). For depression, the response rates were the following: lamotrigine, 45% (14 / 31); gabapentin, 26% (8 / 31); and placebo, 19% (6 / 31). The response rate observed during phase I was highly similar to that in the whole study using all three phases of the cross-over trial; it was 50% (5 / 10) for lamotrigine, 33% (3 / 9) for gabapentin, and 18% (2 / 11) for placebo. In addition, when the response data were analyzed as a function of a positive response in the preceding phase, only 23% of lamotrigine responders, 50% of gabapentin responders, and 0% of placebo responders were also partial responders in the previous phase, and would thus have entered the next phase somewhat improved. This finding further indicates that there was not a greater percentage of lamotrigine-responsive patients who were responders in the preceding phase. Moreover, there were no significant differences at the baseline level on any of the supplementary ratings of severity of illness. There was no difference between the response rates based on gender. Both agents were generally well tolerated, with the exception of one patient, who was administered lamotrigine and who developed a rash after the 6-week study phase was over. The rash occurred in week 15 (during the continuation treatment), progressed to toxic epidermal necrolysis, and required the patient to be hospitalized in an intensive care burn unit. The patient recovered fully. A pairwise contrast (lamotrigine versus gabapentin, $F = 5.884$, $P = 0.021$) showed that patients lost weight when they received lamotrigine relative to the weight gained when they received gabapentin.

This study suggests that lamotrigine monotherapy is superior to both gabapentin and placebo treatments in patients with refractory affective disorders. Although cross-over designs have the potential for producing carry-over and other confounding effects, this did not seem to occur in this study, according to the authors, nor did it affect the interpretation of the outcome data based on a variety of considerations. These data suggest that the response rates in this study were not confounded by the treatment phase, nor were they influenced by carry-over effects on the severity of illness. Nonetheless, the 6-week treatment phases and total study period of 18 weeks is a short period in which to assess the efficacy or persistence of response. A very high percentage (92%) of this bipolar sample was rapid cycling, which is substantially greater than the general population estimates of this course specifier (DSM-IV). Both refractory unipolar and bipolar patients were included in this preliminary study. In addition, the direct application of these preliminary monotherapy results to community treatment guidelines is limited, given that a combination treatment is the norm and monotherapy regimens are rarely used in clinical practice. In contrast to the weight gain observed during treatment with gabapentin, patients lost weight while receiving lamotrigine therapy during this 6-week trial, further increasing the possibility of a better side-effects profile on weight than other mood stabilizers such as lithium or valproate. However, and despite this study's controlled condition and vigorous data analysis, its applicability to the larger population of patients with bipolar disorder, especially with the rapid-cycling course, remains limited. It is worth noting that the cross-over design, taking into consideration the rapidly changing nature of the rapid-cycling course, might interfere with our ability to draw solid conclusions (Maj, 2001). Additionally, there was no clear differentiation between previous treatments' ineffectiveness and patient intolerance thereof.

Walden *et al.* (2000) reported an open longitudinal investigation, where 14 patients with rapid-cycling bipolar disorder were treated for 1 year with either lithium or lamotrigine as a mood stabilizer. Out of the seven patients with lithium, three out of seven (43%) had fewer than four and four out of seven (57%) had four or more episodes. In the lamotrigine group, six out of seven (86%) had fewer than four, and one out of seven (14%) had more than four affective episodes (depressive, manic, hypomanic, or mixed). In fact, three out of seven (43%) of the patients who were on lamotrigine therapy were without any further affective episodes. There was no evidence of a preferential antidepressant versus antimanic efficacy. Although the study is limited by the small number of patients, the results are in line with other investigations, suggesting efficacy for lamotrigine and a suboptimal response for lithium in rapid-cycling bipolar disorder. These preliminary data need to be confirmed with controlled double-blind studies.

Despite the generally positive outcomes of the previously cited studies on the use of lamotrigine in the treatment of rapid-cycling bipolar disorder, more controlled studies with longer courses are needed to clarify the role of this promising agent.

Lithium

Despite being the oldest among the pharmacological armamentarium in the treatment of bipolar disorder, lithium continues to draw attention to its utility as an effective agent in the treatment of different aspects and phases of this disorder, and especially in the rapid-cycling course. While some researchers continue to demonstrate and advocate for lithium efficacy in the treatment of rapid-cycling bipolar disorder (Baldessarini *et al.*, 2000, 2002; Swann *et al.*, 2000; Viguera *et al.*, 2001; Tondo *et al.*, 2001), others have argued that lithium has a poor efficacy in treating rapid-cycling bipolar disorder, even when supplemented by antidepressants and neuroleptics (Post *et al.*, 2000; Bowden, 2001).

Baldessarini *et al.* (2000) concluded, in a study evaluating the factors associated with rapid-cycling status, that this subtype of bipolar disorder was strongly associated with type II diagnosis, higher average pre-lithium episode frequency and percentage time ill, and weakly with female sex, but not with greater overall morbidity during treatment. In 360 DSM-IV BP-I ($n = 218$), and BP-II ($n = 142$) disorder subjects (64% women) followed over an average of 13.3 years, researchers evaluated factors associated with rapid-cycling status with bivariate and multivariate techniques, and response to lithium maintenance treatment (recurrence rates, time ill, survival analysis of time to recurrence on lithium). Their results indicated that the rapid-cycling risk (15.6% of cases) was 5.1 times greater in BP-II versus BP-I subjects (30.3% versus 6.0%), in minor excess in women versus men (17.9% versus 11.5%), and associated with premorbid cyclothymia, depressive first episodes, older onset age, and being employed or married. Before lithium, rapid-cycling versus non-rapid-cycling cases had more mean total (3.9 / 1.2), manic, and depressive episodes/year, and greater percent time ill (60% versus 38%). During treatment, prior rapid-cycling status was unrelated to time to first recurrence and other measures of morbidity and improvement, including percent time ill, although depressive episodes were 2.7 times more frequent, and there was 13.7% less chance of full protection from all recurrences in rapid-cycling cases. Limitations of the study included that it was naturalistic, without random assignment or blind assessment. However, its length and the number of subjects studied make its conclusions noteworthy.

On the other hand, Swann *et al.* (2000) reported that at least four previous depressive or 12 previous manic episodes are associated with reduced antimanic

response to lithium. They found that response to lithium, but not to divalproex or placebo, worsened with increased depressive or manic episodes. A history of more than 11 manic or four depressive episodes was associated with response to lithium that did not differ from placebo. Effects of previous depressive and manic episodes appeared independent, and could not be accounted for by increased rapid cycling or mixed states.

These cross-sectional data cannot distinguish whether this represents progressive development of lithium resistance with repeated episodes, or patients who had frequent episodes that were lithium-resistant from the start. The reported increased episodes could be associated with an increased number of lithium discontinuations, which might lead to neurophysiological changes adversely affecting response to lithium, but not to divalproex. However, previous favorable response to lithium in the present study predicted a favorable response in the index episode, arguing against loss of lithium response with repeated episodes of treatment. Further, most patients have similar responsiveness to lithium before and after lithium discontinuation.

Viguera *et al.* (2001) compared the clinical characteristics of 360 women and men with DSM-IV BP-I or BP-II disorder before and during clinical lithium maintenance monotherapy in a mood-disorders clinic. They utilized preliminary bivariate comparisons, multivariate analysis, and survival analysis of time stable during treatment. They found that women ($n = 229$) versus men ($n = 131$) were more likely to have BP-II disorder (1.6 times), 3.2 years older at illness onset, more often depressed-before-manic (1.4 times), considered unipolar depressive 1.9 years longer, and started maintenance treatment 5.5 years later. However, women differed little from men before treatment in overall morbidity, average episode frequency, and risk of suicide attempts. Contrary to prediction, women showed non-significantly superior responses to lithium treatment and a significant 60% longer median time before a first recurrence during treatment, despite 7% lower average serum lithium concentrations. Women were diagnosed as bipolar later than men, with corresponding delay of lithium maintenance treatment that proved to be at least as effective as in men. A possible interpretation of this study's results might be a confirmation of the hypothesis that the increased rate of rapid cycling in women is probably a reflection of the increased treatment with antidepressants. Frequency of episodes did not seem to differ greatly before the treatment with lithium started, taking into consideration that women were more misdiagnosed as unipolar depressed, and that they had more depressed episodes than men.

To clarify further the role lithium plays in the thyroid gland's function, Kupka *et al.* (2002) reported the lack of association between lithium exposure and the high rate of autoimmune thyroiditis in bipolar disorder. The thyroid peroxidase

antibodies (TPO-Abs) of outpatients with DSM-IV bipolar disorder ($n = 226$), a population control group ($n = 252$), and psychiatric inpatients of any diagnosis ($n = 3190$) were measured. The TPO-Abs were more prevalent in bipolar patients (28%) than population and psychiatric controls (3–18%). The presence of TPO-Abs in bipolar patients was associated with thyroid failure, but not with age, gender, mood state, rapid cycling, or lithium exposure. Thyroid failure was present in 17% of bipolar patients and more prevalent in women. It was associated with lithium exposure, especially in the presence of TPO-Abs, but not with current rapid cycling, although an association may have been masked by thyroid hormone replacement. The authors concluded that thyroid autoimmunity was highly prevalent in this sample of outpatients with bipolar disorder and not associated with lithium treatment. These variables appear to be independent risk factors for the development of hypothyroidism, especially in women with bipolar disorder.

Divalproex sodium

Swann (2001) analyzed the prediction of treatment response in acute mania in controlled clinical trials with divalproex. For predictive factors, 179 subjects in three parallel groups (divalproex, lithium, and placebo) were evaluated over a period of 21 days by using structured interviews. For the follow-on study, 372 stabilized patients were randomized to three groups: divalproex, lithium, or placebo. The results showed that patients with manic episodes with depressive symptoms or with rapid cycling exhibited good response to divalproex. It was concluded that a high number of both manic and depressive prior episodes is predictive of poor response to lithium and favorable response to divalproex. The results of this study add to the available evidence of the utility of divalproex sodium in the treatment of rapid-cycling bipolar disorder.

Olanzapine

There have been few reports about the use of olanzapine in rapid-cycling bipolar disorder (Demopulos *et al.*, 2000; Bhana and Perry, 2001), Demopulos *et al.* (2000) published a preliminary report of a cohort of patients with rapidly cycling bipolar I disorder who participated in the double-blind, placebo-controlled 3-week study of acute mania. Their results indicated that olanzapine 5–20 mg/day monotherapy ($n = 19$) was significantly superior to placebo ($n = 25$) in improving YMRS scores relative to baseline (-14 versus -4, $P = 0.05$). Additionally, significantly more olanzapine than placebo recipients had improvements of $\geq$ 30% from baseline YMRS scores (84 versus 36%, $P = 0.002$). However, their sample size was too small to draw any generalizable conclusions.

Quetiapine

Ghaemi *et al.* (2001) reported limited results with 40 BP-I rapid-cycling subjects to be followed in up to 1 year of open prospective follow-up of quetiapine treatment, with or without a concomitant mood stabilizer. Sixteen subjects were recruited at the time of presentation. Assessments were done utilizing HAM-D, YMRS, along with GCI-BP and a daily mood chart. Patients entered the study with any mood symptomatology severe enough to require added medication intervention. Eight subjects received concomitant lithium and/or divalproex or concomitant lamotrigine. Only one patient was taking an antidepressant (fluoxetine). The results showed that the mean dosage of quetiapine was 159.4 ± 161.5 mg/day. Preliminary data analysis at weeks 4, 8, and 12 indicated improvement in both HDRS and YMRS ratings. At week 8, depressive symptom improvement tended towards statistical significance, but not at week 12. Manic symptom improvement was statistically significant at weeks 4 and 12. CGI-BP ratings indicated improvement in both manic and depressive symptoms for week 2 onwards, with statistical significance for manic symptoms at week 4, and overall bipolar illness at weeks 4 and 8. Drop-out and side-effect data were also analyzed. Weight change was minimal, with a mean amount of 1.2 lb (0.5 kg) lost at 14.9 weeks' mean follow-up. It was concluded in this preliminary analysis of a partially recruited data set that early indications at 3-month follow-up are that quetiapine improves rapid-cycling symptoms in bipolar disorder. Further controlled studies will definitely be needed to clarify the role of quetiapine in the management of bipolar disorder generally, and in rapid cycling in particular.

Combination therapy

The need sometimes to combine mood stabilizers in the treatment of rapid-cycling bipolar disorder has received more recognition lately (Sachs *et al.*, 2000b; American Psychiatric Association, 2002), especially in the face of the fact that many patients with rapid-cycling bipolar disorder do not achieve bimodal stabilization with the currently available treatment strategies (Calabrese *et al.*, 2001).

Calabrese *et al.* (2001) reported in two studies evaluating combination therapy in rapid cycling in bipolar disorder with and without comorbid substance abuse. The first study evaluated the spectrum of efficacy of combined lithium and divalproex treatment over 6 months in a prospectively defined cohort of 215 patients with rapid-cycling BP-I or BP-II disorder. Data are from the open stabilization phase of an ongoing and still blinded 20-month maintenance study designed to compare the efficacy of lithium monotherapy with divalproex monotherapy after 6 months of treatment with both medications concurrently.

Table 3.2 Baseline characteristics and outcome of subjects in two ongoing rapid-cycling, 6-month combined lithium and divalproex maintenance treatment

	Without ADA ($n = 215$)	With ADA ($n = 84$)
Characteristics		
Female	64	38
Bipolar I	31	66
Bipolar II	69	34
Circular continuous	92	98
Cycling		
Outcome		
Mood stabilization	25	17
Early full remission of ADA	NA	25
Premature discontinuation		
Poor compliance	29	44
Refractory depression	20	16
Refractory hypomania/mania/mixed states	6	9

Values are percentage unless otherwise specified.
ADA, alcohol and drug abuse; NA, not applicable.

Inclusion criteria included the presence of rapid cycling and an episode of hypomania or mania within the 3 months prior to study entry, along with the absence of comorbid substance abuse. Patients were mostly women with BP-II disorder presenting in the depressed phase of their illness. The median number of affective episodes meeting DSM-IV criteria in the 12 months prior to study entry was eight. Patients were required to have minimum therapeutic concentrations of 0.8 mmol/l of lithium and 50 μg/ml of valproate. Both intent-to-treat analyses and responder analyses on completers were carried out. Of the 55 patients who failed to be randomly assigned because they were non-responsive to combined treatment, 76% were experiencing refractory depression and 24% were experiencing refractory hypomania/mania/mixed states. Of the completers, only one-half met criteria for a marked bimodal response and were randomly assigned to the maintenance phase of the study; 61% of patients met criteria for a marked antidepressant response, and 88% met criteria for a marked antimanic response (Tables 3.2 and 3.3).

The second study evaluated the spectrum of efficacy of combined treatment with lithium and divalproex in a cohort of 84 patients with rapid-cycling BP-I or BP-II disorder comorbid with a current history of either abuse of, or dependence on, alcohol, cannabis, and/or cocaine. Data are derived from the open stabilization

Table 3.3 Responder analyses on completers after 6 months of combined lithium and divalproex in bipolar rapid cycling

	Without ADA ($n = 109$)	With ADA ($n = 28$)
Mood stabilization	50	37
Time required (months)	4.7	5.4
Marked antimanic effect	88	77
Cycling into depression (n)	42	16
Marked antidepressant effect	61	59
Cycling into hypomania/mania/mixed states (n)	13	9

Values are percentages unless otherwise specified.
ADA, Alcohol and drug abuse.

phase of an ongoing and still blinded 6-month maintenance study designed to compare the efficacy of lithium monotherapy with the combination of lithium and divalproex after 6 months of open stabilization with the combination. Inclusion criteria included presence of rapid cycling and an episode of hypomania or mania within the 3 months preceding study entry, and meeting DSM-IV criteria for either abuse of, or dependence on, alcohol, cannabis, and/or cocaine. All patients were required to attend a 12-step-based intensive outpatient chemical dependence treatment program. Patients enrolled were mostly men with BP-I disorder presenting in the depressed phase. However, manias and mixed states were more commonly observed at study entry as compared with the cohort of non-comorbid patients with rapid cycling. The median number of affective episodes meeting DSM-IV criteria in the 12 months prior to study entry was eight. Of the 28 subjects who were not randomly assigned because they were non-responsive to combined treatment, 64% were experiencing refractory depression and 36% were experiencing refractory hypomania/mania/mixed states. Twenty-five percent of patients met criteria for an early remission to their alcohol or drug-abuse disorder at the end of open stabilization. The responder analyses indicated that, of 39 completers, only 37% met criteria for a marked bimodal response and were randomly assigned to the maintenance phase of the study; 59% of patients met criteria for a marked antidepressant response, and 77% met criteria for a marked antimanic response (Tables 3.2 and 3.3).

The final results of these two studies will shed long-awaited light on the efficacy of the, apparently needed, combined pharmacotherapy for this challenging subtype of bipolar disorder, especially with its high comorbidity rate with alcohol- and substance-related disorders.

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4

Bipolar I and bipolar II: a dichotomy?

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Introduction

The distinction between unipolar and bipolar forms, rooted in the work of Pierre Falret (1851) and Jules Baillarger (1854), was later established by Karl Kleist (1928, 1953) and his school (Neele, 1949; Leonhard, 1957), and subsequently validated by Angst (1966), Perris (1966), and Winokur *et al.* (1969), who showed that clinical, familial, and course features supported the nosological differentiation between unipolar and bipolar disorders (Angst and Marneros, 2001; Marneros, 2001). However, there are many areas of overlap between those extremes, pointing up the question of possible clinical subtypes in the interface of depressive and manic extremes of affective illness (Akiskal, 2002a).

Bipolar disorder occurs in multiple forms and degrees of severity. The recognition of the existence of so-called milder forms of manic-depressive illness has been a major endeavor in the last decade. The distinctions hinge on the classification of elated states and this poses some difficulty because it depends on the arbitrary gradation of severity and duration. Bipolar disorder with mania and strict unipolar depression without manic or hypomanic episodes would represent the extremes of a spectrum (Akiskal, 1983); recurrent depressions with hypomania would occupy a middle territory (Akiskal, 2002b). Goodwin and Jamison (1990) point out that the exploration of spectrum models of manic-depressive illness would enhance research on genetic markers and modes of genetic transmission, provide an approach for identifying individuals at risk for the development of bipolar illness, and permit the evaluation of treatments for milder forms, including the question of whether early intervention could lessen the chance of progression to bipolar illness. In fact, a great number of individuals with the so-called soft or subsyndromal states belong to the bipolar spectrum by virtue of their positive family histories, their pharmacological response, and their tendency to progress to full clinical disorder. Regarding nosological classification, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn (DSM-III: American Psychiatric Association,

1987) (DSM-III) was a symptom-based diagnostic system that resulted in a narrowing of the diagnosis of schizophrenia and a broadening of the diagnosis of affective disorders, particularly bipolar affective disorders (Dunner, 1998). In DSM-III, the bipolar mood disorders included bipolar disorder, cyclothymic disorder, and atypical bipolar disorder. The mood-disorder definitions were slightly modified in DSM-IIIR (American Psychiatric Association, 1987), including bipolar disorder, cyclothymia, and bipolar disorder not otherwise specified, which included bipolar II, and the criterion of duration for manic episode was deleted. Two aspects not included in DSM-III or DSM-IIIR were rapid cycling and bipolar II as a separate disorder, which were incorporated by DSM-IV. In contrast, The *ICD-10 Classification of Mental and Behavioural Disorders* (ICD-10: World Health Organization, 1993) does not recognize bipolar II disorder as a specific nosologic category.

Bipolar II disorder, sometimes wrongly called "soft bipolar disorder," is actually a severe pathology, as it resembles a milder form of classic manic-depressive illness in regards to symptom intensity, but implies a higher episode frequency, comorbidity, suicidal behavior, and rapid cycling (Vieta *et al.*, 1997a, 1999). In DSM-IV, hypomanic episodes occurring in response to treatment with antidepressant pharmacotherapy would not count toward the diagnosis of bipolar II but would instead be termed substance-induced hypomania. Many clinicians consider antidepressant-induced mania or hypomania to be an indication of the capacity to develop mania or hypomania spontaneously and therefore a sign of a type of bipolar mood disorder. Besides, DSM-IV requires a duration of 4 days or more as minimal criteria for hypomania, while other authors have proposed a brief hypomania reducing the duration of symptoms to 1–3 days (Wicki and Angst, 1991; Angst, 1995, 1998).

Failing to identify minor elated states leads to misdiagnosis of bipolar-spectrum patients as unipolar. A recent study found that 37% of bipolar patients had been misdiagnosed with unipolar depression at first presentation (Ghaemi *et al.*, 2000). A prior study showed that only 9% of bipolar II patients were accurately diagnosed (Vieta *et al.*, 1994). In fact, it may be that current diagnostic criteria lack the sensitivity to detect the full range of conditions within the bipolar spectrum. Moreover, episodes of hypomania rarely lead to treatment, so the accurate diagnosis depends on how rigorously the clinician queries about hypomania, the recollections of patients, and the interview with the relatives. A wrong diagnosis would condition the treatment and would affect the course and prognosis of bipolar patients.

A still unresolved issue is whether bipolar II disorder represents an autonomous type of bipolar disorder or a transitory condition between unipolar and bipolar I disorder. In this chapter, we will try to offer a review of some of the studies that

have focused on the distinctions and similarities between bipolar I and bipolar II disorders, and to draw some conclusions about the validity of such a dichotomy.

Is there a true dichotomy between bipolar I and bipolar II disorder?

Epidemiologic studies

There are similarities across countries in patterns of bipolar disorder (Weissman *et al.*, 1996). In regard to gender, bipolar I disorder occurs with equal frequency in both men and women but bipolar II disorder may be more common in women (American Psychiatric Association, 1994).

The prevalence rate of bipolar disorder depends on how it is defined; many prevalence studies have required the presence of mania for a bipolar diagnosis to be recorded. The lifetime prevalence rates of bipolar disorder have been settled in 1.2% by Regier *et al.* (1988) and 1.6% by Kessler *et al.* (1994). Weissman and Myers (1978) found that bipolar I and bipolar II disorders each had a lifetime prevalence of 0.6%, which combine to 1.2% for all bipolar patients. Schatzberg (1998) suggested that bipolar disorders appear in approximately 1.3% of the population, with a prevalence rate of 0.8% for bipolar I and 0.5% for bipolar II. From a dimensional point of view (bipolar spectrum), this lifetime prevalence would increase to at least 5% (Lewinsohn *et al.*, 1995; Angst, 1998; Szádocky *et al.*, 1998). The prevalence rate of the group of brief hypomania, characterized by short episodes of 1–3 days' duration, was 2.2% (Angst, 1995).

Benazzi (1997) studied the prevalence of bipolar II disorder in a sample of major depressive outpatients in a private setting. Hypomania was diagnosed according to DSM-IV criteria, but antidepressant-induced hypomania was not excluded. The author found that 45% of patients attending a private clinic had bipolar II disorder. This rate is even higher than the 10–40% previously reported in clinical samples (Akiskal and Mallya, 1987; Bourgeois, 1996; Cassano *et al.*, 1992).

Age at onset

The first onset of bipolar disorder usually occurs by the second or third decade of life, although prepubertal and pubertal illness onset is no longer uncommon. McMahon *et al.* (1994) found that patients with affective disorder in both parental lines experienced an earlier onset. It seems that an earlier onset of illness might be associated with greater case complexity, episode severity, and comorbidity (Sachs and Thase, 2000).

The age of initiation of the disease seems to be higher in bipolar II patients (Gershon *et al.*, 1982; Vieta *et al.*, 1997a; Tondo *et al.*, 1998); nevertheless, other studies did not find differences in age-at-onset distributions between bipolar I and bipolar II patients (Benazzi, 1999; Coryell *et al.*, 1985; Egeland *et al.*, 1987;

Table 4.1 Differential quantitative features between bipolar I and bipolar II disorder: mean ± standard deviation

Variable	Bipolar I		Bipolar II		*t*	*P*
Age	35.6	11.9	39.7	12.3	–1.25	NS
Previous episodes	6.3	4.2	12.6	7.5	–3.67	0.001
Manic episodes	3.7	3.4	0	0	NA	
Hypomanic episodes	3.2	3.7	7.0	5.4	–2.96	0.006
Depressive episodes	2.6	2.2	5.6	4.1	–3.28	0.003
Hospitalizations	3.0	3.3	1.0	1.2	3.43	0.001
Age at onset	21.9	8.0	31.2	9.7	–4.01	<0.001

NS, not significant; NA, not applicable.
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McMahon *et al.*, 1994). Benazzi (1999) has suggested that the discrepant results across the studies might be related to different criteria at onset, samples, settings, diagnostic criteria, diagnostic interview, interviewers, methods of analysis, and cohort effect.

Clinical course and outcome

Dunner *et al.* (1976) distinguished bipolar II from bipolar I disorder on the basis of hospitalization for depression and excited periods that did not require hospitalization. According to the American Psychiatric Association (1994), the essential feature of bipolar I disease is a clinical course consisting of the occurrence of one or more manic or mixed episodes, and the essential feature of bipolar II disorders is a clinical course characterized by the occurrence of one or more major depressive episodes with at least one hypomanic episode.

Vieta *et al.* (1997a), after studying differential features between bipolar I and bipolar II disorders, found that bipolar II patients had had a greater number of previous episodes, but had been hospitalized and had presented psychotic symptoms less frequently (Table 4.1 and 4.2). The authors concluded that bipolar II disorder was less severe than bipolar I with regard to symptom intensity, but was more severe with respect to episode frequency. Similar results with respect to the higher number of recurrences in bipolar II patients have been found by other authors (Ayuso-Gutiérrez and Ramos-Brieva, 1982; Coryell *et al.*, 1987; Pallanti *et al.*, 1999), although other studies did not confirm these findings (Koukopoulos *et al.*, 1980; Cassano *et al.*, 1989). With regard to severity, Benazzi (1999) observed that recurrences, psychosis, and chronicity were higher in bipolar I patients. When

Table 4.2 Differential qualitative features between bipolar I and bipolar II disorder

	Bipolar I		Bipolar II			
Variable	No.	%	No.	%	χ^2	*P*
Sex					2.03	NS
Male	17	45	5	23		
Female	21	55	17	77		
Marital status					NA	
Single	22	58	8	36		
Married	11	29	12	55		
Separated	4	10	0	0		
Widowed	1	3	2	9		
First episode					0.13	NS
Manic/hypomanic	17	45	8	36		
Depressive	21	55	14	64		
Rapid cycling					0.35	NS
Present	5	13	5	23		
Absent	33	87	17	77		
Seasonal pattern					0.21	NS
Present	17	45	12	55		
Absent	21	55	10	45		
Psychotic symptoms					11.64	<0.001
Yes	34	90	10	45		
No	4	10	12	55		
Suicide attempts					0.00	NS
Yes	12	32	6	27		
No	26	68	16	73		
Familial history					NA	
Bipolar I	5	13	2	9		
Bipolar II	1	3	4	18		
Unipolar	8	24	6	27		
Other	10	26	4	18		
None	13	34	6	27		
Familial history of suicide					0.85	NS
Yes	8	22	2	9		
No	28	78	20	91		

NS, not significant; NA, not applicable.

Reproduced with permission from Vieta *et al.* (1997a).

we analyze all these data, it is essential to consider the influence of treatment because many patients, before being diagnosed as bipolar II, could have been misdiagnosed as personality disorders or unipolar depressive disorder, which would have precluded the use of mood stabilizers that facilitated treatment with tryciclic antidepressants, with a high risk of drug-induced switching (Vieta, 1999). Figure 4.1 illustrates the natural course of some bipolar I and bipolar II patients when antidepressant use was strictly controlled and all patients received mood stabilizers.

Coryell *et al.* (1987, 1995) reported that bipolar II disorder seemed to be phenomenologically stable, with a relatively low percentage of patients who became bipolar I during follow-up. This would support the long-term validity of the bipolar II category and the hypothesis of a true dichotomy. Akiskal *et al.* (1995) performed an 11-year follow-up of a sample who presented a major depressive episode. The results showed that 3.9% developed a full-blown manic episode, becoming bipolar type I, and 8.6% presented with at least one episode of hypomania, confirming that they belonged to bipolar II disorder. Unipolar patients who switched to bipolar II disorder were characterized by early age at onset, recurrent depression, high rates of divorce or separation, high rates of scholastic and/or job maladjustment, isolated antisocial acts, drug abuse, and a broad *mélange* of atypical depressive symptoms with borderline taint. Mood lability was the most specific predictor of which depressions would prospectively switch to bipolar II disorder. The study testifies to the fact that bipolar II disorder is a complex affective disorder with biographical instability deriving from an intense temperamental dysregulation (Akiskal, 2002a, b). Other authors have suggested that the depressive phase of bipolar II disorder features more atypical symptoms than unipolar depression (Benazzi, 2000). Akiskal *et al.* (1983) proposed eight criteria that are believed to be predictive of "bipolarization" from depression: (1) treatment-induced hypomania; (2) family history of bipolar disorder; (3) strong inheritability; (4) depression with hypersomnia and motor slowing-down;

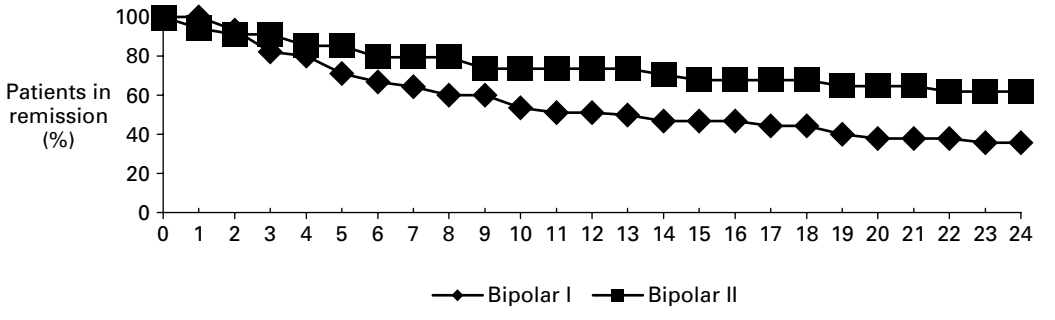

Fig. 4.1 Course of bipolar I and bipolar II disorders. Reproduced with permission from Vieta (1999).

(5) psychotic depression; (6) continuous multigenerational familial transmission; (7) postpartum onset; and (8) early onset. They suggested that these episodes should be called "pseudounipolar depression" and that the condition would show its bipolar nature afterwards. Bourgeois *et al.* (1996) confirmed the significantly higher frequency of these markers on bipolar disorder. Goldberg *et al.* (2001) found that depressed patients with psychosis at the index depressive episode were significantly more likely than non-psychotic patients to demonstrate mania or hypomania at follow-up.

With regard to outcome, Tsuang *et al.* (1979) found that, when marital, residential, occupational, and psychiatric symptoms were combined, outcome was good in 64% of bipolar I patients, intermediate in 14%, and poor in 22%. Endicott *et al.* (1985) described a more chronic course in bipolar II than in bipolar I disorder; this difference not only accounted for affective symptoms but also for the presence of other psychiatric problems between episodes. Coryell *et al.* (1989) found comparable degrees of psychosocial disability over time in bipolar II and bipolar I patients, although bipolar II patients were particularly likely to report work impairment at the end of a 5-year follow-up. Other authors have found that bipolar I disorder was more incapacitating than bipolar II disorder (Vieta *et al.*, 2002a). As far as social impairment and functioning between episodes are concerned, more than one-third of bipolar patients seem to have some chronic symptoms; some of this pathology is sequelae of the episodes themselves, and much of it reflects the absence of prophylactic or poor treatment (Goodwin and Jamison, 1990). Judd *et al.* (2002) studied the weekly symptomatic status of patients with bipolar I disorder during a prospective long-term follow-up; the results showed that symptomatic structure was primarily depressive rather than manic, and subsyndromal and minor affective symptoms predominated. A study by Tohen *et al.* (2000) with 219 cases of first episode of major affective disorder with psychotic features (159 manic or mixed bipolar patients) showed that syndromal recovery was attained by most patients (98.6% of bipolar or mixed patients) soon after hospitalization, but only one-third were functionally recovered by 24 months (40.4% of bipolar or mixed patients); functional recovery was associated with older age at onset and shorter hospitalization. The psychosocial impairment related to relapse persists for years in a great number of bipolar patients (Coryell *et al.*, 1993; Keck *et al.*, 1998).

Rapid cycling generally represents a transient phase in the course of bipolar disorder, with a prevalence rate lower than 20% in most studies (Akiskal *et al.*, 2000). It is more likely to arise from a bipolar II base (Coryell *et al.*, 1992; Baldessarini *et al.*, 2000), thus alternating at least four depressive or hypomanic episodes per year.

Several studies have reported a higher risk of suicide in bipolar II patients (Dunner *et al.*, 1976; Stallone *et al.*, 1980; Dunner, 1983; Goldring and Fieve, 1984; Arató *et al.*, 1988). Rihmer and Pestality (1999) reviewed the rate of lifetime history of suicide attempts and found it was attempted by 17% of bipolar I patients, 24% of bipolar II patients, and 12% of unipolar major depressive patients. In addition, bipolar II patients were relatively overrepresented among suicide victims. It was not only the personal history of suicide attempts, but also the family history of completed suicide in first-degree relatives that was significantly higher in bipolar II patients as compared to unipolar major depressives (Rihmer, 2002). Interpersonal conflicts, marital instability, and/or family breakdown were found to be particularly more frequent among bipolar II patients with respect to bipolar I and unipolar depressive patients, which, in the opinion of the authors, might contribute to the high suicidality. Kupfer *et al.* (1988) found higher past suicide attempts in a group of bipolar II patients than in a group of unipolar depressive patients.

Other authors have shown that bipolar II patients with personality disorders had a higher suicidal risk (Vieta *et al.*, 1999). The presence of comorbidity seemed to have no relevant impact on the clinical course of bipolar II patients except for suicidality (Vieta *et al.*, 2000). Previous studies did not show significant differences between bipolar I and bipolar II patients with respect to suicidal behavior (Coryell *et al.*, 1989; Vieta *et al.*, 1997b). These discrepancies may be due to different definitions of bipolar II disorder, biases derived from the setting, and comorbidity. In fact, it has been suggested that the exclusion of personality traits and substance abuse might eliminate some of the differences between bipolar I and bipolar II patients (Cooke *et al.*, 1995). There is some evidence that bipolar II disorder is more likely than unipolar disorder or bipolar I disorder to occur with other psychiatric diagnoses (Endicott *et al.*, 1985).

Pathophysiology

Unfortunately, most of the studies do not compare bipolar I and bipolar II disorders. We will comment on some of the studies that take into account bipolar subtypes.

Family studies and genetics

Family studies are useful for an understanding of the pathophysiology of bipolar disorders and then to evaluate the dimensional model and the category model. Some studies have concluded that bipolar II patients seem to have more bipolar II and unipolar relatives and fewer bipolar I relatives than bipolar I patients do (Coryell *et al.*, 1984; Fieve *et al.*, 1984). Coryell *et al.* (1984) not only found that

bipolar II probands were significantly more likely to have bipolar II relatives than were non-bipolar or bipolar I probands, but also that bipolar II probands were slightly more likely than non-bipolar probands and slightly less likely than bipolar I probands to have relatives with bipolar I illness. A higher morbid risk of depression among relatives of bipolar II patients with regard to the group of unipolar depressive patients has been described (Kupfer *et al.*, 1988). Gershon *et al.* (1982) noted that bipolar I and bipolar II disorders were more frequent in relatives of bipolar I and II patients than in relatives of unipolar depressives and controls. A study from Andreasen *et al.* (1987) showed higher familial loads of bipolar I disorders in bipolar I subjects and an increase of bipolar II illness in the relatives of bipolar II probands. In contrast with the results of Andreasen *et al.* (1987), Heun and Maier (1993) found that morbid risks for bipolar I disorder were equivalent in relatives of bipolar I and bipolar II patients and lower in relatives of unipolar subjects. However, the familial load for bipolar II disorder was higher in bipolar II than in bipolar I subjects, and lower in unipolar depressives and in controls. Bipolar II disorder has been reported to be the most prevalent affected phenotype in both bipolar I and bipolar II families and the only expressed phenotype in half of the bipolar II families (Simpson *et al.*, 1993).

With regard to genetics, a recent study from McMahon *et al.* (2001) found that paternal allele sharing on 18q21 was greatest in pairs where both siblings had bipolar II–disorder. Prospective analysis confirmed the finding that bipolar II–bipolar II siblings pairs showed significantly greater paternal allele sharing. Paternal allele sharing across 18q21–23 was also significantly higher in families with at least one bipolar II–bipolar II sibling pair. In these families, multipoint affected sibling pair linkage analysis produced a peak paternal LOD score of 4.67 versus 1.53 in all families. Therefore, affected sibling pairs with bipolar II discriminated between families who showed evidence linkage to 18q and families who did not. Families with a bipolar II sibling pair produced a increased lod score and improved linkage resolution.

Neuroimage

Kato *et al.* (1994) studied brain phosphorus metabolism in patients with bipolar I and bipolar II disorder using magnetic resonance spectroscopy. Phosphocreatine levels were lower in patients with bipolar II in the three states (euthymic, hypomanic, and depressed) compared to controls. High values of phosphomonoester were found in bipolar II patients in the hypomanic and depressive states, but phosphomonoester values in the euthymic state did not differ from controls. Intracellular pH of bipolar II patients in all phases was similar to control values, whereas euthymic bipolar I patients had lower pH values. The authors suggested that brain high-energy phosphate metabolism might be impaired in bipolar II

patients and that there might be pathophysiological differences between bipolar I and bipolar II.

Differences have been found between bipolar I and II disorders on magnetic resonance imaging scanning and on the presence of vascular abnormalities, including Raynaud's phenomenon, migraine, and migraine equivalents (Ferrier *et al.*, 2001). Endicott (1989) found a positive correlation between bipolarity and a cluster of disturbances, including classic migraine headache, the peripheral vascular disturbance of Raynaud's disease, enuresis, vague episodic phenomena similar to migraine prodrome, fingernail biting, and learning disorders; most of the psychophysiological conditions showed a higher incidence in bipolar II patients with respect to bipolar I patients.

By contrast, periventricular hyperintensities have been reported to be more common in bipolar I patients than in bipolar II patients and normal comparison subjects (Altshuler *et al.*, 1995). It would be necessary to increase the number of brain-imaging studies that separate bipolar I from bipolar II patients to know whether a pathophysiologic brain marker could distinguish between bipolar I and bipolar II disorders.

There were no quantitative magnetic resonance imaging studies of bipolar II patients until Hauser *et al.* (2000) measured temporal lobe and ventricular structures in bipolar I, bipolar II, and control subjects. Their results showed that there were no differences in temporal lobe or hippocampal volume estimates in the third ventricle area and lateral ventricle-to-cerebrum area ratio among diagnostic groups. The lateral ventricle area and the lateral ventricle-to-cerebrum area ratio were significantly larger in bipolar I patients than either bipolar II patients or control subjects only in the left hemisphere. Furthermore, these measures were approximately twice as large in the bipolar I patients as in the other groups. This study concluded that bipolar I disorder, particularly in males, might show different neurobiological alterations compared to bipolar II or control subjects.

Positron emission tomography was used in a recent study by Berns *et al.* (2002) to determine whether patients with bipolar II disorder had altered regional brain responses to novel motor sequences with respect to healthy subjects. The results showed that, in the comparison subjects, a spatial attention circuit in the superior parietal lobe and supplementary motor area was activated in response to the introduction of the new sequence. Bipolar II patients did not display this activation pattern; instead, a widespread limbic network was activated in response to the new sequence.

Future neuroimaging research should study comparative functional neuroimaging with single-photon emission computed tomography and positron emission tomography of bipolar I disorder and bipolar II disorder. Neuroimaging could be useful in validating diagnostic subtypes, although the results to date are too unspecific (Benabarre *et al.*, 2002).

Neurochemical studies

Siah *et al.* (1999) showed a trend towards higher platelet 5-hydroxytryptamine (5-HT) levels in bipolar I and II depressions when compared to normal controls, whereas there was no difference in platelet 5-HT levels between bipolar I and II depressed patients. The finding of increased platelet 5-HT levels in bipolar depressed patients compared to normal controls is consistent with the results of previous studies (Wirz-Justice and Puhringer, 1978; Stahl *et al.*, 1983), and might suggest an increase in presynaptic 5-HT reuptake, presumably resulting from diminished synaptic 5-HT availability in this condition. When bipolar I and II patients were pooled, there was a trend toward a weak positive correlation between platelet 5-HT and 21-item Hamilton Depression Rating Scale scores in the patient groups, suggesting that the presumed deficiency of serotoninergic function might be related to the severity of depression. There were no differences in plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) levels between the three groups. Goodwin and Post (1975) had also found no difference in cerebrospinal fluid MHPG levels between bipolar I and bipolar II. In contrast, some studies suggest that reduced urinary MHPG levels may be present only in bipolar I but not in bipolar II depressed patients (Muscettola *et al.*, 1984; Schatzberg *et al.*, 1989). Further studies are needed to explore the biochemical distinctions and similarities between bipolar I and bipolar II disorders.

On the other hand, Emamghoreishi *et al.* (1997) showed that the baseline Ca^{2+} concentration was significantly higher in the B lymphoblasts from patients with bipolar I disorder, but not bipolar II disorder or major depression, than in healthy subjects or psychiatric patients with non-mood disorders. There were higher basal Ca^{2+} concentrations in T lymphocytes in male bipolar I patients, but not in men with bipolar II patients or major depression, than in healthy male comparison subjects. Phytohemagglutinin-stimulated Ca^{2+} concentrations did not differ among groups, but the percentage differences from basal Ca^{2+} levels were lower in bipolar I and depressed patients than in healthy subjects. The authors suggested that trait-dependent factors account, at least partly, for the higher basal lymphocyte Ca^{2+} concentration in bipolar I subjects.

Neurophysiology

With respect to sleep electroencephalography, no differences between bipolar I and unipolar depressed patients have been reported by Giles *et al.* (1986), but they did find differences between unipolar patients and bipolar II patients: bipolar II patients had longer rapid-eye-movement (REM) latencies, more non-REM time, and hypersomnia. Ansseau *et al.* (1984, 1985) found that depressed bipolar II patients had more variability in REM latency, as well as a trend toward more sleep-onset REM periods than bipolar I patients.

Treatment

There are few studies that compare bipolar I and bipolar II patients with respect to treatment response.

Tondo *et al.* (1998) studied lithium maintenance treatment in bipolar I and II patients. Their findings showed that lithium had superior benefits in type II patients, with significantly greater reduction of episodes per year and of the percentage of time ill. Reduction of depressive morbidity was similarly strong in both bipolar I and bipolar II diagnoses. In a recent study, Tondo *et al.* (2001) found similar results and concluded that long-term lithium maintenance treatment in compliant patients without comorbid substance use-disorder remained effective, even in subgroups of supposedly poor prognosis, such as patients with mixed episodes, psychotic episodes, or rapid cycling. Only about a quarter of the patients in this study experienced complete remission during maintenance treatment, suggesting that full protection was not commonly achieved with lithium or with alternative treatments. Some clinical factors found early in the course of illness (age at illness onset, and a longer interval between first and second lifetime episodes) or early in treatment with lithium (rapidity of recovery from the index episode at the start of lithium treatment, and a longer interval to the first subsequent recurrence) were significantly associated with a better long-term treatment response as indicated by the overall proportion of time ill during treatment.

Other studies found evidence of beneficial effects of lithium for both mania and depression in bipolar I patients and for mainly depressive episodes in bipolar II patients (Dunner *et al.*, 1976; Fieve *et al.*, 1976; Quitlin *et al.*, 1978; Kane *et al.*, 1982; Peselow *et al.*, 1982; Tondo *et al.*, 1997). Koukopoulos *et al.* (1980) found significant differences in lithium prophylaxis as a function of episode sequence: the bipolar II patients with the hypomania–depression–euthymic interval course were the best lithium responders. A higher incidence of axis-II disorders among bipolar II patients could affect drug responses. Other authors have replicated the significantly more favorable prophylactic response among the mania–depression–euthymic interval course (Grof *et al.*, 1987; Haag *et al.*, 1987; Maj *et al.*, 1989; Faedda *et al.*, 1991); in contrast, in the above-mentioned study of Tondo *et al.* (2001), the sequence of manic and depressive episodes was not associated with treatment response. Goodwin and Jamison (1990) suggested that the poor results in patients with the depression–mania–euthymic interval course might reflect the impact of tricyclics given to treat depression; the mania following depression could be drug-induced, and such manias might be relatively resistant to lithium treatment.

There was a suggestion for a higher prophylactic efficacy of carbamazepine versus lithium in bipolar II patients compared to bipolar I in one study (Greil *et al.*,

1998), which deserves replication. Data on the comparative efficacy of valproate are scant.

With a sample of rapid-cycling bipolar patients, Calabrese *et al.* (2000) studied the safety and efficacy of lamotrigine in a double-blind, placebo-controlled study. The results suggested that lamotrigine might be a well-tolerated and effective mood stabilizer with prophylactic properties when used as monotherapy in some patients with rapid cycling. Differences favoring lamotrigine were consistently greater for bipolar II than bipolar I patients. An open study is also supporting the efficacy of lamotrigine in bipolar II disorder (Vieta *et al.*, 2003), though an unpublished double-blind trial could not separate its effects from placebo in this particular population. Another anticonvulsant, topiramate, seemed to be more useful for the hypomanic phase (Vieta *et al.*, 2002b).

Regarding antidepressant treatment, its impact is positive for unipolar patients but unclear and sometimes self-defeating for bipolar patients because antidepressant treatment, especially tricyclic antidepressants, implies an important risk of switch induction or cycle acceleration. In bipolar I patients the treatment aims to prevent manic relapses; consequently, lithium is the primary treatment in bipolar I patients because of its prophylactic effect on mania, and also because it has greater antidepressant efficacy in bipolar I depressive disorder. On the other hand, in bipolar II patients it is very important to control and prevent depressive episodes; consequently, lamotrigine and antidepressant treatment (mostly represented by the selective serotonin reuptake inhibitors), which have less propensity for hypomania induction, may be useful (Bourgeois, 2002). In practice, the decision to use concurrent mood stabilization during the treatment of bipolar II depression must be made on a case-by-case basis, with age at onset, cycle length, past history of rapid cycling, patient gender, and prior frequency and severity of hypomanias important considerations (Thase and Sachs, 2000).

Atypical antipsychotics have also been tried in bipolar II disorder, though no randomized, double-blind trials are yet available (Crespo and Vallejo, 2002; Vieta, 2003). A cohort of bipolar II hypomanic patients was treated with adjunctive risperidone by Vieta *et al.* (2001a), with good results. Efficacy was fully comparable to that found in bipolar I manic patients (Vieta *et al.*, 2001b), thus supporting the dimensionality of the (hypo)manic spectrum. Besides, doses correlated with the intensity of symptoms, being higher for manic than for hypomanic patients (Vieta *et al.*, 2001b). Other atypicals have been reported to be useful in the treatment of patients within the bipolar spectrum, including bipolar I and II. Olanzapine (Vieta *et al.*, 2001c) and quetiapine (Vieta *et al.*, 2002c) may show some promise, even in the "softer" range of bipolarity.

Conclusion

From a clinical and therapeutic point of view, bipolarity looks clearly dimensional. The strongest support for the theory that bipolar II disorder "breeds true" comes from genetic studies. Pathophysiological and neuroimaging studies are still inconclusive. The dimensionality of the bipolar spectrum runs against the existence of a true dichotomy between bipolar I and bipolar II. In fact, as far as the molecular level, it seems to be uncategoric. Dichotomies are useful for education, communication, and simplification; unfortunately, simplicity is useful but untrue, whereas complexity is true, but useless. In clinical practice, we may use current classifications, such as DSM-IV, as categoric backgrounds that may help to establish the treatment and prognosis. However, the presence of mixed symptoms in many bipolar II patients, their not-so-rare switch into mania, and the need for vigorous treatment to deal with the high frequency of relapse may make the apparent dichotomy less likely to shed light on the nature of bipolarity and the needs of our patients.

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5

Recurrent brief depression as an indicator of severe mood disorders

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Introduction

Bipolar spectrum

The bipolar spectrum is currently the focus of very intensive research, which is hampered by two interrelated biases, one methodological and one commercial. Epidemiological and clinical research in the field of bipolar disorders deals with disorders/syndromes defined according to the diagnostic manuals and uses methods tailored to them, which are not suitable for assessing subthreshold morbidity (minor and recurrent brief depression, recurrent and brief hypomania). This has significant implications for the differentiation between depression and bipolar disorder. As a consequence, major depressive disorders (MDD) are overdiagnosed and heterogeneous; they include many bipolar II (BP-II) cases, of which the hypomanic component does not reach the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV: American Psychiatric Association, 1994) or *ICD-10 Classification of Mental and Behavioural Disorders* (World Health Organization, 1992) diagnostic threshold for hypomania. This means that drug trials selecting patients on the basis of an MDD diagnosis are also dealing with heterogeneous groups, which include hidden BP-II subjects prone to switch into hypomania.

Moreover, current bipolar research is biased towards mania and neglects bipolar depression. The large majority of modern treatment studies on mood stabilizers select patients with mania and exclude those with BP-II disorders, although the latter are much more prevalent than the former both in clinical practice and among relatives of bipolar patients. In addition, BP-II patients have traditionally been excluded from drug trials using modern antidepressants.

As we have found, bipolar subjects identified by diagnostic criteria of DSM-IV (American Psychiatric Association, 1994) or ICD-10 (World Health Organization, 1992) form only the tip of the iceberg of the bipolar spectrum; below the diagnostic threshold are a large number of subjects with unidentified

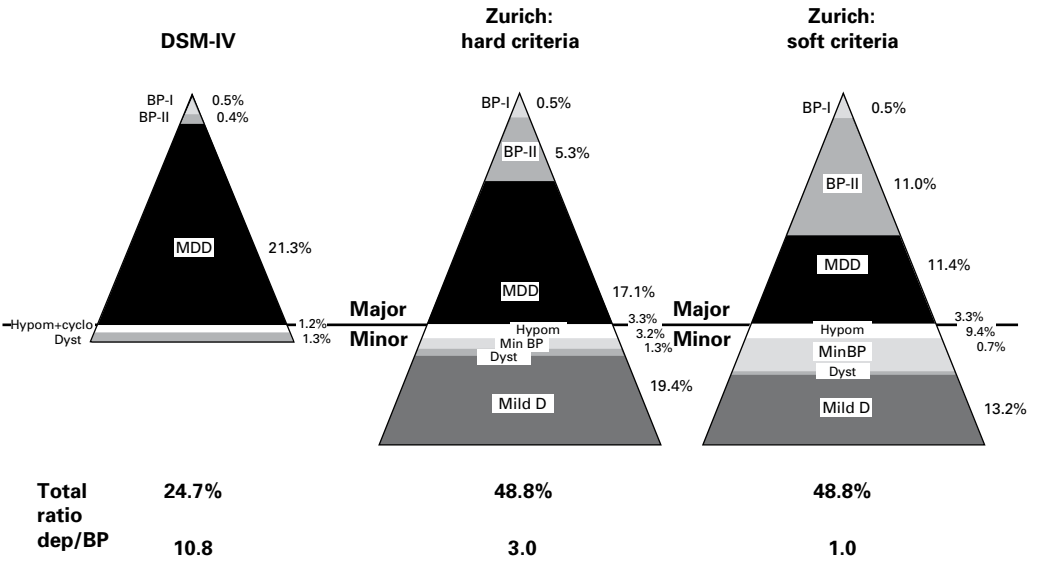


Fig. 5.1 Cumulative prevalence rates of the bipolar spectrum. BP-1, bipolar disorder I; MDD, major depressive disorder; Hypom, hypomania; Dyst, dystonia; D,/Dep, depression; BP, bipolar; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*. Reprinted with slight modifications from Angst, J. and Gamma, A. (2002). Prevalence of bipolar disorders: traditional and novel approaches. *Clin. Approaches Bipolar Disord.,* **1**, 10–14, by permission of Cambridge Medical Publications.

BP-II, minor bipolar disorders, and hypomania (Angst *et al.*, 2003a; Angst and Gamma, 2002). Figure 5.1 illustrates the cumulative prevalence rates of the bipolar spectrum, with its subgroups, as diagnosed in the Zurich study across six interviews from the age of 20 to 40 (Angst *et al.*, 2003a; Angst and Gamma, 2002). The tip of the iceberg consists of 0.55% BP-I disorder, below which we found 5.3% BP-II disorders defined by hard Zurich criteria and a further 5.7% suspected BP-II cases defined as major depressive episodes (MDE) with hypomanic symptoms. In the same paper, we also proposed a new group of minor bipolar disorders (MinBP) with a prevalence rate of 3.2% (hard definition) and 6.2% (soft definition). This important MinBP group consists of depressives (dysthymia, minor depression, and recurrent brief depression (RBD)) who, in addition, manifested hypomanic syndromes (hard definition) or hypomanic symptoms (soft definition).

Figure 5.1 shows that a hard definition of bipolarity identifies about one-quarter of all mood-disorder cases as bipolars, whereas a soft definition, including suspect cases, identifies about half of such cases as bipolars. This finding is especially relevant in regard of MDD, which was found to be no more prevalent than BP-II disorders. A soft definition of BP-II disorders enables us to identify most hidden bipolar cases, which are usually misdiagnosed as MDD. For more details, see Angst *et al.* (2003a).

Recurrent brief psychiatric syndromes

Although the relevant concepts were established a decade ago, recurrent brief psychiatric syndromes are still not fully researched. They are characterized by a special course pattern, with frequently recurring (at least monthly) brief episodes, lasting between a few days and less than 2 weeks. Recurrent brief mood and anxiety disorders include recurrent brief hypomania (RBM) (Angst, 1992), RBD (Angst, 1988), and recurrent brief anxiety (RBA) (Angst and Wicki, 1992). Recurrent brief psychiatric syndromes were not conceptualized as new disorders but as elements of the manic, depressive, and anxiety spectra. Diagnoses of RBD and MDD are not mutually exclusive in our studies. In the same year a patient may manifest an episode of MDD and many brief episodes of depression, qualifying for RBD. The association may also be found during the course of an illness over years. The combination of recurrent brief psychiatric syndromes with the corresponding major disorders, for instance major depression, bipolar disorder, panic disorder, or generalized anxiety disorder, has great clinical relevance in terms of impairment and treatment.

Associations of RBD with MDDs were termed early on "combined depression" by analogy with "double depression" (MDD + dysthymia; Montgomery *et al.*, 1989, Merikangas *et al.*, 1990). Combined depression (CD) has been shown to be more severe than pure MDD in the community (Angst *et al.*, 1990) and in clinical samples (Pezawas *et al.*, 2002b). The increased risk of suicide attempts and the severe clinical condition observed in CD are intriguing, since CD does not differ from either MDD or RBD with respect to the required psychopathological depression criteria. It is important for the understanding of the concept to bear in mind also that the hierarchy of the DSM-IV system, for example, determines that patients with either "pure" MDD or CD are both diagnosed as MDD. We may therefore assume that this subgroup of depressive patients may have contributed more than "pure" MDD to clinical impairment in DSM-IV-based studies on MDD.

This chapter begins by analyzing the associations between RBD (Angst, 1988), RBM (Angst, 1992), and RBA (Angst and Wicki, 1992). All three recurrent brief psychiatric syndromes share an ultrarapid cycling pattern of mood symptoms. In association with MDEs, they clearly increase impairment and worsen treatment outcomes. Given this greater clinical severity of CD, it is reasonable to hypothesize that BP-II disorders combined with RBD also represent more severe clinical conditions than pure BP-II forms. The main goal of this chapter, then, is to test this hypothesis by comparing diagnostic subgroups of mood disorders with and without RBD in a large number of validating clinical variables, including family history, course, personality, and comorbidity. Cases associated with RBD will hereafter be termed "combined" (e.g., combined BP II disorder, combined MDD, combined MinBP).

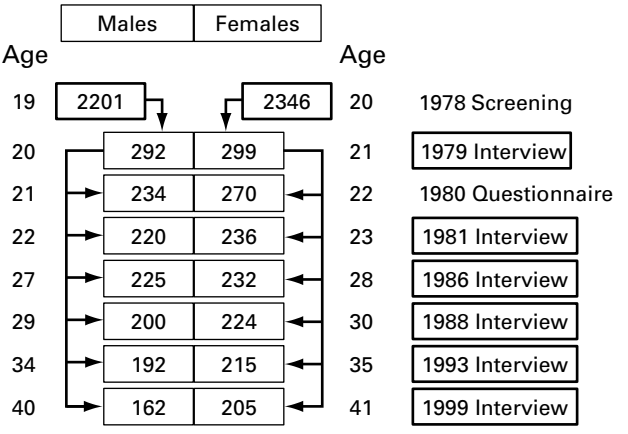


Fig. 5.2 Design of the Zurich cohort study.

Methodology

Sample

The Zurich study is based on the population of the canton of Zurich, which accounts for approximately one-sixth of the population of Switzerland. In a first stage of the study (1978) 4547 subjects (male, 2201; female, 2346) were screened using the Symptom Check List 90-R (SCL-90R). Derogatis's (1977) subsample selected for interview consisted of 591 subjects, two-thirds of whom were high-scorers on the SCL-90R (85th percentile or more) and one-third were randomly selected from those with lower scores. By weighting the two strata, it is possible to extrapolate to a representative group of 2599 persons of the general population of the same age.

The male subsample ($n = 292$) was screened at the age of 19 and the female subsample ($n = 299$) at the age of 20; to date they have been interviewed six times between the ages of 20 and 40 (male) and 21 and 41 (female). Figure 5.2 shows the design of the Zurich study.

Interviews

The six interviews were conducted in 1979, 1981, 1986, 1988, 1993, and 1999. After 20 years, 60% of the sample remained in the study and there had been no significant distortion of the sample by attrition; the proportion of the two strata of high- and low-scorers on the SCL-90 remained stable (Eich *et al.*, 2003). The interviews were carried out mainly by trained clinical psychologists and psychiatrists with the Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology (SPIKE: Angst *et al.*, 1984). The interview has

been shown to have good diagnostic validity in depressed hospitalized and ambulatory patients (Illes, 1981; Pfortmüller, 1983; Busslinger, 1984; Meier, 1985); an interrater reliability study showed good specificity and sensitivity (Angst *et al.*, 2003c) for the syndromes of depression and anxiety.

Definitions

Bipolar spectrum

A spectrum of bipolar disorders was defined as follows (for a detailed description of the bipolar spectrum, see Angst *et al.* (2003a)):

(1) BP-I disorder: DSM-IV criteria
(2) BP-II disorders: Zurich criteria using two definitions:
    (a) a hard syndromal definition required the presence of hyperactive or mood symptoms plus three of seven symptoms of mania plus personal or social consequences
    (b) a soft definition required only the presence of manic symptoms. No episode-length criterion was applied, as we could find no empirical evidence for its validity
(3) MinBP: the definition of MinBP required the diagnosis of dysthymia, minor depression (MinD), or RBD plus a hypomanic syndrome (a) or hypomanic symptoms (b).
(4) Cyclothymia was diagnosed in cases where dysthymia was combined with hypomania or hypomanic symptoms and where more days than not had been spent in affective states during the 12 months prior to an interview.

Depressive spectrum

The depressive spectrum was as follows:

(1) MDD: DSM-IIIR
(2) Dysthymia: DSM-IIIR
(3) MinD: the diagnosis of MinD is often defined by any depressive symptoms present over at least 2 weeks (Judd *et al.*, 1994); in the Zurich study we restricted the definition to syndromes with three to four of the nine DSM-IIIR criterial symptoms, because under this threshold there was almost no treatment-seeking or impairment
(4) RBD.

Recurrent brief psychiatric syndromes

(1) RBD required the presence of the major depressive syndrome according to DSM-IIIR symptom criteria (five of nine symptoms) with brief duration (less

than 2 weeks, usually 1–3 days) and frequent recurrence (at least monthly over the previous 12 months) plus work impairment

(2) The definition of RBM required the presence of a hypomanic syndrome (Angst *et al.*, 2003a) of brief duration (1–3 days) and frequent recurrence (at least monthly over the previous 12 months). In addition, we tentatively defined a diagnosis of recurrent brief hypomanic symptoms (RBMS) with brief duration and high recurrence

(3) RBA was diagnosed in the presence of a DSM-III syndrome of generalized anxiety disorder of brief duration (less than 2 weeks) and frequent recurrence (at least monthly over the previous 12 months; Angst and Wicki, 1992).

Combined syndromes

This paper will concentrate on combined major depression and combined bipolar disorders.

As stated earlier, we defined combined major depression as the association of MDD with RBD; combined BP-II disorders as the association of BP-II with RBD; and combined MinBP as the association of MinBP with RBD. The combined groups will be compared with the pure groups in order to test the hypothesis that the combined are more severe than the pure syndromes.

Rapid cycling and seasonality

Rapid cycling was diagnosed if the subjects reported having suffered from four or more episodes of depression or hypomania per year; brief episodes with a length under the diagnostic thresholds of DSM-IV were included.

Seasonality was assessed by questions on the presence of the episodes in spring, summer, fall, and winter.

Treatment and distress

Treatment was defined as consultation of doctors or psychologists for mood syndromes. Distress as a consequence of manic and depressive symptoms was estimated on an analogue scale from 0 to 100 (thermometer) over the 12 months prior to the interview.

Personality

A personality trait of mood instability (ups and downs) was assessed by the question: "Would you say you were one of those people who have frequent ups and downs?"

A diagnosis of depressive personality disorder (DPD) was derived from the General Behavior Inventory of Depue *et al.* (1981; items 16, 20, 36, 47, 56, 62, 71

corresponding to the seven items of DPD in DSM–IV); unlike DSM–IV we required not just five but all seven items to be present at least sometimes.

Anxious personality features were assumed to be present if the subject answered yes to both of the following questions:

1. As a child or adolescent were you more anxious than your peers?
2. Do you feel your anxieties impaired your development?

Neuroticism (N), extroversion (E) and aggression (A) were measured by the Freiburg Personality Inventory (FPI) of Fahrenberg and Selg (1970) using a questionnaire with 212 items given at the fourth and fifth interviews (ages: males, 29/30; females, 34/35). These three factors – aggression, extroversion, and neuroticism – were derived from large Swiss population samples (6315 males, 1381 females).

Impulsivity/irritability was represented by subfactor 4 of the FPI.

Statistics

SAS for Windows version 8.01 was used. For group comparisons, chi-squared tests, Fisher's exact tests, and Kruskal–Wallis tests were applied. Prevalence rates and standard errors were computed by Stata 7.0 with adjustment for sample stratification. Cumulative prevalence rates refer to the sum of 1-year prevalence rates across all interviews. For certain analyses, logistic regression and biserial correlations were computed.

Results

Recurrent brief psychiatric syndromes and their overlap

The main focus of this chapter is the relationship of the two mood spectra with recurrent brief psychiatric syndromes (RBD, RBM, and RBA), with particular emphasis on RBD. An association is very frequent: Table 5.1 demonstrates that 44% of BP-II cases and 39% of MDD cases received an additional diagnosis of RBD; in addition 71% of MinBP cases were associated with RBD. Furthermore, over one-third of mood-disorder cases also received a diagnosis of RBA.

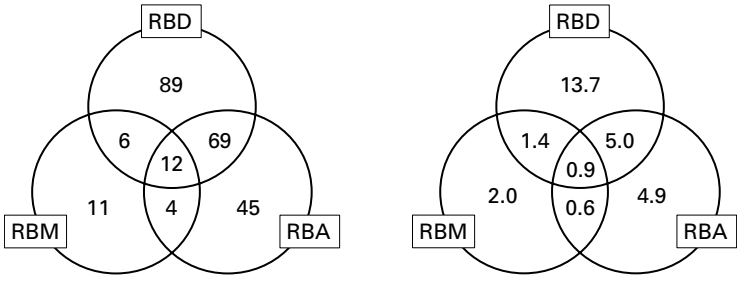
This raises the question of the interrelationship between RBD, RBM, and RBA. Figure 5.3 shows their overlap computed as odds ratios: it is intriguing that the highest associations were found between RBA and RBD (OR = 5.2) and RBA and RBM (OR = 3.8). However, RBM was more closely associated with RBA than with RBD (OR = 2.9), which underlines the important role of anxiety in brief hypomania and bipolar disorders in general, as shown in Table 5.1. The associations are very similar in the case of RBMS.

Figure 5.3 shows the overlap on the basis of prevalence rates.

Table 5.1 Recurrent brief depression (RBD), recurrent brief hypomania (RBM), and recurrent brief anxiety (RBA): association with mood disorders

Diagnoses	BP-II ($n = 89$) (%)	Minor BP ($n = 59$) (%)	Hypomania ($n = 23$) (%)	MDD ($n = 101$) (%)
RBD (rbdr7999)	43.8	71.2		38.6
RBM (rbm8199)	20.2	17.0	17.4	
RBD + RBM (rbmd7999)	55.1	72.9	17.4	
RBA	43.8	32.2	8.7	35.3

BP, bipolar; MDD, major depressive disorder.



Association	OR (95% CI)
RBD×RBM	2.9 (1.4–5.9)
RBD×RBA	5.2 (3.4–8.0)
RBM×RBA	3.8 (1.7–8.2)

Fig. 5.3 Longitudinal associations between recurrent brief psychiatric syndromes. Left side: number of cases; right side: weighted prevalence rates. Odds ratios are adjusted for sex and stratified sampling. RBD, recurrent brief depression; RBM, recurrent brief mania/hypomania; RBA, recurrent brief anxiety; OR, odds ratio; CI, 95% confidence interval.

The value of RBD, RBM, and hypomanic symptoms as a predictor of BP-II disorder

Of 132 first observed cases of RBD, 32% developed manic symptoms prospectively and a further 15% developed BP-II/MinBP disorders (the categories are not mutually exclusive).

There was considerable stability of RBD over the years; 31% of RBD cases received a diagnosis of RBD again in a later interview.

Three of 23 cases of RBM (11.5%) were followed by BP-II disorder, and 8% of the 38 cases with BP-II disorder were preceded by RBM.

Of the subjects with hypomanic symptoms, seven of 122 cases (5.7%) developed BP-II disorders prospectively; in a follow-up, seven of 38 BP-II cases (18%) were found to have manifested hypomanic symptoms in earlier interviews.

Combined versus pure mood disorders (Table 5.2)

Gender

A marked female preponderance (88%) was only found in combined major depression (MDD + RBD). In most other groups with sufficiently large numbers, the female preponderance was marginal (53–60%).

Diagnostic overlap

RBM overlapped with pure BP-II disorder, combined BP-II, and combined MinBP in about 20% of cases; if symptoms (RBMS) were included, that overlap rose to about 35%.

The group of pure MinBP (without RBD) is small and not conclusive. The high rates of RBA (40–59%) among all subgroups of mood disorders associated with RBD are remarkable; this is compatible with the high odds ratio (OR) of 5.2 shown in Figure 5.3.

Family history

From a genetic point of view, the results are very interesting: they demonstrate that, compared to pure BP-II and pure MinBP, the combined-disorder groups tended to have higher rates of positive family histories for mania, depression, and anxiety. It is important that, compared to the control group, none of the pure depressed groups had an elevated rate of a family history of mania.

Clinical characteristics

A number of variables reflect the severity of the illness. Most demonstrate the greater severity of illness in the combined groups: higher rates of subjective or social consequences of their hypomanic symptoms (therefore meeting more often the strict criteria for hypomania), higher rates of treatment and medication for depression, and higher distress scores due to depression. On the other hand, none of the subjects reported being distressed in any way by hypomanic symptoms.

Table 5.2 Bipolar II (BP-II), minimum bipolar (MinBP), and major depressive disorder (MDD) subclassified by presence of recurrent brief depression (RBD)

	1 BP-II RBD ($n=39$) (%)	2 BP-II ($n=50$) (%)	3 MDD RBD ($n=39$) (%)	4 MDD ($n=62$) (%)	5 MinBP RBD ($n=42$) (%)	6 MinBP ($n=17$) (%)	7 RBD pure ($n=60$) (%)	8 Controls ($n=138$) (%)	1–7 *P*
Prevalence rates (age 20–41 years)	4.3	6.7	3.5	7.9	6.0	3.4	7.5	42.4	
Females	59.6	57.7	**87.9**	57.9	54.0	67.9	53.2	42.5	0.4804
RBM									
RBM threshold (RBM)	20.5	20.0			21.4	5.9			NC
RBMS subthreshold + RBM	35.9	34.0			33.3	17.7			NC
Cyclothymia (>49% days/1 year)					14.3	23.5			NC
Recurrent brief anxiety	**59.0**	32.0	**43.6**	17.7	**40.5**	11.8	**43.3**	4.9	0.0003
Family history (FH)									
FH + depression	**71.8**	50.0	**74.4**	57.9	**68.3**	64.7	55.8	30.0	0.0373
FH + mania	**20.5**	**10.4**	2.9	4.0	**10.0**	**11.8**	4.4	4.2	0.0001
FH + anxiety	**48.7**	34.0	**48.7**	19.3	**43.9**	23.5	**34.6**	15.4	0.0001
Clinical consequences									
Suicide attempts	**38.5**	16.0	**25.6**	22.6	**7.1**	4.9	11.7	2.7	0.0001
Subjective or social consequences of hypomania	**53.9**	48.0			**40.5**	29.4			NC
Consequences of hypomania or depression	**64.1**	55.1	61.1	42.9	**47.6**	47.1	36.0		
Lifetime treatment of depression	**82.5**	60.0	**69.2**	50.0	**66.7**	52.9	46.7		0.0078
Work impairment	100	82.0	100	89.9	100	82.4	100		NC
Maximum distress depression (mean)	86.9	80.6	85.1	83.3	81.3	81.7	77.4		0.1717
Onset and course									
Age of onset (mean) (years)	**12.0**	13.3	**12.3**	15.3	**12.6**	14.4	16.1		0.0002
Age of first treatment (mean) (years)	21.7	22.8	22.0	23.4	23.2	22.3	22.6		0.0002
Course									
Recurrent	100	95.2	81.8	90.9	100	90	100		NC

Chronic		4.8	**18.2**	9.1		10			NC
Rapid-cycling depression	**69.2**	54.0	**61.5**	48.4	**90.5**	76.5	98.3		0.0001
Rapid-cycling (mania depression)	**82.2**	**82.0**	**61.5**	48.4	**100**	88.2	98.3		0.0001
Seasonal depression (fall/winter)	**64.1**	55.1	**61.1**	42.9	47.6	47.1	36.0		0.1014
Spring depression	**20.5**	12.2	**19.4**	3.6	**19.1**	5.9	4.0		0.0278
Summer depression	7.7	2.0	5.6	0	2.4	0	4.0		NC
Atypical depression DSM-IV	69.2	30.6	52.8	39.3	45.2	35.3	32.0	6.0	0.0001
Atypical depression: Zurich criteria	**82.1**	44.9	**58.3**	42.9	**45.2**	41.2	34.0	6.0	0.0001
Personality "ups and downs"	**41.0**	36.0	**20.5**	19.4	**35.7**	23.5	13.3	3.8	0.0126
Depressive personality disorder	**33.3**	8.9	**14.3**	8.3	**29.0**	5.9	**27.3**	4.3	0.0047
Anxious personality	**33.3**	10.0	**25.6**	4.8	**23.8**	11.8	**16.7**	3.8	0.0038
Sociopathy (including adulthood)	12.8	8.0	5.1	11.3	4.8		3.3	1.6	NC
Conduct problems (adolescence)	28.2	**47.9**	17.1	**25.5**	24.4	**29.4**	23.4	20.2	0.0558
Thefts	7.7	18.8	17.1	16.0	7.5	23.5	2.2	10.5	NC
Truancy	18.0	18.8	8.6	14.0	5.0		8.7	2.1	NC
Runaway	10.3	8.3	5.7	8.0		11.8		1.05	NC
Frequent fights	5.1	20.8	5.7	6.0	10.0		8.7	5.3	NC
Offenses	33.3	24.0	18.0	25.8	11.9	23.5	15.0	6.0	0.2194
Freiburg Personality Inventory at age 35 years									
Aggressiveness	20.6	18.3	17.8	12.6	19.5	20.4	18.8	14.6	0.6914
Extroversion	**16.9**	19.9	**13.9**	19.4	**17.5**	18.0	**16.9**	18.5	0.0161
Neuroticism	**20.4**	17.5	**20.0**	16.9	**20.5**	17.7	**18.7**	13.1	0.0889
Impulsivity/irritability	**25.3**	21.3	**23.0**	22.1	**22.8**	21.2	**22.3**	17.1	0.0001
Comorbidity									
Anxiety disorders	**71.8**	58.0	**69.2**	45.2	**50.0**	23.5	**51.7**	13.0	0.0072
DSM-III panic disorder	15.4	18.0	20.5	4.8	16.7	5.9	11.7	1.6	0.2314

Table 5.2 (*cont.*)

	1 BP-II RBD ($n=39$) (%)	2 BP-II ($n=50$) (%)	3 MDD RBD ($n=39$) (%)	4 MDD ($n=62$) (%)	5 MinBP RBD ($n=42$) (%)	6 MinBP ($n=17$) (%)	7 RBD pure ($n=60$) (%)	8 Controls ($n=138$) (%)	1–7 P
Repeated panic attacks	**38.5**	34.0	**51.3**	16.1	**31.0**	5.9	**36.7**	6.5	0.1378
DSM-III general anxiety disorder	**43.6**	34.0	25.6	24.2	**26.2**	11.8	21.7	3.8	0.3615
Agoraphobia	15.4	16.0	18.0	8.1	11.9	11.8	8.3	3.8	NC
Social phobia	**30.8**	20.0	**33.3**	14.5	**23.8**	11.8	**16.7**	3.8	0.1715
Specific phobia	**28.2**	18.0	**25.6**	14.5	16.7	17.7	6.7	6.0	0.1121
Obsessive-compulsive disorder	**23.8**	11.4	**22.2**		17.4		6.5	2.7	NC
Obsessive-compulsive syndrome	**23.1**	14.0	**28.2**	8.1	11.9	29.4	11.7	9.2	0.0507
Bulimia	2.6	4.1	2.8	5.4	7.1		2.0		NC
Binge-eating	23.1	22.5	16.7	14.3	16.7	11.8	10.0	3.4	0.6136
Substance abuse/dependence	61.5	50.0	23.1	32.3	26.2	47.1	18.3	15.1	0.0001
Alcohol abuse/dependence	56.1	36.0	7.7	25.8	23.8	35.3	11.7	11.9	0.0001
Cannabis abuse/dependence	18.0	20.0	12.8	14.5	7.1	23.5	3.3	6.5	0.0861
Benzodiazepine abuse	10.3	8.0	7.7	11.3	4..8	5.9	5.0	1.0	0.8489
Opiate abuse/dependence	10.3	4.0	5.1	4.8	2.4	11.8		1.1	NC
Psychostimulant abuse/dependence	12.8	10.0	2.6	6.5	2.4	5.9	1.7	3.8	NC
Tobacco dependence	64.1	55.1	47.2	46.3	52.4	64.7	38.0	33.3	0.2121

NC, not computed, small cell occupancy; RBM, recurrent brief mania; RBMS, RBM symptoms; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*

Table 5.3 Mood disorder with recurrent brief depression (RBD) versus mood disorders without RBD: associations with clinical characteristics

Dependent variable	OR	*P*	CI 95%	
Family history of depression	1.99	0.01	1.17	3.39
Family history of mania	1.52	0.36	0.62	3.70
Family history of anxiety	2.56	0.00	1.49	4.38
Suicide attempts	1.29	0.43	0.69	2.40
Lifetime treatment depression	2.12	0.01	1.22	3.68
Seasonal depression	1.37	0.24	0.81	2.30

OR, odds ratio; CI, confidence interval.

Onset and course

In all groups the age of onset of first symptoms was early, occurring in 90% of cases before the age of 21. A chronic course was mainly observed in major depression but not in bipolar spectrum disorders, whose course patterns tended to be characterized by recurrent episodes and very high rapid-cycling rates (80% or more).

Overall, bipolarity was associated with seasonal depression. Seasonal depression in fall and winter was markedly present in all the mood-disorder subgroups, especially in combined BP-II and combined MDD. Rapid-cycling depression was also strongly associated with these two subgroups (69% and 62% respectively); rapid-cycling depression was found in about half of the pure BP-II and MDD cases.

Associations with other psychiatric disorders

Overall, the combined groups showed significantly elevated comorbidity with all subgroups of anxiety disorders, with the exception of agoraphobia. However, we found no systematic relationship between substance abuse/dependence and RBD; but significant differences were found between bipolar and depressive spectrum disorders. Table 5.3 shows the results of a logistic regression that tested associations between all three combined groups (BP-II, Min-BP, MDD with RBD) versus the pure groups (without RBD) of mood disorders (as dependent variable), with some of the characteristics listed in Table 5.2 as independent variables. RBD was significantly associated with a family history of depression (OR = 2.0) and anxiety (2.6) and double the lifetime treatment rate for depression (OR 2.1).

Personality

Combined bipolar and depressive groups (with RBD) demonstrated significantly more personality disorders and certain personality traits, such as mood lability

(assessed as "frequent ups and downs"), anxious personality, and depressive personality disorder, whereas, surprisingly, the reverse trend was present for conduct problems in childhood and adolescence (Table 5.2). The combined groups also showed lower extroversion scores and higher neuroticism scores than the pure diagnostic groups. It is noteworthy that in all three combined groups the impulsivity/irritability scores were significantly higher. A comparison of mean impulsivity scores revealed highly significant differences between the following four groups (Kruskal–Wallis test: 68.5, df = 3, $P < 0.0001$): (1) MDE + RBD: 17.1 (8.1); (2) MDE: 14.7 (7.2); (3) RBD: 18.5 (7.4); and (4) all other subjects of the sample: 11.0 (5.9). High impulsivity/irritability was the most characteristic personality feature of RBD subjects.

Suicide attempts

The significance of RBD is illustrated by the highest suicide attempt rates found in combined BP-II (38.5%) and combined MDD (25.6%). Compared to controls, subjects suffering from pure RBD had a fourfold higher suicide attempt rate (11.7% versus 2.7%), but the suicide attempt rates in pure BP-II subjects was slightly higher (16%) and higher still in pure MDD (22.6%) (Table 5.2). In a logistic regression we found a significant association of suicide attempts (as the dependent variable) with all three diagnoses, BP-II (OR 9.8; 95% confidence interval 3.5–27.4); MDD (11.2; 4.1–30.5); and RBD (2.1; 1.3–3.5).

Disregarding the bipolar–unipolar distinction, we also compared the suicide attempt rates of subjects with MDE, RBD, and its combination. As expected, the combined group (MDE + RBD) had the highest suicide attempt rate, with 32.9%; the rate for the MDE group was 19.5%, for RBD 9.7%, and the rate for all other subjects together (including anxiety disorders, and substance abuse/dependence) was 3.7%.

Considering the hypothesis that a factor underlying impulsive/aggressive behavior (Angst and Clayton, 1998; Mann *et al.*, 1999) might lower the threshold for acting on suicidal ideas, we carried out logistic regression analyses of suicide attempts as the dependent variable. Female gender (OR = 1.9; 1.1–3.3), MDD (OR = 4.5; 2.6–7.9), and RBD (OR = 1.9; 1.1–3.2) were significantly associated with suicide attempts, but this was not the case for impulsivity, aggressiveness, as self-rated personality traits, or a positive family history of suicides.

Discussion

The main findings of this study shed further light on the clinical significance of the *combination* of major mood disorders, BP-II and MDD with RBD versus *pure* major mood disorders without RBD.

Prevalence

The first observation in this regard is that the association of both groups of mood disorders with RBD is very common: it occurred in 44% of BP-II and 39% of MDD. In terms of weighted prevalence rates, the association was even higher, with 64% and 44% respectively. Thus, about half of all subjects with MDEs also manifested RBD. Given the higher recurrence risk of BP versus MDD (Marneros *et al.*, 1991; Angst and Preisig, 1995, Lavori *et al.*, 1996), it is comprehensible that RBD, as a rapid-cycling depressive condition, was more often associated with BP-II than with MDD.

Comorbidity

We hypothesized that combined cases of mood disorders (defined by an association with RBD) were clinically more severe than pure cases. Our epidemiological data clearly confirm that the combined forms of BP-II and MDD differ from the pure groups on many measures: earlier age of onset, higher rates of family history of depression and anxiety, suicidality, treatment, atypicality, comorbidity with anxiety disorders, certain personality disorders and traits (especially impulsivity), and seasonality (in fall/winter as well as spring).

Taken together, these characteristics of combined BP-II and MDD convincingly demonstrate the clinical relevance of the concept of combined mood disorders and of a diagnosis of RBD.

Our failure to find that combined mood disorders had a higher association with substance abuse/dependence than the pure forms is intriguing. It does not support the hypothesis that RBD is a feature of personality disorders. Our findings are in agreement with those of Staner *et al.* (1992) that RBD was not an unspecific expression of axis II disorders. Our data also showed no association between RBD and sociopathy and conduct problems in adolescence. All this is compatible with Pezawas *et al.* (2002b), who also failed to find an association between personality disorders (assessed by Structured Clinical Interview) (SKID II) (Wittchen *et al.*, 1998) and RBD in a study of clinical cases.

All these findings are in line with the hypothesis that RBD is not associated with personality disorders but is linked with affective abnormalities of the personality, such as depressive personality disorders and high impulsivity/irritability scores.

Risk of suicide attempts

The concept of brief depression originated in observations of its frequency among suicide attempters in an emergency clinic and in a psychiatric practice (Gregory, 1908, 1915; Paskind, 1929, 1930).

The findings of our analysis of suicide attempts are puzzling. They confirm an association of RBD with a history of suicide attempts, but its effect as a risk factor alone is smaller than that of MDE or dysthymia. The true clinical significance of RBD is given by its association with MDE. We found the highest suicide attempt rates among combined BP-II subjects (38.5%), compared to 25.6% in combined MDD and to 22.6% in pure MDD; this finding is also linked to the greater psychiatric co-morbidity of combined cases. On the other hand, our earlier finding that suicide attempt rates in combined MDD were several-fold higher (30%) than in the pure forms (7.7%) (Angst *et al.*, 1990, Merikangas *et al.*, 1990) was not confirmed by the new data (where the figures were 25.6% versus 22.6% respectively). This may be in part a consequence of the diagnostic shift of many cases from MDD to BP-II disorder.

Searching for further correlates of the association of RBD with suicide attempts, we also analyzed personality traits measured by the FPI. Although, compared to controls, aggressiveness was higher in all diagnostic subgroups of mood disorders, the latter did not differ from each other. The findings on impulsivity/irritability were important. Here all diagnostic groups differed from controls but, in addition, all groups with RBD scored systematically higher than the pure-mood-disorder groups. Thus we were unable to replicate the findings of Pezawas *et al.* (2002b), who found differences between combined depression and RBD in clinical cases.

We could not examine a postulated impulsivity/aggression factor underlying suicidal behavior, which was extracted by factor analysis from the Brown–Goodwin aggression inventory, Buss–Durkee hostility inventory, and Barratt impulsivity scale (Mann *et al.*, 1999) This factor was found in psychiatric inpatients suffering from a cluster of disorders, e.g., alcohol or drug dependence, borderline personality disorder, cigarette smoking and aggressive, impulsive behaviors. These disorders and behaviors were significantly associated with suicide attempts. Furthermore, aggressiveness/impulsivity was recently shown to be linked to a malfunctioning serotonergic system (Mann *et al.*, 2001; Pezawas *et al.*, 2002b). Since our analysis was based only on multiple variables, this relationship may have been missed on account of power problems. However, biserial correlations and logistic regressions failed to confirm those findings in our study. On the other hand we were able to show that the risk for suicide attempts was linked to gender and to a diagnosis of MDE plus RBD.

What is the nature of RBD?

We do not think that RBD is only a residual syndrome of MDEs, fluctuating in short recurrences, as first described in Sardinia (Carta *et al.*, 1994) or the residuals of dysthymia (Angst and Wicki, 1990). RBD can undoubtedly also precede MDD.

We found a transition from RBD to MDD in 14% of cases and the reverse transition in 25% of cases (Angst, 1990). These findings have been recently supported by another epidemiological study in adolescents and young adults (Pezawas *et al.*, 2003). RBD is therefore best considered as one of many course patterns of the natural history of depression. Moreover, it is clearly not the case that patients suffering from recurrent major depression experience only major episodes. It is well established that half of such patients manifest multiple brief episodes of depression and in addition depressive symptoms under the threshold of RBD or minor depression, including symptom-free intervals in between. This has recently also been reported by Judd *et al.* (1998) on the basis of a prospective long-term study of depression and bipolar disorders (Judd *et al.*, 2002, 2003). We would like to see RBD established as a firm subgroup of the dimension of depression, ranging from symptoms to severe episodes. This seems to be the most plausible concept.

A further-reaching interpretation would be that RBD is the manifest clinical expression of a persisting instability of mood regulation, which may also be expressed as a lowered threshold for exhibiting mood symptoms on stressful life events. RBD patients might be more prone to exhibit depressive symptoms in the presence of stressful environmental factors. This hypothesis is supported by the Early Developmental Stages of Psychopathology study (Pezawas *et al.*, 2003), which found a strong relationship between posttraumatic stress disorder and RBD. The irregular pattern of occurrences of depressive symptoms which are linked to stressful events also supports this hypothesis (Pezawas *et al.*, 2002a). This interpretation would be compatible with the idea of a premorbid personality or chronic low-threshold mood disorder, which is characterized by RBD and frequent ups and downs. The latter has been shown to be a risk and/or vulnerability factor for mood disorders (especially for BP-II). These frequent ups and downs as a personality feature seem to be independent of the positive family history for BP and depression (Angst *et al.*, 2003b). This etiological model postulates two independent types of risk factors: (1) family occurrence of mood disorders; and (2) unstable mood regulation. We could speculate that suicidal behavior and such mood lability share the same underlying biological factor. Mood stabilizers may influence the biological mood lability. This hypothesis is supported by a single case analysis (Pazzaglia *et al.*, 1993) and a case report (Corominas *et al.*, 1998).

Treatment of RBD and CD

There is a growing body of evidence that RBD can be successfully treated by maintenance medication, although there is not one treatment study that has recruited RBD subjects by diagnostic criteria for a controlled trial. Recent methodological advances (Post *et al.*, 1998; Pezawas *et al.*, 2002a), together with published

reports (including open studies) on the successful treatment of almost 70 RBD cases, mainly by serotonergic drugs (Gertz, 1992; Joffe, 1996; Amore, *et al.*, 1998; Corominas *et al.*, 1998; Pazzaglia *et al.*, 1998; Stamenkovic *et al.*, 1998, 2001; Mantgomery, Pezawas *et al.*, 2002a; Verkes *et al.*, 1998) are promising. This is incompatible with the therapeutic pessimism of previous studies (Montgomery *et al.*, 1994; Montgomery, 1997; Kocmur *et al.*, 1998), which discouraged research in this field. Earlier negative controlled studies did not deal with truly representative clinical cases of RBD but recruited chronic suicide attempters with personality disorders (e.g., borderline personality disorder) and psychiatric comorbidity. Such subjects, whose increased impulsivity makes them poor compliers, are very difficult to treat and have also been shown to be non-responders to other treatments (Verkes *et al.*, 1998). Negative reports on RBD treatment may therefore be largely attributable to the selection of patients (Montgomery *et al.*, 1989).

Moreover, the successful treatment of RBD in open single-case studies provides enough evidence on which to base controlled clinical trials without the serious methodological flaws of earlier studies. A first-choice antidepressant treatment trial with substances lacking severe side-effects seems to be justified. As a second-line treatment, mood stabilizers should be considered. The design of such trials should clearly distinguish between pure RBD and combined cases of RBD, because the latter, as mentioned above, are likely to have a long previous history with a chronic course, multiple admissions to psychiatric institutions, suicidality, and treatment resistance (Pezawas *et al.*, 2002b). Conventionally, such patients are not taken into drug trials since they fulfill common exclusion criteria. Therefore no evidence is at present available regarding the optimal treatment regime for this highly prevalent and clinically important group.

Conclusion

The example of RBD demonstrates that severity measures of mood disorders should not be restricted to the number of symptoms and the duration of episodes and consequences but should also include recurrence (course). The concepts of RBD and of combined mood disorders and their integration into psychiatric practice are clinically relevant because they enable psychiatrists to identify a highly prevalent, severely impaired, and often suicidal subgroup of patients. It also opens the way for new therapeutic research.

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6

Atypical depression and its relation to bipolar spectrum

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Introduction: the relationship of atypical depression to bipolar II disorder

The focus of this chapter on the relationship between atypical depression (AD) (different definitions, including *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV): (American Psychiatric Association, 1994) definition) and bipolar (BP) spectrum is the relationship between BP-II and AD, because BP-II is the most common and best-studied disorder of the BP spectrum disorders. BP-II was recently found to be very common in the community (11.0% BP-II versus 11.4% unipolar (UP): Angst *et al.*, 2003) and in major depressive episode (MDE) outpatients (up to 60%: Cassano *et al.*, 1992; Angst, 1996; Benazzi, 1997a, 2001a; Hantouche *et al.*, 1998; Perugi *et al.*, 1998; Akiskal *et al.*, 2000; Benazzi and Akiskal, 2003a). But nevertheless BP-II is still underdiagnosed (Ghaemi *et al.*, 2000). Lumping bipolar-I (BP I) and BP-II together is not supported by the BP-II strong diagnostic stability (Coryell *et al.*, 1995), different family history (more BP-II than BP-I in first-degree relatives of BP-II) (Goodwin and Jamison, 1990; Coryell, 1999), and by linkage studies (McMahon *et al.*, 2001).

The most recent definitions of BP spectrum come from Akiskal and Pinto (1999), Ghaemi *et al.* (2002), and Angst *et al.* (2003). Akiskal and Pinto's definition includes BP-I, BP-II (hypomania and MDE ± cyclothymic disorder), BP-III (antidepressant and stimulant-associated hypomania), and BP-IV (depressive mixed state, that is, a MDE plus some concurrent hypomanic symptoms). The definition of Angst *et al.* (2003) includes BP-II, minor bipolar disorders (hypomania and mild depressions), and single hypomania (with no depression). The diagnostic criteria of Ghaemi *et al.* (2002) for bipolar spectrum disorder include a UP MDE plus signs of bipolarity, such as bipolar family history, antidepressant-induced mania/hypomania, and AD. The bipolar spectrum disorder of Ghaemi *et al.* (2002) links pure UP with BP. Also depressive mixed state (Benazzi and

Akiskal, 2001; Akiskal and Benazzi, 2003;) was found to be a link between pure UP and BP. In the American Psychiatric Association, DSM-IV (1994) bipolar disorders are divided into:

(1) BP-I disorder
(2) BP-II disorder
(3) cyclothymic disorder
(4) bipolar disorder not otherwise specified
(5) manic or hypomanic episodes due to a general medical disorder or substance-induced.

DSM-IV BP-II criteria for hypomania require elevated or irritable mood, lasting at least 4 days, plus at least three (four, if mood is irritable) hypomanic symptoms, an observable change in functioning, a mild episode not due to substances, antidepressants, or medical disorders, and not superimposed on psychotic disorders. DSM-IV BP-II criteria have some problems:

(1) No data support the cut-off of 4 days (Dunner, 1998), while a cut-off of 2 days is supported by data (Akiskal *et al.*, 2000)
(2) There are no clear boundaries between mania and hypomania
(3) Antidepressant-associated hypomania is not classified as BP-II, while follow-up studies found that antidepressant-associated hypomania will have spontaneous hypomania in many cases (Akiskal and Pinto, 1999)
(4) Hypomanic mood is the first criterion, while recent studies (Akiskal *et al.*, 2001; Angst *et al.*, 2003; Benazzi and Akiskal, 2003a, b) found that overactive behavior is at least as important as hypomanic mood
(5) The Structured Clinical Interview for DSM-IV Axis I Disorders–Clinician Version (SCID-CV; First *et al.*, 1997) skip-out stem question on mood does not allow the assessment of the other hypomanic symptoms if it is negative, while Dunner and Tay (1993) and Benazzi and Akiskal (2003a) found that systematic assessment of all past hypomanic symptoms increased the frequency of BP-II diagnoses.

Recent literature review

A comprehensive review of the literature on AD until the early 1990s can be found in Rabkin *et al.* (1996), and an updated review in Angst *et al.* (2002). The diagnostic validity of AD is mainly based on its better response to monoamine oxidase inhibitors (MAOI) rather than to tricyclic antidepressants (TCA) (Rabkin *et al.*, 1996), and on latent class analysis (Kendler *et al.*, 1996; Sullivan *et al.*, 1998). An important limitation of these studies is the inclusion of mainly UP samples. The current definition of AD is mostly based on the Columbia group definition of AD (Rabkin *et al.*, 1996).

In DSM-IV, AD is not classified as a distinct mood disorder, but as a subtype (specifier) of BP MDE and depressive (UP) disorders. DSM-IV criteria for the AD specifier always require mood reactivity, plus at least two symptoms, including weight gain or overeating, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity (plus criteria for concurrent melancholic or catatonic features not met). There are a lack of data supporting the inclusion of mood reactivity (Posternak and Zimmerman, 2002; Rabkin *et al.*, 1996). AD's better response to MAOI than to TCA was not related to any one AD symptom (McGrath *et al.*, 1992), and when only mood reactivity was present, MAOI were not more effective than TCA (Quitkin *et al.*, 1989). Angst *et al.* (2002) found support for a definition of AD where mood reactivity has no priority over the other symptoms. Posternak and Zimmerman (2002) found that mood reactivity was not correlated with the other AD symptoms, while Angst *et al.* (2002) found that it was associated with other AD symptoms. Benazzi (2002a) found that mood reactivity was associated with the other AD symptoms in BP-II, but not in UP (the previous studies combined in the analysis BP-II and UP, and had very different proportions of BP-II).

Surprisingly little research has been done on AD in BP. The DSM-IV-TR 2000 (American Psychiatric Association, 2000) literature review concluded that AD was more common in BP. There is some similarity between the Columbia group definition, and antidepressant response, of AD and the definition of Himmelhoch *et al.* (1991) and antidepressant response of anergic BP depression. Anergic BP depression of Himmelhoch *et al.* (1991) included loss of energy, psychomotor retardation, hypersomnia, and weight gain. Its frequency was 73% among 77 BP outpatients (57.1% were BP-II). Himmelhoch (1999) also reported that melancholic features were present in only 12 of 1100 BP patients. Data on non-melancholic depression in BP can give indirect information about AD, as at least some of the non-melancholic depressions can be AD. Parker *et al.* (2000) found that BP (I + II) versus UP depression was more likely to be melancholic. However, the studies of Parker *et al.* were based on mixed in-/outpatient samples (melancholic depression was reported to be more common in inpatients: American Psychiatric Association, 2000), and BP-I and BP-II were lumped together. Serretti *et al.* (1998) found more AD symptoms in BP-I versus UP inpatients. Mitchell *et al.* (2001) found that BP-I versus UP depression (matched for age) had significantly more hypersomnia and retardation. More hypersomnia in BP depression versus UP depression is reported in standard textbooks (Akiskal, 2000; Goodwin and Jamison, 1990). In Baldessarini's review (2000), anergia and hypersomnia were reported to be typical bipolar features. More AD in BP-II versus UP was found by Angst (1998), Perugi *et al.* (1998), Agosti and Stewart (2001), Angst *et al.* (2002, 2003). No more or less AD in BP-II versus UP was found by McGrath *et al.* (1992), Robertson *et al.* (1996), and Posternak and Zimmerman (2002).

Agosti and Stewart (2001) found more BP-II in AD versus non-AD, but the frequency of BP-II found was very low (12%).

A prospective study found that AD often progressed to BP spectrum (Ebert *et al.*, 1993). Akiskal *et al.* (2000) reported that hypersomnic-retarded depression had 88% specificity for predicting BP outcome. Interpersonal sensitivity (an AD symptom) was found to predict the switching of UP to BP-II (Akiskal *et al.*, 1995). Perugi *et al.* (1998) found that BP-II and BP spectrum were present in 72% of 86 AD outpatients, that BP-II AD ($n = 28$) versus UP ($n = 24$) AD had higher family history of BP, but similar female frequency, age of onset, and MDE recurrences. The power of the sample was however low. Hantouche *et al.* (1998) found that hypersomnia was more common in BP-II MDE ($n = 100$) versus UP MDE ($n = 113$). Angst (1998) found AD more common in the soft BP spectrum versus UP (28.6% versus 6.8%).

Cassano *et al.* (1992) found a similar high frequency of melancholic features between BP-II and UP (AD was not assessed, but, according to DSM-IV, AD diagnosis cannot be made if the criteria of melancholic features are met). In the community study of Levitan *et al.* (1997), MDE with some AD symptoms (overeating, weight gain, hypersomnia) was found to have higher mania frequency versus MDE without these symptoms (BP-II was not assessed). In the community study of Sullivan *et al.* (1998), AD (defined by overeating, weight gain, and hypersomnia) had similar BP-I comorbidity and age of onset versus non-AD (BP-II was not assessed). In the community study of Horwath *et al.* (1992), first onset of mania at 1-year follow-up in UP AD (defined by overeating and oversleeping) versus non-AD was similar and very low. McGrath *et al.* (1992) reported that, among 401 AD, only 10% had BP-II. Robertson *et al.* (1996), comparing 79 UP with 30 BP (I + II), found similar frequency of AD (28% versus 30%), but only 10 BP-II were included. Posternak and Zimmerman (2002) did not find more BP-II in AD versus non-AD, but, in the 579 sample, almost all were UP (28 patients were BP-II (4.8%)). The community study of Angst *et al.* (2003) found that AD versus non-AD had earlier onset, more BP spectrum, females, recurrences, and chronicity. Angst *et al.* (2002) found that BP-II ($n = 89$) had more AD than UP ($n = 101$: 49.5% versus 29.6%).

The author's studies

In the author's studies AD means DSM-IV "atypical features specifier." The studies try to answer the following questions.

Is AD more common in BP-II versus UP?

Frequency of AD was significantly much higher (more than 40%) in BP-II MDE versus UP MDE. In BP-II ($n = 251$) versus UP ($n = 306$) MDE, AD was present in

45.4% versus 25.4% ($P = 0.0000$). In another study, prevalence of BP-II in AD was 64.2% ($n = 140$). These findings are in line with previous reports (Perugi *et al.*, 1998; Angst *et al.*, 2003). Factor analysis of the Montgomery Asberg Depression Rating Scale (which has only two items negatively related to sleep and eating) in 251 BP-II MDE and 306 UP MDE outpatients found three factors in BP-II, one including reduced sleep (negative) and reduced appetite (negative). This factor was not found in UP (Benazzi, 1997a, 1999a, 2000a, 2001a, b; Benazzi and Akiskal, 2003a). Two studies, including only 10 BP-II and 28 BP-II, found no AD frequency difference between BP and UP (Posternak and Zimmerman, 2002; Robertson *et al.*, 1996).

Is BP-II versus UP difference in AD frequency age-related?

UP MDE versus BP-II MDE had significantly higher age. BP-II MDE ($n = 187$) versus UP MDE ($n = 126$) had a significantly higher frequency of AD (49.7% versus 18.2%), persisting when controlled for age (Benazzi, 2003c). Findings suggest that age may not be important for the BP-II versus UP difference in AD. Mitchell *et al.* (2001) suggested instead that BP versus UP depression differences could be related to an age difference.

Is there a difference in AD frequency in BP-II samples when probing for past hypomania focused on overactivity?

Frequency of BP-II MDE versus UP MDE increased when probing for past hypomania, with the SCID-CV focused more on overactivity than on mood. This BP-II sample ($n = 103$) had the same frequency of AD (47.5% versus 45.4%) found in a previous BP-II sample interviewed strictly following the SCID-CV ($n = 251$) (in the same setting and by the same interviewer), and a significantly higher frequency of AD versus UP MDE ($n = 65$, 16.9%: Benazzi and Akiskal, 2003a). Findings support the usefulness of probing for overactivity when assessing past hypomania, as found by Angst *et al.* (2003) and Akiskal *et al.* (2001). The focus on past overactivity was also supported by a factor analysis study of past hypomania using the Mood Disorder Questionnaire (MDQ) (Hirschfeld *et al.*, 2000) in 181 remitted BP-II MDE and UP MDE, which found two factors, one of which had only overactivity items (Benazzi and Akiskal, 2003b).

Is AD frequency still higher in BP-II versus UP when BP-II had a short hypomania?

In BP-II MDE with a history of hypomania lasting less than 4 days, frequency of AD was significantly higher in comparison with UP MDE (Benazzi, 2001c),

suggesting that a strong bipolarity (long episodes of hypomania) may not be required to have more AD in BP-II.

Is AD a predictor of BP-II?

Specificity of AD for predicting BP-II was found to be 82.8% (sensitivity 45.3%) ($n = 161$, BP-II + UP). In the discriminant analysis of some predictor variables for the diagnosis of BP-II (many MDEs, early onset, interpersonal rejection sensitivity, depressive mixed state, and AD), AD was found to be still significant, suggesting that it was a strong predictor compared to the other variables (Benazzi, 2001d). Cross-sectional clinical markers of BP-II could reduce the high underdiagnosis of BP-II (Ghaemi *et al.*, 2000; Benazzi, 2001e).

Can AD increase the probability of UP switching into hypomania?

UP MDE switchers into hypomania during antidepressant treatment had features similar to the BP-II MDE switchers (age of onset, frequency of AD: 50.0%; Benazzi, 1997b).

Is there any difference in AD frequency in early-onset versus late-onset BP-II?

In early- ($n = 99$) versus late-onset ($n = 80$) BP-II MDE, there was a significant AD frequency difference (73.7% versus 51.2%), which however was not significant, controlling for age. This finding suggests that the difference was related to age (Benazzi, 2000b).

Is there any difference between BP-II AD and UP AD?

BP-II AD ($n = 79$) versus BP-II non-AD ($n = 53$) had a significantly lower age of onset. BP-II AD ($n = 79$, $n = 90$) versus UP ($n = 42$, $n = 50$) AD had significantly lower age of onset. Two-way analysis of variance (ANOVA) found that difference in age of onset between BP-II AD and UP AD was related to diagnosis, and not to AD (Benazzi, 1999a, b, 2000c). A different age of onset (McMahon *et al.*, 1994; Robins and Guze, 1970) runs against the view of AD as a distinct mood disorder (Rabkin *et al.*, 1996), and is in line with DSM-IV, where AD is a specifier of BP and depressive disorders.

Is there a link between BP-II and UP AD?

BP-II AD ($n = 124$) versus UP AD ($n = 38$) did not have a significantly different age of onset and MDE recurrences, but did have a significantly higher frequency of

depressive mixed-state and BP-II family history. BP-II non-AD ($n = 110$) versus UP AD did not have a significantly different age of onset, MDE recurrences, depressive mixed-state frequency, and significantly higher frequency of a BP-II family history. UP AD versus UP non-AD ($n = 120$) had a significantly lower age of onset (and not significantly different MDE recurrences, depressive mixed-state frequency, and BP-II family history). These findings support a link between BP-II and UP AD (Benazzi, 2003a).

What is the relationship between AD and age?

In a sample of 525 (BP-I, BP-II, UP) MDE outpatients (43.6% BP-II, 52.3% UP), BP-II with age less than 50 years had significantly more AD than BP-II with age 50 years or more (60.9% versus 26.1%, $P = 0.0000$), and UP with age less than 50 years had significantly more AD than UP with age 50 years or more (34.2% versus 18.1%, $P = 0.0025$). Findings suggest that AD frequency decreases with age (as also shown by Angst *et al.*, 2002). AD frequency was significantly higher in BP-II MDE versus UP MDE with age less than 50 years ($P = 0.0000$), but not in BP-II MDE versus UP MDE with age 50 years or more, suggesting that the higher frequency of AD in BP-II versus UP is mainly due to young patients. BP-II frequency was higher in younger compared with older patients (53.4% versus 32.9%, $P = 0.0000$), and UP frequency was higher in older compared with younger patients (67.0% versus 46.5%, $P = 0.0000$; Benazzi, 2001a). Findings suggest a change in the clinical picture of depression related to age. In a 358 MDE sample (BP-II + UP), AD was present in 55.0% of patients under age 60 years and in 28.1% of patients age 60 years and over ($P = 0.0000$). BP-II frequency significantly decreased between the two age groups (56.4% versus 23.9%, $P = 0.0000$), while UP frequency significantly increased ($P = 0.0000$; Benazzi, 2000d). When AD in patients aged 60 years or more was compared to AD in those under age 60 years, controlling for age, few significant differences were found.

Are there differences between AD and non-AD?

AD frequency was 38.1% in 467 MDE outpatients. Comparison between AD ($n = 121$) and non-AD ($n = 133$) (BP-II + UP sample) found that AD had significantly more BP-II (65.2% versus 39.8%, $P = 0.0000$), lower age of onset ($P = 0.0059$), more females (76.8% versus 61.6%, $P = 0.0089$), more axis I comorbidity (not including substance abuse: 74.3% versus 57.1%, $P = 0.0039$; Benazzi, 1999b). Findings are in line with previous reports (Horwath *et al.*, 1992; Agosti and Stewart, 2001; Angst *et al.*, 2002; Posternak and Zimmerman, 2002).

Is there any difference between early-onset and late-onset AD?

Early-onset (before 18 years) versus late-onset AD (BP-II + UP sample) was significantly associated with female gender (+), number of MDE recurrences (+), BP-II (+), UP (−). Early-onset BP-II AD versus late-onset LO BP-II AD was significantly associated with female gender (+), number of MDE recurrences, depression chronicity (+). The same analysis in UP did not find these associations. Findings suggest that there are differences between BP-II AD and UP AD (Benazzi, 2000e), further supporting the distinction between BP-II AD and UP AD.

What is the relationship between AD and chronic depression?

No significant difference in AD frequency was found between BP-II ($n = 67$) and UP ($n = 69$) chronic depression (chronic MDE and MDE without full interepisode recovery, lasting more than 2 years from index MDE). BP-II (chronic and non-chronic: $n = 95$) depression versus non-chronic UP depression ($n = 81$) had significantly more AD. Chronic UP could be a link between BP-II and non-chronic UP, a finding in line with reports suggesting that chronic depression may be related to BP-II (Akiskal *et al.*, 1995; Coryell *et al.*, 1995). Frequency of depression chronicity was not significantly different (46.3% versus 40.5%) between AD ($n = 164$, BP-II 64.6% of the sample) and non-AD ($n = 162$, BP-II 35.8% of the sample). UP AD had significantly more depression chronicity than UP non-AD and BP-II AD. Chronicity was not significantly different in BP-II AD compared with BP-II non-AD. Chronic AD versus non-chronic AD had significantly more UP. Findings suggest that depression chronicity in AD is mainly related to UP, and may explain why AD was often reported to be chronic (as most previous studies mainly included UP samples; Rabkin *et al.*, 1996). In BP-II, depression chronicity findings related to AD seem different in comparison to UP. In BP-II chronic depression ($n = 87$), early onset was associated with higher AD frequency. Chronic depression in old (> 60 years) versus young (< 60 years) (199 BP-II + 200 UP) found the frequency of AD to be significantly higher in young patients (59.5% versus 27.6%), but when the comparison was controlled for age (ANCOVA), the difference was no longer significant, suggesting that it was related to age (Benazzi, 1999c, d, 2000d, f, 2001f).

Are females more common in AD versus non-AD?

In BP-II MDE ($n = 251$) versus UP ($n = 306$) MDE, AD was present in 45.4% versus 25.4% ($P = 0.0000$). AD was significantly more common in BP-II females versus males, in UP females versus males, in BP-II females versus UP females, and in

BP-II males versus UP males. Female gender was significantly associated with AD but not with diagnosis (by logistic regression). The higher frequency of AD in females versus males was not related to the higher frequency of AD in BP-II versus UP, but to an association between female gender and AD (Benazzi, 1999e). Findings are in line with studies showing more females than males in AD (Agosti and Stewart, 2001; Angst *et al.*, 2002, Posternak and Zimmerman, 2002, and other studies reviewed by Angst *et al.*, 2002).

Is AD a moderate-severity depression?

In a 536 MDE sample (BP-II $n = 241$, UP $n = 295$), severe MDE ($n = 219$) (defined as a Global Assessment of Funtioning (GAF) scale score of 50 or less) had AD in 34.7%, and non-severe MDE had AD in 37.5% ($P = 0.5022$; Benazzi, 1999f). No BP-II versus UP differences were found. The GAF severity cut-off of 50 followed the depression severity definition of Elkin *et al.* (1989). This finding runs against the report that AD is often a moderate-severity depression (Kendler *et al.*, 1996), but is in line with the report that severe AD is not uncommon (35.6% of AD; Sullivan *et al.*, 1998).

Is there a link between depressive mixed state and AD?

Depressive mixed state (defined as a BP-II and UP MDE plus more than two concurrent hypomanic symptoms) was significantly more common (50.0% versus 20.3%) in AD versus non-AD (BP-II + UP sample, $n = 87$), and the association persisted when controlled for BP-II by logistic regression (BP-II could be a confounding factor because it was associated with both AD and depressive mixed state). Among the DSM-IV hypomanic symptoms, AD had significantly more talkativeness, distractibility, and psychomotor agitation (Benazzi, 2001g).

In a second, larger study, depressive mixed state was highly associated with AD (odds ratio = 3.1, $P = 0.000$). UP depressive mixed state ($n = 35$) versus BP-II MDE ($n = 226$) did not have a significantly different age of onset, frequency of AD, or BP-II family history, while UP depressive mixed states versus UP non-depressive mixed state MDE ($n = 116$) had a significantly higher frequency of BP-II family history. These findings suggest a link between BP-II and UP depressive mixed state, including a similar frequency of AD (Akiskal and Benazzi, 2003).

Is there a link between female gender and AD in depressive mixed state?

In a depressive mixed-state outpatient sample ($n = 205$), female gender was significantly associated with atypical features (odds ratio = 2.1, $P = 0.021$; Benazzi, 2003d).

Is psychomotor retardation more common in AD versus non-AD?

In 95 AD patients (80% BP-II, 20% UP), 21.0% had psychomotor agitation, while 0.0% had retardation. The result may be related to the finding that melancholic features were not more common in BP-II MDE versus UP MDE outpatients (19.2% versus 22.6%, $n = 182$; 20.6% versus 25.0%, $n = 161$). MDE with psychomotor agitation (BP-II + UP: $n = 85$) versus MDE without psychomotor agitation ($n = 292$) had a significantly higher frequency of AD (51.7% versus 37.3%), while AD frequency was not significantly different in BP-II-agitated MDE versus UP agitated MDE (Benazzi, 2000g, 2002b, c; Benazzi, *et al.*, 2002).

These results run against previous studies reporting that psychomotor retardation was more common in AD versus non-AD (Horwath *et al.*, 1992; Kendler *et al.*, 1996; Posternak and Zimmerman, 2002), and that melancholic features were more common in BP versus UP depression (Parker *et al.*, 2000). Different samples (inpatient versus outpatient, community versus clinical), different study settings (tertiary care versus non-tertiary care), BP-I and BP-II lumping together, and mainly UP samples in some studies, may be related to the different findings. Himmelhoch (1999) reported that melancholic features were only present in 12 of 1100 BP patients. Prevalence of melancholic features was reported to be higher in the inpatient severe and psychotic MDE (American Psychiatric Association, 2000).

Is there a link between recurrences and AD?

Comparisons among BP-II MDE ($n = 151$), highly recurrent UP MDE (> 4 MDEs: $n = 57$), and low recurrent UP MDE (< 5 MDEs: $n = 32$) found that AD was significantly more common in BP-II MDE versus highly recurrent UP MDE, but also significantly more common in highly recurrent UP MDE versus low recurrent UP MDE. These findings suggest that recurrences may be related to increased frequency of AD in UP MDE (Benazzi, 2003c).

What is the relationship between AD and psychotic features?

Frequency of AD was much lower in psychotic BP (I + II) MDE (6.6%) compared to the frequency of AD found in other BP-II samples of the author. Psychotic versus non-psychotic MDE (BP-I + BP-II + UP) had significantly less AD (Benazzi, 1999g, h).

What is the relationship between AD and menopause?

Female MDE (BP-I + BP-II + UP) with age before 40 years ($n = 283$), versus female MDE with age at or after 40 years ($n = 63$) (the 40-year age cut-off gave a

median age of onset of 52, which is near the median age of onset of menopause, 51 years) found more AD (53.2% versus 31.6%, $P = 0.0019$) and BP-II (47.7% versus 26.9%, $P = 0.0026$) before 40 years (in males there was no significant difference in the BP-II frequency, while AD frequency was significantly reduced after age 40), suggesting that menopause may change the picture of depression (Benazzi, 2000h).

More recent, published, studies of the author on AD have focused on a definition of AD based only on the reversed vegetative symptoms (oversleeping, overeating, weight gain: Benazzi, 2002f), on the impact of AD on trials of antidepressants in BP-II (Benazzi, 2004a), on supporting the subtyping of AD into an early-onset, chronic subtype versus a non-early-onset, non-chronic subtype (Benazzi, 2004b), on the normal-like distribution of atypical symptoms between BP-II and UP MDE, supporting a continuity between the two disorders by finding no zone of rarity (which would be expected because AD is more common in BP-II: Benazzi, 2003c), on testing the DSM-IV definition of AD (Benazzi, 2003d), and on further testing the predictive power for BP-II of AD versus other bipolor validators such as BP family history and depressive mixed state (Benazzi, 2003e).

The author's last sample study on atypical depression

Study methods

Interviewer

The interviewer was a senior clinical and mood disorder research psychiatrist.

Study setting

The study was carried out in a private outpatient psychiatry center (a University of California in San Diego (USA) collaborating center). Private practice is more representative of mood-disorder patients in Italy, where it is the first (or the second, after family doctors) line of treatment of mood disorders, and national mental health services and university centers usually treat the most severe patients. Most individuals can be visited by a private psychiatrist in Italy (reducing a possible selection bias). Authorities believe that mood-disorder patients in tertiary-care centers may not be representative of patients who are usually treated in clinical practice (Akiskal and Pinto, 1999; Goldberg and Kocsis, 1999; Ghaemi *et al.*, 2000; Post *et al.*, 2001).

Patients and interview

Consecutive UP (major depressive disorder (MDD), MDD superimposed on dysthymic disorder) and BP-II outpatients, presenting spontaneously for MDE

treatment, were interviewed. MDD and MDD superimposed on dysthymic disorder were combined in one group (Angst *et al.*, 2000; Judd and Akiskal, 2000). No psychopharmacotherapy before evaluation avoided the inclusion of antidepressant-induced mixed states (Akiskal and Pinto, 1999). Current substance abuse and patients with severe personality disorder were not included (Benazzi, 2000i), as this would confound the diagnosis of BP-II and mixed states (Akiskal *et al.*, 2000). Clinically significant general medical illness and dementia patients were not included. All patients were interviewed during the first visit with the SCID-CV. The SCID-CV is partly semistructured and is based on clinical evaluation (not on simple yes/no answers to structured questions). Clinical evaluation by clinicians trained in BP-II diagnosis using semistructured interviews resulted in more correct diagnoses than strict structured interviewing (Dunner and Tay, 1993; Brugha *et al.*, 2001). All patients were systematically SCID-CV-interviewed for a history of manic/hypomanic episodes, and for DSM-IV hypomanic symptoms during the index MDE. The SCID-CV-structured question on racing thoughts was supplemented by the Koukopoulos and Koukopoulos' definition (1999) of crowded thoughts (head continuously full of ideas that the patient is unable to stop). The SCID-CV skip-out instruction of the stem question about past hypomanic mood was not followed, as a negative answer would not allow assessment of the other hypomanic symptoms. It was shown (Benazzi and Akiskal, 2003a) that systematic assessment of all past hypomanic symptoms increased the frequency of BP-II diagnoses, as overactivity was easier to remember (by patient and family members/close friends) than hypomanic mood (diagnosis of hypomania always required hypomanic mood, which was easier to remember after having remembered overactivity). A history of mania/hypomania was always investigated soon after having made the diagnosis of MDE, before the assessment of study variables, to avoid a possible bias related to knowledge of indicators of bipolarity. BP (I + II) family history was investigated with the Family History Screen (Weissman *et al.*, 2000), a structured interview for psychiatric history of first-degree relatives.

Depressive mixed state (DMX) was defined as an MDE plus more than two concurrent hypomanic symptoms, following Benazzi and Akiskal (2001). The more clinically useful definition of DMX was found to be one based on a minimum number of hypomanic symptoms (three) during MDE versus one based on the combination of specific hypomanic symptoms, by multivariate analyses (Benazzi, 2002e, 2003b). Hypomanic symptoms during the MDE lasted at least 1 week, appeared during the MDE, and were present at the time of the interview.

The DSM-IV 4-days' minimum duration of hypomania for BP-II diagnosis (a cut-off not based on data: Dunner, 1998) was not followed. Instead, at least 2

Table 6.1 Comparisons between atypical depression (AD) and non-atypical depression (N-AD) ($n = 433$)

	AD ($n = 182$)	N-AD ($n = 251$)			
Variable: mean (SD), %			*T/Z*	df	*P*
Unipolar	24.1	51.3	–5.7		0.0000
Bipolar II	75.8	48.6	5.7		0.0000
Female gender	74.1	58.9	3.2		0.0010
Age at index MDE (years)	40.2 (13.5)	46.4 (15.3)	–4.3	431	0.0000
Age at onset of first MDE (years)	22.2 (10.6)	29.7 (14.0)	–6.0	431	0.0000
> 4 MDEs	76.3	69.3	1.6		0.1084
MDE symptoms > 2 years	44.5	37.0	1.5		0.1161
Axis I comorbidity	58.2	45.8	2.5		0.0108
MDE severity by GAF	51.3 (7.9)	50.0 (9.8)	1.4	431	0.1409
Psychotic features	2.7	11.9	–3.4		0.0005
> 2 hypomanic symptoms during index MDE	63.1	35.8	5.6		0.0000
Bipolar (I + II) family history	50.8	32.1	3.9		0.0001
Irritability	60.4	47.4	2.6		0.0075
Psychomotor agitation	31.8	21.5	2.4		0.0156
Distractibility	76.3	62.9	2.9		0.0030
More talkativeness	22.5	14.7	2.0		0.0369
Racing/crowded thoughts	75.2	58.9	3.5		0.0004
Mood reactivity	100	74.5			
Weight gain	36.8	1.9	9.6		0.0000
Overeating	46.7	3.1	10.9		0.0000
Hypersomnia	63.7	7.1	12.5		0.0000
Leaden paralysis	69.2	17.1	10.9		0.0000
Interpersonal rejection sensitivity	85.1	40.6	9.3		0.0000

MDE, major depressive episode; GAF, Global Assessment of Functioning.

days of hypomania were required for BP-II diagnosis, following previous reports (Akiskal *et al.*, 1977; Cassano *et al.*, 1992; Coryell *et al.*, 1995; Akiskal, 1996; Angst, 1998; Akiskal *et al.*, 2000; Benazzi, 2001c). Most present-study BP-II patients had had more than one episode of hypomania. Often, family members or close friends supplemented the clinical information during the interview. Study variables are reported in Table 6.1.

Statistics

Means were compared with the *t*-test, proportions were compared by the two-sample test of proportion. Univariate and multivariate logistic regression was used to study associations. Two-way ANOVA was used to study interaction. Maximum-likelihood logit estimation was used for discriminant analysis. STATA Statistical Software, Release 7, was used (Stata Corporation, College Station, TX, USA). *P*-values were two-tailed, and the probability level was $P < 0.05$.

Results

Frequency of AD was 182/433 (42.0%). AD versus non-AD (Table 6.1) had significantly more BP-II, females, lower age, lower age of onset, more axis I comorbidity, fewer psychotic features, more DMX, more BP family history, and more hypomanic and atypical symptoms.

To test if AD associations with female gender, early onset, DMX, and BP family history were specific features of AD, or were due to its association with BP-II (which could be a confounding factor, as it was associated with all these variables), multivariate logistic regression controlled for BP-II was used. Logistic regression of AD versus females gender found OR = 1.9, $z = 3.2$, $P = 0.001$, and when controlled for BP-II found OR = 1.9, $z = 2.9$, $P = 0.003$. Logistic regression of AD versus onset found OR = 0.9, $z = -5.4$, $P = 0.000$, and when controlled for BP-II found OR = 0.9, $z = -4.2$, $P = 0.000$. Logistic regression of AD versus DMX found OR = 3.0, $z = 5.5$, $P = 0.000$, and when controlled for BP-II found OR = 2.4, $z = 4.2$, $P = 0.000$. Logistic regression of AD versus BP family history found OR = 2.1, $z = 3.0$, $P = 0.002$, and when controlled for BP-II found OR = 1.6, $z = 1.8$, $P = 0.062$. To test if the association between AD and axis I comorbidity was specific for AD, or was instead related to a common early age of onset, multivariate logistic regression was used. Logistic regression of AD versus axis I comorbidity found OR = 1.6, $z = 2.5$, $P = 0.011$, and when controlled for onset, found OR = 1.4, $z = 1.6$, $P = 0.093$.

To test if the association between AD and BP-II was related to early onset (both had an early onset), multivariate logistic regression was used. Logistic regression of AD versus BP-II found OR = 3.3, $z = 5.5$, $P = 0.000$, and when controlled for onset, found OR = 2.5, $z = 4.0$, $P = 0.000$. Two-way ANOVA was also used to find if the lower age of onset in AD versus non-AD was related to an interaction between AD and BP-II. The result was that AD had $F = 23.2$, $P = 0.000$, BP-II had $F = 26.9$, $P = 0.0000$, and there was an interaction between AD and BP-II ($F = 4.7$, $P = 0.0306$). Discriminant analysis of BP-II, female gender, early onset, DMX, and

Table 6.2 Discriminant analysis of bipolar II (BP-II), female gender, early onset, major depressive episode with more than two concurrent hypomanic symptoms (depressive mixed state; DMX), and BP family history for predicting atypical depression ($n = 433$)

Variable	Coefficient	Z	P
BP-II	0.4	1.3	0.188
Female	0.5	2.0	0.046
Onset	–0.0	–3.4	0.001
DMX	0.6	2.1	0.031
BP family history	0.2	0.9	0.329

BP family history for predicting AD ($n = 433$ sample) is presented in Table 6.2. Results found that AD was significantly associated only with female gender, early onset, and DMX. BP-II AD versus UP AD (Table 6.3) had significantly lower age of onset, more recurrences, more depression chronicity, more depressive mixed state, more BP family history, and more irritability. AD symptom frequency was not significantly different.

Sensitivity, specificity, correctly classified, and receiver-operating characteristics (ROC) area of AD, BP family history, early onset of first MDE, many MDE recurrences (> 4), and DMX for predicting BP-II diagnosis, by logistic regression, are presented in Table 6.4. Results showed that AD had a high specificity for predicting BP-II, second only to BP family history. Discriminant analysis of AD, BP family history, early onset of first MDE, many MDE recurrences, and DMX for predicting BP-II diagnosis are presented in Table 6.5. Results showed that AD was a near-significant predictor of BP-II compared to the other variables.

Associations among AD symptoms in the whole sample are presented in Table 6.6. Mood reactivity was significantly associated with all AD symptoms, apart from leaden paralysis (4/5). All the other AD symptoms were significantly associated with each other. Associations among AD symptoms in the BP-II subsample are presented in Table 6.7. Mood reactivity was significantly associated with 3/5 AD symptoms. The other AD symptoms were often, but not always, significantly associated with each other (7/10). Associations among AD symptoms in the UP subsample are presented in Table 6.8. Mood reactivity was not significantly associated with any AD symptom. The other AD symptoms were often, but not always, significantly associated with each other (8/10).

A comparison of AD symptoms between mood-reactive (MR) and non-mood-reactive (N-MR) MDE patients is presented in Table 6.9. Findings showed that AD symptoms were significantly more common in MR MDE.

Given the strong significant association between BP-II and AD, the association between BP-II and mood reactivity was tested. Logistic regression of BP-II versus mood reactivity found OR = 2.0, $z = 2.6$, $P = 0.009$.

Table 6.3 Comparisons between bipolar II atypical depression (BP-II AD) and unipolar (UP) AD

	BP-II ($n = 138$)	UP ($n = 44$)			
Variable: mean (SD), %			*T/Z*	df	*P*
Female gender	73.9	75.0	–0.1		0.8846
Age at index MDE (years)	39.9 (13.0)	41.1 (14.9)	–0.5	180	0.6077
Age at onset of first MDE (years)	21.3 (9.8)	25.2 (12.4)	–2.1	180	0.0329
> 4 MDEs	81.8	59.0	3.0		0.0020
MDE symptoms > 2 years	50.0	27.2	2.6		0.0080
Axis I comorbidity	59.4	54.5	0.5		0.5661
MDE severity by GAF	50.9 (7.9)	52.7 (7.8)	–1.3	180	0.1885
Psychotic features	3.6	0.0	1.2		0.2019
> 2 hypomanic symptoms during index MDE	68.8	45.4	2.8		0.0051
Bipolar (I + II) family history	59.7	27.2	3.7		0.0002
Irritability	66.6	40.9	3.0		0.0024
Psychomotor agitation	33.3	27.2	0.7		0.4494
Distractibility	79.7	65.9	1.8		0.0606
More talkativeness	25.3	13.6	1.6		0.1054
Racing/crowded thoughts	78.2	65.9	1.6		0.0998
Mood reactivity	100	100			
Weight gain	39.8	27.2	1.5		0.1313
Overeating	47.8	43.1	0.5		0.5863
Hypersomnia	62.3	68.1	–0.6		0.4860
Leaden paralysis	71.7	61.3	1.3		0.1933
Interpersonal rejection sensitivity	84.0	88.6	–0.7		0.4554
n atypical symptoms	4.0 (1.0)	3.8 (0.9)	1.1	180	0.2386

MDE, major depressive episode; GAF, Global Assessment of Functioning.

Conclusions

Frequency of AD was 42.0%, in line with the findings of Nierenberg *et al.* (1998) in a large UP sample. AD versus non-AD had significantly more BP-II, more females, lower age of onset, more axis I comorbidity, fewer psychotic features, more DMX, more BP family history, more hypomanic and atypical symptoms, in line with previous reports (Kendler *et al.*, 1996; Rabkin *et al.*, 1996; Levitan *et al.*, 1997; Sullivan *et al.*, 1998; Sotsky and Simmens, 1999; McGrath *et al.*, 2000; Williamson *et al.*, 2000; Benazzi and Akiskal, 2001). More BP-II in AD was reported in some recent studies (Angst, 1998; Perugi *et al.*, 1998; Agosti and Stewart, 2001; Angst

Table 6.4 Sensitivity (SE), specificity (SP), correctly classified (CC), and receiver operating characteristics (ROC) area of atypical depression (AD), positive family history of bipolar (I + II) disorders, early-onset first major depressive episode (MDE), many MDE recurrences (> 4), MDE with more than two concurrent hypomanic symptoms (depressive mixed state: DMX) for predicting BP-II diagnosis, by logistic regression ($n = 405$)

Variable, %	SE	SP	CC	ROC
Bipolar family history	56.6	79.8	66.3	0.68
AD	53.5	76.2	62.7	0.64
DMX	59.3	73.1	64.9	0.66
> 4 MDEs	80.9	40.2	64.4	0.60
Early onset	86.2	39.0	67.0	0.70

Table 6.5 Discriminant analysis of atypical depression (AD), positive family history of bipolar (I + II) disorders, early-onset first major depressive episode (MDE), many MDE recurrences (> 4), MDE with more than two concurrent hypomanic symptoms (depressive mixed state: DMX) for predicting bipolar II diagnosis ($n = 405$)

Variable	Coefficient	*Z*	*P*
Bipolar family history	1.2	3.5	0.000
AD	0.6	1.9	0.054
DMX	0.6	1.9	0.049
> 4 MDEs	0.7	1.8	0.062
Early onset	–0.0	–3.9	0.000

Table 6.6 Associations among atypical depression symptoms in the whole sample ($n = 405$), by univariate logistic regression (odds ratio, *$P < 0.05$; **$P < 0.01$)

	Mood reactivity	Weight gain	Overeating	Hypersomnia	Leaden paralysis
Weight gain	3.1*				
Overeating	9.3**	83.7**			
Hypersomnia	4.6**	8.8**	9.4**		
Leaden paralysis	1.5	3.0**	3.5**	2.6**	
Interpersonal rejection sensitivity	2.2**	2.0*	1.7*	2.4**	2.4**

Table 6.7 Associations among atypical depression symptoms in the bipolar II subsample ($n = 241$), by univariate logistic regression (odds ratio, *$P < 0.05$; **$P < 0.01$)

	Mood reactivity	Weight gain	Overeating	Hypersomnia	Leaden paralysis
Weight gain	3.9				
Overeating	5.3*	69.6**			
Hypersomnia	5.2**	6.2**	6.5**		
Leaden paralysis	1.3	3.1**	3.4**	2.0**	
Interpersonal rejection sensitivity	3.2**	1.1	1.0	1.4	2.2**

Table 6.8 Associations among atypical depression symptoms in the unipolar subsample ($n = 164$), by univariate logistic regression (odds ratio, *$P < 0.05$; **$P < 0.01$)

	Mood reactivity	Weight gain	Overeating	Hypersomnia	Leaden paralysis
Weight gain	1.4				
Overeating	nc	98.3**			
Hypersomnia	3.1	18.5**	18.5**		
Leaden paralysis	1.4	1.5	2.4	3.4**	
Interpersonal rejection sensitivity	1.2	4.4*	2.9*	4.1**	2.0*

Table 6.9 Comparison of atypical depression symptoms between mood-reactive (MR) and non-mood-reactive (N-MR) major depressive episode patients

Atypical symptoms	MR = 344	N-MR = 61	*Z*	*P*
Weight gain	18.0%	6.5%	2.2	**0.0249**
Overeating	24.1%	3.2%	3.6	**0.0002**
Hypersomnia	33.4%	9.8%	3.7	**0.0002**
Leaden paralysis	40.9%	31.1%	1.4	0.1489
Interpersonal sensitivity	62.5%	42.6%	2.9	**0.0035**

et al., 2002, 2003; Benazzi studies in this paper), but not in others (McGrath *et al.*, 1992; Robertson *et al.*, 1996; Posternak and Zimmerman, 2002). Different findings may be related to diagnostic criteria, careful and systematic probing for past hypomania, diagnostic interviews (fully structured versus semistructured),

clinician's training, and to different study settings. Lower age of onset and more females in AD versus non-AD were reported (American Psychiatric Association, 2000; Angst *et al.*, 2002). More DMX in AD versus non-AD is a relatively new finding (Benazzi, 2001g; Benazzi and Akiskal, 2001). However, more irritability (a hypomanic symptom) was also reported by Posternak and Zimmerman (2002), Akiskal (1996, 2000) reported that BP-II depression frequently had a combination of AD and hypomanic symptoms, and DSM-IV-TR (American Psychiatric Association, 2000) stated that BP-II females were more likely to have mixed episodes. Much more BP family history in AD versus non-AD is an important finding, as family history is an important variable, validating a diagnosis (Robins and Guze, 1970). The review of Rabkin *et al.* (1996) concluded that, if AD was related to BP, family history should show more BP. To test if the associations of AD and female gender, early onset, DMX, and BP family history were specific features of AD, or were instead due to its association with BP-II (which was closely related to all these variables), multivariate logistic regression was used. Results showed that the associations between AD and female gender, AD and early onset, and AD and DMX were specific features of AD and were not related to the association between AD and BP-II, but that the association between AD and BP family history was related to the association between AD and BP-II.

It was found that the association between AD and axis I comorbidity was not specific for AD, but could instead be related to a common early age of onset. It was found that the association between AD and BP-II was specific for AD and not related to a common age of onset. Two-way ANOVA was also used to find if the lower age of onset in AD versus non-AD was related to an interaction between AD and BP-II, showing such an interaction. Discriminant analysis of BP-II, female gender, early onset, DMX, and BP family history for predicting AD found that AD was significantly associated only with female gender, early onset, and DMX, supporting the previous multivariate logistic regressions, and suggesting that AD may not be so strongly related to BP-II when compared to these predictor variables. BP-II AD, versus UP AD had a significantly lower age of onset, more recurrences, more depression chronicity, more DMX, more BP family history, and more irritability, while AD symptoms were not significantly different. Results suggest that BP-II AD may be distinct from UP AD, supporting a DSM-IV classification, where AD is not a distinct mood disorder. AD had a high specificity for predicting BP-II, second only to BP family history, when compared to BP family history, early onset, many MDE recurrences, and DMX (which are typical bipolar signs: Benazzi and Akiskal, 2001; Ghaemi *et al.*, 2002). Discriminant analysis of AD, BP family history, early onset, many MDE recurrences, and DMX for predicting BP-II diagnosis found that AD was a near-significant predictor of BP-II compared to the other variables.

The results of these analyses suggest that AD is related to BP-II, and that there are other indicators of bipolarity that are more strongly related to BP-II than AD. However, AD is a cross-sectional sign of BP-II which is more reliable and easy to assess during MDE assessment than onset, family history, and number of recurrences (all variables dependent on memory). AD and DMX can be useful cross-sectional markers of BP-II for the clinician (Benazzi, 2001d), leading to careful probing for past hypomania, and to the search for collateral information from family, close friends, medical records, and previous clinicians. AD may have some specific features, like more females, low age of onset, and DMX, which may be independent of its association with BP-II. The strong association between DMX and BP-II (Benazzi, 2001d; Benazzi and Akiskal, 2001; Akiskal and Benazzi, 2003) and AD and DMX strengthen the link of AD with BP-II.

Mood reactivity was significantly associated with all DSM-IV AD symptoms, apart from leaden paralysis (4/5), in the whole sample. All the other AD symptoms were significantly associated with each other (10/10) in the whole sample. However, when the analysis was made separately in the BP-II and UP subsamples, results were partly different. In the BP-II subsample, mood reactivity was significantly associated with 3/5 AD symptoms, while in the UP subsample it was significantly associated with no AD symptom (0/5). In the two subsamples the other AD symptoms were often, but not always, significantly associated with each other (7/10, 8/10). Given the strong association between BP-II and AD found in the present study and in previous studies (Angst, 1998; Perugi *et al.*, 1998; Agosti and Stewart, 2001; Angst *et al.*, 2002, 2003; Benazzi studies in this paper), the association between BP-II and mood reactivity was tested by logistic regression, finding a strong association. The results of the present study in the BP-II subsample are in line with the finding of Angst *et al.* (2002) of a significant association between mood reactivity and the other DSM-IV AD symptoms. The results of the present study in the UP subsample are also in line with Posternak and Zimmerman (2002), who found a lack of correlation between mood reactivity and the other AD symptoms. In these two studies UP and BP-II patients were combined in the analysis, as shown in Table 6.6. An important difference between these two studies is the number of BP-II patients included, which was very small in the study by Posternak and Zimmerman (2002). In the present study, a large number of BP-II patients were included, making it more comparable to the study by Angst *et al.* (2002). However, in contrast to these two studies, UP and BP-II subsamples were also studied separately (Tables 6.7 and 6.8), leading to findings which could explain the opposite findings of the above two studies.

The results of the present study seem to suggest that the inclusion of mood reactivity among the symptoms of AD may be different in BP-II versus UP. In BP-II, mood reactivity could be included in AD, while in UP it could not be included.

This conclusion is also supported by differences found between BP-II AD and UP AD (Benazzi, 1999a, b, 2000c, e).

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7

Agitated depression: spontaneous and induced

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Sometimes it is more "inward anxiety and trembling," a painful tension; sometimes it is an anxious restlessness, which finds an outlet in the most varied gestures, in states of violent excitement, and in heedless attempts at suicide. These moods are most frequently found in the periods of transition between states of depression and mania; they are, therefore, probably most correctly regarded as mixed states of depression and manic excitability (Kraepelin, 1913).

The inner unrest is the constant thing, while the motor unrest is variable (Lewis, 1934).

Introduction

The greatest shortcoming of psychiatry is the near complete lack of knowledge of the pathophysiological processes underlying our clinical entities. Kahlbaum (1863) was the first to distinguish clearly between symptomatic clinical pictures and the disease process that was responsible for them. Kraepelin took this concept a step further and based the idea of the disease process (*Vorgang*) on the conditions under which the disease starts, its course, and outcome. This method of clinical psychiatry achieved the separation of manic-depressive illness from dementia praecox. But the real identity of the pathophysiological process underlying the clinical entities still remains obscure. Our psychiatric nosology is entirely based on phenomenology and course.

We do, however, have important tools at our disposal, which are the psychoactive drugs. The response to these drugs not only indicates the pharmacological action of the drug itself but also provides important clues about the nature of the neuropathologic process upon which the drug acts. Thus far we have not fully profited from these responses to enhance our understanding of clinical entities and improve our nosology. On the contrary, clinical entities are taken as firm

points of reference and the response of a clinical syndrome to a drug is used to qualify the action of that drug. For instance, if a number of depressed patients improve on lithium or carbamazepine we conclude that these drugs have antidepressant properties. We do not question the nature of the processes that underlie what we call depression according to our present nosology. Further, if a depressed patient becomes agitated on antidepressants, it is labeled an adverse reaction instead of considering it a potentially normal reaction of an excited or excitable neuronal substratum: that we are in fact treating a mixed state. It does not occur to us that in some cases what presents itself with depression of mood, anhedonia, anxiety and other "depressive" symptoms may be linked to, or caused by, excitatory processes.

A century and a half ago W. Griesinger had this intuition without the help of modern psychopharmacology:

> By using the expression "psychic depressive states" we did not mean to imply that the basic nature of these states is inactivity and weakness and suppression (depression) of the psychic or cerebral processes that underlie them. We have much more reason to assume that very intense states of irritation of the brain and excitation of the psychic processes are very often the cause of such states; but the end result of these (psychic and cerebral) states as far as mood is concerned is a state of depression or psychic suffering. (Griesinger, 1861).

Agitated depression and psychotic depression are crucial issues today because their nosological position as depressive states does not correspond to their response to antidepressant treatments, which on the contrary may increase or induce agitation, insomnia, and suicidal or other violent acts. Agitated melancholia and agitated depression used to be considered mixed affective states but the Diagnostic and Statistical Manual of Mental Disorders (DSM: American Psychiatric Association, 1968, 1980, 1987, 1994) and *ICO-10: International Statistical Classification of Diseases and Related Health Problems* (World Health Organization, 1992) systems do not consider them as such. The main reason for this was probably the very good response of these conditions to electroconvulsive therapy (ECT). With the introduction of tricyclic antidepressants and selective serotonin reuptake inhibitors, the poor response, in contrast to the beneficial response of non-agitated and non-psychotic depressions, became clear. Actually, antidepressant drugs may exacerbate these conditions, as we discuss in this chapter, and as is well known among clinicians.

Melancholia agitata

From classical antiquity to the end of the nineteenth century, melancholia was described in various forms, many of which would today be considered mixed

affective states. The first and one of the best descriptions of agitated melancholia is found in *Diseases II* by Hippocrates (1988):

> Anxiety: the patient feels something like a thorn stinging his innards. He flees from light and from people, loves the dark and he is caught by panic . . . he is terrified and sees frightening visions, dreadful nightmares and sometimes dead people. The disease attacks most people in spring.

Aretaeus (1735) stated that melancholics suffer from "violent rage and sadness and awful dejection." The nosologists of the eighteenth century, such as Boissier de la Croix de Sauvages (1768) and Cullen (1785a), classified among the melancholias such forms as *melancholia phrontis*, *melancholia moria*, *melancholia saltans*, *melancholia errabunda*, *melancholia silvestris*, *melancholia furens*, and *melancholia enthusiastica*.

Heinroth (1818) abandoned the intellectualistic conception of melancholia and considered it a disease of the mood *(Gemüth)*. In his classification of the morbid conditions of the soul, he placed *melancholia metamorphosis* among states of exaltation *(hypersthenia)*, whereas among the manias he listed *melancholia saltans*. Among the mixtures of exaltation with weakness *(hyperasthenia)*, he cited *ecstasis melancholica*, *melancholia furens*, *mania melancholica*, and *athymia melancholico-maniaca* (timidity with melancholia and rage).

Griesinger (1845) considered melancholia a disease of the affects (intense, altered emotional states), distinguishing them into two major classes: (1) the expansive, affirmative ones, such as happiness, joy, and hope; and (2) the depressive, negative ones, such as dejection, sadness, and fear. He placed rage in an intermediate position between the two kinds of affect. Griesinger described, among the states of mental depression, melancholia in the strict sense, melancholia with destructive tendencies, and melancholia with persistent excitement of the will. As noted earlier, he had the great insight that processes of cerebral excitation may be the cause of psychic pain and depression. Griesinger saw the cause of melancholia in a state of hyperesthesia, and Kahlbaum (1863) saw the cause in a state of hyperthymia. As Schmidt-Degenhardt (1983) points out, there is an evident contrast with the concept of depression, which implies suppression or weakening of brain processes.

The first to use the term *melancholia agitans* was Richarz in 1858 in his remarkable work *On the Nature and Treatment of Melancholia with Excitement (Melancholia Agitans)*, in which he differentiates "racing thoughts" of agitated melancholia from the *flight of ideas* of mania. He introduced the term *melancholia agitans* instead of *melancholia activa* because it better suited the aimless restlessness of the patient. More commonly termed as *melancholia agitata*, it was widely employed in the second half of the nineteenth century, and it was later replaced by *Angstmelancholie* and eventually *agitated depression*.

With the introduction in 1851 of *folie circulaire* by Falret (1851), a significant number of melancholias became a component of a more complex disease entity and lost their nosologic independence. This nosographic evolution eventually led to the creation of *manic-depressive insanity* by Kraepelin in 1899 and the definitive substitution of the concept of melancholia with that of depression. Many psychiatrists had proposed substituting the term *melancholia*, which had become too vague, with other terms such as *tristimania*, proposed by Rush (1830), *lypemania* by Esquirol (1838), *dysthymia* by Flemming (1844), and *vecordia melaena* by Kahlbaum (1863).

In the first edition (1883) of his textbook, Kraepelin placed *melancholia activa* among the excited states and distinguished it from *melancholia periodica*, which is in any case marked by delirious or delusional ideas and anxious agitation. Only *melancholia of circular insanity*, marked by psychic and physical inhibition, corresponds to the clinical picture of the present disorder *major depression*. In the second (Kraepelin, 1887) and third (Kraepelin, 1889) editions, Kraepelin distinguished between *melancholia activa*, very agitated, and *melancholia simplex*. In the fourth edition, published in 1893, he replaced *melancholia activa* with *Angstmelancholie*, to emphasize better the component of anxiety in this condition. In the fifth edition (Kraepelin, 1896), he introduced *melancholia of the age of involution*: "with the name of melancholia we designate all pathological anxious depressions of older age which do not represent parts in the course of other psychic disorders." The clinical picture also comprised delusions, especially of guilt but also of persecution, and hypochondriacal ideas. The similarity with the old *melancholia agitata* is evident. Kraepelin included *Angstmelancholie* in *involutional melancholia*.

In the eighth edition (Kraepelin, 1913), Kraepelin subsumed *involutional melancholia* into *manic-depressive insanity*, accepting the results of the catamnestic investigation carried out by his student Dreyfus (1907) on Kraepelin's same patients in Heidelberg. In essence, Dreyfus showed that involutional melancholia was a mixed state of manic-depressive insanity. In his foreword to Dreyfus's *Melancholia*, Kraepelin wrote with evident regret: "Nevertheless, it is to be foreseen that the old clinical form of Melancholia, one of the oldest in psychiatry, will completely disappear because it contains mainly manic-depressive features." What he could not have foreseen was that, by the end of the twentieth century, agitated depression, which had replaced melancholia, in all likelihood would also lose its status as a mixed state.

In the following decades, the concept of melancholia was replaced in European psychiatry by the concept of endogenous depression and in the USA by the concept of depressive reaction according to Meyer's (1951) idea of reaction types. Under the impact of DSM-III (American Psychiatric Association, 1980), the term *major depression* replaced worldwide the terms of *melancholia*, *endogenous depression*, and

depressive reaction. The term *involutional melancholia* remained in use for a long time, and it was still present in DSM-II (American Psychiatric Association, 1968). It was abandoned as the name of a separate entity in DSM-III, and the term *melancholia* was relegated to a subclassification at the fifth digit: *major depressive episode with melancholia*: "a term from the past in this manual used to indicate a typically severe form of depression that is particularly responsive to somatic therapy." This subclassification may be seen as an effort to preserve the oldest term in psychiatry. Certainly the syndrome described here would have been called *melancholia simplex* in the past, but it does not bring out the dramatic picture of anxiety, fear, rage, and delusional ideas that have traditionally been associated with the term *melancholia* and are still seen in clinical practice today. The term *melancholia* would have better suited the form described as *major depressive episode with psychotic features*.

Another key shift in DSM-III was the introduction of the term *bipolar disorder* in place of *manic-depressive illness*. In this regard, the authors fully share Jamison's (1995) view:

> the word "bipolar" seems to me to obscure and minimize the illness it is supposed to represent ... and it minimizes the importance of mixed manic and depressive states, conditions that are common, extremely important clinically, and lie at the heart of many of the critical theoretical issues underlying this particular disease.

Mixed affective states and agitated depression

Many authors clearly described mixed affective states well before Kraepelin, including Lorry (1765), *mania melancholica*; Heinroth (1818), *melancholia mixta catholica*, *melancholia furens*; Guislain (1852), *melancholie maniaque*; and Griesinger (1845), *melancholia with persistent excitement of the will*. Kraepelin conceptualized and described mixed states in a systematic way. He made them the cornerstone of the manic-depressive entity. In conceiving the manic-depressive mixed states, Kraepelin started from the excitement or depression of the three domains of psychic life: (1) the intellect (train of thought rather than its contents); (2) mood; and (3) volition, expressed in psychomotor activity.

Distinguishing between the foregoing three domains of psychic life has been a constant idea in western culture and stems both from Plato's (1994) three elements of the soul – rational, emotional, and appetitive – and from Aristotle's (1970) psychic powers (faculties) – rational, sensory, and appetitive. Via the equivalent faculties of Kant (1800) – the rational, the sense of pleasure or pain, and the appetitive faculty – these distinctions have had a great influence on psychiatry and

the understanding and classification of psychic disorders as well as the conception of mixed manic disorders in particular, as discussed later.

In the fifth edition of his textbook (1896), Kraepelin introduced the concept of *mixed states* and described *manic stupor*. In the sixth edition (Kraepelin, 1899), he presented the entity of *manic-depressive insanity* and described the mixed states: mania with inhibition of thought, manic stupor, querulous mania, states of transition, and depression with flight of ideas. In the seventh edition (Kraepelin, 1904), he introduced among the mixed states depressive agitation and mania with poverty of ideas.

In the eighth edition of his textbook (Kraepelin, 1913), starting from *mania*, which consists of flight of ideas, exalted mood, and hyperactivity, Kraepelin described *depressive* or *anxious mania*. Flight of ideas is evident in the speech of the patient, who continuously spins out thoughts and often shows a real passion for writing. The mood is anxiously despairing and is manifested in great restlessness and senseless pressure of activity. Ideas of sin and persecution or hypochondriacal delusions are frequently present. The degree of excitement in this condition is such that the noun *mania* seems appropriate, and, given the prominence of anxiety, the adjective *anxious* seems more suitable than *depressive*. This syndrome certainly comes close to the old *melancholia agitata*. The next mixed state is *excited depression (erregte Depression)* with inhibition of thought, great restlessness, and anxious and despondent mood. The difference between these two syndromes is the presence of flight of ideas in the first and inhibition in the second.

Although the previous two mixed forms originate, according to Kraepelin, from a manic state, the third one originates from a state of depression and is called *depression with flight of ideas*: "in a usual picture of depression, inhibition of thought may be replaced by flight of ideas ... They cannot hold fast their thoughts at all; constantly things come crowding into their heads." Kraepelin also states: "in such cases we have to do with the appearance of a flight of ideas which only on account of the inhibition of external movements of speech is not recognizable. The patients are almost mute and are rigid in their whole conduct and are of cast-down and hopeless mood." As discussed later, in many cases there is, in fact, no inhibition at all. The patient moves and talks freely and complains about crowded thoughts, whereas the mood is despondent. These two Kraepelinian mixed states seem similar to the present agitated depression, which is discussed later. Kraepelin explained the coexistence of manic and depressive symptoms with the hypothesis that the three areas of psychic function (mood, thought, and volition) do not evolve in a synchronous way in mixed states. The frequent occurrence of mixed states during periods of transition between two opposite phases lends support to this hypothesis.

In 1888, Clouston from Edinburgh described *excited motor melancholia*, a term that stresses the excitatory nature of the agitation. In 1899, a monograph appeared on *Mixed States of Manic Depressive Insanity* by Kraepelin's pupil Weygandt, based on a study carried out in Heidelberg. He focused on only three types of mixed state: manic stupor, unproductive mania, and agitated depression (*agitirte Depression*) with depressed mood, psychomotor excitement, and flight of ideas. This is the first time to the authors' knowledge that the term *agitated depression* was used. Weygandt pointed out the similarity with agitated forms of involutional melancholia and, similar to Lange (1928), Specht (1908), and Thalbitzer (1908), considered *melancholia agitata* a mixed state of manic-depressive insanity, in contrast to Wernicke's (1906) school of thought, which viewed it as a form of anxiety psychosis.

Stransky, in 1911, wrote in Aschaffenburg's handbook that the anxiety of *melancholia agitata*, or *depression with anxious excitation*, does not contain mixed elements. He also remarked that inhibition of thought is not always present in manic stupor, and motor inhibition does not affect facial expressiveness. He did not consider dysphoric mania a mixed state because the basic mood is an expansive one.

In 1928, Lange discussed mixed states and noted that classic, pure clinical pictures of mania or depression are rarely found. He recognized *melancholia agitata* as a mixed state. Among the mixed states, he described a form that he named *excitable depression (anregbare Depression)*, marked by inner anxiety and lack of motor agitation. Some patients present with inhibition of thought, and some have flight of ideas. If they are somehow stimulated, these patients show motor agitation and exaggerated expressive movements. Lange pointed out that in many patients depressive mood and motor inhibition coexist with hyperactivity of thought.

Interest in mixed states was waning by the 1920s. In 1923, Jaspers wrote that the issue of mixed states "did not have any further development, and this was very natural since elements of understanding psychology had been considered as objective components and factors of psychic life." Schneider (1962) was more hasty: "We no longer believe in manic-depressive mixed states. Anyway, what may look like this is a change or a switch, if it pertains to Cyclothymia at all."

On purely psychopathologic grounds, without any knowledge of the underlying neuropathologic alterations, it is difficult to make significant progress in this field. The present interest in mixed states is due to the adverse effects of antidepressants and the beneficial effects of lithium, anticonvulsant mood stabilizers, and atypical antipsychotics.

At present, agitated depression has lost its status as a mixed state, not only in the DSM system, but also in the view of most psychiatrists worldwide. Apart from the

impact of the conceptual shifts that are mentioned subsequently, another reason may be the great efficacy of ECT in both agitated and retarded depression. The nosologic differences between the two forms were probably overshadowed by the similar therapeutic outcome. ECT is as effective (Gruber *et al.*, 2000) or more effective in agitated depression than on any other form of depression (Koukopoulos *et al.*, 1995). ECT is effective in both mania and depression (Small, 1985). With the widespread use of antidepressants, coupled with the diminishing use of ECT, the different response of agitated and psychotic depression has become increasingly clear. Agitated depression was considered a subtype of major depressive disorder in the *Research Diagnostic Criteria* (RDC: Spitzer *et al.*, 1978) but was not carried over in DSM-IIIR (American Psychiatric Association, 1987) or DSM-IV (American Psychiatric Association, 1994).

In the criteria of major depressive episode, agitation is listed as the fifth symptom: "psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)" (American Psychiatric Association, 1994). This seems as if agitation and retardation are equivalent symptoms.

Over the course of more than 2000 years, the disease entity *melancholia* has become the syndrome *agitated depression* and now a symptom, *agitation*, of a depressive episode. This evolution has had an enormous impact on therapeutic approaches to depression. The kind of treatment is determined by the diagnosis of a disease or a syndrome and less by a symptom. Thus, major depressive episodes with or without agitation are treated in the same way, and the result is disastrous in many cases of agitated depression. Both symptoms and course worsen.

A significant inverse symmetry may be seen in the evolution that occurred with the concept of depression. In the beginning, it was a symptom that could be present in many conditions. Ziehen (1902) objected to the term *manic-depressive insanity* on the grounds that Kraepelin had conflated a disease, *mania*, with a symptom, *depression*, and he proposed, as many others did, the term *manic-melancholic insanity*. Then, in the entity *manic-depressive insanity*, depression became a syndrome, the depressive phase of the illness. Today, depression is understood as a morbid entity and every physician is entitled to offer antidepressant treatment to nearly all patients with despondent mood diagnosed as meeting the DSM-III criteria for a major depressive episode with or without agitation. Agitated depression is not considered a mixed state in DSM-IV or in ICD-10. Most psychiatrists (World Health Organization, 1992) today consider it a form of depression with anxiety.

In recent years, a growing number of psychiatrists (Himmelhoch *et al.*, 1976a; Koukopoulos *et al.*, 1989; Dell'Osso *et al.*, 1991; Akiskal, 1992; Koukopoulos *et al.*, 1992; Swann *et al.*, 1993; Bourgeois *et al.*, 1995; Perugi *et al.*, 1997; Benazzi, 2000)

have expressed disenchantment with the official view, proposing agitated depression as a mixed form of affective disorders. The DSM system opposes this view because agitated depressives do not simultaneously meet the criteria for mania and major depression. Schatzberg (1998) finds

> a number of key differences in the seeming overlap of symptoms: manic or mixed patients demonstrate a decreased need for sleep while agitated depressives complain of insomnia. The bipolar patient has increased thinking and increased speech, while agitated depressives have especially depressive ruminations and decreased speech. The increased motor activity of the agitated depressive is purposeless and unpleasant, while in bipolar patients it is often aimed at some grandiose goal.

One could object that the state of depression inevitably modifies the excitatory symptoms and vice versa. The DSM system not only conceives a mixed state as an overlap of manic and depressive symptoms, but also requires the rare simultaneous presence of a full manic and a full depressive syndrome. The symptoms of agitated depression are of a different kind, as their response to treatment demonstrates. The current interest in this topic stems from the clinical observation that antidepressant drugs exacerbate agitation, insomnia, anxiety, and suicidal ideas in these patients (Koukopoulos *et al.*, 1992).

The parallelism between drive, mood, and thought

Normal human behavior, and especially behavior during affective episodes, has created the impression that good mood is allied with good drive and fluent thinking and vice versa. Hypomania with euphoric mood with hyperactivity, and depression with retardation are typical examples of this parallelism. Cullen (1785b), who ascribed the state of excitement and state of collapse (asthenia, depression) to changes in nervous power, remarked that "these different states of the brain are expressed in the body by strength or debility, alacrity or sluggishness; and in the mind by courage or timidity, gaiety or sadness."

This bipolarity is certainly a clinical reality, but the mixture of elements of excitement with elements of depression (inhibition) creates clinical pictures called *mixed states*. These elements manifest themselves as symptoms and the clinical pictures are syndromic sets of symptoms. As Goodwin and Jamison (1990) state, "mixed states can be broadly defined as the simultaneous presence of depressive and manic symptoms." Nevertheless, physicians cannot help associating them with an underlying, analogous physiopathologic alteration that they try to modify by treatment. Part of the problem lies in the term *depression*, which probably displaced melancholia because it was thought to convey the meaning of a state of mood rather than that of a disease entity. Clinicians and laypersons automatically

relate such a state of depressed mood to lower activity of the nervous system, as Cullen did, and physicians today prescribe antidepressants to most patients who look and behave depressed, just as they prescribe antimanic medication for those who behave in an excited way. This concept of depression being caused by lower nervous activity is also borne out by the medical terms and popular expressions for despondent mood in most languages: like the Latin *depressio*, the German *niedergedrückt*, the English *downcast* or *down in the dumps*, the French *abattement*, the Spanish *abatido*, and the Italian *essere giù*, they all imply being low. Nosology and therapy of the so-called functional psychoses can be based only on their phenomenology, course, and outcome. The extensive use of effective psychotropic drugs, however, sheds new light and provides meaningful information on the underlying neurophysiologic conditions.

There is important clinical evidence, in fact, that excitatory brain processes may cause despondent mood, anxiety, and symptoms of inhibition. Stages II and III of mania, as described by Carlson and Goodwin (1973), with their dysphoric mood, panic, and hopelessness, are a perfect example of a condition that phenomenologically looks like a mixed state but neurophysiologically is a purely manic state, and useful treatments are exclusively antimanic.

The same applies to dysphoric mania, which is still considered a mixed state (Secunda *et al*., 1987; Post *et al*., 1989; McElroy, 1997). The useful treatments are antimanic ones, and typically, under their effect, euphoria replaces dysphoria before the patient becomes euthymic or depressed. A similar phenomenon may occur between excitement and psychomotor inhibition. In manic stupor, there is no inhibition of thought, as Kraepelin believed. The patient does not speak, but when he or she recovers, the patient discloses that there were so many thoughts in his or her head racing so fast that the patient could not utter them. Also in the few cases of mania with poverty of ideas that the authors have seen, the patients have reported that their heads were so full of thoughts that they could not express them or hold a conversation. As with mood in dysphoric mania, here too the inhibitory symptoms are solely due to an increase in the levels of excitement, and treatment is exclusively antimanic. Should they really be considered mixed states?

The case of agitated depression is different. As discussed subsequently, elements of clear excitement are bound together with authentic depressive elements. It is ironic that today agitated depression has lost its status as a mixed state, whereas manic stupor and dysphoric mania are still considered as such.

Clinical picture of agitated depression

Depressed anxious mood and inner, psychic agitation dominate the clinical picture. Psychomotor agitation is present in many cases, but not in all. In the

cases without psychomotor agitation, the inner unrest is the main symptom. This inner agitation makes the patient very anxious and fearful, hence the condition is very difficult to distinguish from anxiety, as will be discussed later. The inner unrest manifests itself with irritability or feelings of unprovoked rage, racing or crowded thoughts, talkativeness, and dramatic descriptions of psychic pain. A typical feature of agitated depression is the absence of retardation in speech and movement; yet, there is an inhibition of purposeful activity, which in more severe cases is nearly complete. In mild forms, the patient is quite active and sometimes anxiously hyperactive. Complete anhedonia and lack of interest are marked in all cases. Psychic pain is particularly severe and is often accompanied by suicidal thoughts and impulses. In more severe forms, the psychic pain is constant while in milder cases there is lability of mood and emotional reactivity. Early insomnia, often sustained by racing thoughts, is common.

Clinical forms of agitated depression

The following clinical forms can be distinguished.

Psychotic agitated depression

These patients present with depressed mood, restlessness, anxiety, delusions of guilt and persecution, hypochondriacal ideas and, often, strong suicidal impulses. The similarity of this syndrome with that of other psychotic depressions that do not present with motor agitation is notable (Nelson and Bowers, 1978; Frances *et al.*, 1981). In the latter, the patient lies silently in bed. On questioning, the patient describes an intense inner agitation, often located in the chest, abdomen, or head. A young patient said he felt "blades ripping through his guts" – a similar image to that employed by Hippocrates. Some patients describe racing or crowded thoughts.

Agitated depression (non-psychotic) with psychomotor agitation

Patients do not present with delusions or hallucinations. The picture is dominated by depression, anxiety, and motor agitation similar to that described in the RDC criteria (Spitzer *et al.*, 1978). The patient may complain of crowded thoughts.

Minor agitated depression

The patient does not appear outwardly agitated, or the motor agitation is limited, but there is total lack of retardation. The patient speaks fluently and moves normally. The patient complains of intense inner agitation. The psychic pain of the patient is relentless, and the patient feels unable to perform normal tasks or enjoy anything. Frequently the patient complains of racing or crowded thoughts

Table 7.1 Minor agitated depression

Patient displays:	Patient complains of:	Partner reports:
Depressed mood	Anxiety	Continuous complaining
Psychic agitation	Inner tension	Occasional overt expression of irritability
Vivacious facial expression	Muscular tension, subjective feelings of irritability and unprovoked feelings of rage	
Dramatic descriptions of suffering	Crowded or racing thoughts	Occasional sexual hyperactivity
Lack of retardation	Early or middle insomnia	
Spells of weeping	Suicidal ideas and impulses	
Talkativeness		
High diastolic blood pressure		
Emotional lability		
Impulsive suicidal attempts		

(Table 7.1). We propose the term *minor agitated depression* or *minor mixed depression* because the syndrome is less severe and requires lower doses of medication.

The term *minor agitated depression* is replacing the term *excited anxious depression* proposed by us in the past (Koukopoulos, 1999). We are now proposing the term *minor* to indicate the lesser severity in comparison with the other two forms and because it is simpler. This syndrome is similar to Kraepelin's (1913) *depression with flight of ideas* and Lange's *excitable depression* (Lange, 1928), as described earlier.

These patients fully meet the DSM-III criteria for major depression. Because of the absence of psychomotor agitation, they do not meet the RDC criteria for agitated depression and do not meet the criteria for a DSM-IV mixed affective episode because of the absence of a clear manic syndrome. Yet this form should be considered as a mixed state not only for the racing thoughts that are undoubtedly a sign of excitation, for the irritability, and for the emotional lability, but also for the course of this disorder and the reaction to antidepressant treatment. Because of the lack of inhibition and because of the intense expression of their suffering, these patients are often diagnosed as presenting with reactive or personality disorders. The syndrome may resemble *hysteroid dysphoria* (Liebowitz and Klein, 1981; Klein and Liebowitz, 1982) because of the vivacious expression of their suffering. These syndromes may occur spontaneously or appear during antidepressant treatment.

An interesting split is often observed between motor agitation and racing or crowded thoughts. Their relationship appears to be inversely proportional. Mental excitement is more frequent and more intense in patients who do not show marked motor agitation. There is a striking analogy with manic states, in which the presence of delusional ideas is inversely proportional to psychomotor excitement. This phenomenon may have played a decisive role in the success of political and religious fanatics who created a vast popular following. It can be assumed that, if their delusional or semidelusional ideas had been accompanied by patent motor excitement, they would not have had the same charismatic influence on their audience.

Because the term *agitation* usually means motor agitation, as in the RDC, and neglects the cases of mental and psychic agitation, the term *mixed depression* (MxD) is suggested for all the clinical forms of agitated depression.

It is also suggested that the old term *melancholia* be reused for the psychotic form of agitated depression. This name not only represents a great psychiatric tradition, but also fully conveys the tragic human experience of these patients and bears out a deeply significant fact – that the major psychiatric syndromes have remained unchanged over the course of thousands of years. If they are not disease entities, they surely are what Kraepelin would have called *natural realities*.

Flight of ideas, racing and crowded thoughts

In all three forms of agitated depression delineated here, many patients complain of a disturbance of the train of thought that they call *crowded or racing thoughts* or other similar names. In the literature, this is often called *depression with flight of ideas*. This disturbance is, in many respects, different from the flight of ideas observed in manic state.

Flight of ideas in manic patients is expressed verbally in an abundance of words or pressured or clearly logorrheic speech. When racing thoughts are present in depressed patients, speech is limited or at normal tempo.

In flight of ideas, the content of these ideas and somehow the pattern of thoughts are reflected in the content and pattern of the speech itself. In racing thoughts, there is not such a close relationship. On the contrary, the patient talks about the thoughts and reports on their course and their content and his or her own sensations. Racing thoughts are not expressed directly in the speech. The patient repeats monotonous laments, but the great energy involved in these depressive lamentations and in this speech denote the mixed depressive–manic nature of this symptom. In some cases, there is a certain degree of pressured speech.

The agitated melancholic patient complains of this course of thought as a torment, but the exalted (manic) patient never complains about his or her flight

of ideas. This observation by Richarz, in 1858 in his paper on *melancholia agitans*, is fully confirmed by the patients seen today.

Richarz (1858) also observed that in mania thoughts tend to form strings of ideas *(Reihenbildung von Vorstellungen)* that link together by their content, alliteration, or assonance. In racing thoughts, the ideas come and go rapidly as if they were hunting each other or continuously overlapping without any link between them.

In Braden and Qualls' (1979) work, the phenomenon is described by their patients with metaphors implying rotation: like a whirlpool, a hurricane, a centrifuge. A patient of the authors said, "I felt like the thoughts were circling around in my head and somehow I felt trapped by them." Another young woman said her thoughts were "like a raging river breaking through a dam and flooding my mind."

In other cases, the phenomenon could be called *crowded thoughts*; the patient complains that his or her head is full of thoughts of all kinds, not merely depressive ones and sad memories, but prevalently trivial thoughts of little significance for the patient. Not infrequently, patients report the presence of musical tunes that they keep hearing in their heads. The most important feature of these crowded or racing thoughts is that they afflict the patient not only through their meaning but also by the way they manifest themselves; there must be something unrelentingly painful and oppressive in their impact on the patient's mind.

A male patient said, "I felt attacked by them." Another male patient who tried unsuccessfully to shoot himself in the head said afterwards that he did it to stop his thoughts. This patient was of depressed mood and kept quiet. These kinds of thoughts are typically intense at night and often prevent the patient from falling asleep.

Depressive ruminations are different. They consist of only a few thoughts that carry the anxieties and fears of the patient, and they are constantly present or recur frequently. The patient complains of their content but not of their course. There are naturally cases of transition between crowded thoughts and ruminations, and making the distinction may be difficult.

Flight of ideas, racing thoughts, and crowded thoughts are clearly excitatory phenomena. Neuronal hyperactivity must underlie them. This hyperactivity is dramatically confirmed by the effect of antidepressant medication, especially given without typical and atypical neuroleptics. The thoughts are further accelerated and intensified; the patient becomes exasperated to such a point that sometimes he or she wants to commit suicide. This worsening may be induced within the space of a few days or even hours. In many cases, the suicidal impulses induced by antidepressants seem to be linked to the acceleration of the thoughts and to the worsening of the agitation. Typical and atypical neuroleptics, on the contrary, are of great benefit.

Restlessness, inner agitation, and anxiety

I was awfully restless, I kept wringing my hands and pulling my hair. I couldn't sit still but had to keep pacing around all the time. I was not able to read or listen to music, I couldn't play the piano, I couldn't concentrate at all, I was unable to eat or sleep. I was irritable and constantly tired, I suffered from fears of going insane, of having contracted AIDS or syphilis and these thoughts would not leave me alone. I started thinking of oblivion, about suicide. I was so restless that I began to think of ending my life just to get some peace of mind.

This young woman called her agitated depression a *horror*.

Other patients exhibit much less psychomotor agitation, but they clearly suffer from inner agitation. They describe it as intense inner tension and use metaphors such as "I feel like I'm bursting inside," or "I feel a violent force inside me as if I wanted to smash everything," or "I feel there are blades tearing through my guts." They describe an internal shaking or an electrical current passing through the body. This tension is also manifested as muscular tension or pains. Diastolic blood pressure is found typically increased to 90 or 100 mmHg. Psychomotor agitation and inner agitation are equally significant. Both are worsened by antidepressants and improved by neuroleptics. Psychic agitation is a subjective symptom, but it has objective manifestations observable by others, and the descriptions given by the patients are so characteristic as to make this symptom as reliable as any other aspect of affect and mood.

Closely related to this inner tension and agitation is a feeling of rage arising without external provocation and in most cases not directed against anything. The patient just complains about it. In other cases, there is irritability and, at times, verbal and rarely physical violence, usually within the family environment, as noted by Lange (1928). In extreme cases, this rage, combined with hopelessness, is the cause of the violent character of suicide attempts, of which *raptus melancholicus* is the utmost example. At least some suicide–homicide cases are due to agitated depression. The difference from manic aggressiveness is that in manic patients anger is provoked by some external cause and is directed outward.

The clinical picture comprises depressed mood, total anhedonia, exhaustion, and inability to perform simple tasks or take part in usual activities, and it is marked by intense anxiety and fears – fear of everything or psychotic fears, often hypochondriacal, especially the fear of losing one's mind. The devil figures frequently in these fears. One of the most common colloquial expressions for feeling low and fearful is "the blues," which originates from an old English expression alluding to an attack by "the blue devils."

Anxiety seems highly related not only to psychomotor agitation, but also to inner, psychic agitation. An interesting debate on anxiety in manic-depressive

insanity, and particularly on *melancholia agitata*, took place at the beginning of the twentieth century, between Westphal and Koeplin (1907) on one side and Specht (1908) on the other. The former authors, following Wernicke (1906), who considered anxiety the basis of *Angstpsychosen*, maintained that anxiety overwhelms depressive inhibition and dominates the clinical picture, producing restlessness, agitation, and flight of ideas. Wernicke believed that the increased production of anxious thoughts could lead to flight of ideas, pressured speech, and agitation. A similar idea was advanced by Weitbrecht in 1963. Mentzos (1967), in his monograph on mixed states in 1967, proposed a distinction between anxious agitated depression and excited depression with flight of ideas.

Specht (1908) saw agitation and flight of ideas as manic elements and considered *melancholia agitata* and *agitated depression* as mixed manic-depressive states. He made the same assessment of melancholic delusions and proposed classifying every mixed state with depressive mood as melancholia. As far as anxiety is concerned, he thought that the inhibition present in depressions of circular insanity dampens the anxiety, which is, on the contrary, freely manifested in cases without inhibition. Inhibition depresses all emotions and reactions, but anxiety is often completely absent in retarded depression. The anxiety found in typical depression (major depressive episode) is an emotional reaction to the painful experience of the depression itself. Human beings react with anxiety to stress factors of much lesser entity. This anxiety improves with antidepressant medication. Often, it is the first symptom to disappear.

The anxiety observed in agitated depression seems to be of a different kind, inherent in the agitation itself. These two types of anxiety, assessed with limited semiologic tools, seem almost identical. The subjective suffering is similar, and they produce the same fears. Yet the anxiety present in agitated depression appears to be a form of excitation or arousal. By more careful examination of the patients, a substantial difference emerges between on the one hand the anxiety of anxiety disorders, which consists of a feeling of apprehension, fearfulness, or impending doom, and the anxiety that often accompanies depressive episodes, which consists of fear of being worthless, fear of facing others, and fear of not getting better, in short, fear of something, and on the other hand, the inner tension of agitated depression. This latter anxiety seems similar to the two former types of anxiety but is substantially different. Patients of considerable introspective capacity describe this inner agitation as a great energy that strikes and possesses their minds and sometimes their bodies too, in a way that annihilates their capacity to think, feel, concentrate, or do anything.

Racing thoughts have the same annihilating effect, probably because they are conveyed by this abnormal energy. It becomes impossible for the patient to cope with all of this because of the overwhelming sensation of total impotence. The total

inactivity, the despair, the undirected and groundless rage, and the violent suicidal impulses, all the essential elements of classic melancholia and of the more mundane agitated depression of today, seem to be caused by that ominous, dark force. The long-standing western tradition that has always associated the colour black with melancholy and depression is probably linked to this force within the patient. This force is so violent that it cannot be anything but manic in nature. It improves rapidly under the effect of neuroleptic drugs, whereas it can worsen dramatically under the effect of antidepressants, especially if given without neuroleptics or discrete doses of benzodiazepines or anticonvulsant drugs. ECT is the most effective treatment (Koukopoulos *et al.*, 1992; Gruber *et al.*, 2000). A young woman called her agitated depression *black mania*, a term also used by Jamison (1995). Why this manic energy, rather than improving drive and mood, instead annihilates psychic life, must be due to the depression itself and a tentative explanation is offered below.

Role of temperament

Many hypotheses have been advanced to explain the genesis of mixed states. Kraepelin's (1904) idea of the unsynchronized transition between the two phases and the consequent hypothesis of the patient being "trapped in the switch process" may be accepted for transitional mixed states but not for the permanent ones. The most important mixed states either start as such or they become mixed under the effect of treatment. Himmelhoch *et al.* (1976a, b) advance the hypothesis of a double bipolar and unipolar heredity to explain the manic elements in a state of depression. McElroy (1997) thinks that the agitation may be driven by hypomania.

Akiskal (1992; Akiskal *et al.*, 1998) advances the ground-breaking hypothesis that mixed states arise from the intrusion of an affective episode into an opposite affective temperament or one with a high degree of chronic instability, such as the cyclothymic temperament. Thus, dysphoric mania results from the intrusion of a manic episode in a depressive temperament, and depressive mixed states arise from the intrusion of a depressive state into a hyperthymic (hypomanic) temperament. Marneros (2001) also agrees with this interpretation.

The authors' view is similar to that of Akiskal. The premorbid temperament of depressed patients with motor or psychic agitation is marked by a high degree of excitability, emotional reactivity, and energetic drive. Many hyperthymic people and all cyclothymic and irritable people have such features, especially women, who make up the vast majority of agitated depressive patients. People with such temperaments react intensely to stimuli in general and particularly to emotionally charged ones. They tend to have passionate love affairs, deeply felt disappointments, intense reactions to pleasure or frustration, deep artistic and religious

experiences, and powerful fits of anger when irritated. The escalation of anger from initial irritation to outright rage typifies their reactive processes under stress or emotional stimuli. Their temperamental energy intensifies their emotions, and the emotions fire their energy. The authors' hypothesis is the following: when a sad or stressful event provokes a depressive reaction, or a seasonal or endogenous depression occurs in such a person, the psychic reaction is intense and exacerbates the depression itself. In turn, the emotional reaction heightens and unleashes this energy, which produces manic symptoms, such as restlessness and racing thoughts, while it also triggers anxiety and aggravates the depressive psychic pain. This tight interweaving of manic traits and depressive states of agitated depression makes it an authentic mixed state.

The nature and definition of agitated depression

Agitated depression should not be considered a depressive syndrome in which some manic or hypomanic symptoms coexist. No such symptoms can be present in agitated depression or in agitated mixed states in general. They are certainly symptoms of an excitatory nature, but there is nothing manic or hypomanic in depressive mixed states if we accept expansiveness as the essential feature of mania or hypomania. The cardinal symptom of agitated depression is psychic agitation with or without motor agitation and this agitation torments the patient and inhibits every activity and every pleasure. Even the racing thoughts are very different from the manic flight of ideas. The flight of ideas is expressed in speech and even facilitates, together with expanded emotion, literary creativity. Racing thoughts of agitated depression are not verbalized and are very tormenting to the point that some patients wish to die just to stop them. Kraepelin's conception of mixed states was the coexistence of manic and depressive symptoms. Nevertheless, in all the forms of agitated depression he described, from melancholia activa of 1883 to the evolutional melancholia and the excited depression of 1913, he emphasized the inner motor agitation of the patient. Since psychic agitation is very intense also in patients with motor agitation and even in psychotic agitated depression there is often a tormenting, inner agitation, it should be considered as the fundamental symptom of all these depressive mixed states.

But what is this agitation from the psychopathological point of view? Kraepelin and all the authors at the turn of the nineteenth century defined it with the term *anxiety*, *Angst*. On the other hand, agitation is synonymous with anxiety in lay and psychiatric language. Day reviews and highlights the ambiguities of the term *agitation* (Day, 1999). In the Hamilton scale for depression, psychic agitation has the meaning of psychic anxiety. Furthermore, patients suffering from agitated depression express their suffering in terms of anxiety and anxious fears. Patients,

however, specially endowed with powers of introspection describe a type of psychic agitation in a totally different way from anxiety. They describe it as an ominous force that agitates them and is more physical, more somatic, coming more from their body than from their psyche. They cannot cope with it. A woman explained her desire to die just in order to escape her body – she could not live inside it any longer. The old theme of black and darkness reappears. The same woman said that "everything was dark and I was in a very narrow dark place where I could not live. It was something physical, very physical," she insisted. Other patients describe it as a physical, tremendous energy that makes them feel like exploding, their heads or chests bursting or imploding. Often these painful sensations are felt in the epigastrium. Such an agitation cannot be caused by anything less than excitatory processes. Indeed, it calms down with typical or atypical neuroleptics and is exacerbated by antidepressants.

But why does it inhibit all mental activities? Probably because the excitation emerges in the midst of a major depression. One seems to be seeing the reaction of very energetic temperaments to the depressive event. People with such temperaments are overreactive in general to all environmental and psychic events. No event is more traumatic than depression. On the other hand, agitated depressions are often triggered by life events which may be more or less important but to which they react immediately in a disproportionate manner. In a certain sense, their reaction to antidepressants may also be viewed as disproportionate and it could be considered as an exaggerated neuronal reaction. This reaction is indeed not only very intense and dramatic to the patient but often manifests itself within hours of the first intake of the antidepressant drug. Equally dramatic and swift is also the benefit given by the appropriate sedative. We saw three cases where the agitated syndrome disappeared within 24 h after the intake of small doses of neuroleptics and benzodiazepines and another three after olanzapine. One day we will certainly have adequate means to measure neuronal activity and reactivity. Affective temperaments can be viewed as an overall expression of different degrees of nervous activity and reactivity.

That something permanently distinct exists in patients with agitated depression has been posited by many authors who propose that agitated depression is a distinct clinical entity. One of the arguments is that these patients have had in their lives other episodes of agitated or psychotic depression. This observation is correct. But these patients at other times have simple depressions or manias or hypomanias. It therefore clearly belongs to the manic-depressive spectrum, but certainly is distinct as a syndrome from simple major depression. Its peculiarity as a syndrome is the mixed nature of the phenomenology and the underlying pathology. What creates the permanent predisposition throughout life is the temperament of these patients together with their susceptibility to depression.

The temperamental reactions of all persons are often similar in type but they are not constant. Other factors contribute, such as life situation and age. Old age has often been recognized as the age at which agitated and anxious depressions are more frequent. Involutional melancholia is an atypical example. The relationship between affective disorders and age is certainly very complex. The perimenopausal years, for example, are a time of increased emotional lability and reactivity. The mean age at onset of agitated depression in our sample was 45.9 for men and 44.9 for women.

Diagnostic criteria of agitated depression

Full depressive syndrome and inner unrest are both essential elements of this syndrome. The presence of motor agitation is sufficient to make the diagnosis, as in the RDC criteria, because it also confirms the presence of psychic agitation. The absence of motor agitation creates the diagnostic problem of distinguishing anxiety from the particular inner unrest of agitated depression. In order to clarify the differential diagnosis between anxiety and inner agitation, pending more systematically validated criteria, we used a set of criteria different from that proposed in our previous paper (Koukopoulos, 1999). Along with major depression and inner agitation, at least three of the following symptoms must be present:

(1) racing or crowded thoughts
(2) irritability or an unprovoked feeling of rage
(3) absence of signs of retardation
(4) talkativeness
(5) dramatic descriptions of suffering or frequent spells of weeping
(6) mood lability and marked emotional reactivity
(7) early insomnia

Such symptoms are of an excitatory, not depressive, nature and indicate the absence of inhibition. Early insomnia is often sustained by racing or crowded thoughts. These criteria were, however, validated by the external criterion of the effect of antidepressant treatments. A total of 113 cases had simple depressions that became agitated (with at least three of the above symptoms) when treated with antidepressants.

Patients and method

During the years 1990–1999 we have examined and treated 212 (152 women; 72%) patients suffering from agitated depression as defined above. All met DSM-IIIR criteria for major depression. Sixty-seven cases presented with agitated depression (non-psychotic) with psychomotor agitation. The others suffered from minor agitated depression (77 cases), as defined above, and psychotic agitated depression (68 cases). Transient agitated depressive states were not included. A minimum of

Table 7.2 Nosologic diagnosis of 212 patients according to sex and polarity

	Male	Female	Total	%
Bipolar I	20	36	56	27
Bipolar II	15	51	66	31
Unipolar depression	12	56	68	32
MxD	14	8	22	10

MxD, first episode of agitated (mixed) depression.

2 weeks' duration was required. All these patients were examined, evaluated, and treated by the authors at the Centro Lucio Bini in Rome. The previous course of the disorder, treatments, and present condition were evaluated with all available medical records and with the cooperation of at least one family member. Table 7.2 shows the distribution of these patients by gender and polarity of their previous course; the age at first affective episode was 31.9 for women and 37.6 for men; the age at index episode of agitated depression was 44.9 for women and 44.5 for men. One hundred and eleven patients had had earlier episodes of agitated depression. The age at onset of the first episode of agitated depression as first affective episode was 44.5 years.

The mean Hamilton-D score was 23.8 (range 14–39) for all patients; 27.2 (range 17–39) for patients with psychotic agitated depression; 25.3 (range 16–36) for cases with agitated depression (non-psychotic) with psychomotor agitation; and 20.0 (range 14–32) for patients with minor agitated depression.

The mean duration of the episodes of agitated depression was 4.6 months (range 1–48 months).

Spontaneous and induced agitated depression

The episode started as an agitated depression in 99 (47%) cases. In the other 113 (53%) cases, the episode started as a simple depression without symptoms of agitation, and later it turned into an agitated depression. The mean duration of the simple depression was 4.7 months (1–36 months). The shift from simple to agitated depression occurred in association with various treatments, mainly antidepressants, but also other treatments with stimulant effect (Table 7.3). The onset of agitated depression took place either immediately or within a few days to a few weeks. The great majority of agitated depressions emerged during treatment with tricyclic antidepressants (58 cases), selective serotonin reuptake inhibitors (45 cases), other antidepressants (27 cases), and seven cases during maintenance treatment with antidepressants. The small number of cases (four) associated with monoamine oxidise inhibitors is probably due to the limited use of these

Table 7.3 Treatments associated with onset of agitated depression

Tricyclic antidepressants	58
Selective serotonin uptake inhibitors	45
Monoamine oxidase inhibitors	4
Other antidepressants	27
Steroids	6
Levothyroxine	4
Caffeine	4
Lithium withdrawal	4
Neuroleptic withdrawal	2
Maintenance antidepressants	7

agents in Italy, but the possibility that these agents may be less agitating cannot be ruled out. Six cases were associated with steroids, four with levothyroxine, four with excessive caffeine intake, four with lithium withdrawal, and two with neuroleptic withdrawal. Eighty-three women (55% of all women) and 30 men (50% of all men) became agitated in association with the above-mentioned treatments. The previous course of these 113 patients was: bipolar I (BP) for 27 patients, BP-II for 47 patients, unipolar depression for 34 patients and five were first affective episodes. If we compare them to the total numbers of the different groups, we find that 48% of the BP-I, 71% of the BP-II, and 50% of the unipolar patients had induced agitated depressions. The preponderance of BP-II patients is to be noted. The age at onset of the mixed episode was 48.4 years for the induced group and 41.7 years for the spontaneous group. The duration of the mixed episode was 4 months for the induced group and 5.4 months for the spontaneous group. There was no difference between the spontaneous and induced groups with regard to severity or outcome.

Among our 212 agitated depressions, 68 (47 women and 21 men) also had psychotic symptoms. As psychotic symptoms we considered hallucinations, delusions, both congruent and non-congruent (true delusions and not mere fears or doubts), and the presence of a state of mental confusion and grossly disturbed behavior. Of these patients, 22 (32%) were spontaneous, i.e., the psychotic symptoms emerged spontaneously and not in association with pharmacological treatment. In the other 46 patients, the psychotic symptoms emerged in association with antidepressant treatment. Of these 46 patients, 30 patients had a BP-I course (54% of all BP-I patients), 14 had a course of BP-II (21% of all BP-II patients), 19 had a previous course of recurrent depression (28% of all unipolar patients), and five were first affective episodes of psychotic depression. It should be underlined that all the 14 BP-II patients who had a psychotic agitated depression were induced by antidepressants.

Latent agitated depression

There are cases of depression that, though without manifest psychic or motor agitation and not delusional, rapidly become agitated after the institution of antidepressant drug treatment. All antidepressants can induce this effect in certain patients but the most rapid triggering is seen with selective serotonin reuptake inhibitors. Probably the cases of suicidal or other violent acts attributed to selective serotonin reuptake inhibitors in recent years may be due to the agitation induced by the drugs in patients who were already agitated or prone to agitation, and not due to adverse pharmacological reactions. Reading the clinical descriptions of these cases, it is clear that the suicidal ideas have emerged from a state of agitated depression (Teicher *et al.*, 1990; Healy, 1994), the psychomotor component of which is often seen as akathisia (Drake and Ehrlich, 1985). We propose the term *latent agitated depression* for these depressions prone to agitation. How can they be identified? According to our observations, the most reliable signs are:

1. total lack of inhibition in speech and movement
2. rich description of their depressive suffering
3. early or middle insomnia rather than late insomnia

These signs are not of absolute value but may suffice to suspect a latent agitated depression and make one more cautious with treatment. One should start with an antimanic, antianxiety medication, or, if antidepressants are used in the beginning, a sedative should be added. In any case, sedative treatment is the best protection against suicide, as Fawcett *et al.* (1993) emphasize.

Treatment

In the majority of our depressed patients, the emergence of psychotic features, motor agitation, or intense psychic agitation was associated with antidepressant treatments or was exacerbated by them. The basic rule for their treatment, therefore, was to suspend antidepressants if they were being administered or not to administer them until psychotic symptoms and agitation had subsided. The best results are obtained by initiating treatment with old or new neuroleptics, benzodiazepines, anticonvulsants, and lithium. Perhaps the most rapid effect is achieved by a combination of neuroleptics and benzodiazepines. Haloperidol and clonazepam are equally effective. In cases of minor agitated depression, even lower doses of haloperidol and clonazepam, such as 2 mg, may be effective in as little as 48 h. In more resistant cases, higher doses are required. ECT is rapidly effective. Table 7.4 shows the treatments given to the patients who fully recovered.

Table 7.4 Treatments associated with full improvement of mixed depression episodes ($n = 120$)

Electroconvulsive therapy	51
Neuroleptic	40
Antiepileptics	40
Lithium	38
Olanzapine	22
Benzodiazepines	30

Outcome

One hundred and twenty patients (57%) fully recovered. Forty-two patients (20%) showed partial improvement demonstrated by a mean Hamilton-D score of 11 (range 9–15). Fifty (23%) patients did not improve significantly and four of these patients committed suicide.

Treatment with olanzapine

We have found olanzapine to be particularly effective in the treatment of agitated depression. Thirty-three patients were treated with olanzapine at a mean daily dose of 5.5 mg (range 2.5–15 mg). Twenty-two patients (67%) recovered fully, five (15%) recovered partially, and six (18%) did not improve. The therapeutic delay of olanzapine was short, with a mean of 7.65 days (range 1–30 days; SD = 6.67). Three cases improved substantially within 24 h.

Olanzapine was administered alone in nine cases. In the remaining cases benziodiazepines or anticonvulsants were added. Our observations about the effectiveness and speed of action of olanzapine in similar cases confirm earlier reports (Parker, 2002). Parker and Malhi (2001) advance the hypothesis that atypical antipsychotics may have an antidepressant effect, particularly in treatment-resistant melancholic depression, and suggest the term *atypical anti-depressants*. We maintain, as explained above, that the antidepressant effect is due to the antimanic action of these agents in cases of depression of a mixed nature.

Agitated depression followed by simple depression

In many cases the resolution of the psychic agitation also swiftly brings to an end the depressive symptoms. In other cases, especially those with motor agitation or psychotic features, a phase of simple, more or less inhibited depression follows.

This has also been observed by other authors (Glassman *et al.*, 1975; Spiker *et al.*, 1985). We treated this pure depressive phase with antidepressant drugs. In this pure depressive phase, any antidepressant treatment may be effective. The traditional amitriptylin seems the most suitable because it is the least likely to trigger agitation. In our view the mixed depressive phase followed by a simple depression corresponds to the pattern of manic-depressive cycle starting with mania and followed by depression. There, too, the manic phase is treated with antimanic agents and the depression is susceptible only to antidepressant treatments. Agitated depression was followed by simple depression in 64 cases (30%). In their previous course, these patients were bipolar I ($n = 20$), bipolar II ($n = 17$), unipolar depression ($n = 22$), and five cases were first episode agitated depression. We hold that it is no coincidence that 28% of bipolar patients present the same cycle pattern consisting of mania followed by depression, which in most cases is of a simple or clearly inhibited type (Kukopoulos *et al.*, 1980).

Many clinicians, on an empirical basis, have always treated these patients first with neuroleptics and then with antidepressants and many authors, starting with Klein and Davis (1969), have recommended this line of treatment. ECT is even more effective in mixed depressive states than in non-mixed depressions. The less frequent use of ECT in recent years (in Italy, unfortunately, for political and not medical reasons), coupled with the widespread use of antidepressants, has worsened the condition of these seriously ill patients, who often suffer longer duration of episodes, longer hospitalization, and higher risk of suicide.

It may be argued that the treatment of the agitated phase with neuroleptics and other antimanic agents favors the onset of a depressive phase, but this is also true for the typical mania–depression cycle where it is clear that neuroleptics only accentuate the natural evolution of the manic–depressive cycle, i.e., the depression, more or less severe, that follows the manic phase. ECT, with its antidepressant and antimanic action and its particular effectiveness in mixed depressive states, had cloaked the essential difference between mixed and simple depression. But as far as response to treatment is concerned, the same thing happened with the frequently biphasic course of agitated and psychotic depression. Glassman *et al.* (1975) made the first observation of a simple depression following a psychotic depression after neuroleptic treatment in 1975, though their interpretation was different from ours. ECT sweeps away mixed and simple depression in the course of the same series of sessions, and this is conceivable. But what reveals the singular nature of mixed depressive states is the fact that, often, after one to three ECT sessions, the whole syndrome resolves abruptly. We have seen complete recovery after only one ECT. This outcome seems analogous to that obtained in milder cases after a few days of neuroleptic–benzodiazepine treatment and especially with olanzapine treatment. This rapid response is hard to explain but it demonstrates that

excitatory and depressive phenomena do not simply coexist but are interdependent in their emergence and evolution, and are probably caused by the same pathophysiological alteration. An additional explanation could be that, once the excitatory phenomena have subsided, the highly energetic temperament of these patients quickly overrides the depression, obviating the need for antidepressant treatment. In other cases depression sets in and antidepressant treatment is necessary for weeks or months. This biphasic evolution of many cases of agitated depression may be the basis of the doubts and hesitations of many clinicians about its treatment (Erfurth *et al.*, 2001).

Conclusions

Agitated depression should be considered a mixed affective state given its phenomenology and response to treatments. Antidepressants worsen the condition of these patients and, in many cases, induce agitation or psychosis in cases with otherwise simple depression. The authors propose new diagnostic criteria for agitated depression and introduce the term *minor agitated depression* for the cases with psychic agitation without motor agitation or psychotic symptoms. Three forms of agitated depression (mixed depression) are described: (1) psychotic agitated depression; (2) agitated depression with psychomotor agitation; and (3) minor agitated depression. All these forms may be induced or aggravated by antidepressants and improve with mood-stabilizing and antipsychotic treatments, as well as ECT.

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8

Schizoaffective mixed states

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Introduction

Hardly any studies on schizoaffective mixed states exists. However, an exception is the Cologne study carried out by Marneros *et al*. in the 1980s and 1990s (Marneros *et al*., 1991). The rarity of research on schizoaffective mixed states is, on the one hand, a paradox, but on the other hand, an understandable phenomenon. Why a paradox? There are two reasons: first, while schizoaffective disorders are well established as diagnostic categories in both *Tenth Revision of the International Classification of Diseases* (ICD-10: World Health Organization, 1991) and *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV: American Psychiatric Association, 1994), it has also been determined that schizoaffective disorders have to be divided according to their mood component into unipolar and bipolar types, a fact that implicates the occurrence of schizoaffective mixed states (American Psychiatric Association, 1994; Marneros *et al*., 1989a–c; 1990a, b; 1991; Marneros and Angst, 2000). Second, both diagnostic systems, ICD-10 and DSM-IV, define a schizoaffective mixed episode, as shown in Tables 8.1 and 8.2. Therefore, it is to be expected that clinicians and researchers applying either ICD-10 or DSM-IV criteria diagnose *schizoaffective mixed episode*. But neither clinical nor practical experience, as well as a study of the literature, supports such an assumption.

Then, why do these obvious deficits seem understandable? Mainly due to two reasons: first, the definition of schizoaffective disorders is – in spite of their long history and clinical reality – still diffuse and uncertain. Second, the clinical and psychopathological picture of schizoaffective mixed states is difficult for non-specialized physicians to detect.

In such cases, schizophrenic, manic, and depressive symptoms form a rather unclear and diffuse conglomerate – sometimes dominated by schizophrenic symptoms, sometimes dominated by affective symptoms, each in a varying way. Sometimes the depressive symptomatology is very strong, hiding manic elements,

Table 8.1 Schizoaffective disorders (F25) according to *Tenth Revision of the International Classification of Diseases* (ICD-10: World Health Organization, 1991)

G1. The disorder meets the criteria of one of the affective disorders (F30., F31., F32.) of moderate or severe degree, as specified for each category
G2. Symptoms from at least one of the groups listed below must be clearly present for most of the time during a period of at least 2 weeks (these groups are almost the same as for schizophrenia (F20.0–F20.3))
G3. Criteria G1 and G2 above must be met within the same episode of the disorder, and concurrently for at least part of the episode. Symptoms from both G1 and G2 must be prominent in the clinical picture
G4. Most commonly used exclusion clause. The disorder is not attributable to organic mental disorder (in the sense of F00–F09), or to psychoactive substance-related intoxication, dependence, or withdrawal (F10–F19)

Table 8.2 Diagnostic criteria for 295.70 schizoaffective disorder *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV: American Psychiatric Association, 1994)

A. An uninterrupted period of illness during which, at some time, there is a major depressive episode, a manic episode, or a mixed episode concurrent with symptoms that meet criterion A for schizophrenia. Note: The major depressive episode must include criterion A1: depressed mood
B. During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms
C. Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness
D. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition
Specify type:
Bipolar type: If the disturbance includes a manic or a mixed episode (or a manic or a mixed episode and major depressive episodes)
Depressive type: if the disturbance only includes major depressive episodes

and sometimes the reverse is the case. The ability to diagnose a *schizoaffective mixed episode* needs much more experience and training than required to diagnose an affective mixed episode, which is also much more difficult to determine than a pure manic or pure depressive episode.

Developments of the definition of schizoaffective disorders

Perhaps the paradox of the extremely rare research on schizoaffective mixed states can be better understood when one considers the development of the definitions,

concepts, and nosological allocations of schizoaffective disorders. The information that follows provides a summary of this development.

The term "schizoaffective" was introduced in 1933 by the American psychiatrist John Kasanin in his paper "The acute schizoaffective psychoses", published in the *American Journal of Psychiatry*, originally presented at the American Psychiatric Association annual meeting in Philadelphia the previous year (Kasanin, 1933). But descriptions of what was later called schizoaffective disorder are much older. Perhaps the German psychiatrist Karl Kahlbaum can be considered the first psychiatrist in modern times to describe schizoaffective disorders as a separate group in *vesania typica circularis* (1863). Kahlbaum applied cross-sectional and longitudinal aspects. Later, Kraepelin recognized a "great number" of cases having the characteristics of both groups of psychoses, dementia praecox and manic-depressive insanity. He also recognized the existence of such cases, which seriously challenged the clear dichotomy between schizophrenia and mood disorders (Kraepelin, 1920; see also Marneros and Angst, 2000). Such cases were also recognized by Kurt Schneider, who distinguished between concurrent and sequential types and called them "cases-in-between" (*Zwischen-Fälle*) (Schneider, 1959). But John Kasanin gave these "cases-in-between" their present name, although the cases described by him are only partly related to what we today define as schizoaffective disorder. ICD-9 defined *schizoaffective psychosis* (295.7) as a psychosis in which conspicuous manic or depressive symptoms are mixed with schizophrenic symptoms (World Health Organization, 1968). The diagnosis can only be made when affective and schizophrenic symptoms are prominent. How unclear this ICD-9 was can be demonstrated by its synonyms: amongst others, one finds terms such as "cycloid psychoses" or "schizophreniform psychoses, affective type," which are nowadays seen as fundamentally different syndromes (Perris, 1986; Pichot, 1986; Strömgren, 1986; Marneros and Pillmann, 2004).

What we presently define as schizoaffective disorders (for example, the definitions provided by the World Health Organization (ICD-8, 1968; ICD-10, 1991) or American Psychiatric Association (DSM-IV, 1994), as well as empirical definitions (Marneros *et al.*, 1986), is much more strongly related to Kurt Schneider's "cases-in-between" than to Kasanin's "schizoaffective psychoses."

Pierre Pichot, who analyzed Kasanin's concept, observed (1986) that Kasanin's paper contained three main chapters:

1. General considerations are presented regarding the alleged pessimism of the Kraepelinian nosology and the specificity of American psychiatry, with Adolf Meyer's teachings and the psychoanalytic approach being particularly emphasized. Kasanin then suggests the separation (from the "nuclear constitutional cases" of schizophrenia) of a subgroup of patients defined by special criteria, probably etiologically related to emotional conflicts of a mainly sexual nature. This, in turn, prompts him to suggest that "psycho-therapy is strongly

indicated, and [that] a thorough analytic procedure would be in the best interest of the patient if one wishes to prevent the recurrence of such attacks."

2. A synthetic description of schizoaffective psychoses is introduced based on nine cases, which can be summarized into four points:

   (a) "The patients are between twenty and thirty . . . in excellent physical health." The personality "is not very much different from the general run of people in the community," and the "social and industrial adjustment" is normal.
   (b) There is "definite and specific environmental stress," although some of the cases reported by Kasanin are not very convincing in this respect.
   (c) There is "a very sudden onset in a setting of emotional turmoil, with a distortion of the outside world and presence of false sensory impressions in some cases." The symptomatology is made up of "a blending of schizophrenic and affective symptoms." "Absence of passivity and of withdrawal are good prognostic features."
   (d) "The cases presented describe a single episode with a return to a perfectly normal adjustment." Kasanin states that "there is usually a vague history of a previous breakdown" and that "these psychoses tend to repeat themselves."

3. Detailed observations of five of the nine cases are presented. The literature quoted by Kasanin in support of his concept includes classical references to Kraepelin, Bleuler, Lange, and four American papers. In particular, two contributions by Dunton, who, in 1910 had described a "cyclic (or intermittent) form of *dementia praecox*" were quoted, as well as two French papers by Henri Claude "in which concepts of *schizomanie*, *schizophrenie*, and *demence précoce* are discussed" (Pichot, 1986).

The history of the development of the concepts of the schizoaffective disorders was already described by Maj (1984), Marneros and Tsuang (1986), and Marneros (1999, 2001). As Pichot (1986) pointed out, the official American history of the disorder "schizoaffective" can be followed in the successive editions of DSM from the American Psychiatric Association. DSM-I (American Psychiatric Association, 1952) describes, among the "schizophrenic reactions," their "schizo-affective type." The criteria used in DSM-I are different from Kasanin's original description. No mention is made of sudden onset, shortness of episode, or complete recovery.

DSM-II (American Psychiatric Association, 1968) included the category "schizophrenia, schizoaffective type." The definition, however, had become brief and noncommittal: "Patients showing a mixture of schizophrenic symptoms and pronounced elation and depression." ICD-8, published in the same year, contained the same category (World Health Organization, 1968).

In 1978, the Task Force on Nomenclature and Classification of the American Psychiatric Association published the draft of DSM-III (American Psychiatric Association, 1978). It included a special category, schizoaffective disorders, which

was completely distinct from schizophrenic disorders. The criteria proposed as essential were "a depressive or manic syndrome ... that preceded or developed concurrently with certain psychotic symptoms thought to be incompatible with a purely affective disorder." The DSM-III draft stated, "[t]he term schizoaffective has been used in many different ways ... at the present time there is a controversy as to whether this disorder represents a variant of Affective Disorder of Schizophrenia, a third independent nosological entity, or part of a continuum between pure Affective Disorder and pure Schizophrenia." The separate listing is justified by "the accumulated evidence that individuals with a mixture of 'affective' and 'schizophrenic' symptoms, as compared with individuals diagnosed as having schizophrenia, have a better prognosis, a tendency towards acute onset and resolution, more likely recovery to [a] premorbid level of functioning, and an absence of an increase of prevalence of schizophrenia among family members."

Two years later, in the final printed edition of DSM-III (APA, 1980), the category had practically disappeared. The manic episode and the major depressive episode now included cases "with mood-incongruent psychotic features" which, in the draft, would have belonged to the schizoaffective disorders. It is true that DSM-III has formally retained a category called schizoaffective disorders but, being without diagnostic criteria, it was considered a residual class "for those instances in which the clinician is unable to make a differential diagnosis between Affective Disorders and either Schizophreniform Disorder or Schizophrenia."

A new category, schizophreniform disorder, appears. As Pichot (1986) pointed out, this category is very similar to Kasanin's original schizoaffective psychosis as far as the evolution is concerned: "The duration ... is less than six months ... [there is] a tendency towards acute onset and resolution ... [and] recovery to premorbid levels of functioning," but the symptomatic criteria are those of schizophrenia, with the exception of "a greater likelihood of emotional turmoil and confusion." No mention is made of affective symptoms (Pichot, 1986).

In DSM-III-R (American Psychiatric Association, 1987), schizoaffective disorders were reborn – this time classified independently from both schizophrenia and affective disorders in the category "psychotic disorders not elsewhere classified" and with their own diagnostic criteria, as well as with subtypes, namely bipolar type and depressive type. In DSM-IV, published in 1994, schizoaffective disorders belonged to the category "other psychotic disorders" with almost the same diagnostic criteria and the same subtypes as in DSM-III-R. This time, the mixed bipolar symptomatology was recognized as well.

ICD-9 continued the tradition of ICD-8. In ICD-10, after bouncing around like a ping-pong ball during successive draft publications, schizoaffective disorders landed in a category of their own within schizophrenia and delusional disorders, with an extensive description, as well as with five subcategories:

(1) schizoaffective disorders, at the present manic
(2) schizoaffective disorders, at the present depressive
(3) mixed schizoaffective disorder
(4) other schizoaffective disorders
(5) schizoaffective disorders not otherwise specified

The evolution of the concept and definitions of schizoaffective disorders continues. Many aspects remain to be clarified, and many questions still require answers. Most diagnostic systems only recognized the concurrent form of schizoaffective disorders, not the sequential one. But operational research showed no differences in any investigated dimension between concurrent and sequential schizoaffective disorders (Marneros *et al.*, 1986; 1988a–c; 1991).

As we previously pointed out (Marneros, 1999), the ongoing evolution of concepts and definitions of schizoaffective disorder lead to enduring uncertainty. The question: What are the schizoaffective disorders? remains unanswered, which is also a reason why only meager research results exist in the complicated field of schizoaffective mixed states.

Current research in schizoaffective mixed states

Schizoaffective mixed states in the Cologne study

As mentioned above, for the most part, systematic research on schizoaffective mixed states has not been published. An exception is research performed as a part of the Cologne study (1986–1991). The Cologne study, which is a longitudinal study comparing schizophrenic, affective, and schizoaffective disorders, has been published in several presentations and in a monograph, which also includes an extensive English summary (Marneros *et al.*, 1991). A total of 402 patients were followed-up for an average of 25 years after the onset of their illness. The diagnoses, obtained longitudinally, were as follows: schizophrenic disorders ($n = 148$), schizoaffective disorders ($n = 101$), affective (mood) disorders ($n = 106$).

A distinction was made between "episode" (which is only a cross-sectional diagnosis) and "illness" or "disorder" (which are longitudinal diagnoses). The "episodes" (cross-sectionally defined) were classified according to slightly modified DSM criteria into schizophrenic, affective (depressive, manic, manic-depressive mixed), schizoaffective (schizodepressive, schizomanic, schizomanic-depressive mixed) and non-characteristic episodes.

The diagnoses of an "illness" or "disorder" were made only longitudinally and took into account all types of episodes occurring during the whole course. The final diagnoses were longitudinally defined as follows:

- schizophrenic disorders: only schizophrenic episodes during the whole course
- affective (mood) disorders: only depressive, manic, or manic-depressive mixed episodes during the whole course

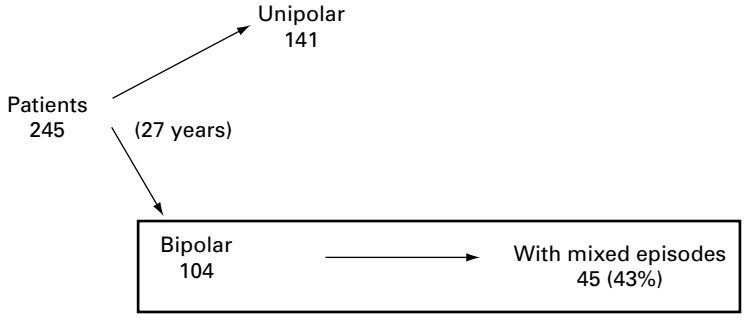

Fig. 8.1 Frequency of mixed episodes in bipolar patients in the Cologne study.

- schizoaffective disorders:
  a. at least one schizoaffective episode within the course (schizodepressive, schizomanic, schizomanic-depressive mixed episode)
  b. all sequential manifestations of schizophrenic and affective episodes, independent of the type and number of other episodes

This definition has been proved empirically. No differences concerning investigated levels were found (Marneros *et al.*, 1991).

Mood, schizoaffective, and schizophrenic disorders were compared longitudinally (average follow-up 25.1 years from onset). Both mood and schizoaffective disorders were divided into bipolar and unipolar types, and they were investigated both as a voluminous group (bipolar affective and schizoaffective disorders as a single group), and individually (bipolar affective versus bipolar schizoaffective: Marneros *et al.*, 1989a–c; 1990a, b). The main results regarding mixed episodes in bipolar patients in the Cologne study can be summarized as follows.

At the end of the observation time (for patients with mood disorders, 27 years), 145 patients were classified as unipolar and 104 as bipolar. Of the bipolar patients, 43% showed at least one mixed episode (either affective or schizoaffective mixed episode; Fig. 8.1).

The 104 bipolar patients showed 685 episodes during the investigation period. One hundred and seventeen episodes (17%) were mixed bipolar episodes, affective and schizoaffective (Fig. 8.2).

Patients with mixed episodes were found to have the following characteristics:

- more frequently females
- more frequently a family history of affective disorders
- more and longer episodes
- more often a poorer long-term outcome

The syndromatological instability during course is interesting. Only 1% of the patients showed a monomorphous affective-mixed course, which means that during the whole course, only affective mixed episodes occurred. Four percent

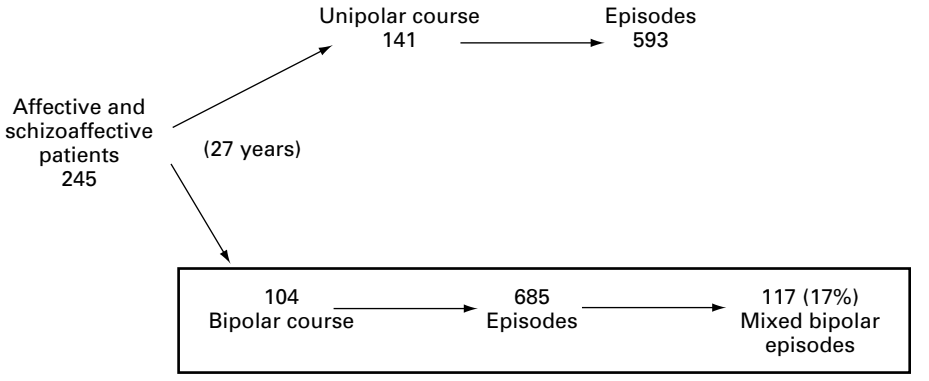

Fig. 8.2 Frequency of mixed episodes in bipolar patients in the Cologne study.

of the patients showed a course dominated by affective mixed episodes, which means that the majority of the episodes fulfill the criteria of affective mixed states. Similarly, only 1% of the bipolar patients had a monomorphous schizoaffective mixed course, which means that only schizoaffective mixed episodes occurred during the whole course. Four percent of the bipolar patients had a course dominated by schizoaffective mixed states, which means that the majority of episodes fulfill the criteria of schizoaffective mixed episodes.

The Halle Bipolarity Longitudinal Study

The Halle Bipolarity Longitudinal Study (HABILOS) (Marneros *et al.*, 2004) examines, amongst others, schizoaffective mixed states. The study population involved inpatients of the Department of Psychiatry and Psychotherapy of the Martin-Luther University Halle-Wittenberg, Germany. It is part of a voluminous Affectivity Project and involves all inpatients with manic, schizomanic, affective, and schizoaffective mixed episodes treated between 1993 and 2000. The diagnostic criteria of the above-mentioned episodes were: ICD-10, DSM-IV criteria and, additionally for mixed states, Cincinnati (McElroy *et al.*, 1992) and Pisa criteria (Perugi *et al.*, 1997). The characteristics of the study population are given in Table 8.3.

All patients were first assessed as inpatients and later re-examined as outpatients (mean follow-up time: 5.1 years). Several instruments, which assessed psychopathology, illness history, personal history, disability, functioning, quality of life, and other constructs, were applied (Table 8.4).

Results

Characteristics of episodes

Episodes were defined according to ICD-10, DSM-IV, and Cincinnati criteria. Nevertheless, findings presented in this chapter regarding episodes are limited to

Table 8.3 Characteristics of the study population

Total number of patients	277
Female	135 (48.7%)
Age at first illness episode (mean, range)	32.3 years (13.0–66.2)
Age at the end of the follow-up period (mean, range)	47.9 years (20.6–90.1)
Duration of the illness (mean, range)	15.7 years (1.2–58.3)
Prospective period (mean, range)	5.1 years (1.0–9.7)
Total number of episodes	2119

Table 8.4 Instruments of the Halle Bipolarity Longitudinal Study (HABILOS)

Scope	Instrument
Axis I diagnosis DSM-IV	SCID-I (Wittchen *et al.*, 1997)
Axis II diagnosis DSM-IV	SCID-II (Fydrich *et al.*, 1997)
History of illness	Rating of episodes (Marneros *et al.*, 1991)
Medication	Documentation of medication (Marneros *et al.*, 1991)
Depressive symptoms	CDRS (Mason *et al.*, 1993)
Manic symptoms	BDI (Beck *et al.*, 1961)
	YMRS (Young *et al.*, 1978)
Psychotic symptoms	MSS (Krüger *et al.*, 1997)
Personality	PANSS (Kay *et al.*, 1987)
Temperament	NEO-FFI (Costa and McCrae, 1989)
Social biography	TEMPS-A Questionnaire (Akiskal *et al.*, 2002)
Premorbid functioning	SOBI (Marneros *et al.*, 1991)
Social disability	PAS (Cannon-Spoor *et al.*, 1982)
Social functioning	DAS-M (Jung *et al.*, 1989)
Global functioning	SOFAS (American Psychiatric Association, 1994)
Quality of life	GAS (Spitzer *et al.*, 1978)
	WHOQOL-Bref (WHOQOL Group, 1998)

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*; SCID-I, Structured Clinical Interview for DSM-IV (Axis I); CDRS, Cornell Dysthymia Rating Scale; BDI, Beck Depression Inventory; YMRS, Young Mania Rating Scale; MSS, Manie-Selbstbeurteilungsskala (English, SRMI – Self-Report-Mania Inventory); PANSS, Positive and Negative Syndrome Scale; NEO-FFI, Neo-Five Factor Inventory; TEMPS-A, Temperament Scale – Autoversion; SOBI, Sociobiographical Interview; PAS, Premorbid Adjustment Scale; DAS-M, Disability Assessment Schedule; SOFAS, Social and Occupational Functioning Assessment Scale; GAS, Global Assessment Scale; WHOQOL, WHO Quality of Life.

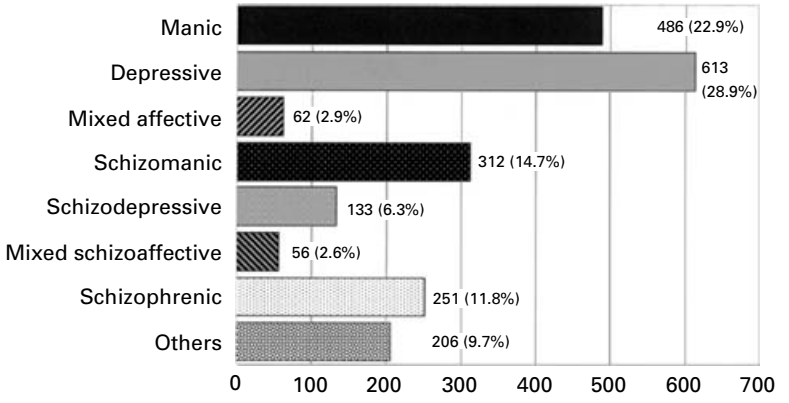

Fig. 8.3 Types of episode ($n = 2119$).

the ICD-10 definition. Out of the 2119 episodes evaluated, the most frequent type of episode was the depressive one ($n = 613$; 29% of all episodes). Mixed episodes were found to be the rarest type of episodes: there were only 118 affective and schizoaffective mixed episodes (ICD-10) (6%) and the frequency of mixed affective episodes ($n = 62$; 3%) was almost identical to that of mixed schizoaffective episodes ($n = 56$; 3%; Fig. 8.3).

These findings of HABILOS confirm the results from other studies that the most frequent type of episodes in bipolar disorders is the depressive type (Marneros and Brieger, 2002; Marneros *et al.*, 1990a, b; 1991; see chapter 2).

Interestingly, although the inclusion criterion for the study population was the presence of "bipolar episodes" (i.e., manic, schizomanic and mixed), 251 episodes (12%) fulfilled the ICD-10 criteria of a schizophrenic episode, in addition to the depressive and schizodepressive episodes. This is compatible with findings showing a syndromal instability in the course of bipolar disorder (Marneros *et al.*, 1990b; 1995; Marneros and Pillmann, 2004). This finding repeatedly demonstrates that ICD and DSM criteria of disorders not involving syndrome changes during longitudinal course are not sufficient to define "diseases." According to the longitudinal criteria proposed by Marneros *et al.* (1986, 1991), mood disorders with "syndrome shift" into schizophrenic syndromes and vice versa fulfill the criteria of the "sequential type" of schizoaffective disorders.

Duration of episodes

Based on methodological considerations, we decided to evaluate, as a first step, the length of episodes according to length of inpatient treatment. Obviously, this is not the real duration of an episode, but it certainly serves as an indicator for the real duration of an episode. Mixed episodes are, according to classical but also new

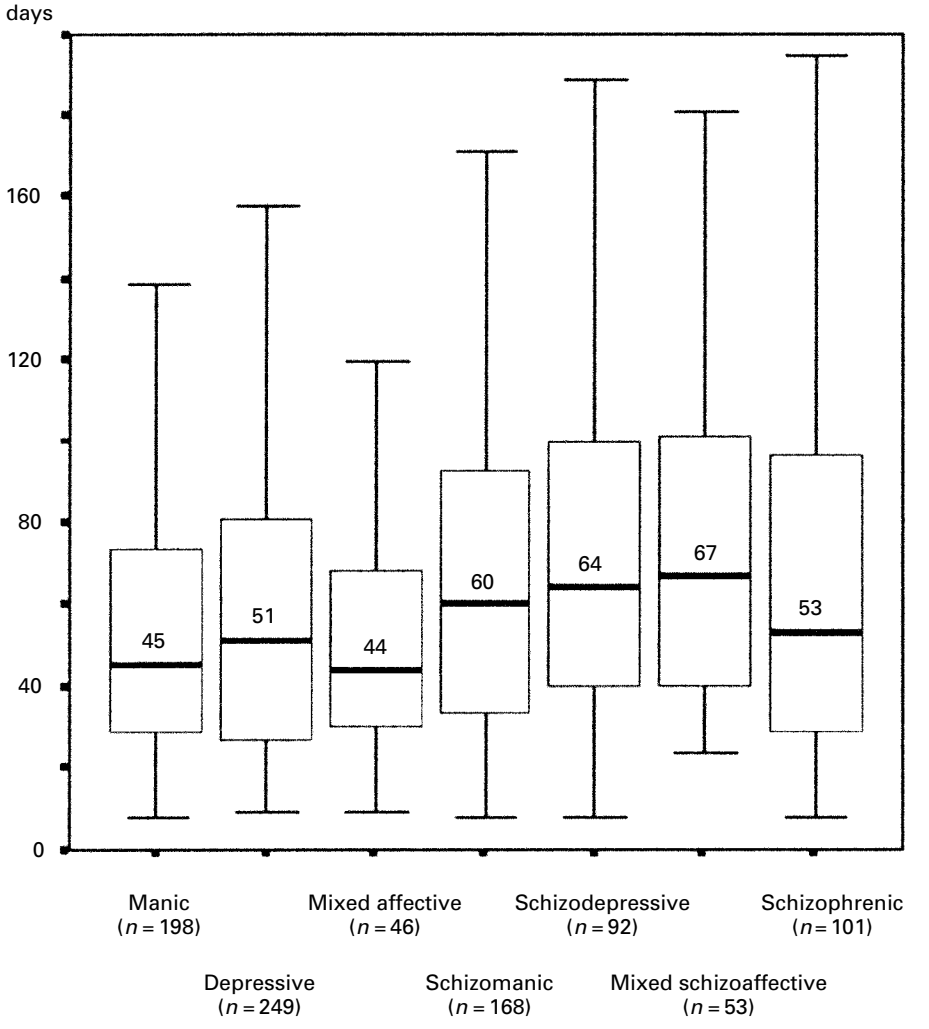

Fig. 8.4 Duration of episodes (length of hospitalization).

literature on the topic, the longest-lasting episodes (Kraepelin, 1899; Weygandt, 1899; Marneros *et al.*, 1991).

The findings of HABILOS showed no significant differences in episode length between different episode types (Fig. 8.4). On a purely descriptive level, the mixed schizoaffective episodes had the longest duration of all types of episode. Descriptively, mixed affective episodes had almost the same duration as pure manic episodes – the shortest of all. These findings are contrary to our previous findings (Marneros *et al.*, 1991). The explanation we have is that, while almost none of the patients with mixed episodes in the Cologne study received anticonvulsants as mood stabilizers, in contrast the vast majority of the HABILOS patients with mixed episodes received

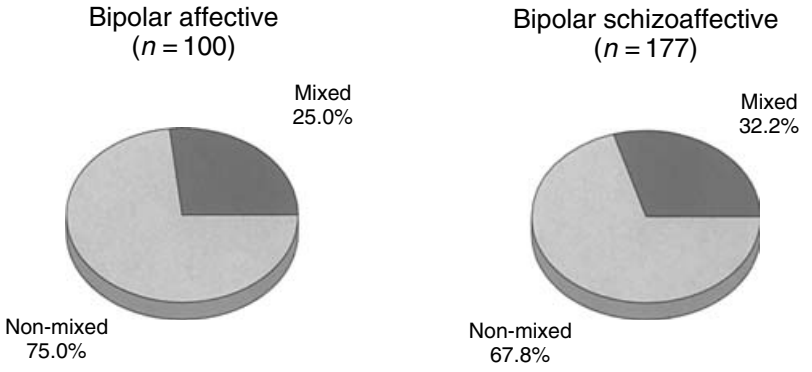

Fig. 8.5 Frequency of patients with at least one mixed episode.

anticonvulsants, especially valproate, carbamazepine, and lamotrigine. The positive response of mixed states to the above-mentioned mood stabilizer have been repeatedly documented (Calabrese *et al.*, 2000; see Chapter 3). Perhaps this is an effect of the new mood stabilizers. Additionally, none of the patients in the Cologne study received atypical neuroleptics because the study was closed before atypical neuroleptics were introduced, while almost all patients with mixed states of the HABILOS received atypical neuroleptics. The positive response of patients with mixed states to typical neuroleptics is also documented (Tohen, 2000; see chapter 16). Perhaps treatment with atypical neuroleptics or even a combination of novel neuroleptics with novel mood stabilizers, is another factor contributing to the shortness of episodes. Finally, one should not overemphasize these findings, as statistically the length of duration of treatment was identical for all episode types. More indepth analysis will be needed.

Frequency of patients having mixed episodes

Following the "empirical longitudinal diagnosis of schizoaffective disorder" (Marneros *et al.*, 1986, 1991), we were able to allocate all the HABILOS patients into two categories:

(1) bipolar affective patients, who had only affective episodes (depressive, manic, mixed) but no schizoaffective or schizophrenic episodes during the entire course of their illness
(2) bipolar schizoaffective patients, with at least one schizoaffective episode during the illness course, or when schizophrenic and affective episodes occured sequentially (see Chapter 1)

Applying this clinical and longitudinal classification, 100 patients were diagnosed as *bipolar affective* and 177 as *bipolar schizoaffective*. The high proportion of schizoaffective courses may reflect the specialization of our hospital in such disorders. As shown in Figure 8.5, 25% of the bipolar affective patients had at least

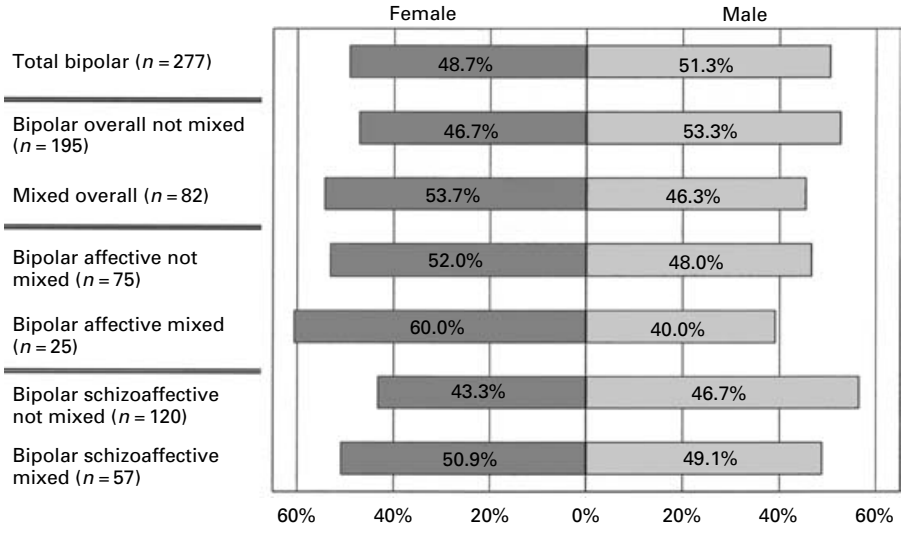

Fig. 8.6 Gender distribution.

one mixed episode, while 32.2% of the bipolar schizoaffective patients had at least one mixed episode (not statistically significant difference).

Gender distribution

The findings of the HABILOS confirmed the findings of former investigations, that females are overrepresented in the group of affective mixed states (McElroy *et al.*, 2000; Marneros *et al.*, 1991), although this difference did not reach significance. The overrepresentation of females in the group of mixed states, however, was only found in the group of pure affective mixed states, but not in that of schizoaffective mixed, where gender is almost equally represented. This is possibly a result of the impact of the schizophrenic symptomatology. It is well known that in schizophrenia the percentage of males is equal to that of females, if not higher. Taking into consideration that the gender distribution in the whole bipolar group of the HABILOS is almost equal – as was expected – we can conclude that the findings regarding the gender distribution in the subgroups (like mixed states) could also be assumed to be representative (Fig. 8.6).

Initial episode and first manifestation of a mixed episode

Only 14% of "schizoaffective patients" and 20% of "mixed pure affective patients" had a mixed initial episode (Table 8.5).

Mixed episodes can manifest any time during the course of the illness. Nevertheless, more than 40% of all patients with mixed episodes had their first mixed episode after the fourth illness episode (Fig. 8.7).

Table 8.5 Types of initial episode

	Bipolar affective disorders ($n = 100$)		Bipolar schizoaffective disorders ($n = 177$)	
	Non-mixed ($n = 75$)	Mixed ($n = 25$)	Non-mixed ($n = 120$)	Mixed ($n = 57$)
Manic	28 (37.3%)	6 (24.0%)	13 (10.8%)	2 (3.5%)
Depressive	45 (60.0%)	13 (52.0%)	25 (20.8%)	21 (36.8%)
Mixed affective		5 (20.0%)		
Schizomanic			29 (24.2%)	6 (10.5%)
Schizodepressive			7 (5.8%)	1 (1.8%)
Mixed schizoaffective				8 (14.0%)
Schizophrenic			41 (34.2%)	13 (22.8%)
Not exactly classifiable	2 (27%)	1 (4.0%)	5 (4.2%)	6 (10.5%)

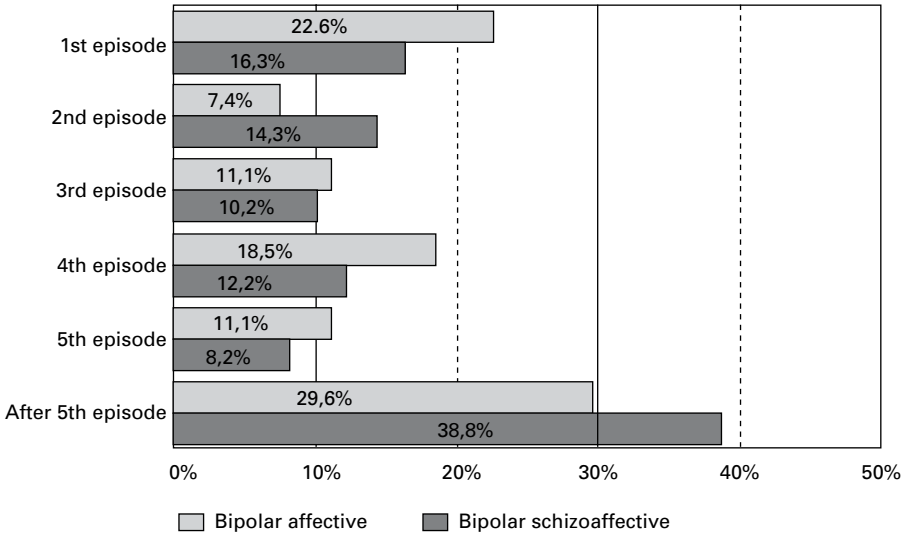

Fig. 8.7 Time of first manifestation of a mixed episode.

Disability pensions

In both groups – bipolar affective and bipolar schizoaffective disorders – patients having mixed episodes are overrepresented in receiving disability payments due to their illness. This is especially the case in the mixed schizoaffective group, with almost 60% of the patients receiving disability pensions. But also in the group of pure affective mixed episodes, a rate of 52% seems rather high. This means that patients with mixed schizoaffective episodes have a less favorable prognosis and more

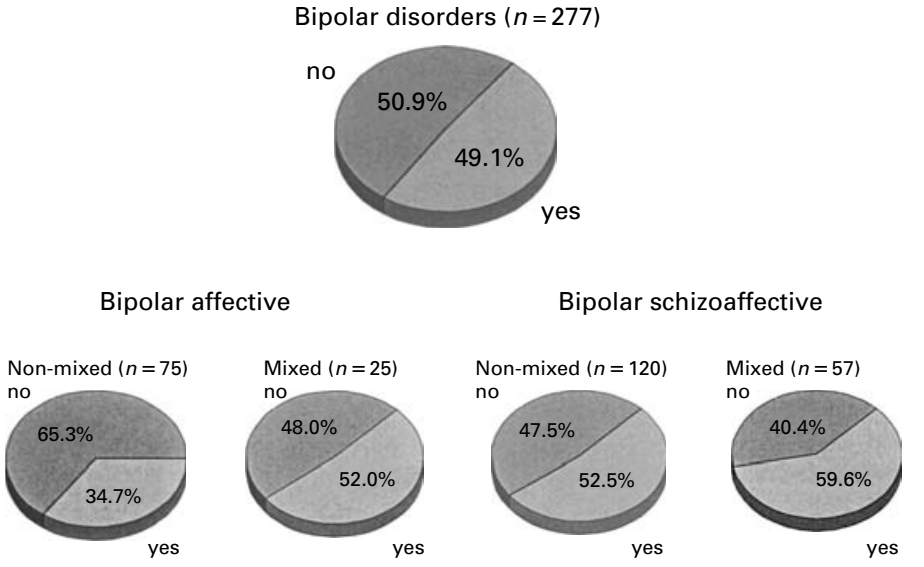

Fig. 8.8 Patients receiving disability pensions.

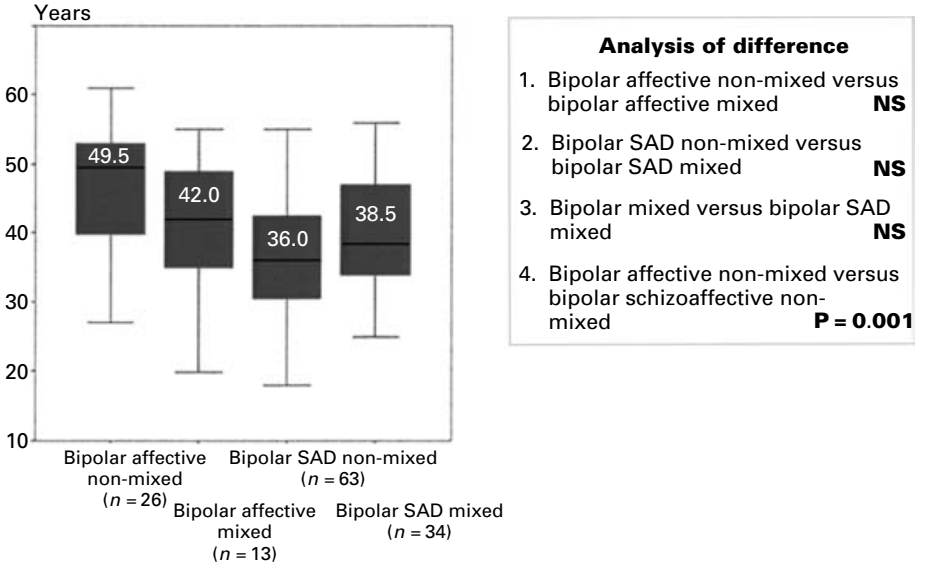

Fig. 8.9 Age when disability payments were first granted. NS, not significant; SAD, seasonal affective disorder.

disability. As Figure 8.8 shows, at the time of investigation, half of the patients with bipolar disorder were receiving disability pensions as a result of their mental illness.

In the group of schizoaffective mixed and non-mixed patients, disability pensions were granted at the age of approximately 36 years – a very low age.

In the state of Saxony-Anhalt (Germany), where this study was carried out, all disability payments were granted at a mean age of 50.2 years in 1999. According to the official statistics, the age when disability payments were granted for affective, schizophrenic, and other psychotic disorders, was 7.2 years (males) and 14.2 years (females) earlier than the mean age of 50.2 years. Therefore, schizoaffective patients and affective patients having mixed episodes were younger when their disability payments were granted than the controls (Fig. 8.9).

Conclusions

In spite of existing definitions and criteria for mixed schizoaffective episodes in both ICD-10 and DSM-IV, very little work on the topic has been carried out. The main reason is the uncertainty of how to define schizoaffective disorders and a still-ongoing evolution of their concepts. Perhaps another difficulty is the exact estimation of a very complicated symptomatology with schizophrenic, depressive, and manic components during a schizoaffective mixed episode. Nevertheless, the findings, both from the Cologne study and from the HABILOS, show that at a rate of more than 30%, the frequency of schizoaffective mixed episodes is high and equivalent to that in pure affective disorders.

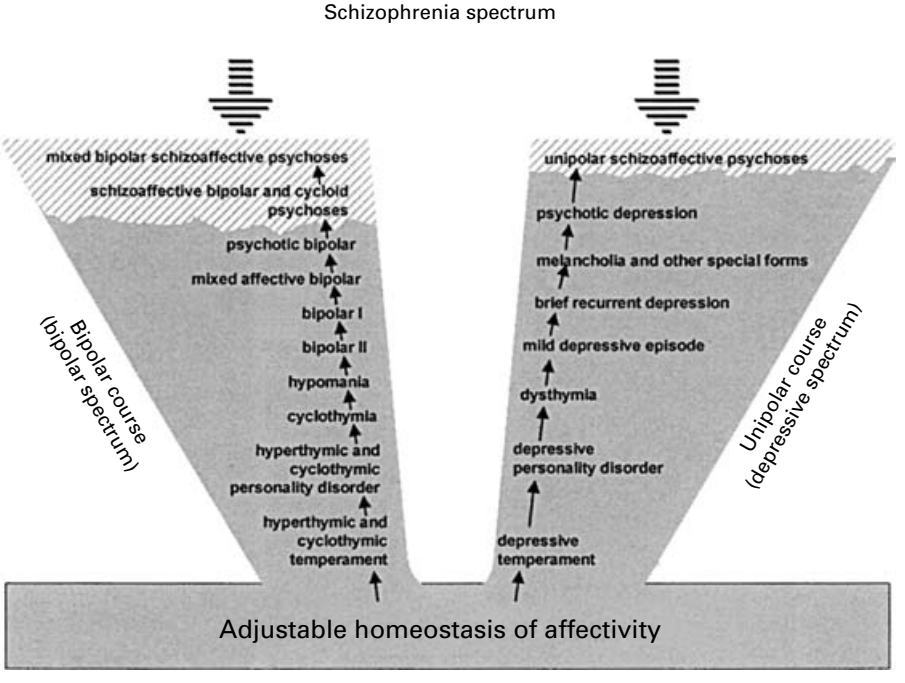

Fig. 8.10 The affective continuum.

There are many similarities between schizoaffective and affective mixed episodes, but also relevant differences: for example, there are no gender differences in patients having schizoaffective mixed episodes – perhaps a result of the impact of the schizo-element. The age at onset is lower, the duration of schizoaffective mixed episodes can be longer, and the patients having schizoaffective mixed episodes exhibited more inability to work at a younger age.

These results support the assumption that not only are schizoaffective mixed episodes frequent, but they also represent the most severe form of bipolar disorder standing on the top of a continuum – as we previously pointed out (Marneros, 1999, 2000), and as is illustrated in Figure 8.10.

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9

Acute and transient psychotic disorder: an atypical bipolar disorder?

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Introduction

Karl Kleist, the main creator of the concept of "cycloid psychoses," wrote in 1928 that many of the cases allocated by Kraepelin into the group of "mixed states" would better be described as "cycloid psychoses." In Kleist's opinion, cycloid psychoses are bipolar disorders, but do not belong to the category of manic-depressive insanity (Kleist, 1928, 1953). Cycloid psychoses are the essential component of what the World Health Organization (WHO, 1992) defined as "acute and transient psychotic disorder (ATPD)" (ICD-10 F23). We investigated the ATPD by carrying out the Halle Study on Brief and Acute Psychotic Disorder (HASBAP), which is a longitudinal comparative study (Marneros *et al.*, 2000, 2002; Pillmann *et al.*, 2001; 2002a, b; Marneros and Pillmann, 2004). The HASBAP compares patients with acute and transient psychotic disorders with patients diagnosed as having schizophrenia or bipolar schizoaffective disorder, as well as with a mentally healthy control group. In a further step, we now combine the findings of HASBAP with the findings of the Halle Bipolarity Longitudinal Study (HABILOS), already presented in Chapter 1. In this chapter, we longitudinally compare patients diagnosed as having ATPD from the HASBAP with patients diagnosed as having affective or schizoaffective mixed states belonging to the HABILOS group.

Definitions of acute and transient psychotic disorders

As ATPD (ICD-10 F23), the WHO defines psychotic states having an acute or abrupt onset, usually a good prognosis, and typical symptoms. They may or may not be associated with acute stress (Table 9.1).

Table 9.1 "Acute and transient psychotic disorders" according to ICD-10 (F23: World Health Organization, 1992)

G1. There is acute onset of delusions, hallucinations, incomprehensible or incoherent speech, or any combination of these. The time interval between the first appearance of any psychotic symptoms and the presentation of the fully developed disorder should not exceed 2 weeks
G2. If transient states of perplexity, misidentification, or impairment of attention and concentration are present, they do not fulfill the criteria for organically caused clouding of consciousness as specified for F05, criterion A
G3. The disorder does not meet the symptomatic criteria for manic episode (F30), depressive episode (F32), or recurrent depressive disorder (F33)
G4. There is insufficient evidence of recent psychoactive substance use to fulfill the criteria for intoxication (F1x.0), harmful use (F1x.1), dependence (F1x.2), or withdrawal states (F1x.3) and (F1x.4). The continued moderate and largely unchanged use of alcohol or drugs in amounts or with the frequency to which the individual is accustomed does not necessarily rule out the use of F23; this must be decided by clinical judgment and requirements of the research project in question
G5. Most commonly used exclusion clause. There must be no organic mental disorder (F00–F09) or serious metabolic disturbances affecting the central nervous system (this does not include childbirth). (The duration of the disorder must not exceed 3 months in subtypes F23.0, F23.3, and F23.8; it must not exceed 1 month in the subtypes F23.1 and F23.2, which include schizophrenic symptoms)

Acute onset

The acute onset is defined as the change from a non-psychotic to a clearly psychotic state within 2 weeks or less. The distinction between "abrupt" and "acute" onset is recommended because there is some evidence that the prognosis of ATPD with abrupt onset (less than 48h) could be more favorable.

Typical syndromes

The typical syndromes are first, the quickly changing and variable manifestations called "polymorphic," and second, the presence or lack of typical schizophrenic symptoms.

Acute stress

The association with acute stress follows the tradition of the "reactive" or "psychogenic" psychoses (Strömgren, 1986). Nevertheless, ATPD can be manifested without an association with acute stress, which makes its presence not decisive for the diagnosis.

Table 9.2 Subtypes of acute and transient psychotic disorder (World Health Organization, 1992) according to ICD-10

Acute polymorphic psychotic disorder
with symptoms of schizophrenia (F23.1)
without symptoms of schizophrenia (F23.0)
Acute schizophrenia-like psychotic disorder (F23.2)
Other acute predominantly delusional psychotic disorders (F23.3)
Other acute and transient psychotic disorder (F23.8)
Unspecified acute and transient psychotic disorder (F23.9)

Table 9.3 Acute polymorphic psychotic disorder without symptoms of schizophrenia

A. The general criteria for acute and transient psychotic disorders (F23) must be met
B. Symptoms change rapidly in both type and intensity from day to day or within the same day
C. Any type of either hallucinations or delusions occurs, for at least several hours, at any time from the onset of the disorder
D. Symptoms from at least two of the following categories occur at the same time:
• Emotional turmoil, characterized by intense feelings of happiness or ecstasy, or overwhelming anxiety or marked irritability
• Perplexity, or misidentification of people or places
• Increased or decreased motility, to a marked degree
E. If any of the symptoms listed for schizophrenia (F20.0–F20.3), criterion G(1) and (2), are present, they are present only for a minority of the time from the onset, i.e., criterion B of F23.1 is not fulfilled
F. The total duration of the disorder does not exceed 3 months

According to the WHO, a full remission can be achieved within 2 or 3 months, but often even after a few weeks or a few days. Nevertheless, some patients may develop persistent alterations. The present state of knowledge, however, does not allow for a definition of prognostic predictors.

The HASBAP shows that the ATPDs are mostly independent from associated acute stress. The factor "acute stress" does not have any defining, but also not any prognostic, value in regard to the long-term prognosis of ATPD (Marneros and Pillmann, 2004).

It is essential to note that the WHO defines some subgroups of ATPD, Table 9.2.

The most important group is that of the acute polymorphic psychotic disorder (Table 9.3). The majority of patients diagnosed as having ATPD fulfill the criteria

Table 9.4 Acute polymorphic psychotic disorder with symptoms of schizophrenia

A. Criteria A, B, C, and D of acute polymorphic psychotic disorder (F23.0) must be met.
B. Some of the symptoms for schizophrenia (F20.0–F20.3) must have been present for the majority of the time since the onset of the disorder, although the full criteria need not be met, i.e., at least one of the symptoms in criteria G1(1)a to G1(2)c
C. The symptoms of schizophrenia in criterion B above do not persist for more than 1 month

Table 9.5 Diagnostic criteria for brief psychotic disorder according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV: American Psychiatric Association, 1994)

A. Presence of one (or more) of the following symptoms: • Delusions • Hallucinations • Disorganized speech (e.g., frequent derailment or incoherence) • Grossly disorganized or catatonic behavior
Note: Do not include a symptom if it is a culturally sanctioned response pattern
B. Duration of an episode of the disturbance is at least 1 day but less than 1 month, with eventual full return to premorbid level of functioning
C. The disturbance is not better accounted for by a mood disorder with psychotic features, schizoaffective disorder, or schizophrenia, and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition
Specify if: With marked stressor(s) (brief reactive psychosis): if symptoms occur shortly after and apparently in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the person's culture Without marked stressor(s): if psychotic symptoms do not occur shortly after, or are not apparently in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the person's culture With postpartum onset: if onset is within 4 weeks postpartum

of this subgroup. Our studies have shown that the polymorphic symptomatology is also of essential diagnostic and prognostic validity (Marneros and Pillmann, 2004).

ICD-10 differentiates acute polymorphic psychotic disorders with symptoms of schizophrenia from acute polymorphic psychotic disorders without such symptoms (Table 9.4).

However, the distinction of the acute polymorphic psychotic disorders in a group "with symptoms" and another one "without symptoms of schizophrenia" is absolutely useless. No defining or prognostic validity has been found (Marneros and Pillmann, 2004).

Another crucial point is that subgroups of acute polymorphic psychotic disorder have the strongest relationship to the most essential predecessors of the concept of ATPDs namely the cycloid psychoses and *bouffée délirante* (Pillmann *et al.*, 2001; Pillmann and Marneros, 2003; Marneros and Pillmann, 2004).

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV: American Psychiatic Association, 1994) has a similar category to ICD-10, the "brief psychotic disorder" (298.8) (Table 9.5).

By definition, patients fulfilling the DSM-IV BP criteria also fulfill the ICD-10 criteria for ATPD, but not those of other ICD-10 psychotic groups. In other words, all DSM-IV brief psychosis patients are also ICD-10 ATPD, but the converse is not true. "Brief psychosis" of DSM-IV does not differ from other ATPDs as defined by ICD-10 in all essential parameters. There is no necessity to consider them as a separate diagnosis (Pillmann *et al.*, 2002a, b; Marneros and Pillmann, 2004).

The predecessors of the acute and transient psychotic disorders

When looking at the synonyms given by the WHO for ATPDs (Table 9.6), we cannot help but recognize their predecessors. However, the most essential predecessors are cycloid psychosis and *bouffée délirante*, which show relevant similarities to the subgroup of ATPD "acute polymorphic psychotic disorders."

Table 9.6 Synonyms for acute and transient psychotic disorder

- Acute (undifferentiated) schizophrenia
- *Bouffée délirante*
- Cycloid psychosis
- Oneirophrenia
- Paranoid reaction
- Psychogenic (paranoid) psychosis
- Reactive psychosis
- Schizophrenic reaction
- Schizophreniform attack or psychosis
- Remitting schizophrenia
- Good-prognosis schizophrenia

Cycloid psychoses

The most closely related concept to that of acute psychotic disorders of the ICD-10, as well as that of brief psychotic disorders of the DSM-IV, is the concept of cycloid psychoses. It was created and developed by the so-called "three Karls": Karl Wernicke, Karl Kleist, and Karl Leonhard. It was originated by Karl Wernicke and further developed by the work of his pupil, Karl Kleist (who also provided the name "cycloid"). It was then completed by the work of Kleist's pupil, Karl Leonhard (see also Perris, 1986; Marneros, 1999; Sigmund and Mundt, 1999; Marneros and Angst, 2000; Beckmann and Franzek, 2001; Marneros and Pillmann, 2004). The concept of the "three Karls" focused mainly on clinical and later also on genetic findings (Neele, 1949; von Trostorff, 1968).

The theoretical roots of the concept can be easily traced back to the work of Augustin Morel (1857) and to his concept of degeneration. Perris (1986) pointed out that it was very likely Valentin Magnan who, for the first time, linked an acute polymorphic psychotic disorder to a state of degeneration. In the 1880s, Magnan, inspired by Morel, described in some detail a psychopathological condition characterized by sudden onset, polymorphous symptomatology, and a recurrent course in successive generations of "degenerate" families (*syndromes épisodiques des dégénérés, bouffée délirante des dégénérés*). The concept of "degeneration psychosis" (no longer linked to the hypothesis of "degeneration") won acceptance in Germany and laid the foundation for the concept of "cycloid psychoses."

Many important German authors of the first quarter of the twentieth century (e.g., Bonhoeffer, 1907; Schröder, 1918, 1920, 1922, 1926; Birnbaum, 1923; Binswanger, 1928) published important work on "degenerative psychoses" (Perris, 1986). Paul Schröder, who stressed the polymorphism of the picture of "degenerative psychoses" (1920), was aware of the criticism about the concept of degeneration and wrote: "albeit one should be more concerned with the essence of a problem rather than with its name, a bad name has a detrimental effect on the problem." He changed the term "degenerative psychoses" to "metabolic psychoses" (from the Greek verb *metaballein*, which translates to "prone to change") to stress the polymorphism and the variability of such psychotic disorders. But the term "metabolic psychoses" has never been established (Pillmann *et al.*, 2001; Pillmann and Marneros, 2003; Marneros and Pillmann, 2004). The concept of cycloid disorder was mainly focused on clinical and prognostic aspects, but later also on genetic findings (Neele, 1949; von Trostorff, 1968; Franzek and Beckmann, 1998).

Karl Kleist, the most influential pupil and coworker of Wernicke at the University of Halle-Wittenberg and later Professor of Psychiatry in Rostock and Frankfurt, defined cycloid psychoses as bipolar disorders, but not identical to

Kraepelin's "manic-depressive insanity." Kleist's conclusions were based on clinical, prognostic, and family findings (Kleist, 1924, 1925, 1926, 1928, 1953).

Leonhard (1957) allocated the cycloid psychoses into three pairs:

(1) the anxiety–happiness psychosis
(2) the excited–inhibited confusion psychosis
(3) the hyperkinetic–akinetic motility psychosis

The three pairs of cycloid psychoses conceived by Leonhard were in accordance with Kleist's view that they were bipolar disorders (while differing essentially from manic-depressive illness).

The anxiety–happiness psychosis is characterized by continuous changing between severe all-pervasive anxiety and ecstatic happiness. It is possible that only one pole – anxiety or ecstasy – becomes manifest. Anxiety is often associated with delusions and hallucinations. While the experience of anxiety is overwhelming, its intensity fluctuates, and patients can suddenly turn to a state of ecstatic happiness. In the happiness–ecstasy phase, the patients experience a feeling of revelation and of closeness to God. They feel like wanting to help others, to save them, to make them as happy as they themselves are. A peculiarity of the affects in this condition is their changing character during the episode. Clear-cut depressive or clear-cut manic mood is not recognizable or long-lasting.

The excited–inhibited confusion psychosis is characterized by thought disturbances which become incoherent and perplexed, in the excited phase but do not continue in the inhibited pole. Incoherence is mostly manifest in an inconsequential choice of themes or by an inconsequential use of different languages. In the most extremely inhibited form, the patient becomes mute. A wondering perplexity is present. Hallucinations and delusions are frequently present. Most often, a polymorphous, rapidly changing pattern characterizes the episodes of illness.

The main characteristic of the hyperkinetic–akinetic motility psychosis is a disturbance of motility. In the hyperkinetic type, there is an increase in reactive and expressive movements and in pseudospontaneous movements. In contrast to the increased activity of many patients, they do not suffer pressure of speech. The patients remain mute in the hyperkinetic phase. In the akinetic phase, only a few isolated movements are carried out. In extreme cases, the patient may lie completely motionless in a stupor and in cataplexia. The difference to catatonia lies in the fact that the way in which movements are carried out is not qualitatively disordered in motility psychoses (Leonhard, 1961).

The 1974 study by Perris comprised a clinical and family investigation of 60 patients and their first- and second-degree relatives. The author recognized at the beginning of the study that a clear-cut distinction among the three different subtypes of cycloid psychoses proposed by Leonhard (1957) was not always possible. An admixture of symptomatology of all three pairs appeared to be

Table 9.7 Diagnostic criteria for 'cycloid psychosis' according to Perris and Brockington (1981)

1. An acute psychotic condition, not related to the administration or abuse of any drug or to brain injury, occurring for the first time in subjects in the age range 15–50 years
2. The condition has a sudden onset with a rapid change from a state of health to a full-blown psychotic condition within a few hours or at most a very few days
3. At least four of the following must be present:
   - Confusion of some degree, mostly expressed as perplexity or puzzlement
   - Mood-incongruent delusions of any kind, most often with a persecutory content
   - Hallucinatory experiences of any kind, often related to themes of death
   - An overwhelming, frightening experience of anxiety, not bound to particular situations or circumstances (pananxiety)
   - Deep feelings of happiness or ecstasy, most often with a religious coloring
   - Motility disturbances of an akinetic or hyperkinetic type which are mostly expressional
   - A particular concern with death
   - Mood swings in the background and not so pronounced to justify a diagnosis of affective disorder
4. There is no fixed symptomatological combination: on the contrary, the symptomatology may change frequently during the episode and shows a bipolar characteristic

more the rule than the exception. Perris did not find any convincing evidence that a differentiation into "ideal" subtypes would have a practical value. This knowledge led Perris (together with Brockington) to develop operational criteria for cycloid psychoses, ignoring Leonhard's differentiation of the three subgroups (Perris and Brockington, 1981, Table 9.7).

The Perris studies verified the abrupt or acute onset of cycloid disorder in general, but also anecdotally: "One of the investigated patients, who has been followed for several years and who has suffered several episodes, always becomes ill in the middle of the night after having gone to bed in a state of complete health" (Perris, 1974). Prodromal symptoms were found to be very rare, and when they occurred, they most often consisted of irritability and poor sleep. No seasonal dependence of onset was found. The development of psychotic symptoms was also very fast. They were mingled together without any discernible pattern and continuously changed, not only from day to day, but also in most instances from one hour to the next. The occurrence of schizophrenic first-rank symptoms (Schneider, 1959; Marneros, 1984) was very common. Further studies of Perris in cooperation with Brockington (Brockington *et al.*, 1982a, b) showed a very poor concordance between cycloid and schizoaffective psychoses. Only 20 of 108

patients who met the criteria of schizoaffective psychoses (mostly schizomanics) were diagnosed as cycloid. Patients identified as cycloid showed a significantly better short-term and long-term outcome than did other psychotic patients. Although the knowledge about epidemiology of cycloid psychotic disorder is still scanty, Perris assumed that 10–15% of psychotic patients are cycloid.

Bouffée délirante

Bouffée délirante is another important synonym given by the WHO for ATPD. It can be regarded as the French root of ATPD and brief psychoses. The modern concept of *bouffée délirante* of francophonic psychiatry is based on operational criteria, including sudden onset, specific symptomatology, and the evolution of the disorder (Pichot, 1986a; Pull *et al.*, 1983). The concept of the *bouffée délirante* has been influential in French psychiatry for more than a century (Appia, 1964; Pichot 1986a, b). In the 1880s, Valentin Magnan (1835–1916) described for the first time a psychopathological condition named *syndromes épisodiques des dégénérées* or *bouffée délirante des dégénérées*. The concept created by Magnan was completed by his pupils Legrain and Saury (Legrain, 1886; Saury, 1886; Magnan and Legrain, 1895).

It was Henri Ey who renewed interest in the entity of *bouffée délirante*, which he refined and contrasted to a more narrowly defined concept of schizophrenia (Ey, 1954). In this theoretical framework, the *bouffée délirante*, among other acute psychoses, displays a level of destructuration intermediate to manic-depressive illness and schizophrenia. Hallmarks of this intermediate level of psychopathological disturbance are oneiroid phenomena (Ey, 1954). It is this intermediate level of disturbance that explains the benign prognosis of the *bouffée délirante*. The diagnosis conforms with the desire of many French psychiatrists to put more weight on course than on symptomatology and to separate the acute psychoses from schizophrenia (Pull *et al.*, 1984). Hence, the French psychiatric school, even after the incorporation into its nosology of Kraepelinan dementia praecox and later of Bleulerian schizophrenia, has retained the category *bouffée délirante* as an independent mental disorder (Pichot, 1982). *Bouffée délirante* has its place in French psychiatry, as documented by its inclusion in the classification system of the Institut National de la Santé et de la Recherche Médicale (INSERM, 1969) and the formulation of operational criteria by Pull *et al.* (1983, 1984, 1987) and the continuing publication of case reports, theoretical articles, and clinical studies. The term, however, is not always used very strictly by French psychiatrists (e.g., it has also been applied to substance-induced delirious states: Devillières *et al.*, 1996).

The operational criteria that have been developed by Pull and his colleagues (1983) are shown in Table 9.8.

The frequency of patients found with *bouffée délirante* was much lower when applying the criteria used by Pull and coworkers (1983) than was the frequency of

Table 9.8 Diagnostic criteria for *bouffée délirante* (Pull *et al.*, 1983)

1. Age of onset: approximately 20–40 years
2. Onset: acute, without any prior psychiatric history (other than identical episodes)
3. No chronicity: active phases fade away completely in several weeks or months, possibly recurring under the same form: the patient remains devoid of all abnormalities in the interval
4. Characteristic symptoms (all of the following):
   - Delusions and/or hallucinations of any type
   - Depersonalization/derealization and/or confusion
   - Depression and/or elation
   - Symptoms vary from day to day even from hour to hour
5. Not due to any organic mental disorder, alcoholism, or drug abuse

patients found with the acute polymorphic psychotic disorders of the ICD-10 and cycloid psychosis when applying the criteria used by Perris (Pillmann *et al.*, 2003b; Marneros and Pillmann, 2004). They can be assumed to be a part of the acute polymorphic psychotic disorders, as defined by the WHO (Pillmann *et al.*, 2003b; Marneros and Pillmann, 2004).

Other predecessors

Another synonym for ATPD is that of "atypical psychoses," which is mainly a Japanese concept (Perris, 1986). The creator of the concept of atypical psychoses in Japan was Hisatoshi Mitsuda, who presented this topic for the first time in 1941. Atypical psychoses are characterized by an acute onset of illness, a favorable prognosis, and a tendency toward relapse. They show strong similarities with the concept of cycloid psychoses. In contrast to Kleist and especially to Leonhard, Mitsuda had doubts regarding the full remission of all cases with atypical psychoses (Mitsuda, 1965; Kimura *et al.*, 1984; overview in Fukuda, 1990). According to family studies by Mitsuda and Fukuda (1974), atypical psychoses have to be regarded as separate from both schizophrenia and depressive psychoses and from the epileptic psychoses, although some overlaps may occur. It has been assumed that atypical psychoses, as defined by the Japanese psychiatrists, have some similarities to epileptic psychoses. This assumption could not be supported in the HASBAP (Röttig, 2001; Marneros and Pillmann, 2004).

Reactive or psychogenic psychoses are also among the synonyms given by the WHO for ATPD. So-called reactive/psychogenic psychoses have a very strong tradition, mainly in Scandinavia (Strömgren, 1986). The basic concept was developed by August Wimmer (1916) in parallel with Karl Jaspers (1913). According to

Strömgren (1986), the reactive/psychogenic psychoses include emotional syndromes (depressions, excitations), syndromes with disturbance of consciousness (delirious states, dissociative states, twilight states, fugues), and paranoid (delusional) states (sensitive delusions of reference, litigious paranoia, incarceration psychoses, delusional psychoses in the deaf, and delusional psychoses in other forms of sensory deprivation). The original broad concept of reactive psychoses is still being used in Scandinavia, where up to 13–30% of all psychiatric admissions are diagnosed with reactive psychosis (Dahl, 1986; Opjordsmoen, 2001). The concept has been strongly advocated by Strömgren (1986, 1987). More recently, Ungvari has pleaded for the acceptance of an independent category reactive psychoses (Ungvari and Mullen, 2000; Ungvari *et al.*, 2000).

Dream-like states, independent of organic conditions and not identical to schizophrenia, have been described by Mayer-Gross (1924) in Germany. Schizophrenia-like emotional psychoses were described by Staehelin (1931, 1946) and Labhardt (1963) in Switzerland, and emotional psychoses by Störring and by his pupil Boeters in Germany (Störring *et al.*, 1962; Störring, 1969; Boeters, 1971). Psychiatrists in Spain, Portugal, Italy, Greece, Hungary, Bulgaria, and Russia described states very similar to those mentioned above (overview in Perris, 1986). They shared clinical and prognostic features with the above-described disorders.

What are acute and transient psychotic disorders?

The creation by the WHO of the category of ATPD in the ICD-10, as well as the creation by the American Psychiatric Association of a category of brief psychosis in DSM-IV, reflects the efforts to gather other psychotic disorders referring in some extent from classical schizophrenia and of course of affective disorders. Both systems include them in the "schizophrenic spectrum." But the WHO, in spite of creating this new category, remains uncertain about its accuracy:

> The nomenclature of these acute disorders is as uncertain as their nosological status [. . .] Systematic clinical information that would provide definitive guidance on the classification of acute psychotic disorders is not yet available, and the limited data and clinical tradition that must therefore be used instead do not give rise to concepts that can be clearly defined and separated from each other. (WHO, 1992).

This is quite true, but also a challenge for research on the topic. That became yet another reason to design and carry out the HASBAP.

The most systematic and voluminous study on the topic – the HASBAP – gave some answers to essential questions which can be found in the first book written on the topic (*Acute and Transient Psychoses* by Marneros and Pillmann, 2004).

Summarizing the findings of the HASBAP, it can be said that ATPD, as defined by the ICD-10, are disorders:

- mainly concerning females
- with possible onset in all ages of adult life, but usually between the 30th and 50th years of life
- having an acute or even abrupt onset
- with an onset only rarely dependent on acute severe stress
- with a very short psychotic period
- with a very good response to antipsychotic drugs
- with a usually favorable outcome, in spite of the fact that they are usually recurrent

People suffering from ATPD can be described as follows: a majority of patients with ATPD have an average education, occupational status, and level of functioning, with no significant difference from the mentally healthy population. They have an average level of social interaction and activities, as well as the same frequency of stable heterosexual partnerships as mentally healthy people do. But, because of the recurrence of their illness, it is possible in some socioeconomic systems, especially in times of high unemployment, to be excluded from the labor market. Nevertheless, even in such situations, they do not usually lose their autarky.

There are some significant differences between acute and transient psychotic disorders and schizophrenia. Summarizing the findings of the HASBAP, it can be noted that there are significant differences between ATPD and schizophrenia regarding:

- gender distribution
- age at onset
- premorbid level of functioning and social interactions
- onset, development, duration, and phenomenology, as well as structure of symptomatology
- level of postepisodic functioning and outcome in general

But it seems that a subgroup of ATPD – the "acute schizophrenia-like psychoses" – has a closer relationship to schizophrenia and schizoaffective disorders.

According to the findings of the HASBAP, the question of the nosological independence of the ATPD in general, but especially of their core group – the brief polymorphic psychoses – must be rejected. This is not only due to the many and relevant overlaps in all the domains investigated with the other two psychotic groups, and, considering the knowledge available, with the major affective disorders, but mainly because of their syndromatic instability. Even if the group of schizophrenia-like psychoses is excluded, and, if only the more homogeneous group of acute polymorphic psychoses is considered, then it is still clear that 60% of patients with more than one episode have other kinds of episode (especially affective and schizoaffective) than ATPD episodes during the course. The changeability of type of

episodes during the course, namely the manifestation of episodes belonging to other major disorders, is one of the most important arguments – although not the only one – against the assumption that ATPD, or its subgroup acute polymorphic psychoses, is a separate nosological entity.

The same findings (i.e., family, premorbid, course, outcome data and, especially, kind of episode) support the assumption that the brief polymorphic psychoses are also related to the affective spectrum.

Methods of the HASBAP

In order to determine the relationship between ATPDs especially with regard to the relationship between the core groups of the acute polymorphic psychotic disorders and the bipolar affective and schizoaffective disorders, we combined them and compared the findings of the HABILOS, described in chapter 1, with the previously mentioned HASBAP. The HABILOS has been described elsewhere in this book, therefore, we only give a short description of the HASBAP in this chapter:

The HASBAP combines three methodological approaches:

(1) a prospective approach, studying a consecutively recruited inpatient sample with a diagnosis of ATPD or brief psychotic disorder
(2) a case-control design in which every patient of the original index cohort was matched for age and gender with two clinical groups and a non-clinical control group
(3) a longitudinal approach for all three clinical groups

The sample investigated in the HASBAP comprised all inpatients with ATPD treated as inpatients at the Department of Psychiatry and Psychotherapy of Martin–Luther University Halle-Wittenberg from 1993 to 1997. The hospital is situated in the city of Halle, Germany, and takes patients from the city, as well as from the surrounding communities, which comprise both rural and industrial areas. It can be said that Halle University Hospital serves a large municipal and suburban area with a non-selective admission policy. Moreover, ATPD are acute and usually dramatic psychotic states that – considering the German health care system – nearly always lead to inpatient treatment. The HASBAP sample can be regarded as representative of a clinical inpatient population with ATPD. With some restrictions, the findings of this study might also be regarded – because of the above-mentioned reasons – as a reasonable approximation of ATPD in general, and not only for inpatients.

The number of patients fulfilling the criteria of ATPD during this period amounted to 42 patients. For the present analysis, three patients were excluded because they had shown affective or schizoaffective mixed states during earlier episodes, leaving a group size of 39 patients. The control groups comprised gender- and age-matched:

Table 9.9 Instruments used for assessment and evaluation in the Halle Study on Brief and Acute Psychotic Disorder

Sociobiographical interview (SBI)
ICD-10 and DSM-IV checklists
Schedules for Clinical Assessment in Neuropsychiatry (SCAN)
World Health Organization Psychological Impairments Rating Schedule (WHO/PIRS)
World Health Organization Disability Assessment Schedule (WHO/DAS)
Global Assessment Scale (GAS)
Positive and Negative Syndrome Scale (PANSS)
Neuroversion, Extroversion, Openness Five-Factor Inventory (NEO-FFI)

ICD-10, *Tenth Revision of the International Classification of Diseases*; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn.

(1) patients with an acute episode of "positive" schizophrenia
(2) patients with an acute episode of bipolar schizoaffective disorders
(3) surgical patients without any mental disorder

The basic instruments applied in the various stages of the HASBAP are shown in Table 9.9.

The statistical comparisons between ATPD and the bipolar group included a number of combinations:

1. ATPD versus bipolar affective mixed states versus bipolar schizoaffective mixed states
2. polymorphic subgroup of ATPD versus bipolar affective mixed states versus bipolar schizoaffective mixed states
3. ATPD versus all mixed states (affective plus schizoaffective)
4. polymorphic subgroup of ATPD versus all mixed states (affective and schizoaffective)
5. ATPD versus the groups of bipolar affective mixed states, bipolar schizoaffective mixed states, non-mixed bipolar affective disorders, and non-mixed bipolar schizoaffective disorders

Results

ATPD versus bipolar affective mixed states versus bipolar schizoaffective mixed states

We first intended to ascertain what differences, if any, exist between ATPD and the bipolar mixed states of bipolar affective disorders, as well as the mixed states of bipolar schizoaffective psychoses – mixed states, respectively. Therefore, these groups were compared on the basis of a large number of variables, including age

at onset, gender, birth complications, developmental abnormalities, "broken-home" situation in the family of origin, educational level, long-term heterosexual partnership, occupational status, personality, symptomatology at follow-up, general level of functioning, and social disability. For these and all following comparisons, the group of ATPD patients only comprised patients who never during the course of their illness had an episode that fulfilled the criteria of a mixed affective or schizoaffective episode. Table 9.10 shows the variables with significant differences between the groups.

The main findings shown in Table 9.10 can be summarized as follows:

- Women predominate in ATPD and, to a lesser extent, in bipolar affective mixed states, while there is a slight preponderance of males in bipolar schizoaffective mixed states. The differences between ATPD and bipolar schizoaffective mixed states are statistically significant.
- ATPD and bipolar affective mixed states have a higher age at onset than bipolar schizoaffective mixed states. The differences are significant at trend level.
- ATPD patients were significantly more often of asthenic/low self-confident personality type than affective or schizoaffective mixed states. ATPD were also significantly less often obsessoid or sthenic/self-confident than bipolar schizoaffective mixed states.
- At follow-up, ATPD patients less often received disability pension than bipolar affective mixed states and bipolar schizoaffective mixed states. The difference from the schizoaffective mixed states was significant.
- In the NEO-FFI, ATPD patients showed higher scores on conscientiousness and agreeableness than bipolar schizoaffective mixed states.

Polymorphic subgroup of ATPD versus bipolar affective mixed versus bipolar schizoaffective mixed states

Since the results of the HASBAP indicate that the polymorphic subgroup of ATPD (F23.0 and F23.1) are the most homogeneous group of ATPD as regards their core form (Marneros and Pillmann, 2004), the above comparisons were repeated with only the polymorphic subgroup of ATPD. Table 9.11 shows the results.

As shown in Table 9.11, the gender ratio remained essentially the same as in the voluminous group of ATPD. The age at onset was slightly lower for acute polymorphic psychosis than for ATPD in general, and no longer differed significantly from schizoaffective mixed states. The proportion of asthenic/low self-confident personalities in ATPD-polymorphic subtype remained high, as did the high rating of conscientiousness, but not of agreeableness, in ATPD. One new association occurred: there was a significantly lower number of suicide attempts in acute polymorphic psychoses than in schizoaffective mixed states.

Table 9.10 Significant differences between acute and transient psychotic disorder (ATPD), affective mixed states, and schizoaffective mixed states

	ATPD ($n = 39$) n (%)	Bipolar affective mixed states (BAD-MIX: $n = 16$) n (%)	Bipolar schizoaffective mixed states (BSAP-MIX: $n = 32$) n (%)	Statistical analysis[a]
Gender				
Female	30 (76.9)	11 (68.8)	15 (46.9)	ATPD > BSAP-MIX**
Male	9 (23.1)	5 (31.3)	17 (53.1)	
Age at onset	35.4 ± 11.4	37.0 ± 11.3	29.3 ± 10.5	ATPD > BSAP-MIX BAD-MIX > BSAP-MIX[b]
Disability pension at follow-up[c]	4 (10.3)	5 (35.7)	17 (65.4)	ATPD < BAD-MIX*** ATPD < BSAP-MIX***
Premorbid personality[c]	$n = 35$	$n = 11$	$n = 23$	
Obsessoid	8 (22.9)	5 (45.5)	11 (47.8)	ATPD < BSAP-MIX*
Sthenic/highly self-confident	5 (14.3)	5 (45.5)	7 (30.4)	ATPD < BSAP-MIX*
Asthenic/low self-confident	19 (54.3)	0	4 (17.4)	ATPD > BSAP-MIX** ATPD > BAD-MIX**

Table 9.10 (*cont.*)

	ATPD ($n = 39$) n (%)	Bipolar affective mixed states (BAD-MIX: $n = 16$) n (%)	Bipolar schizoaffective mixed states (BSAP-MIX: $n = 32$) n (%)	Statistical analysis[a]
Nervous-tense	3 (8.6)	1 (9.1)	1 (4.3)	NS
Dimensional personality scores (NEO-FFI)[c]	$n = 32$	$n = 15$	$n = 27$	
Neuroticism	1.89 ± 0.58	2.22 ± 0.65	2.01 ± 0.68	NS
Extroversion	2.06 ± 0.52	1.98 ± 0.50	1.87 ± 0.51	NS
Openness for experiences	2.17 ± 0.38	2.08 ± 0.44	2.33 ± 0.48	NS
Agreeableness	2.73 ± 0.43	2.39 ± 0.41	2.53 ± 0.42	ATPD > BAD-MIX*[d]
Conscientiousness	2.76 ± 0.44	2.31 ± 0.71	2.43 ± 0.50	ATPD > BAD-MIX*[e]

[a] Only pairwise comparisons with significant differences (χ^2-test or Fisher's exact test, two-tailed) are shown.

[b] Differences overall significant in ANOVA ($P = 0.027$); pairwise comparisons given are significant on trend level ($P < 0.1$) in Scheffé test.

[c] Reduced n, because some patients could not be followed up or information was insufficient to rate this item.

[d] Differences overall significant in ANOVA ($P = 0.027$); pairwise comparisons given are significant ($P < 0.05$) in Scheffé test.

[e] Differences overall significant in ANOVA ($P = 0.010$); pairwise comparisons given are significant ($P < 0.05$) in Scheffé test.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; NS, no significance.

NEO–FFI, NEO Five-Factor Inventory; ANOVA, analysis of variance.

Table 9.11 Comparison of the polymorphic subtype of acute and transient psychotic disorder (ATPD) with affective and schizoaffective mixed states

	ATPD($n = 25$) n (%)	Bipolar affective mixed states (BAD-MIX: $n = 16$) n (%)	Bipolar schizoaffective mixed states (BSAP-MIX: $n = 32$)	Statistical analysis[a] n (%)
Gender				
Female	20 (80.0)	11 (68.8)	15 (46.9)	ATPD > BSAP-MIX*
Male	5 (20.0)	5 (31.3)	17 (53.1)	
Age at onset	34.5 ± 8.0	37.0 ± 11.3	29.3 ± 10.5	BAD-MIX > BSAP-MIX[b]
Disability pension at follow-up[c]	2 (8.0)	5 (35.7)	17 (65.4)	ATPD < BSAP-MIX***
Number of suicide attempts	0.40 ± 0.65	0.87 ± 0.92	1.41 ± 2.08	ATPD < BSAP-MIX[d]
Premorbid personality[c]	$n = 35$	$n = 11$	$n = 23$	
Obsessoid	5 (22.7)	5 (45.5)	11 (47.8)	ATPD < BSAP-MIX*
Sthenic/highly self-confident	5 (22.7)	5 (45.5)	7 (30.4)	ATPD < BSAP-MIX*
Asthenic/low self-confident	10 (45.5)	0	4 (17.4)	ATPD > BSAP-MIX**
				ATPD > BAD-MIX**

Table 9.11 (*cont.*)

	ATPD($n=25$) n (%)	Bipolar affective mixed states (BAD-MIX: $n=16$) n (%)	Bipolar schizoaffective mixed states (BSAP-MIX: $n=32$)	Statistical analysis[a] n (%)
Nervous-tense	2 (9.1)	1 (9.1)	1 (4.3)	NS
Dimensional personality scores (NEO-FFI)[c]	$n=19$	$n=15$	$n=27$	
Neuroticism	1.88 ± 0.50	2.22 ± 0.65	2.01 ± 0.68	NS
Extroversion	2.12 ± 0.62	1.98 ± 0.50	1.87 ± 0.51	NS
Openness to experiences	2.14 ± 0.41	2.08 ± 0.44	2.33 ± 0.48	NS
Agreeableness	2.66 ± 0.42	2.39 ± 0.41	2.53 ± 0.42	NS
Conscientiousness	2.80 ± 0.41	2.31 ± 0.71	2.43 ± 0.50	ATPD > BAD-MIX*[e]

[a] Only pairwise comparisons with significant differences (χ^2-test or Fisher's exact test, two-tailed) are shown.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; NS, no significance.

[b] Differences overall significant in ANOVA ($P = 0.025$); pairwise comparisons given are significant ($P < 0.1$) in Scheffé test.

[c] Reduced n, because some patients could not be followed up or information was insufficient to rate this item.

[d] Differences overall significant in ANOVA ($P = 0.048$); pairwise comparisons given are significant ($P < 0.05$); in Scheffé test.

[e] Differences overall significant in ANOVA ($P = 0.019$); pairwise comparisons given are significant ($P < 0.05$); in Scheffé test.

NEO-FFI, NEO Five-Factor Inventory; ANOVA, analysis of variance.

Table 9.12 Significant differences between acute and transient psychotic disorder (ATPD) and all mixed states

	ATPD ($n = 39$) *n* (%)	All mixed states ($n = 48$)	Statistical analysis[a] *n* (%)
Gender			
Female	30(76.9)	26(54.2)	$P = 0.028$
Male	9(23.1)	22(45.8)	
Age at onset (years)	35.4 ± 11.4	31.8 ± 11.3	NS
Disability pension at follow-up[b]	4(10.3)	22(55.0)	$P < 0.001$
Premorbid personality[b]	$n = 35$	$n = 33$	
Obsessoid	8(22.9)	16(47.1)	$P = 0.027$
Sthenic/highly self-confident	5(14.3)	12(35.3)	$P = 0.036$
Asthenic/low self-confident	19(54.3)	4(11.8)	$P < 0.001$
Nervous-tense	3(8.6)	2(5.9)	NS
Dimensional personality scores (NEO-FFI)[b]	$n = 32$	$n = 42$	
Neuroticism	1.89 ± 0.58	2.09 ± 0.67	NS
Extroversion	2.06 ± 0.52	2.06 ± 1.90	NS
Openness to experiences	2.17 ± 0.38	2.16 ± 2.24	NS
Agreeableness	2.73 ± 0.43	2.73 ± 2.48	$P = 0.013$
Conscientiousness	2.76 ± 0.44	2.76 ± 2.39	$P = 0.003$

[a] χ^2-test or Fisher's exact test, two-tailed for categorical variables, *t*-test for continuous variables.
[b] Reduced *n*, because some patients could not be followed up or information was insufficient to rate this item.
NEO-FFI, NEO Five-Factor Inventory.

ATPD versus all mixed states (affective plus schizoaffective)

Bivariate comparisons were calculated for ATPD and all mixed states were combined (affective and schizoaffective). The results are shown in Table 9.12.

The results are largely similar to those obtained in the multivariate comparisons reported above. The lower age at onset observed for ATPD in comparison with schizoaffective mixed states was no longer significant when affective and schizoaffective mixed states were grouped together.

Polymorphic subgroup versus all mixed (affective and schizoaffective)

Accordingly, we calculated bivariate comparisons between ATDP-polymorphic subtype and all mixed states combined. The results are reported in Table 9.13.

Again, the results were quite similar to those of the multivariate comparisons.

Table 9.13 Significant differences between acute and transient psychotic disorder (ATPD: polymorphic subtype) and all mixed states

	ATPD ($n = 25$) n(%)	All mixed states ($n = 48$) n(%)	Statistical analysis[a]
Gender			
Female	20(80.0)	26(54.2)	$P = 0.030$
Male	5(20.0)	22(45.8)	
Age at onset (years)	34.5 ± 8.0	31.8 ± 11.3	NS
Disability pension at follow-up[b]	2(8.0)	22(55.0)	$P = 0.001$
Number of suicide attempts	0.40 ± 0.65	1.23 ± 1.8	0.028
Premorbid personality[b]	$n = 22$	$n = 34$	
Obsessoid	5(22.7)	16(47.1)	NS
Sthenic/highly self-confident	5(22.7)	12(35.3)	NS
Asthenic/low self-confident	10(45.5)	4(11.8)	$P = 0.004$
Nervous-tense	2(9.1)	2(5.9)	NS
Dimensional personality scores (NEO-FFI)[b]	N = 19	N = 42	
Neuroticism	1.88 ± 0.50	2.09 ± 0.67	NS
Extroversion	2.12 ± 0.62	2.06 ± 1.90	NS
Openness to experiences	2.14 ± 0.41	2.16 ± 2.24	NS
Agreeableness	2.66 ± 0.42	2.73 ± 2.48	NS
Conscientiousness	2.80 ± 0.41	2.76 ± 2.39	$P = 0.006$

[a] χ^2-test or Fisher's exact test, two-tailed for categorical variables, t-test for continuous variables.
[b] Reduced n, because some patients could not be followed up or information was insufficient to rate this item.
NEO-FFI, NEO Five-Factor Inventory.

ATPD versus the groups of bipolar affective mixed, bipolar schizoaffective mixed, bipolar affective non-mixed, and non-mixed bipolar schizoaffective disorders

Finally, we also included the non-mixed subtypes of bipolar affective and schizoaffective disorders (i.e., patients who never during the course of their illness experienced an episode that qualified as mixed episodes). The results of these comparisons, now comprising five groups, are provided in Tables 9.14a and 9.14b.

For some of the comparisons, the statistical power was quite small due to the low number of patients in some subgroups. We therefore calculated the comparisons for the combined groups of mixed and non-mixed bipolar disorders (affective and schizoaffective). The results are given in Table 9.15. Generally, they confirm the picture given in the preceding tables.

Table 9.14a Significant differences between acute and transient psychotic disorder (ATPD), affective mixed states, and schizoaffective mixed states (part 1)

	ATPD ($n = 39$) n (%)	Bipolar affective mixed states (BAD-MIX: $n = 16$) n (%)	Bipolar schizo affective mixed states (BSAP-MIX: $n = 32$)	Bipolar affective – never mixed (BAD-NOMIX: $n = 30$) n (%)	Bipolar schizoaffective never mixed (BSAP-NOMIX: $n = 48$)	Statistical analysis[a]
Gender						
Female	30(76.9)	11(68.8)	15(46.9)	16(51.6)	21(42.9)	ATPD > BSAP-NOMIX*
						ATPD > BAD-NOMIX*
						ATPD > BSAP-MIX**
Male	9(23.1)	5(31.3)	17(53.1)	15(48.4)	28(57.1)	
Age at onset	35.4 ± 11.4	37.0 ± 11.3	29.3 ± 10.5	35.9 ± 12.3	28.2 ± 10.3	ATPD > BSAP-NOMIX
						BSAP-NOMIX > BAD-NOMIX[b]
	$n = 39$	$n = 14$	$n = 26$	$n = 26$	$n = 42$	
Disability pension at follow-up	4(10.3)	5(35.7)	17(65.4)	17(65.4)	34(81.0)	ATPD < BAD-MIX***
						ATPD < BSAP-MIX***
						ATPD < BAD-NOMIX***
						ATPD < BSAP-NOMIX***
						BAD-MIX > BSAP-NOMIX**

[a] Only pairwise comparisons with significant differences (χ^2-test or Fisher's exact test, two-tailed) are shown.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; NS, no significance.

[b] Differences overall significant in ANOVA ($P = 0.002$), pairwise comparisons given are significant on trend level ($P < 0.1$) in Scheffé test.

Table 9.14b Significant differences between acute and transient psychotic disorder (ATPD), affective mixed states, and schizoaffective mixed states (part 2)

	ATPD *n* (%)	Bipolar affective mixed states (BAD-MIX) *n* (%)	Bipolar schizoaffective mixed states (BSAP-MIX)	Bipolar affective – never mixed (BAD-NOMIX) *n* (%)	Bipolar schizoaffective never mixed (BSAP-NOMIX)	Statistical analysis[a]
Premorbid personality[c]	$n = 35$	$n = 11$	$n = 23$	$n = 13$	$n = 20$	
Obsessoid	8(22.9)	5(45.5)	11(47.8)	8(61.5)	12(60.0)	ATPD < BSAP-MIX* ATPD < BSAP-NOMIX** ATPD < BAD-NOMIX*
Sthenic/highly self-confident	5(14.3)	5(45.5)	7(30.4)	5(38.5)	4(20.0)	ATPD < BSAP-MIX*
Asthenic/low self-confident	19(54.3)	0	4(17.4)	0	3(15.0)	ATPD > BSAP-MIX** ATPD > BAD-MIX** ATPD > BAD-NOMIX*** ATPD > BSAP-NOMIX**
Nervous-tense	3(8.6)	1(9.1)	1(4.3)	0	1(5.0)	NS
Dimensional personality scores (NEO-FFI)[c]	$n = 32$	$n = 15$	$n = 27$	$n = 27$	$n = 41$	

Table 9.14b (*cont.*)

	ATPD *n* (%)	Bipolar affective mixed states (BAD-MIX) *n* (%)	Bipolar schizoaffective mixed states (BSAP-MIX)	Bipolar affective – never mixed (BAD-NOMIX) *n* (%)	Bipolar schizoaffective never mixed (BSAP-NOMIX)	Statistical analysis[a]
Neuroticism	1.89 ± 0.58	2.22 ± 0.65	2.01 ± 0.68	1.80 ± 0.65	1.88 ± 0.51	NS
Extroversion	2.06 ± 0.52	1.98 ± 0.50	1.87 ± 0.51	1.96 ± 0.43	1.95 ± 0.51	NS
Openness to experiences	2.17 ± 0.38	2.08 ± 0.44	2.33 ± 0.48	2.23 ± 0.46	2.33 ± 0.52	NS
Agreeableness	2.73 ± 0.43	2.39 ± 0.41	2.53 ± 0.42	2.57 ± 0.37	2.57 ± 0.42	NS
Conscientiousness	2.76 ± 0.44	2.31 ± 0.71	2.43 ± 0.50	2.56 ± 0.45	2.59 ± 0.60	NS

[a] Only pairwise comparisons with significant differences (χ^2-test or Fisher's exact test, two-tailed) are shown.

$^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; NS, no significance.

[b] Differences overall significant in ANOVA ($P = 0.002$), pairwise comparisons given are significant on trend level ($P < 0.1$) in Scheffé test.

[c] Reduced *n*, because some patients could not be followed up or information was insufficient to rate this item.

Table 9.15 Comparison of acute and transient psychotic disorder (ATPD) with all mixed states combined and all non-mixed bipolar disorders

	ATPD $n = 39$ n (%)	All mixed states(BIP-MIX: $n = 48$ n (%)	All bipolar disorders – never mixed (BIP-NOMIX: $n = 80$) n (%)	Statistical analysis[a]
Gender				
Female	30 (76.9)	26 (54.2)	37 (46.3)	ATPD>BIP-MIX* ATPD>BIP-NOMIX**
Male	9 (23.1)	22 (45.8)	43 (53.8)	
Age at onset	35.4 ± 11.4 $n = 39$	31.8 ± 11.3 $n = 40$	31.1 ± 11.6 $n = 68$	NS
Disability pension at follow-up[b]	4 (10.3)	22 (35.7)	51 (65.4)	ATPD<BIP-MIX*** ATPD<BIP-NOMIX*** BIP-MIX>BIP-NOMIX*
Premorbid personality[b]	$n = 35$	$n = 34$	$n = 33$	
Obsessoid	8 (22.9)	16 (47.1)	20 (60.6)	ATPD<BIP-MIX* ATPD<BIP-NOMIX**
Sthenic/highly self-confident	5 (14.3)	12 (35.3)	9 (27.3)	NS
Asthenic/low self-confident	19 (54.3)	4 (11.8)	3 (9.1)	ATPD>BIP-MIX** * ATPD>BIP-NOMIX***
Nervous-tense	3 (8.6)	2 (5.9)	1 (3.0)	NS
Dimensional personality scores (NEO-FFI)[b]	$n = 32$	$n = 15$	$n = 27$	
Neuroticism	1.89 ± 0.58	2.22 ± 0.65	2.01 ± 0.68	NS
Extroversion	2.06 ± 0.52	1.98 ± 0.50	1.87 ± 0.51	NS
Openness to experiences	2.17 ± 0.38	2.08 ± 0.44	2.33 ± 0.48	NS
Agreeableness	2.73 ± 0.43	2.39 ± 0.41	2.53 ± 0.42	ATPD >BIP-MIX*[c]
Conscientiousness	2.76 ± 0.44	2.31 ± 0.71	2.43 ± 0.50	ATPD >BIP-MIX*[d]

[a] Only pairwise comparisons with significant differences (χ^2-test or Fisher's exact test, two-tailed) are shown. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; NS, no significance.

[b] Reduced n, because some patients could not be followed up or information was insufficient to rate this item.

Notes to Table 9.15 (*cont.*)

[c] Differences overall significant in ANOVA ($P = 0.035$); pairwise comparisons given are significant ($P < 0.05$) in Scheffé test.
[d] Differences overall significant in ANOVA ($P = 0.012$); pairwise comparisons given are significant ($P < 0.05$) in Scheffé test.
NEO-FFI, NEO Five-Factor Inventory; ANOVA, analysis of variance.

Conclusions

At the beginning of this chapter, we reported the opinion of Karl Kleist, who was the main creator of cycloid disorders and also one of the most important antagonists of Emil Kraepelin. He wrote that many cases described by Emil Kraepelin as mixed states could be better described as "cycloid psychoses."

Cycloid psychoses, according to Kleist, are bipolar disorders, but differ from manic-depressive illness. After Kleist's publications, the concept of cycloid disorders created interest in psychiatrists outside Germany, such as Carlo Perris in Sweden (Perris, 1986), Frank Fish (1964), Ian F. Brockington (Brockington *et al.*, 1982a, b) in the UK, and Mario Maj in Italy (1990) (see also Marneros and Pillmann, 2004). Therefore, there is an international, but limited, acceptance of cycloid psychoses. Nevertheless, the WHO integrated this concept in the category of ATPD (F23) of ICD-10. In particular, one subgroup of ATPD, called "polymorphic psychotic disorder," has considerable concordance with the concept of cycloid disorders (Pillmann *et al.*, 2001). In spite of some similarities between ATPD and "classical" bipolar disorders, there are some differences. Patients with ATPD are more frequently females, at their onset they have a better prognosis, and they more frequently have an asthenic polymorphic personality than bipolar patients. The comparison between ATPD and schizoaffective mixed states showed that the prognosis of ATPD is much better than in schizoaffective mixed states, and that females are significantly more frequently represented in the group of ATPD. However, in spite of some similarities in phenomenology, there are also differences between the two groups.

Our investigations showed that ATPD, especially the core group – the polymorphic psychotic disorders and therefore also the so-called cycloid disorders – are not identical with manic-depressive illness. This is evident because the occurrence of the full syndrome of mania or the full syndrome of major depression are exclusion criteria. We have also shown further differences in other investigations (Marneros *et al.*, 2000, 2002, 2003; Pillmann *et al.*, 2001, 2002a, b, 2003a; Marneros and Pillmann, 2004). The longitudinal investigations support an interpretation that locates the polymorphic psychotic disorders on a continuum between schizophrenia

and mood disorders, building together with the schizoaffective disorders the bridge between the two classical types of major psychiatric disorders.

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10

Bipolar disorder in children and adolescents

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Introduction

There is no doubt that children and adolescents may experience classical Kraepelinian (1921) or *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-type bipolar disorder (BP-I, II, mixed, rapid-cycling; American Psychiatric Association, 1994). However, as discussed in detail below, many BP children and adolescents have very short and frequent periods of mania, hypomania, or depression and, more controversially, some have continuous mood lability and irritability (Nottelman *et al.*, 2001). Children and adolescents with BP disorder usually have poor psychosocial outcome, increased risk for suicide, substance abuse, and psychosis (Lewinsohn *et al.*, 1995, 2000; Strober *et al.*, 1995; Geller *et al.*, 1998a, b, 2000a, b, 2001; Birmaher, 2001), indicating the need for accurate diagnosis and prompt treatment of this illness.

Since the research on BP disorder in children and adolescents is in its earlier stages, below we present the extant literature following in most part the criteria described by Robins and Guze (1970) to validate a psychiatric disorder, including the presence of a reliable diagnosis that can be differentiated from other psychiatric disorders, specific course, family history, response to treatment, and biological characteristics. Because of their scarcity, no biological studies are presented in this chapter.

Prevalence

A large adolescent community study, using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (6–18) epidemiologic version (K-SADS) (Chambers *et al.*, 1985), found that, similar to adult epidemiological studies, DSM-IV bipolar disorder was approximately 1% (Lewinsohn *et al.*, 1995). However, most adolescents had BP-II (periods of major depression and hypomania) and cyclothymic disorders. Another 6% of the sample showed

Table 10.1 Clinical manifestations of bipolar disorder in children and adolescents

Typical phenotype (DSM-IV) (bipolar I and bipolar II)
Many of these children have rapid-cycling and mixed bipolar presentations
Typical phenotype but for a short time (DSM-IV BP NOS)
Many have rapid-cycling and mixed episodes
Broad phenotype
Continuous mood lability, mood swings, affective storms, irritability, anger, aggressiveness, periodic agitation, explosiveness, recurrent severe temper tantrums, ADHD-like symptoms

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn;
BP NOS, bipolar not otherwise specified;
ADHD, attention-deficit hyperactivity disorder.

subsyndromal BP symptoms, defined in the study as the presence of a distinct period of abnormally and persistently elevated, expansive, or irritable mood. In clinical samples the incidence of BP disorder in children and adolescents has ranged from 2% to 15% depending on the nomenclature system, assessment instruments, and methodology used to diagnose patients' psychiatric disorders and sample origin (e.g., inpatient versus outpatient; Geller *et al.*, 1995; 1998a, b; Wozniak *et al.*, 1995; Axelson *et al.*, 1998).

Clinical diagnoses

Based on the literature and our clinical experience, the following three types of BP presentations in youth can be identified (Nottelmann *et al.*, 2001) (Table 10.1):

(1) patients with typical DSM-IV BP characteristics
(2) patients with DSM-IV BP characteristics but whose symptoms are of short duration
(3) children and adolescents with continuous mood lability, irritability, and severe temper outbursts

Patients with Kraepelinian or DSM-IV classical BP disorder display the cognitive, emotional, and behavioral BP symptomatology described in adult BP populations, with a great proportion having mixed and rapid cycles. These youths usually represent the minority of BP disorder cases seen at the clinics. In contrast, most BP children and adolescents do not have the time duration (7 days for mania and 4 days for hypomania) required by the DSM nomenclature and are usually diagnosed as BP-not otherwise specified (NOS). These patients usually display mixed or very-rapid-cycling presentations but it is not clear whether they can be

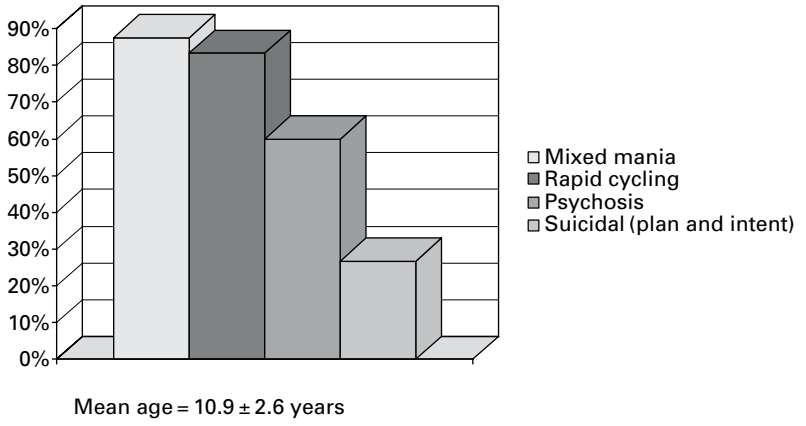

Fig. 10.1 Prepubertal bipolar disorder.

classified as such because the DSM-IV definitions of rapid-cycling or mixed state require that the periods of mania or hypomania last 7 or 4 days respectively.

There are few phenomenological studies of BP disorder in children and adolescents. These studies include one or more of the BP presentations described above. Geller *et al.* (1998b, 2002b) studied 93 children (mean age: 11 years) diagnosed with BP disorder and compared them with 81 children with attention-deficit hyperactivity disorder (ADHD) and no mood disorders, and 94 normal controls. To enter the study children needed to have grandiose ideation and/or elated mood. Compared to ADHD and normal control children, the BP group had an increased incidence of psychosis and suicidality (Fig. 10.1). Most children (80%) had very rapid fluctuations in their mood with very short periods of mania, sometimes lasting for only a few hours. Irritability, hyperactivity, and short attention span did not differentiate children with BP disorder from those with ADHD. Only symptoms specific for BP disorder, including grandiosity, elation, flight of ideas, and hypersexuality, differentiated the two groups.

Data from our own outpatient clinical population at Western Psychiatric Institute and Clinic (WPIC) indicate that child and adolescent BP disorder presents predominantly with brief episodes of manic symptoms that reach the DSM-IV threshold for severity. In examining a database of KSADS-P intake interviews of 1926 pediatric patients referred to the WPIC child mood and anxiety outpatient services from 1985 to 1995, we identified 120 patients (6.2% of the sample) who met the DSM-IV symptom criteria for a manic episode. The median episode duration of manic symptoms was found to be 1–2 days. Only 19% of the manic patients had episodes of manic symptoms that lasted the 1 week or longer which is the DSM-IV duration criterion for a manic or mixed episode.

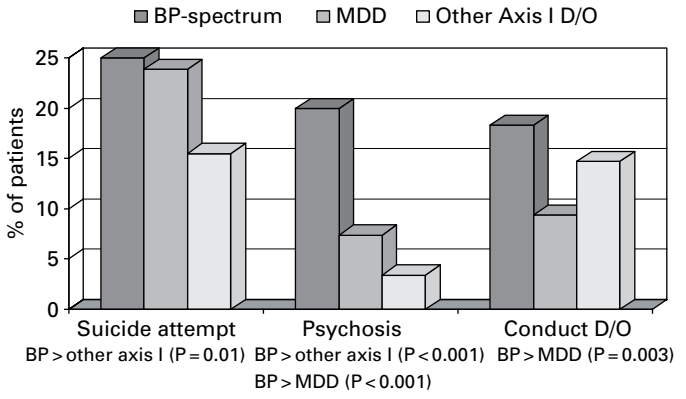

Fig. 10.2 Western Psychiatric Institute and Clinic (WPIC) mood and anxiety disorder outpatients. BP, bipolar; MDD, major depressive disorder; D/O, disorder.

Similar to other studies, the youth presenting with manic symptoms to the WPIC outpatient services had severe psychopathology that was often more serious than other children and adolescents presenting for clinical treatment (Fig. 10.2). Compared to non-BP youth presenting with a major depressive disorder (MDD, $n = 916$), children and adolescents with manic symptoms had significantly higher rates of psychosis (20% versus 7%) and conduct disorder (18% versus 11%). Youth presenting with manic symptoms also had higher rates of psychosis (20% versus 3%) and suicide attempts (25% versus 16%) compared with youth who met criteria for other non-MDD, non-BP Axis I disorders ($n = 679$).

Depression during the current psychiatric episode was a pervasive feature of children and adolescents who presented to our outpatient services with manic symptoms. Approximately 66% of these patients had moderate or worse depressed mood and 78% of them met three or more DSM-IV criteria for MDD during the current psychiatric episode. Forty-five (38%) of the children and adolescents who presented with manic symptoms were also given a clinical diagnosis of MDD during the current psychiatric episode. The high rates of mixed states and cycling between depression and manic symptoms were similar to the ones reported in Geller and colleagues' study, reported above. Also, as in the study by Geller *et al.* (1998b), irritability was a non-specific symptom that did not differentiate BP youth from youth with other disorders. Irritability was present in 93% of youth presenting with manic symptoms, while irritability was present in 89% of youth with MDD and 60% of youth with other Axis I disorders.

In addition to the BP presentations described above, there is a more controversial group of children who have been diagnosed as BP (Table 10.1). These children do not have typical manic/depressive symptoms but ongoing mood lability, very low frustration tolerance, agitation, frequent severe temper outbursts,

Table 10.2 Consequences of bipolar disorder

- Poor academic functioning
- Interpersonal and family difficulties
- Increased risk for suicide
- Increased use of tobacco, alcohol, and other substances
- Behavior problems
- Legal difficulties
- Increased health services utilization (e.g., hospitalizations)

irritability, ADHD-like symptomatology, sometimes silliness, and short periods of dysphoria (Wozniak *et al.*, 1995; Biederman, 1998). Since these children have "continuous manic symptoms" without accompanying elation or grandiosity, it is difficult to differentiate them from other psychiatric disorders and in particular ADHD or oppositional defiant disorder (ODD).

This last group of children represents the majority of patients currently referred to our clinics to rule out BP disorder. They usually have heterogeneous psychiatric disorders (e.g., ADHD, ODD, Asperger's disorder, recurrent MDD) accompanied by mood lability. An undetermined proportion of these children are likely to have BP disorder.

It is imperative to improve the diagnostic accuracy of BP disorder in youth. Early-onset BP disorder has severe negative psychosocial and academic consequences that can be potentially ameliorated by proper diagnosis and treatment (Table 10.2). In addition to delay in proper treatment, BP youth who are misdiagnosed as simply ADHD or depressed often receive stimulant medication and/or antidepressants that, without concomitant mood-stabilizer treatment, may worsen the course of illness.

To identify BP disorder in youth, clinicians as well as researchers need to take into account the following issues:

(1) As stated before, it appears that the manic/hypomanic symptoms in youth frequently do not persist long enough to meet the time duration criteria required by the DSM-IV for a manic and hypomanic episode (Klein *et al.*, 1985; Geller *et al.*, 1995, 1998a, b; Wozniak *et al.*, 1995; Geller and Luby, 1997; Axelson *et al.*, 1998; Biederman, 1998). These shorter periods of mania or hypomania can be easily overlooked and patients can be misdiagnosed with unipolar depressions, ADHD plus MDD, and personality disorders (e.g., borderline).

(2) Childhood-onset BP disorder is frequently manifested by mixed or very-rapid-cycling episodes of very short duration instead of the classical DSM-IV mixed and rapid-cycling DSM-IV classification (Akiskal *et al.*, 1985; Klein

et al., 1985; Bowring and Kovacs, 1992; Carlson and Weintraub, 1993; Carlson, 1995; Geller *et al.*, 1995, 1998a, b; 2000a, b; 2002a, b; Lewinsohn *et al.*, 1995, 2000; Weller *et al.*, 1995; Wozniak *et al.*, 1995; Axelson *et al.*, 1998).

(3) Most children and adolescents with BP disorder have comorbidity with ADHD and behavior-disruptive disorders (Bowring and Kovacs, 1992; Carlson, 1995; Geller *et al.*, 1995, 1998a, b, 2002a; Kovacs and Pollock, 1995; Lewinsohn *et al.*, 1995, 2000; Weller *et al.*, 1995; Wozniak *et al.*, 1995; Axelson *et al.*, 1998; Biederman, 1998). These comorbid conditions usually confound the diagnosis of BP disorder in youth.

(4) It appears that early-onset BP disorder conveys a worse course and outcome than BP disorder that started during adulthood (Geller *et al.*, 2002a, b).

(5) The child's emotional, cognitive, and behavioral developmental stages need to be taken into consideration when assessing symptoms of BP disorder (e.g., fantasies versus grandiosity; Bowring and Kovacs, 1992; Carlson, 1995).

(6) Environmental factors (e.g., family conflicts, parental psychopathology, negative life events) may affect the clinical presentation and course of illness (Geller *et al.*, 2002b).

(7) Overdiagnosis of BP disorder in children and adolescents also has serious consequences, as youth with other psychiatric conditions are unnecessarily exposed to medications with significant risk for side-effects and do not receive potentially therapeutic treatments for their actual disorder.

Longitudinal course

Lewinsohn *et al.* (1995) evaluated 1709 high-schoolers (ages 16.6 ± 1.2 years old, 54% females, 91% Caucasian) with the K-SADS Present and Epidemiological versions and found 1% (18) with BP disorder (mainly BP-II and cyclothymia) and 5.7% (97) with subsyndromal BP symptoms. These patients were reinterviewed 14 months after intake and compared with 316 subjects with MDD and 845 normal controls. The BP patients had the worse course, with a median duration for their index episode of illness of 80 weeks. Also they had more functional impairment, psychosis, suicidality, comorbid anxiety and disruptive disorders, and mental health utilization than the other two groups (Fig. 10.3). The subjects with subsyndromal BP symptoms had levels of impairment and comorbidity that were comparable to the BP group.

Strober *et al.* (1995) reported results from a 5-year naturalistic, prospective follow-up of a small sample ($n = 54$) of inpatient adolescents with BP-I disorder utilizing semiannual assessments. Although the absolute likelihood of recovery (≥ 8 weeks with < 2 symptoms) was high in the sample as a whole, 20% of the sample had suicide attempts requiring medical attention and time to recovery

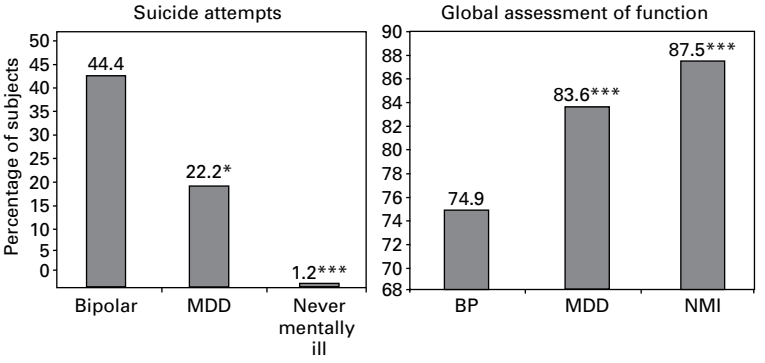

Fig. 10.3 Bipolar disorder in high-school students. MDD, major depressive disorder; BP, bipolar disorder; NMI, never mentally ill. Asterisks, significant *P*-values less than 0.05.

varied significantly by polarity of the index episode. Recovery was most rapid in subjects with pure mania (mean, 9 weeks) or mixed states (mean, 11 weeks) at intake, followed by subjects who were cycling at the time of presentation (mean, 15 weeks). In contrast, a strikingly protracted time to recovery was observed in subjects with pure depression at intake (mean, 26 weeks). Forty-four percent of the subjects who recovered from their index episode had one or more relapse by completion of the 5-year follow-up. Subjects with cycling or mixed episodes at intake had the highest probability of recurrence (mixed/rapid cyclers: 60% versus 40% around week 60 after intake). If minor depression and hypomania were included, the recurrence was approximately 60% for patients whose index episode was mania or depression, 70% for mixed, and 80% for rapid cyclers.

Geller *et al.* (2002a) followed a group of 93 outpatients aged 10.9 ± 2.7 years old (57% prepubertal, 39% females, 89% Caucasian) every 6 months for 2 years. Most of the sample ($\geq 70\%$) had comorbid disorders with ADHD and/or oppositional defiant disorder, psychosis (60%) and rapid cycling (77%). At intake the mean duration of the index episode was 3.6 years. After 1 year, approximately 37% of the sample showed recovery (no mania or hypomania and a Child-Global Assessment Scale (C-GAS) ≥ 60 for 2 weeks) but the rates of relapse/recurrence were 38%. After 2 years of follow-up, the proportions of subjects who recovered from mania and who relapsed after recovery were 65.2% and 55.2%, respectively. The mean time to recovery was 36 weeks. Relapse occurred after a mean of 28 weeks. Living with an intact family improved the chance of recovery and low level of maternal warmth increased the risk to relapse. Only 50% of the sample was treated with antimanic medications and there were no demographic or clinical predictors of relapse/recurrence.

Recently a multicenter pilot study (Birmaher, 2001) evaluated 73 outpatient adolescents with BP-I (mean age 17.1 ± 1.8 years, 75% female, 84% Caucasian)

with the K-SADS Present and Epidemiological version and followed them every 4 months with the Longitudinal Interval Follow-up Evaluation (LIFE) for 4–224 weeks (mean 76 ± 62 weeks). Approximately 68% of the subjects recovered (LIFE psychiatric status rating = 1–2 for 8 weeks) in 20–40 weeks. It took significantly longer for the mixed (mean = 58 weeks) BP patients to recover than those with manic (mean = 42 weeks) or depressive (mean = 20 weeks) presentations. Despite the high recovery rate, 59% of the patients had at least one recurrence, with mixed BP patients having more recurrences and shorter periods before the onset of the recurrent episode (mania = 79 weeks, depression 30 weeks and mixed 26 weeks, $\chi^2 = 6–8$, df = 2, $P = 0.03$). During the follow-up time, almost all patients were on psychotropic medication and 26% of the follow-up time patients received three medications (e.g., mood stabilizer, antidepressants, and stimulants). Moreover, 70% had hospitalizations and the patient's BP illness caused a severe family, interpersonal, and economic burden.

In summary, the few longitudinal studies have helped to validate the diagnosis of BP disorder in youth and have shown that this illness, in particular the mixed and rapid-cycling subtypes, is protracted and causes significant psychosocial and academic impairment.

Family history

Very few bottom-up (first-degree relatives of children and adolescents) and top-down (offspring of BP children) studies have been published (DelBello and Geller, 2001).

Bottom-up studies

Strober *et al.* (1998) found that, compared with adolescents with schizophrenia, youth with BP disorder have a high prevalence of first- (and second-) degree relatives with BP disorder. Likewise, Faraone *et al.* (1997) found that children with ongoing mood lability and severe temper outbursts diagnosed with "continuous" BP disorder had significantly more first-degree relatives with BP disorder than children with only ADHD. These results suggest that these children (or at least some) may indeed be suffering from BP disorder. The problem with this study, however, is that children were not directly interviewed and the assessment was only done with the K-SADS-Epidemiologic version (Orvashel *et al.*, 1982) that does not adequately evaluate BP disorder in children.

Top-down studies

Taking into account all the difficulties in diagnosing BP disorder in children described above, it appears that, in comparison with offspring of parents with non-BP disorders, and normal children, offspring of BP parents are five to seven

times more likely to develop BP disorder. However, offspring of BP parents are also at risk of developing depression, anxiety, and disruptive disorders. The results of these studies (Table 10.3) should be carefully examined because of the difficulties in diagnosing children with BP disorder and due to the following methodological problems:

(1) small sample sizes with few young children
(2) lack of longitudinal follow-up
(3) inclusion of a heterogeneous group of parents (BP and unipolar)
(4) lack of controls
(5) retrospective assessments
(6) offspring assessments not conducted blind to parental diagnosis
(7) no direct assessment of offspring
(8) lack of analysis of developmental influences on psychopathology
(9) use of unspecified diagnostic criteria
(10) lack of standardized assessments of psychopathology and family history
(11) no assessments of parental comorbid psychiatric disorders
(12) no psychiatric assessment of the proband's spouse
(13) no measurement of the effects of environmental stresses
(14) no evaluation of the presence of subsyndromal symptoms and whether severe disruptive disorder symptoms are part of the clinical picture of BP disorder during childhood
(15) lack of control for intrafamilial correlations

An ongoing study at the University of Pittsburgh Medical Center, USA, in a large sample of children of BP and non-bipolar parents, taking into account the above limitations, will help to clarify the initial symptoms of BP disorder in children. For example, answers are being sought for questions such as: is the psychiatric symptomatology in the offspring of BP parents the way that BP non-mood disorder manifests in young children, prodromal symptoms of BP disorder, or the manifestations of other non-mood psychiatric disorders?

Treatment

There are no randomized controlled trials (RCT) for bipolar disorder in children and adolescents. Open studies in samples of children and adolescents with more typical DSM or Kraepelinian or DSM-type BP syndromes have suggested that approximately 40–80% respond to lithium, valproate, and carbamazepine (e.g., Geller and Luby, 1997; Kowatch *et al.*, 2000) Despite the response and overall tolerance to these medications, most of these patients usually require other medications to control their mood (e.g., the atypical antipsychotics) or for the management of their comorbid disorders (e.g., stimulants for ADHD). Patients

Table 10.3 High-risk studies (only those with offspring < 18 years old)

Author	BPD parents: sample size	BPD-offspring: sample size (ages)	Control offspring (parent's clinical status)	Follow-up	Standardized interview: offspring/direct interviews	Standardized interview: parents/spouse diagnosis.[a]	Family history/blind interviews/ psychosocial assessment
McKnew *et al.* (1979)	13	30 (5–15)	N	Once (4 months later)	N/Y	Y/N	N/Y/N
Conners *et al.* (1979)	59 unipolar + bipolar	130 (ages ?)	N	N	N/N	Y/N	N/N/N
Waters and Marchenko-Bauer (1980)	16	50 (> 15)	N	N	Y/Y	Y/Y	N/N/N
Cytryn *et al.* (1982)	13	19 (5–13)	21 ("normal"?)	N	N/Y	Y/N	N/Y/N
Decina *et al.* (1983)	31	24 (7–14)	18 ("normal" ?)	N	N/?	N/N	N/N/N
Kuyler *et al.* (1980)	49	49 (6–18)	N	N	N/N	Y/Y	N/N/N
Zahn-Waxler *et al.* (1984)	7	7 (1–2.5 years old)	20 ("normal"?)	Once (2.5 years old)	Lab observation	Y	N/N/N
Kashani *et al.* (1985)	5	9 (7–17)	41 (unipolar)	N	Y/Y	?/Y	N/Y/N
LaRoche *et al.* (1985)	22	39 (5–18)	N	N	N/Y	Y/N	N/?/Y
Gershon *et al.* (1985)	20	29 (6–17)	37 ("normal")	N	Y/Y	Y/Y	N/Y/N
Klein *et al.* (1985)	24	37 (15–21)	22 (psychiatric)	N	Y/	Y/Y	N/Y/N

Pellegrini *et al.* (1986)	16	23 (7–18)	33 ("normal"?)	N	Y/Y	YY	?/Y/Y
LaRoche *et al.* (1987)	21	37 (8–25)	N	Twice (3–7 years)	Y/Y	Y/Y	Y/N/Y
Hammen *et al.* (1987, 1990)	13	18 (8–16)	Unipolar (22) medical (14) normal (36)	q 6 months × 3 years	Y/Y	Y/Y	N/N/Y
Nurnberger *et al.* (1988)	23	53 (15–25)	1–2 years	1–3 years	Y/Y	Y/Y	N/?/N
Zahn-Waxler *et al.* (1988)	7	7 (5–6 years old)	12 (psychiatric disorders)	Twice	Y/Y	Y/Y	N/Y/N
Gregoroiu-Serbanecu *et al.* (1989)	47	72 (10–17)	72 ("normal"?)	N	Y/Y	N/Y	Y/N/Y
Radke-Yarrow *et al.* (1992)	2	44 (1.5–8)	80 (unipolar)	Once (3 years later)	N/Y	Y/Y	Y/Y/N
Todd *et al.* (1996)	60	50 (6–17)	N	N	Y/Y	Y/N	Y/N/N
Chang *et al.* (2000)	37	60	N	N	Y/Y	?/N	N/N/N

[a] Not all the spouses were interviewed.

N, no; Y, yes; BPD, bipolar disorder.

with mixed presentations and/or rapid cycles appear to have a poorer response to the mood stabilizers. More recently, open studies have shown that BP children and adolescents may respond to the atypical antipsychotics (e.g., Frazier *et al.*, 2001). In contrast, studies including children with very short periods of mania/depression and "continuous" symptoms of BP disorder have contradictory responses to the mood stabilizers. However, more RCT studies with large samples are indicated.

Summary

For the past decade it has become clear that children and adolescents may experience DSM-IV BP syndromes. However, it appears that most of these children and adolescents have shorter episodes of mania, hypomania, and depression, higher prevalence of mixed and rapid episodes, and worse prognosis than their adult counterparts. Epidemiological, follow-up, family, and treatment studies have helped to validate the presence of BP disorder in children and adolescents but further studies are needed, especially to validate the diagnosis of BP disorder in youth, in particular those with very rapid or continuous mood lability. It is of critical importance to be aware of the BP diagnosis in children and adolescents and to be able to differentiate from other psychiatric disorders (e.g., ADHD, ODD) because BP children and adolescents have a poor prognosis and are at risk for suicide and development of other psychiatric conditions (e.g., substance abuse, behavior problems) unless they have the appropriate treatment.

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11

Atypical features of bipolarity in old age

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Introduction

Studying an elderly cohort confers several special advantages compared to younger or mixed-age populations. In the first instance, one has available a lifelong clinical course that has already unfolded. This allows for tracking of age of onset and describing long-term clinical patterns in a way that is much more practical than extensive prospective studies of younger patients. Second, genetic patterns of inheritance can be more fully explored as the exposure in first-degree relatives, especially children and siblings, will be much longer than in studies of younger probands. Third, an elderly cohort offers the opportunity to study lesions of the brain, thus casting more light on localization and pathogenesis, which can be extrapolated back to potential neurophysiological patterns in younger bipolars. Finally, outcome studies of the elderly can reveal differential rates of mortality and psychosocial vulnerability which can be compared to controls, other mood disorders, and neuropsychiatric conditions of late life.

Atypical features

These special aspects of study in the elderly result in features of bipolarity which are quite different from the usual cohorts of bipolar disorder whose mean age of onset is in the early 20s (Weissman *et al.*, 1991). Not surprisingly, atypical features described in this chapter will include:

(1) late age of onset
(2) prolonged latency from first depression to first mania
(3) high prevalence of neurologic comorbidity
(4) presence of cognitive impairment
(5) poor outcome characterized by increased mortality and finally increased nosologic confusion related to the presence of neurologic comorbidity and the similarity of secondary mania to other neurological conditions with disinhibition syndromes (Shulman, 1997)

Age of onset and clinical course

Age of onset can be an important variable that distinguishes subtypes of mania and bipolar disorder in order to improve understanding of underlying pathogenesis (Young and Klerman, 1992). While the vast majority of bipolar disorders in a general population occur early in life (Goodwin and Jamison, 1984), elderly bipolar patients report a mean age of onset of mood disorder which ranges from age 40 to 47 years and an onset of mania that ranges from age 51 to 60 years (Chen *et al.*, 1998). This latter group used a cut-off for "late onset" at 60 years but Wylie *et al.* (1999) have suggested that median age at onset in mixed-age patients could reasonably be used as a cut-off point between early and late onset. Clearly, the mean age of onset is also influenced by the cut-off for the age considered "elderly". In the Wylie *et al.* (1999) sample, their "elderly" bipolar patients were over the age of 60 and had a median age of onset of approximately 50 years. While no clear-cut convention for "late onset" has been established in an elderly population, the work by Wylie *et al.* (1999) suggests that an age of approximately 50 years would seem a reasonable marker for future use. Using this cut-off for a late-onset group of elderly bipolar patients, they found an increased prevalence of psychotic features and an increase in cerebrovascular risk factors.

In another study of elderly bipolar subjects with a mean age of 74 years, an increase in vascular comorbidity was found in a late-onset group defined by a cut-off point of age 50 years (Hays *et al.*, 1998). In this study, despite the elderly cohort and late-onset subjects, the proportion of patients with a positive family history was extremely high (83%), even for the late-onset group. Generally, within an elderly bipolar population, there has been a trend towards a higher rate of positive family history in those with an earlier age of onset (Hays *et al.*, 1998; Stone, 1989). For elderly individuals with comorbid neurological disorders there is a tendency to have a lower rate of family history (Tohen *et al.*, 1994). However even in the neurological subgroup of patients, a significant positive family history in first-degree relatives still applies at approximately 30%.

In a Finnish study, the annual rate of hospitalization by age for all bipolar patients has been recorded by Rasanan *et al.* (1998). Although the peak 1-year incidence occurred in middle age for both sexes, almost 20% of all first admissions for mania still occurred after the age of 60. This is consistent with the bimodal distribution found in a number of bipolar studies (Angst, 1978; Petterson, 1977; Sibisi, 1990). Two studies (Spicer *et al.*, 1973; Sibisi, 1990) found the highest inception rates for males to be in late life and for females the inception rates tended to be highest in middle age or later.

Whether age of onset is determined by episode or hospitalization can make a significant difference. Community surveys such as the Epidemiologic Catchment Area (ECA) study (Weissman *et al.*, 1991) and the National Comorbidity Study (Kessler *et al.*, 1997) report the mean age of onset of bipolar disorders as 21 years.

This is in stark contrast to the previous data based primarily on first admission. Generally, in mixed-age studies of manic inpatients, the mean age of onset is 30 years (Goodwin and Jamison, 1990; Tohen *et al.*, 1990). It is noteworthy that very few elderly bipolar patients are reported to have experienced their first manic episode before the age of 40 (Snowdon, 1991; Shulman *et al.*, 1992). A number of theories have attempted to explain the discrepancy between the early onset of community-based studies and the relatively late onset of hospitalized elderly bipolar patients. Bipolar patients may "burn out" or die by the time they reach old age. Furthermore, the late peak in hospital admissions may represent a group who are suffering from neurologic comorbidity and require hospitalization because of the severity of their illness or associated vascular risk factors. Certainly more work examining age of onset is needed.

In approximately half of index cases of mania in late life, the first affective episode is a depression which is similar to the proportion in mixed-age populations (Stone, 1989; Snowdon, 1991; Broadhead and Jacoby, 1990; Shulman *et al.*, 1992). However what distinguishes the elderly bipolar patient in terms of clinical course is the very long latency (on average 15 years) before mania becomes manifest (Shulman and Post, 1980). Furthermore, a delay of at least 25 years (ranging up to 47 years) between first depression and first mania occurs in about one-quarter of these patients. In further defining the clinical course, it is noteworthy that following a first episode of depression, approximately half of the cohort went on to develop three distinct depressive episodes before experiencing their first manic episode (Shulman and Post, 1980; Broadhead and Jacoby, 1990; Snowdon, 1991). This prolonged latency followed by a "conversion" to bipolarity after many years of an apparently unipolar diagnosis raises the notion of secondary mania associated with neurologic comorbidity as an important aspect of late-life bipolar disorders.

There is a small group of elderly bipolar patients whose clinical course is characterized by manic episodes only and who meet the criteria for unipolar mania (Shulman and Tohen, 1994). In this latter study, subjects were required to experience at least three distinct manic episodes without evidence of a major depression for a minimum period of 10 years from the time of the first manic admission. Of considerable interest is the difference in age of onset in this subgroup of unipolar manic patients. Here the age of onset was significantly lower at 41 years compared to a mean of 65 years for the bipolar elderly manics. Thus, the unipolar manic patients were among the very few elderly bipolar patients whose illness began early in life (Shulman and Tohen, 1994). This raises possible differences in pathogenesis and genetic vulnerability.

Mortality outcome has been reported in two studies with a mean of 6 years' follow-up data (Dhingra and Rabins, 1991; Shulman *et al.*, 1992). In the study by Dhingra and Rabins (1991), approximately one-third of the original cohort had

died at follow-up. Shulman *et al.* (1992) found a significant difference in mortality in an elderly manic group compared to an age- and sex-matched group of unipolar depressives. At the end of the 6-year mean follow-up period, 25 of the 50 manic patients were dead compared with only 20% of the depressed patients. After 5 years of follow-up, the probability of remaining alive was 90% for those with unipolar major depression and only 65% for patients with mania. At 10-year follow-up, the probability of remaining alive was 75% for the depressives and only 30% for the manic group. It should be noted that the data for the study were for hospitalized manic patients and studies of mortality outcome in outpatients are now needed.

Neurologic comorbidity

Retrospective cohort studies of mania in late life have established a very clear association between bipolarity in old age and a heterogeneous group of neurological disorders (Shulman and Post, 1980; Shulman *et al.*, 1992; Shulman and Singh, 1999). Even when compared to age-and sex-matched cases of depression where the prevalence of neurologic disorders was 8%, the elderly bipolar patients had a significantly higher rate of heterogeneous neurologic comorbidity (36%) (Shulman *et al.*, 1992). Within the elderly manic subgroup, a very late onset of mania was even more likely to be associated with neurologic disease (71%) compared to those with multiple previous episodes (28%) (Tohen *et al.*, 1994). Thus, very-late-onset mania is strongly associated with neurologic comorbidity as well as an increased mortality most likely related to the presence of cerebrovascular disease. This was true in 10 of 14 patients whose first affective episode was manic in nature. Furthermore, comprehensive reviews of mixed-age populations with "secondary mania" show a variety of both common and exotic neurologic conditions (Strakowski *et al.*, 1994; Verdoux and Bourgeois, 1995). However, in both cohorts, cerebrovascular disease predominates in terms of its association with mania, especially right-sided lesions involving the orbital-frontal and temporal cortices. This was most pronounced in those elderly bipolars with very-late-onset mania (Tohen *et al.*, 1994).

The evidence for localization in geriatric mania is based primarily on individual case reports and case series (Starkstein *et al.*, 1990). However, Braun *et al.* (1999) pooled all case reports involving focal unilateral cortical lesions and confirmed the trend for right-sided lesions to produce manic syndromes while left-sided lesions were associated with depressive symptomatology. Similar to other reports, the brain lesions described in the literature were dominated by cerebrovascular pathology and in particular cerebral infarction.

In neuroimaging studies, two areas of research have strengthened the association between cerebrovascular disease and manic syndromes (McDonald *et al.*, 1999). The first is the finding of an increase in subcortical hyperintensities on

magnetic resonance imaging scans. These hyperintensities are associated with hypertension, diabetes mellitus, and arteriosclerotic heart disease. The second major neuroimaging finding, led by Japanese investigators (Kobayashi *et al.*, 1991; Fujikawa *et al.*, 1995), is the presence of silent cerebral infarctions. These investigators have shown a progressive age-related increase in silent cerebral infarctions ranging from 6% in middle-aged individuals to greater than 20% in an elderly subgroup. Compared to late-onset depression and early-onset mood disorder, the highest frequency of silent cerebral infarctions occurs in the late-onset manic subgroup (Fujikawa *et al.*, 1995). Conceptually, these individuals fall into the category of secondary mania with a relatively lower incidence of family history in first-degree relatives and a higher prevalence of cerebrovascular risk factors.

Recent volumetric studies of bipolar patients show a trend towards diffuse cerebral atrophy (Steffens and Krishnan, 1998; Young *et al.*, 1999). These studies need replication and further elaboration of their significance.

Cognitive impairment

One of the unique elements of studying an elderly cohort is the expected higher prevalence of cognitive dysfunction that may affect outcome and potentially treatment response. In preliminary studies of manic syndromes in late life, there has been a consistent association of cognitive dysfunction. Berrios and Bakshi (1991) found elderly manic patients to be more cognitively impaired and to have scored higher on the Hachinski Scale, reflecting cerebrovascular pathology, when compared to a matched group of elderly depressives. Furthermore, Dhingra and Rabins (1991) reported scores of less than 24 on the Mini-Mental State Examination in almost one-third of their elderly manic patients during a 5–7-year follow-up. An earlier suggestion that the increased incidence of first admission rates for mania at the extremes of old age might be due to the onset of a dementing illness (Spicer *et al.*, 1973) has not been substantiated by the few outcome studies available (Stone, 1989; Shulman *et al.*, 1992). However this issue still requires clarification and long-term follow-up, including documentation of cognitive function. This is especially true since the finding by Alexopoulos *et al.* (1993) that patients with depressive pseudodementia, if followed for more than 3 years, will develop an irreversible dementia.

Preliminary studies have suggested that cognitive impairment will affect treatment response (Wylie *et al.*, 1999; R. C. Young, personal communication, 2002). Recent interest has focused on executive performance in elderly bipolars and initial findings on a variety of tests of executive and frontal function show impairment in elderly manic patients compared to controls (R. C. Young, personal communication, 2002).

Nosologic confusion

Depending on whether one is conversant with the neurological or psychiatric literature, terms such as "disinhibition syndrome" may be replaced with the concept of "secondary mania." The actual description of these two syndromes however is virtually identical (Shulman, 1997). In particular, it is the high rate of neurologic comorbidity that causes difficulty for categorization of the heterogeneous manic syndromes seen in old age. For example, the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV: American Psychiatric Association, 1994) established a category of "mood disorder due to a general medical condition" (293.83) indicating that "the disturbance is the direct physiologic consequence of a general medical condition." However, in an elderly subpopulation, even when there is a close temporal association, it is difficult to determine whether the medical or neurological comorbidity is a "direct physiologic consequence," simply an associated finding, or just a precipitant. Thus, the assumption of an etiological relationship is highly questionable.

Krauthammer and Klerman (1978) proposed the notion of secondary mania and posit a close temporal relationship between the medical/neurological condition and the manic syndrome. They stipulated that there should be no family history and no prior history of mood disorder and took pains to distinguish secondary mania from the syndrome of delirium.

Most recently, investigators have proposed a concept of vascular mood disorder including both vascular depression and vascular mania (Krishnan and McDonald, 1995; Alexopoulos *et al*., 1997; Steffens and Krishnan, 1998). The original notion of 'vascular depression' rests on a number of clinical observations and imaging findings, including a higher prevalence of cognitive dysfunction, increased cerebral atrophy and hyperintensities in late-onset depression (Alexopoulos *et al*., 1997). This subtype of depression was also associated with greater functional disability, higher morbidity and mortality, as well as a lower genetic predisposition compared to early-onset patients. Using a similar template, Steffens and Krishnan (1998) detailed the criteria for a vascular mania subtype (Table 11.1).

Proposed subtypes

Based on the available literature, Shulman and Herrmann (2002) have proposed four subtypes that may have heuristic value for further research.

(1) Primary bipolar disorder: this subtype should be used for those early-onset patients who continue to show mood disorder into old age. Despite the fact that relatively few of these individuals appear in studies of hospitalized elderly bipolar patients, it is likely that community and outpatient samples of elderly bipolar patients will reveal a higher proportion of the subtype.

Table 11.1 Proposed criteria for vascular mania subtype specifier

A.	Mania occurring in the context of clinical and/or neuroimaging evidence of cerebrovascular disease or neuropsychological impairment
B1.	Clinical manifestations may include history of stroke or transient ischemic attacks, or focal neurological signs or symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait disturbance, weakness of an extremity)
B2.	Neuroimaging findings may include white- or gray-matter hyperintensities (Fazekas *et al.*, 1998 criteria >2 ; or lesion >5 mm in diameter and irregular in shape), confluent white-matter lesions, or cortical or subcortical infarcts
B3.	Cognitive impairment manifested by disturbance of executive function (e.g., planning, organizing, sequencing, abstracting), memory, or speed of processing of information
The diagnosis is supported by the following features:	
1.	Mania onset after 50 years of age or change in the course of mood disorder after the onset of vascular disease in patients with onset before 50 years of age
2.	Lack of family history of mood disorders
3.	Marked disability in instrumental or self-maintenance activities of daily living

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Specify vascular subtype (can be applied to the current or most recent manic episode in bipolar disorder) if A and B1 or B2 or B3.

(2) Latent bipolar disorder: this subgroup is related to elderly bipolars whose onset began in middle age as a first episode of depression but who "converted" to mania much later in life, often after a prolonged latency and repeated depressive episodes. In this subgroup, it is postulated that cerebral factors may be responsible for the "conversion" from a unipolar depressive pattern to that of bipolarity.

(3) Secondary mania (disinhibition syndromes): this is largely a late-onset subtype without prior history of mood disorder and a lower but still significant familial predisposition. It is necessary to find a neurological or other systemic medical disorder that is associated with the manic syndrome. The proposed vascular mania subtype would fall into this subgroup.

(4) Unipolar mania: this is a much smaller but potentially heuristically valuable subgroup who have a course of manic-only episodes, generally of early onset and persisting over a prolonged period of time. Their similarity to patients with chronic frontal disinhibition is of interest but requires further investigation.

Atypical treatment issues

While pharmacokinetic and pharmacodynamic factors dictate a significant alteration in dosage, the general approach to treatment of bipolarity is not fundamentally different in an elderly population (Shulman and Herrmann, 2002). The narrow therapeutic range for pharmacological therapies in old age is an important consideration in ongoing management. Some interesting questions remain with respect to the atypical features of bipolar disorder in the elderly. First and foremost is the question of the impact of secondary mania on treatment and outcome. Will patients with frank neurologic lesions and a diagnosis of secondary mania respond in a way similar to the so-called primary bipolar subgroup? Further, how does cognitive dysfunction affect treatment outcome? Because of the narrow therapeutic range, do combination therapies in old age have a greater role in order to accommodate for limiting side-effects of individual drugs such as lithium carbonate and atypical neuroleptic agents such as olanzapine and risperidone? Can we use lower dosages of these drugs in combination, thereby limiting side-effects but maintaining effectiveness?

Finally, it has been proposed that the vascular subtype of mania may have specific implications for treatment. Instead of the usual mood stabilizers such as lithium, divalproex, and the atypical neuroleptic olanzapine, drugs that target cerebrovascular disease may be more appropriate for this subgroup. The calcium channel blocker nimodipine was used as an augmenting agent to standard antidepressant therapy in a group of patients suffering from "vascular depression" (Taragano *et al.*, 2001). These researchers were able to show a significant decrease in depressive symptoms and a low rate of recurrence with this agent used to treat cerebrovascular disease. Whether this effect can be translated to vascular mania remains to be determined.

Some specific geriatric issues do influence the use of lithium carbonate in the elderly. First and foremost is the fact that lithium is excreted exclusively by the kidneys (Hardy *et al.*, 1997) and aging effects lead to a very significantly altered elimination half-life. Combined with a decrease in the volume of distribution, marked reductions in lithium dosage are necessary.

From a pharmacodynamic viewpoint, sensitivity also appears to be increased in old age (Shulman and Herrmann, 1999). It is clear that adverse reactions and lithium toxicity at so-called normal adult serum levels are a common problem (Roose *et al.*, 1979; Smith and Helms, 1982; Murray *et al.*, 1983;). There is still a lack of clear guidelines regarding maintenance serum levels for the elderly, although by and large the figure of 0.5 mmol/l has been most commonly used as a target (Shulman *et al.*, 1987; Shulman and Herrmann, 2002).

Because the elderly are more likely to consume other drugs because of comorbid medical conditions, drug interactions with lithium carbonate remain a special concern. In particular, the diuretics which can decrease lithium clearance and

significantly increase serum lithium levels are a potential hazard. Other medications that have been implicated in raising serum lithium levels include the angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs such as indometacin (Shulman and Herrmann, 1999).

Case reports suggest that divalproex is still a fairly safe medication in the elderly, although there have been no systematic studies in this subpopulation. There is some evidence that it is surpassing lithium as a first-line mood stabilizer treatment in old age, despite the fact that there are few hard data to support this change in prescription pattern (Dinan, 2002).

Isolated case reports suggest only limited experience with other mood-stabilizing agents such as gabapentin, lamotrigine, olanzapine, risperidone, and quetiapine in the elderly (Shulman *et al.*, 1997; Jeste *et al.*, 1999; Tohen *et al.*, 1999).

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12

Comorbidity in mixed states and rapid-cycling forms of bipolar disorders

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Relevance of comorbidity

In recent years, much has been written on the comorbidity of bipolar disorders with other mental illnesses. Several studies have reported distinct patterns showing how bipolar disorders and other mental disorders co-occur (Brieger, 2000; McElroy *et al.*, 2001). Generally, in patients with bipolar disorders, there is an unexpected excess of co-occurring anxiety disorders and substance-abuse disorders. Concerning personality disorders, there is some evidence that patients with bipolar disorders show higher rates than the normal population, but lower rates than patients with unipolar affective disorders (Brieger *et al.*, 2003a). Such results are descriptive. Therefore, one has to examine the relevance of these findings. Some analyses have cast doubt as to whether one can simply assume that the more disorders a patient suffers from, the more impaired he or she is (Strakowski *et al.*, 1992; Brieger *et al.*, 2002a). Nevertheless, in several studies, comorbidity tended to be a complicating factor (Zimmerman and Mattia, 2000; McDermut *et al.*, 2001). In addition to other elements, it may lead to an increase in the length of hospital stay (Wancata *et al.*, 2001).

A useful definition of comorbidity is the "joint occurrence of two or more mental disorders occurring with each other and/or with medical conditions" (Klerman, 1990). Classical psychiatrists, such as Karl Jaspers (1973), postulated that all signs of an illness should be subsumed under a single diagnosis, which usually implies that this "main diagnosis" is meaningful in terms of prognosis and outcome. Nowadays, in operational diagnostic systems, such as *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV: American Psychiatric Association, 1994) and *Tenth Revision of International Classification of Diseases* (ICD-10: World Health Organization, 1993), comorbidity is the rule, not the exception (Merikangas, 1990). But, nevertheless, "diagnosis and need for treatment

are not the same" (Spitzer, 1998). Questions of methodology are important in understanding comorbidity (Brieger and Marneros, 2000). The growing importance of spectra, of subthreshold, and of the subsyndromal disorders in psychiatry, as well as the suspension of exclusionary principles, has led to an increase in comorbidity, which makes it complicated to appraise the potential consequences of two co-occurring disorders.

There is some indication that mixed states and rapid-cycling forms of bipolar disorders may have a worse prognosis than "typical" forms (Marneros and Brieger, 2002), although when looking at empirical data, the difference may be neither as great nor as clear as is often assumed. One central question is whether mixed states and rapid-cycling forms of bipolar affective disorders show patterns of comorbidity that differ from those observed in other forms of bipolar affective disorders. If that were true, it would make a case for viewing mixed states and rapid-cycling forms of bipolar affective disorders as distinct groups. A basic problem here is the difference between cross-sectional and longitudinal observations. Since the times of Kahlbaum (1863) and Kraepelin (1909–1915), there has been a consensus that, in psychiatric research, longitudinal observation is superior to cross-sectional observation. Nevertheless, both the co-occurrence of two mental disorders and the occurrence of mixed states and rapid-cycling forms of bipolar affective disorders may be transient with potential low long-term stability. It is an overt weakness of present diagnostic systems, such as DSM-IV and ICD-10, that they pay little (or almost no) attention to such a long-term course. At the same time, it becomes increasingly clear that complex interactions between long-term and subsyndromal features of a disorder are important for its prognosis (Marneros and Brieger, 2002).

Medical conditions and neuropsychiatric disorders

The comorbidity of medical conditions and bipolar affective disorders is a topic that warrants systematic research. The interaction between bipolar affective disorders and disorders of thyroid axis has received more attention than most other medical conditions. Nevertheless, no clear picture has emerged. It has been discussed that patients with mixed bipolar disorders may exhibit more thyroid hormone deficiency than controls (Zarate *et al.*, 1997; Chang *et al.*, 1998; McElroy *et al.*, 2000), but there are also negative studies that have found no differences between bipolar affective patients with or without mixed episodes as regards thyroid hormones (Joffe *et al.*, 1994), including a retrospective chart analysis prepared in our department (Reinelt, 2003). A recent study of 443 bipolar patients (Cassidy *et al.*, 2002) showed no indication of "overt or subclinical thyroid disease" in mixed manic episodes. In regard to rapid-cycling bipolar disorders,

several studies have not been able to support the idea that rapid cycling is related to thyroid dysfunction (Joffe *et al.*, 1988; Post *et al.*, 1989; Bartalena *et al.*, 1990), including a large study of almost 500 bipolar affective patients (Kupka *et al.*, 2002). However, there are reports in favor of this possibility (Extein *et al.*, 1982; Cowdry *et al.*, 1983; Bauer et al., 1990; Oomen *et al.*, 1996). Therefore, a higher frequency of co-occurring thyroid dysfunction has neither been proven nor ruled out for either mixed or rapid-cycling bipolar affective disorders, although some indications of such a relationship may exist. Mood-stabilizing medication, especially lithium, may affect the thyroid axis and complicate such analyses, as most bipolar affective patients will have previously received a mood stabilizer.

A report on a series of 13 patients with epilepsy and manic episodes (Kudo *et al.*, 2001) showed that, compared to bipolar affective controls, the patients with epilepsy and mania had less severe manic and depressive episodes. Interestingly, the majority of the patients with mania and epilepsy (8 out of 13) had a rapid-cycling course pattern with regard to mood episodes. Although there is no clear general estimate concerning the frequency of manic episodes in epilepsy, temporal lobe epilepsy has been reported to be among the leading causes of organic bipolar affective disorder (Rundell and Wise, 1989). Additionally, the etiological relationship between epilepsy and manic episodes is not clear. Rapid-cycling bipolar disorder has also been reported in a series of five patients with primary idiopathic dystonia (Lauterbach *et al.*, 1992).

Rapid cycling has been reported in various other neuropsychiatric disorders, such as head injury (Zwil *et al.*, 1993), stroke (Berthier, 1992), learning disability (Jan *et al.*, 1994; Raghavan *et al.*, 1995), or rarer illnesses, such as cerebral sarcoidosis (Walbridge, 1990) or tuberous sclerosis (Hagenah *et al.*, 1999). For mixed bipolar affective disorders, we are only aware of one report of a mixed bipolar affective episode following head injury (Bamrah and Johnson, 1991). Overall, one must be careful to equate such cases of rapid cycling in organic brain disease with "idiopathic" rapid cycling in bipolar affective disorder concerning symptomatic presentation. Instead, in some reports, the symptomatology seems to be "very atypical" and would not necessarily meet DSM-IV criteria for bipolar affective disorder. Nevertheless, in organic brain disease, rapid-cycling-like syndromes may be either more frequent than mixed bipolar affective episodes or more often noticed by clinicians, as they may have a higher relevance for acute treatment (i.e., the treatment could become longer or more complicated). In some cases, the fluctuating course of organic brain disease might mimic rapid-cycling forms (or even mixed states) in bipolar affective disorders.

Although it has been discussed that patients with mixed bipolar affective disorders may show more neuropsychological impairment than other bipolar affective patients, no such evidence was shown in a recent empirical study

(Basso *et al.*, 2002). As the authors of this study readily admit, this single negative study cannot rule out the possibility that subtle differences may exist, but it seems unlikely that they appear on a clinically meaningful level.

Substance-abuse disorders

Substance abuse is far more often found in subjects with bipolar affective disorder than in the general population (Sonne and Brady, 1999; Brieger, 2000). In this respect, alcohol (Winokur *et al.*, 1995) and cocaine (Weiss *et al.*, 1988) have received specific attention. Nevertheless, the overall trend seems to be true for most substances that can be abused, although it may well be that patients with bipolar affective disorder show a certain preference for stimulant drugs (Winokur *et al.*, 1998; Sonne and Brady, 1999; Brieger, 2000).

Already in the 1970s, Himmelhoch *et al.*, (1976) postulated that mixed episodes correlated with higher rates of sedative abuse. Later reports on mixed bipolar affective disorders referred to this observation. There are further empirical reports of higher frequency of substance-abuse disorders in patients with mixed bipolar affective disorders than patients with pure manic episodes (McElroy *et al.*, 1995; Goldberg et al., 1999) or of a higher frequency of dysphoric manic episodes in bipolar patients with substance abuse (Sonne *et al.*, 1994). Nevertheless, other studies with even larger samples have failed to find such differences: Cassidy *et al.* (2001a), for example, looked at 392 bipolar affective patients and found no difference between mixed and pure manic patients with regard to substance-abuse disorders. Similar results were obtained from our own group: in a prospective study of 149 bipolar patients, there were no significant differences in the frequency of substance-abuse disorders in bipolar affective patients with or without mixed affective episodes. Similarly, as shown in the study of Cassidy *et al.* (2001a), on a descriptive and non-significant level, the "mixed" bipolar group had even lower rates of substance-abuse disorders than the pure mania group (Brieger *et al.*, in preparation).

Rapid-cycling bipolar affective disorders may concur with higher rates of substance-abuse disorders (Calabrese *et al.*, 2000), but such an idea is mainly based on clinical observation or preliminary data (Keller *et al.*, 1986; Sonne *et al.*, 1994). One family study reported (without statistical significance) higher rates of substance abuse in families of subjects with rapid-cycling than in families of subjects with non-rapid-cycling bipolar affective disorder (Lish *et al.*, 1993). In our own data set, we have also observed (without significance) that patients with rapid cycling exhibited higher rates of substance-abuse disorders (Brieger *et al.*, in preparation), although our rapid-cycling group is very small ($n = 12$). There is some consideration that patients with substance-abuse disorder and bipolar affective

disorder may have more illness episodes than patients with bipolar affective disorder without substance-abuse disorder (Sonne and Brady, 1999; Calabrese *et al.*, 2000), but not all data support such a hypothesis. Yet, patients with substance abuse and bipolar affective disorders differ from patients with bipolar affective disorders without substance abuse in other respects: they show more hospitalization (Brady *et al.*, 1991), have an earlier age at onset of bipolar disorder (Sonne *et al.*, 1994; Brieger *et al.*, in preparation) and have an overall more unfavorable course of bipolar illness (Sonne and Brady, 1999; Marneros and Brieger, 2002; Brieger *et al.*, in preparation).

Anxiety disorders

There is a fundamental relationship between bipolar affective disorder and anxiety disorders (including obsessive-compulsive disorder: OCD) (Perugi *et al.*, 1999; Zarate and Tohen, 1999; Brieger, 2000), which has been shown by epidemiological (e.g., Kessler, 1999) and clinical (e.g., McElroy *et al.*, 2001; Perugi *et al.*, 2001) studies. Panic disorder, social phobia, and OCD seem to have a specific relationship with bipolar affective disorder (Chen and Dilsaver, 1995a, b; Perugi *et al.*, 1999).

One series of factor analyses (Cassidy *et al.*, 1998a, b, 2001a, 2001b) delineated five independent factors in mania: (1) dysphoric mood; (2) psychomotor pressure; (3) psychosis; (4) increased hedonic function; and (5) irritable aggression. The factor 'dysphoria' strongly correlated with anxiety. Based on these studies, an alternative set of six diagnostic criteria for mixed episodes was proposed (Cassidy *et al.*, 2000), which (with a threshold of two symptoms) consisted of (1) anxiety; (2) depressed mood; (3) anhedonia; (4) guilt; (5) suicide; and (6) fatigue. In this concept, anxiety is an integral aspect of mixed bipolar affective phenomenology, as was earlier observed by Post *et al.* (1989). Furthermore, a comparison between patients with mixed mania and agitated depression (Swann *et al.*, 1993) proved that these two groups were (at least partially) similar in respect to observed anxiety.

These observations support the idea that dysphoria and bipolar mixed states are characterized by elevated levels of dimensional anxiety. This is in agreement with the theories of Akiskal, Koukopoulos, and others, who have postulated that mixed bipolar affective disorders are the product of an admixture of anxiety or depressive symptoms (or such temperaments) with manic episodes (Koukopoulos and Koukopoulos, 1999; Akiskal and Pinto, 2000; Akiskal *et al.*, 2002). In a comparison of bipolar patients with pure and mixed manic episodes, we found that patients with mixed mania exhibited higher rates of anxious temperament than patients with pure mania (Brieger *et al.*, 2003b). Here, anxious temperament may be interpreted as a trait marker with longitudinal stability. Nevertheless, there are studies that do not support such an idea and have found no significant difference between patients with mixed and pure manic episodes concerning dimensional

anxiety. For example, one Italian study found no differences concerning self-rated or observer-rated anxiety (Dell'Osso *et al.*, 2000) in 90 patients with mixed and pure mania with psychotic features.

Patients with mixed bipolar affective disorder may also exhibit higher frequencies of full-blown anxiety disorders than patients with pure mania. This was already observed in the Iowa study (Winokur *et al.*, 1969). A later study (Feske *et al.*, 2000) showed that, amongst bipolar affective patients, those with a depressive or mixed episode fulfilled criteria of an anxiety disorder in roughly half of cases, while this was only the case in every fifth patient with a pure manic episode. Yet, partially negative studies can also be found: in a comparison of patients with mixed mania, pure mania, and bipolar depression with psychotic features, only two differences concerning anxiety disorders were reported: depressive patients had higher rates of OCD and simple phobia (Dell'Osso *et al.*, 2000).

The temporal relationship between anxiety disorder and mixed bipolar affective disorder remains complex. A certain proportion of panic disorders in bipolar affective patients presents during hypomanic episodes, while social phobia nearly always precedes (hypo)mania (Perugi *et al.*, 2001). Therefore, Perugi *et al.* conclude that in such patients panic disorder may be a reflection of mixed (hypo)manic symptomatology (Perugi *et al.*, 2001).

Altogether there is some indication that mixed bipolar affective episodes correspond with an elevated risk for co-occurring anxiety disorders and higher rates of trait anxiety (or anxious temperament). Concerning OCD, it was once observed (Strakowski *et al.*, 1998) that OCD occurred more often in mixed mania than in pure mania, although full-blown OCD had a relatively lower prevalence than many other psychiatric disorders – a result stemming from a rather small sample size (12 patients in both groups).

We are not aware of substantial data that support the idea that rapid cycling has a special link to anxiety disorders, including OCD.

Personality disorders

Personality disorders in affective disorders occur at higher rates (Brieger *et al.*, 2003a). Nevertheless, interactions between personality and affective disorder are complex (Akiskal *et al.*, 1983): is the assessed personality a predisposing or complicating factor, or is it a result or an epiphenomenon of the affective disorder? The present diagnostic system of personality disorders has undergone fundamental critique (Livesley, 1998). The relevance of comorbid personality disorders in affective disorder may be more complex than generally assumed; for example, there is an indication that only specific patterns of personality disorders have a prognostic value (Brieger *et al.*, 2002a). With regard to mixed episodes, there is

some indication that they may (at least partially) result from an admixture of a certain personality type or a certain temperament to an affective episode – a theory that has been advocated most of all by Hagop Akiskal (Akiskal, 1996; Akiskal *et al.*, 1998). There are now several studies supporting such a hypothesis (Dell'Osso *et al.*, 1991; Akiskal *et al.*, 1998; Brieger *et al.*, 2003b), although the observed differences between pure and mixed manic patients in respect to temperament are not significant enough to explain the difference fully. Furthermore, methodologically, the distinction between mood "state" and temperament "trait" cannot always be made satisfactorily. Concerning personality as assessed by the five-factor model (Costa and Widiger, 1994), we found no difference between patients with pure and mixed manic episode in a relatively small sample (Brieger *et al.*, 2002b).

We are not aware of any studies that have linked rapid cycling to the presence of a personality disorder.

Other psychiatric disorders

There is a large diagnostic overlap between attention-deficit hyperactivity disorder (ADHD) and bipolar disorder in children and adolescents (Geller *et al.*, 2002b). Geller *et al.* (2002a, b, c) have outlined a "prepubertal and early adolescent bipolar disorder phenotype," which may be superior to DSM-IV criteria in recognizing bipolar children and adolescents. Still, in their sample of 93 subjects with a "prepubertal and early adolescent bipolar disorder phenotype," 86.5% suffered from comorbid ADHD, 87.1% showed rapid cycling (77.4% ultradian!), and 54.8% presented with mixed mania. As only 16 of 93 subjects with bipolar disorder had no ADHD, it seems futile to analyze the effect of comorbid ADHD on bipolar disorder. Rather, one has to acknowledge that (at least with the present diagnostic criteria of ADHD), the great majority of childhood and adolescent cases of bipolar disorders present with rapid (and even ultradian) cycling and with co-occurring ADHD, and that more than half of the subjects with bipolar affective disorder exhibit mixed episodes.

We are not aware of any studies that have looked specifically at the relationship between mixed states or rapid-cycling forms of bipolar affective disorders and eating disorders, sexual and gender-identity disorders, somatoform disorders, or dissociative disorders.

Furthermore, we have not discussed the relationship between psychotic and schizophrenic disorders and "atypical" forms of bipolar affective disorders, as this lies outside the realm of this chapter. Where to draw the line between bipolar affective disorders, schizophrenic disorders, and schizoaffective disorders is a

fundamental question of concept and phenomenology, and not a question of comorbidity.

The general effect of comorbidity

The majority of patients with a bipolar affective disorder and a co-occurring psychiatric disorder suffer from more than one additional disorder (McElroy *et al.*, 2001; Vieta *et al.*, 2001). In one analysis from the Stanley Foundation Bipolar Treatment Outcome Network, 35% of all bipolar patients ($n = 288$) had no lifetime comorbid Axis I disorder, 23% had one such comorbid disorder, 18% had two, and 24% had three or more. With regard to current comorbid Axis I disorders, the numbers were as follows: 67% had none, 20% had one disorder, 7% had two disorders, and 6% had three or more disorders (McElroy *et al.*, 2001).

In another comparison of bipolar affective patients ($n = 129$) with or without a current comorbid psychiatric disorder (Vieta *et al.*, 2001), patients with a current comorbid disorder had a history of significantly more mixed episodes than patients without such current comorbid disorders. In our follow-up study ($n = 149$), we came to the same result (Brieger *et al.*, in preparation). Both studies have included Axis I and II disorders and, in our study, this difference is primarily the effect of an excess of cluster C personality disorders in the group of patients with previous mixed episodes. Interestingly, the Stanley Foundation Bipolar Treatment Outcome Network study (McElroy *et al.*, 2001), which looked at only Axis I disorders and not at personality disorders, found no significant difference between patients with or without such comorbid diagnoses in regard to dysphoric mania, whether one looked at lifetime or current comorbidity.

The Stanley Foundation Bipolar Treatment Outcome Network study (McElroy *et al.*, 2001) indicated that patients with comorbid Axis I disorders show more cycle acceleration and possibly more rapid cycling. The latter result barely missed statistical significance, but the study used strict correction for multiple comparisons; therefore, this may have been a false-negative result. Vieta *et al.* (2001) did not come to the same result, but here the smaller sample size has to be considered.

Conclusions

Comorbidity research illustrates the shortcomings of the present diagnostic systems and must therefore go further than merely describing present rates of co-occurring disorders. Instead, it has to uncover trends, relationships, and links between different disorders. Even if one were to suppose that the different definitions of mixed episodes and of rapid cycling described two widely homogeneous groups, the present review does not give much support for the idea that such forms

of bipolar disorder constitute distinct diagnostic categories. Rather, this review supports the idea that rapid cycling and mixed episodes are manifestations of bipolar illnesses, which occupy certain regions of the multidimensional bipolar affective spectrum. Still, this does not contradict the idea that these forms of bipolar affective disorders have a prognostic validity. In all areas of our review, there is the overall tendency that mixed states and rapid-cycling forms of bipolar affective disorder constitute more unfavorable forms of the underlying illness. Mixed affective episodes have a link with anxiety disorders and anxious-dependent personality disorders (cluster C). Rapid cycling may have a link with substance abuse and with certain neuropsychiatric disorders, or, perhaps, these neuropsychiatric disorders may mimic rapid cycling. Undoubtedly, children and adolescents with bipolar affective disorders usually suffer from ultradian cycling and ADHD. All of these co-occurring factors are reasons for the deterioration of the course of a bipolar affective disorder.

It seems simplistic to distinguish between "typical" and "atypical," or between "mixed" and "non-mixed," or between "rapid-cycling" and "non-rapid-cycling" forms of bipolar illness. The reality of bipolar illness is much more complex. Several – mostly dimensional – factors affect the course and prognosis. Amongst these, we count phenomenology of episodes, cycle acceleration, cycle frequency, occurrence of full cycles, early age at onset, comorbid substance abuse, comorbid personality disorders, comorbid anxiety disorders, neuropsychiatric abnormalities, time in depression, and other genetic, biological, psychosocial, and personality factors. We think it is necessary to assess bipolar affective illness in the light of these factors in order to understand it better.

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13

Challenges in the genetics of bipolar disorder

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Epidemiology of mood disorders

Major depressive disorder (MDD) is the leading cause of disability among those age 5 and over, and the second leading source of disease burden, surpassing cardiovascular diseases, dementia, lung cancer, and diabetes (Murray and Lopez, 1996). The dramatic impact of mood disorders on distress to the affected individual and his or her family, lifetime disability, and suicide highlights the importance of etiologic research to inform treatment and prevention.

Community-based rates of mood disorder are essential to deriving estimates of population familial recurrence risk (λ) (Risch, 1990). Population prevalence estimates of mood disorders are available from two community surveys of the USA: the Epidemiologic Catchment Area (ECA) study of five sites in the USA (Robins and Regier, 1991), and the National Comorbidity Survey (NCS) of a probability sample of the USA conducted 10 years later (Kessler *et al.*, 1994). Estimates of base rates of bipolar disorder (or manic episodes) were very low in both studies, averaging 0.8% in ECA and 1.6% in NCS. In contrast, there is a very high lifetime prevalence of MDD in the US population (females, 12% ECA; 21.3% NCS, and males, 5% ECA, 12.7% NCS). Similar base rates of mood disorders have been obtained in international studies as well (Weissman *et al.*, 1996). With respect to demographic factors, the differences between the bipolar and major depression subtypes of mood disorders include the sex ratio that favors women for MDD but is nearly equal for men and women for bipolar disorder, and the age of onset that occurs nearly a decade earlier in MDD than in bipolar disorder (Weissman *et al.*, 1991).

Manic episodes, bipolar disorder, and hypomania are generally rare in children and adolescents. In the few studies reporting rates of these disorders, point, 12-month, and lifetime estimates ranged from 0% to 2.0% (Kashani *et al.*, 1987; Costello *et al.*, 1996; Lewinsohn *et al.*, 1998; Pine *et al.*, 1998). The wide variation in base rates has been attributed to methodologic differences rather than true differences in prevalence. Likewise, the diagnostic criteria for bipolar disorder in

childhood have been quite controversial, and several prospective studies are now under way to define the early manifestations of bipolar illness (National Institute of Mental Health Research Roundtable on Prepubertal Bipolar Disorder, 2001).

Genetic epidemiology of mood disorders in adults

The role of genetic factors in the etiology of bipolar disorder has been suspected for more than a century. Numerous reviews have demonstrated conclusively that genetic factors are involved in the susceptibility to mood disorders, particularly bipolar disorder (Tsuang and Faraone, 1990; Merikangas and Swendsen, 1997; Moldin, 1997; Reus and Freimer, 1997; Sullivan *et al.*, 2000).

Several study designs have been employed to assess the role of genetic factors in disease etiology, including:

(1) family studies, which assess the degree of aggregation of a trait among relatives of affected probands compared to expected rates from the general population
(2) twin studies, which compare concordance rates for monozygotic twins, who have identical genotypes, with those among dizygotic twins, who share an average of half of their genes
(3) adoption studies, which compare the degree of similarity between an adoptee and his or her biological parents, from whom he or she was separated, and between the adoptee and the adoptive parents
(4) association and linkage studies of genetic markers, which examine the relationships between a known genetic trait and disease status either across families or within pedigrees.

Family studies

Although family studies cannot yield direct evidence for the involvement of genes in the causation of a disease, they are a rich source of evidence for examining the correspondence between the observed patterns of expression of a disease and the patterns predicted by specific modes of transmission. A second application of family studies, particularly with respect to clinically defined syndromes such as mood disorders, is the investigation of the validity of diagnostic categories and subtypes thereof through inspection of the degree to which particular symptoms or symptom constellations breed true in families. Whereas the homogeneity of expression of disorders is the goal of the latter studies, information on heterogeneity of expression within families may also be employed to identify variable expressivity of transmitted disorders.

A major advantage of studying diseases within families is that the assumption of homotypy of the underlying factors eliminates the effects of heterogeneity, which are present in comparisons that are made between families. However, all individuals within a particular sibship are not expected to share equal genetic risk because of independent segregation of genes. Nevertheless, if two members are affected, similar etiologic factors can be assumed, and variable forms of expression can be identified. This property of within-family studies should be far more widely applied in other domains of research designed to elucidate etiologic factors.

Although standardized methods for conducting family studies have been well established, there are still remarkably few family studies that employ these study principles, including (Weissman *et al.*, 1986b):

(1) recruitment of a well-characterized homogeneous group of probands with a particular disorder
(2) selection of a control group of individuals who are comparable to the affected probands on all possible confounding factors except the disorder itself
(3) systematic enumeration of all living and deceased relatives according to the degree of relationship to the probands and controls
(4) use of structured diagnostic interviews with relatives using predetermined diagnostic criteria and reliable and valid diagnostic instruments
(5) maintenance of blindness with respect to the diagnostic status of the proband in collecting diagnostic information from the relatives and formulating the final diagnostic estimates
(6) collection of information regarding relatives unavailable for interview in a standardized format from as many informants as possible
(7) inclusion of ancillary information to supplement interview and family history data
(8) development of reliable procedures to integrate material from direct interviews, family history reports, and ancillary medical or psychiatric information in deriving the diagnostic assignment of the probands and relatives
(9) application of sophisticated statistical techniques to control for confounding variables and simultaneously adjust for length of observation of the relatives. Recent developments in biostatistics now permit simultaneous estimation of relative risk and familial clustering (Hedeker and Gibbons, 1996)

Review of empirical evidence

Although numerous family studies of both bipolar and MDD have been conducted during the past 30 years, it is remarkable that only four family studies of bipolar disorder and five studies of MDD meet the above-cited standards of family study

methodology including inclusion of control probands and relatives, application of standardized diagnostic criteria with structured diagnostic instruments, and blindness with respect to the diagnosis of the probands.

Table 13.1 presents a summary of controlled family studies of probands with bipolar disorder and MDD. The weighted average risk ratio (comparing the prevalence of mood disorders among relatives of cases compared to those of controls) for bipolar disorder among relatives of bipolar probands is 10.3, whereas the average risk ratio of MDD among relatives of bipolar probands compared to those of controls is 3.2. This indicates a very high magnitude of familial aggregation of bipolar disorder, similar to that found for many of the major diseases for which the genetic basis has been identified. In contrast, the average risk ratio for MDD among relatives of probands with MDD compared to those of controls was 3.6, indicating only a moderate influence of familial aggregation on non-bipolar mood disorders. Although sex, age, birth cohort, and socioeconomic status are differentially associated with MDD (greater risk among females, later birth cohorts, lower socioeconomic status), there is no evidence that they moderate the familial recurrence risk of mood disorders (Weissman *et al.*, 1986a; Tsuang and Faraone, 1990).

Studies of offspring of mood-disorder probands have contributed substantial information on developmental influences in the expression of mood disorders among youth. The high-risk studies on bipolar disorder have revealed an increased risk of mood disorders among offspring of parents with bipolar illness (Decina *et al.*, 1983; Klein *et al.*, 1986; Radke-Yarrow, 1998). There is now a growing body of research of the developmental manifestations of bipolar disorder, and several high-risk studies of bipolar disorder are under way.

In contrast to bipolar disorder, there are far more high-risk studies of MDD, some of which have now been extended to three generations (Weissman *et al.*, 1997; Warner *et al.*, 1999). Although there is a consistent association between mood disorders among parents and offspring (Downey and Coyne, 1990), nearly all show a lack of familial specificity of mood disorders since the prevalence of anxiety and behavioral disorders are often equally elevated (Weissman *et al.*, 1984a; Merikangas and Angst, 1995; Harrington *et al.*, 1997; Rende *et al.*, 1999). A review of comorbidity of anxiety and depression by Brady and Kendall (1992) suggests that anxiety and depression may be part of a developmental sequence in which anxiety is expressed earlier in life than depression.

With respect to subtypes of bipolar disorder, studies of the familial specificity of the bipolar I–II distinction have yielded inconclusive results. Whereas some studies suggest a continuum from bipolar I to bipolar II to major depression based on familial overlap (Gershon *et al.*, 1986; McMahon *et al.*, 1995), others demonstrate that bipolar II disorder constitutes an independent mood-disorder

Table 13.1 Proportion of first-degree relatives of bipolar (BP) and major depressive disorder probands with a lifetime history of bipolar and major depressive disorder

			Rates/100 subtype in relatives by proband subtype					
Study	Probands (*n*)	Relatives (*n*)	BP–BP	BP–UP	UP–BP	UP–UP	Control–BP	Control–UP
Gershon *et al.* (1975)	Bipolar 54	411	19.6	11.5	11.0	20.1	0.2	0.5
	Unipolar 16	113						
	Controls 75	619						
Gershon *et al.* (1982)	Bipolar 130	739	21.9	2.6	8.0	3.0	0.4	5.7
	Unipolar 30	166						
	Controls 43	265						
Weissman *et al.* (1984b)	Unipolar 133	810			1.5	3.2	1.5	4.1
	Controls 82	591						
Tsuang *et al.* (1985)	Bipolar 100	230	21.2	1.9	11.9	2.3	0.2	4.8
	Unipolar 225	500						
	Controls 160	543						
Heun and Maier (1993)	Bipolar 80	504	7.1	17.1	1.3	19.0	0.9	7.7
	Unipolar 108	306						
	Controls 80	221						
Total rates/100			6.2	12.2	2.2	13.6	0.6	3.8
Relative risk (versus control)			10.3	3.2	3.5	3.6		

UP, unipolar.

Ratio weighted for sample size.

subtype (Heun and Maier, 1993; Bauer and Dunner, 1996). The lack of adequate coverage of cases identified in community and primary care settings by the current diagnostic criteria for depression, as well as the low longitudinal stability of specific depressive subtypes, has led to a re-evaluation of the classification of mood disorders (Angst and Merikangas, 1998; Angst, 1999).

Angst and Merikangas (1998) have argued for a more phenomenologic approach to the classification of depression, based on systematic evaluation of the thresholds for individual symptoms, specific symptoms included in the diagnostic categories, as well as the frequency and duration criteria. A series of subthreshold definitions of depression and anxiety was developed by Angst *et al.* based on a 25-year prospective follow-up of a community sample of a cohort of young adults from Zurich, Switzerland (1984). Numerous other investigators have proposed expanding the criteria for mood and anxiety disorders, primarily based on longitudinal follow-up of clinical and community samples of adults (Judd *et al.*, 1994) and children (Kovacs and Beck, 1977; Lewinsohn *et al.*, 1999). Several investigators suggest that a substantial proportion of those with recurrent depression may actually have a form of bipolar disorder (Pages and Dunner, 1997).

Although the concept of atypical depression has been widely recognized, there is still no consensus regarding the specific diagnostic criteria or its clinical significance. According to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV), the essential features of the atypical specifier are mood reactivity, increased appetite or weight gain, hypersomnia, leaden paralysis, and a long-standing pattern of extreme sensitivity to perceived interpersonal rejection (Alpert *et al.*, 1997; Merikangas *et al.*, 2002a). Atypical depression is discriminated from non-atypical depression on the basis of differential clinical features including an earlier onset, greater chronicity, and more severe symptoms than other depressive subtypes (Angst *et al.*, 2002). Other discriminating factors include differential association with bipolar II disorder, compared to other depressive subtypes (Benazzi, 2000), differential treatment response (Stewart *et al.*, 2002), specific patterns of neuroendocrine challenge response (Schmidt *et al.*, 1997), different patterns of comorbidity, including stronger associations with social phobia and migraine, and some degree of specificity in twin (Kendler *et al.*, 1996) and family studies (Dunner, 1980; Heun and Maier, 1993; Merikangas and Avenevoli, 2002). Although the validity of expression of atypical features in youth is still under investigation, studies of depression in children and adolescents confirm that atypical features do occur in youth as well (Williamson *et al.*, 2000; Angst *et al.*, 2002). Although there is substantial research on this subtype, to our knowledge there are no large-scale family studies of atypical depression in the context of the range of expression of both bipolar and unipolar disorder, as well as anxiety disorders.

Rapid cycling is defined as the occurrence of four or more discrete episodes of mood disorders within a 12-month period, with each episode meeting both duration and symptom criteria for major depressive, manic, mixed, or hypomanic episodes. Rapid cycling occurs in approximately 5–15% of those with bipolar disorder, with a higher prevalence in women. Although not widely studied, there is little evidence for specificity of the familial aggregation of rapid cycling (Post *et al.*, 1984, 1986; Goodwin and Jamison, 1990). Existing family history data support a continuum notion in the familial aggregation of bipolar disorder (Nurnberger *et al.*, 1988; Wehr *et al.*, 1988; Goodwin and Jamison, 1990).

Seasonal affective disorder (SAD) applies explicitly to the major depressive episode in bipolar I, bipolar II, or MDD at characteristic times of the year, occurring more commonly in females. Most episodes initiate during the winter or fall and remit in the spring. They are characterized by hypersomnia, hyperphagia, anergia, carbohydrate craving and weight gain, symptoms more commonly considered atypical in unipolar depression but common in bipolar patients. The atypical symptoms occur in 65–85% of study subjects with seasonal mood disorders, compared to 15–30% of patients unselected for seasonality. Since 50–60% of patients with winter depression have first-degree relatives with MDD, this form of SAD is likely to be a manifestation of the general spectrum of major affective disorders that includes manic-depressive illness (Goodwin and Jamison, 1990). Family history data on seasonal depression do not appear to support this subtype as an independent subtype of major depression (Allen *et al.*, 1993).

Factors associated with familial transmission of mood disorders

The transmission of mood disorders may vary according to polarity, as described above, degree of relationship to the proband, age of onset of the proband, and sex of the proband and relative. Many of the above-cited family studies have explored the relationship between these proband characteristics and those in their relatives.

Relationship to the proband

Numerous studies have presented the rates of mood disorder among both the first- and second-degree relatives of mood-disorder probands (Gershon, 1989). According to expectations of traditional genetic models, risks to all classes of first-degree relatives should be equal for dominant traits, whereas siblings should have increased rates of disorders for recessive traits. The aggregate data for bipolar disorder reveal that the risk of bipolar disorder among parents and siblings is approximately equal for both bipolar disorder and MDD. However, the offspring tend to have elevated rates of bipolar disorder and equal rates of MDD when compared to parents and siblings. In the absence of control data, it is difficult to

interpret the latter finding. However, the elevation in the risk among offspring could result from comorbidity, recall bias, a cohort effect, or assortative mating in the parental generation, or genetic anticipation (Tsuang and Faraone, 1990).

Most genetic models described above predict a decrement in risk of disease according to the degree of relationship to the affected proband. Although a large number of studies have reported rates of mood disorders among both the first- and second-degree relatives, there is only a single controlled study in which the rates of mood disorder were compared between the first- and second-degree relatives with controls (Gershon *et al.*, 1982). The results of this study revealed that the rates of bipolar disorder among first-degree relatives of bipolar probands were approximately twice those of second-degree relatives, which in turn were greater than those of controls. In contrast, there was no elevation in the rates of either MDD or bipolar disorder among the second-degree relatives of MDD probands, nor was there an increased rate of MDD among the second-degree relatives of bipolar probands.

Age of onset

The effect of age of onset on the familial aggregation of mood disorders was first described by Stenstedt (1952) and has subsequently been confirmed in several studies. However, there are numerous possible confounding factors that have not been adequately addressed in these studies, including: recurrence, comorbidity, biased recall, and personality factors. Moreover, the conclusions of the above-cited studies have been based on a dichotomous classification of the age of onset of probands, rather than significant correlations between the age of onset of probands and relatives.

Sex of proband

The effect of the sex of the proband and relative has been systematically investigated for both bipolar disorder and MDD. In general, there is little deviation in family study data from the sex ratio for bipolar and MDD reported in epidemiologic studies. In general, the rates of bipolar disorder are nearly equal in male and female relatives, whereas there is a female preponderance of mood disorders among the relatives with MDD. However, the transmission of both bipolar disorder and MDD has been shown to be unrelated to the sex of the proband, with equal rates of mood disorders among the relatives of male and female bipolar disorder and MDD probands (Merikangas *et al.*, 1985; Faraone *et al.*, 1987).

In summary, the family studies of bipolar disorder and MDD demonstrate a strong degree of familial aggregation of both of these subtypes of mood disorders. However, the evidence is inconclusive regarding the role of shared underlying factors in the expression of these subtypes of mood disorders. The transmission of

Table 13.2 Twin studies[a] of mood disorders

	Monozygotic		Dizygotic		
	n	Concordance (%)	*n*	Concordance (%)	Relative risk
Bipolar disorder					
Rosanoff *et al.* (1935)	23	70	67	16	4.4
Kallman (1953)	27	93	55	24	3.9
Harvald and Hauge (1965)	15	67	40	5	13.4
Allen *et al.* (1974)	15	33	34	0	
Bertelsen *et al.* (1977)	55	51	11	14	3.6
Major depression disorders					
McGuffin *et al.* (1991)[b]	62	53	79	28	1.9
Kendler *et al.* (1992)[b,c]	590	48	440	42	1.2

[a] Studies with ≥15 twin pairs.

[b] *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn revised (DSM-IIIR) criteria.

[c] Females only.

mood disorders appears to be associated with an early age of onset of mood disorders in probands, the bipolar subtype, and recurrent episodes, but not with the sex of the affected proband.

Twin studies of mood disorders

There have been numerous studies which compare the rates of mood disorders among monozygotic and dizygotic twins. The majority of the earlier studies selected probands from inpatient settings or treatment registries. Table 13.2 presents the twin studies of probands with bipolar disorder and MDD in which there were at least 15 twin pairs. The average concordance for mood disorders among monozygotic twins was 60% and 12% for dizygotic twins. There is a fivefold greater rate of concordance for mood disorders among monozygotic than dizygotic twins, thereby indicating the importance of the role of genetic factors in the familial aggregation of bipolar disorder.

Twin studies of mood disorders reveal that genetic factors have a far greater etiologic role in bipolar disorder than in MDD. The relative risks comparing monozygotic and dizygotic twins in two studies were 1.9 (McGuffin and Katz, 1989) and 1.2 (Kendler *et al.*, 1992). Nevertheless, the application of quantitative models that estimate the relative components of the variance attributable to shared genes, common environment, or unique non-shared environment yielded significant degrees of heritability in both studies (i.e., 0.39 in the former and 0.84 in the

latter; McGuffin and Katz, 1989; Kendler *et al.*, 1992). Differences in the results of the two studies could be attributable to difference in sampling (i.e., hospitalized patients in the former study and inclusion of only females from the general population in the latter), or to other methodologic differences.

In addition, Tsuang and Faraone (1990) estimated that the heritability of bipolar depression is 0.59, and a recent meta-analysis of community-based twin studies of MDD yielded a substantially lower heritability estimate of 0.37 (95% confidence interval = 0.28–0.42; Sullivan *et al.*, 2000). This latter estimate also indicates that nearly two-thirds of the liability to MDD *cannot* be attributed to genes. The concordance rates were somewhat lower for males than for females: the range for males was 0.23–0.41 for monozygotic and 0.14–0.34 for dizygotic and the range for females was 0.47–0.67 for monozygotic and 0.32–0.43 for dizygotic pairs.

Early studies of the specificity of transmission of polarity in twin studies were reviewed by Zerbin-Rudin (1969). The largest twin study which systematically investigated differences in concordance among bipolar and MDD twins was presented by Bertelsen and colleagues in 1977. Studies which examined the concordance rates among twins by polarity support a strong degree of specificity of transmission of the two subtypes of mood disorders, with little cross-transmission between bipolar index twins with MDD co-twins, and the converse. The average relative risk for cross-transmission for probands with either MDD or bipolar disorder was 1.5. In contrast, bipolar disorder was found to exhibit a strong degree of specificity, with an eightfold greater risk of bipolar disorder among the co-twins of bipolar monozygotic probands compared to their dizygotic counterparts.

The major conclusion that can be drawn from the current evidence from twin studies is that mood disorders are strongly heritable, with bipolar disorder exhibiting a much greater degree of involvement of genetic factors in its etiology than MDD. Moreover, there is little evidence for the cross-transmission of the two subtypes of mood disorder. Faraone *et al.* (1987) calculated the aggregate variance components from the twin studies of MDD then available and found a significant degree of heritability (i.e., 0.51), a significant contribution of the common environment of the twins (variance 0.42), and nearly no effect of the unique environment in the development of mood disorders. Twin studies of milder mood disorders are difficult to interpret because of differences in diagnostic definitions and inconsistent application of the criterion of hospitalization for affected status (Stenstedt, 1966; Shapiro, 1970; McGuffin and Katz, 1989).

Adoption studies of the mood disorders

Adoption studies are the most powerful design to test the relative contributions of genetic and environmental factors to the etiology of the mood disorders. There are

very few adoption studies of mood disorders, and those that are cited were typically quite small and conducted more than 20 years ago. The chief impediment to adoption studies of mood disorders is the lack of valid information on depression in biologic parents, particularly the biologic father.

The aggregate adoption study data on mood disorders reveal a moderate increase in rates of mood disorders among the biologic compared to adoptive relatives of adoptees with mood disorders (Tsuang and Faraone, 1990). With respect to bipolar disorder, there is little evidence for differential risk among biologic compared to adoptive relatives of adoptees with bipolar disorder. However, the small numbers of bipolar adoptees who have been studied (i.e., fewer than 50) do not provide an adequate test of genetic and environmental influences (Goodwin and Jamison, 1990). The most compelling finding from adoption studies, however, is the dramatic increase in completed suicide among biological relatives of mood-disorder probands (Mendlewicz and Rainer, 1977; Wender *et al.*, 1986).

Genetic epidemiology of mood disorders in youth

Family studies

Despite the abundance of well-controlled family and genetic studies that have employed sophisticated methodology to investigate the transmission of mood disorders among adults, there are only a limited number of controlled family studies that have focused on the manifestation of mood disorders among adolescents (Merikangas and Swendsen, 1997).

Controlled family studies of adult relatives of children with depression as well as offspring of adults with depression provide consistent evidence that MDD has a strong familial component (Weissman, 1987; Neuman *et al.*, 1997; Beardslee *et al.*, 1998; Kovacs and Devlin, 1998). Children of depressed parents are three times more likely to have an episode of MDD than children whose parents are not depressed (Birmaher *et al.*, 1996) and are four times more likely to develop mood disorders (Lavoie and Hodgins, 1994). By the age of 25, children of affectively ill parents have a 60% chance of developing MDD (Beardslee *et al.*, 1993). Risk to children is even greater when both parents exhibit mood disorders (Merikangas *et al.*, 1988). Studies of parents of children with MDD reveal a strong association between child and parent MDD (Puig-Antich *et al.*, 1989; Williamson *et al.*, 1995). Although several studies suggest that early age of onset is associated with increased familial aggregation of depression, the results of recent family and twin studies of youth conclude that prepubertal depression is less heritable than postpubertal depression (Harrington *et al.*, 1997; Silberg *et al.*, 1999).

Controlled studies of offspring of parents with bipolar disorder exhibit a wide variation in the frequency of mood disorders among offspring of affected parents (a range of 23–92%; Hammen *et al.*, 1990; Radke-Yarrow *et al.*, 1992), but collectively suggest a familial component. Rates of mania and bipolar disorder are generally low due to the young age of adolescent offspring in these studies; however, children of bipolar parents show greater specificity of transmission of mood disorders than do children of parents with unipolar depression (Merikangas and Angst, 1995).

Although these studies provide evidence of familial influence in the etiology of mood disorders, they shed little light on possible mechanisms through which such factors may operate to produce affective psychopathology in children. Familial aggregation of depression may result from shared genes, common environmental factors, or a combination thereof.

Twin studies

The role of genetic factors underlying the familial aggregation of depression has been investigated by several twin studies of depressive symptoms and disorders among youth. Reports by Thapar and McGuffin (1994, 1995, 1997), Murray and Sines (1996), Eley and Plomin (1997), and O'Connor *et al.* (1998) conclude that there is a modest degree of genetic influence for childhood depressive symptoms, with greater heritability with age. However, some of these studies suggest that the age-related increase in heritability is limited to males, whereas the influence of the shared environment tends to increase with age in females (Eley and Stevenson, 1999).

Genetic factors may also play a role in the recurrence and stability of depression. The twin study of O'Connor *et al.* (1998) found that the stability of depressive symptoms over a 3-year period was primarily explained by genetic influence; Silberg *et al.* (1999) found similar results among girls but not boys. Although a strong genetic component is implicated, O'Connor *et al.* (1998) warn that it is premature to accept the conclusion that the identified influence of heritability is, in fact, purely genetic, given that recent reports suggest strong and pervasive gene–environment correlations (e.g., evocation of stressful events based upon a genetic predisposition). Consistent with this, Silberg *et al.* (1999) found that individuals who inherited a genetic predisposition for depression also inherited a tendency to experience negative life events. Finally, adoption studies of depression symptoms in children and adolescent found only negligible genetic influence (van den Oord *et al.*, 1994; Eley *et al.*, 1998).

Although evidence suggests that the vulnerability for depression may be inherited, the environmental stressors have also been implicated in the development of

mood disorders in youth (Warner *et al.*, 1995; Goldsmith *et al.*, 1997). Indeed, the family environment of depressed adults is consistently characterized by family and parental discord, divorce, inattention, rejection, and abuse (Angold, 1988; Downey and Coyne, 1990; Rutter, 1989). Parker (1979) found that a parental discipline pattern of affectionless control was strongly associated with depressive disorders in adolescents; studies of bipolar depressives reveal normal parental levels on these dimensions (Parker, 1979). Community studies have documented associations between family dysfunction and depression in children and adolescents (Kandel and Davies, 1982; Garrison *et al.*, 1985; Bird *et al.*, 1988). These associations appear to be a reciprocal relationship between parental depression and child maladjustment (Downey and Coyne, 1990).

Age

There is great variability in the estimates of the initial age of onset of depression. Based on retrospective recall of the onset of depression among adults, the onset of depression has been previously estimated to occur in the late 20s and early 30s. However, the results of recent prospective studies reveal that depression often occurs in childhood. Prior to the recent generation of studies of children and adolescents, estimates of the age of onset of depression were derived from retrospective studies of adults with depression (Angst, 1988) and suggested mid to late adolescence as the most common age of onset of first episode of MDD (Burke *et al.*, 1990; Hammen and Rudolph, 1996; Lewinsohn *et al.*, 1998), although the NCS suggests an average age of onset during early adulthood (24 years for men and 23.5 years for women; Kessler *et al.*, 1993).

Genetic marker studies of mood disorders

Association studies of mood disorders

Association studies investigate the relationship between disease status and a particular marker or allele across families and individuals. Most association studies employ the traditional case-control design in which the prevalence of a putative disease marker is compared among persons with a disorder to persons without the disorder. The most common methodologic error in association studies is the lack of equivalence between the cases and controls on factors which may confound the association between the purported marker and disease.

After exclusion of spurious associations due to methodologic factors or population stratification, associations between a disease and a marker could be attributed to either linkage disequilibrium between genes for the disease and for the marker, or the effect of a single gene that encodes both the marker and the disease.

In genetic case-control studies, the most likely source of confounding is ethnicity because of differential gene and disease frequencies in different ethnic subgroups. Aside from confounding, association studies are particularly prone to false-positive findings due to multiple testing without correction and the low prior probability of a gene–disease association (Wacholder *et al.*, 2000). In addition, there is a strong publication bias against reports of negative association studies (Risch and Merikangas, 1996). The latter problem can be resolved in part by the use of much higher α-levels (i.e., false-positive error rates) in association studies (Hirschhorn *et al.*, 2002).

The loci for several biochemical parameters that are suspected to be involved in either etiology or outcome of the psychiatric disorders have been identified. It is important to note that many of these assignments are based upon a single study, and replication is clearly necessary. Identification of new loci is occurring at such a rapid rate that it is necessary to update the human map monthly. Application of this methodology to psychiatric disorders may be particularly fruitful in identifying major genes that are segregating in informative families.

Review of empirical evidence

Great emphasis has been placed on the association study of various affective spectrum disorders, focusing mostly on polymorphisms. From these studies, no functional differences between the alleles have been described (Johansson *et al.*, 2001). The most noted exception is an insertion/deletion polymorphism located in the promoter region of the serotonin transporter gene (5-HTTLPR), reported to affect the expression of the transporter (Lesch *et al.*, 1996), but there are also non-replications of these results (Rees *et al.*, 1997; Ohara *et al.*, 1998a; Frisch *et al.*, 1999; Seretti *et al.*, 1999). The 5-HTTLPR polymorphism has also been associated with clinical subtypes of depression, including SAD and seasonality (Rosenthal *et al.*, 1998; Sher *et al.*, 1999), but the findings have not been able to be replicated in two subsequent studies (Johansson *et al.*, 2001). Other polymorphisms include an amino acid substitution in catechol-*O*-methyltransferase (COMT) affecting the enzymatic activity (Lachman *et al.*, 1996a, b), which has been linked to bipolar disorder, including the rapid-cycling bipolar disorder subtype, and unipolar depression (Li *et al.*, 1997; Kirov *et al.*, 1998; Ohara *et al.*, 1998b). A repeat polymorphism in the promoter region of a monoamine oxidase A (MAOA) gene has also been reported to influence the transcriptional activity (Kunugi *et al.*, 1999). Unfortunately, conflicting results have been found for both polymorphisms (Biomed European Bipolar Collaborative Group, 1997; Frisch *et al.*, 1999; Kunugi *et al.*, 1999; Schulze *et al.*, 2000).

Linkage studies of mood disorders

Linkage is based on the principle that two genes that lie in close proximity on a chromosome are transmitted to their progeny together. However, if the loci are far apart, crossing over between the maternal and paternal chromosomes may take place during meiosis, thereby producing new combinations of alleles. The farther apart the loci, the greater the probability that crossing over will occur and that the offspring may inherit a recombinant of the two parental chromosomes. Cross-overs can be detected by inspecting the maternal and paternal genome; when a particular chromosome is not identical to the parental chromosome, a cross-over or recombination between the maternal and paternal chromosomes has occurred.

Linkage studies differ from association studies in that linkage is based on an association between genetic markers and putative disease genes *within* families, whereas association is the co-occurrence of a marker and disease *at the level of the general population*. Linkage does not imply that the adjacent gene is etiologically related to the disease; only that it can be used to track possible genes in families. Therefore, one allele at a particular locus may be linked to a disease in some families, whereas the other allele may co-segregate with the same disease in other families. In contrast, associations are detected in case-control studies that compare the prevalence of a marker in patients with a particular illness with the proportion of control subjects who possess the marker. Thus, an association found in patient samples may not extend to their families.

Two major methods of genetic linkage analysis are the LOD score method (Morton, 1955) and the affected sib-pair method, derived from Penrose (1935). The LOD score is defined as the ratio of the log odds of the likelihood of a linkage between two loci within a pedigree to that of the likelihood of independent segregation of the two loci, or a recombination frequency of 1/2. A LOD score $> +3$ represents a probability of 1/1000 of falsely concluding that linkage exists when it is absent, and a LOD score < -2 indicates significant evidence for a lack of linkage between the putative marker and disease. Scientific evidence for acceptance of linkage between a disease and genetic marker was described by Risch (1990), who stated that in addition to a LOD score > 3, a linkage finding should be replicated in a different sample in a different laboratory.

The affected sib-pair method examines the sharing of marker alleles at a locus among affected sib pairs. The null hypothesis of no linkage specifies probabilities of 1/4, 1/2, and 1/4 for sharing 2, 1, and 0 marker alleles among affected sibs. Excess sharing of two haplotypes (or conversely, diminished sharing of haplotypes) provides evidence for linkage. The sib-pair method is a powerful design if the gene is rare and requires no assumption regarding the mode of inheritance of the disorder.

Markers in the candidate region identified by linkage analysis can be used to narrow the location of the disease gene through linkage disequilibrium analysis. Linkage disequilibrium is a population association between two alleles at different loci, and occurs when the same founder mutation exists in a large proportion of affected subjects in the population studied. Usually, the closer the marker is to the disease locus, the greater the proportion of affected subjects who carry the identical allele at the marker (Risch, 2000). However, in measuring the strength of linkage disequilibrium for a given marker, it is also important to select unaffected control subjects from the same population, because an allele shared among affected subjects may also be common in the general population and thus shared by chance rather than due to proximity to the disease locus (Risch, 2000).

Review of empirical evidence

The initial enthusiasm generated by early claims of linkage between bipolar disorder and DNA markers including Xq (Baron *et al.*, 1987; Mendlewicz *et al.*, 1987; Lucotte *et al.*, 1992) and 11p (Egeland *et al.*, 1987) was diminished by subsequent non-replications (Risch and Botstein, 1996). Numerous linkage studies of bipolar disorder have subsequently been reported to regions on all but six chromosomes (Straub *et al.*, 1994; Pekkarinen *et al.*, 1995; Stine *et al.*, 1995; Blackwood *et al.*, 1996; Detera-Wadleigh *et al.*, 1996, 1999; Freimer *et al.*, 1996; McMahon *et al.*, 1997; Moldin, 1997; Smyth *et al.*, 1997; Ewald *et al.*, 1998a, b; Aita *et al.*, 1999; Kelsoe, 1999; Morissette *et al.*, 1999; Kelsoe *et al.*, 2001). Table 13.3 presents a summary of genome-wide linkage studies of bipolar disorder updated from a recent review by Prathikanti and McMahon (2001). Based on a total of 3538 bipolar I disorder scans in affected subjects from 1119 pedigrees reported in 20 samples, the authors conclude that no two studies conclusively implicate the same region. However, suggestive findings emerged for two loci (i.e., 4p12–13 and 13q31–33). The most striking conclusion was that no two studies employed identical ascertainment procedures and there was substantial diversity in sampling and methods. In conclusion, sufficient ambiguities exist to give pause in considering any of these linkage results as unambiguously replicated (Goldin *et al.*, 1997; Reus and Freimer, 1997; Rice *et al.*, 1997; DeLisi *et al.*, 2000; Altmüller *et al.*, 2001; Craddock and Jones, 2001). More recently, McMahon *et al.* (2001) reported replication of the suggestive finding reported earlier by Nöthen *et al.* (1999). The demonstration of the low power of existing linkage studies by Risch and Merikangas (1996) generated a spate of association studies of mood disorders, particularly those employing within-family controls (Merikangas *et al.*, 2002b).

Some other features of mood disorders that complicate genetic analyses are described below.

Table 13.3 Summary of recent bipolar linkage studies

Study	Sample	Pedigrees	Affected subjects	Genotyped pairs	Pair type	Number of markers	Scanned what?	Locus = LOD
Straub *et al.* (1994)	Columbia/ Hadassah University	47	490	443	ERP	5–153 markers per chromosome	Genome-wide	21q22 = 3.4
Ewald *et al.* (1995)	Danish	2	89	87	ERP	12	Chromosome 16p13	16p13 = 2.5
Blackwood *et al.* (1996)	Edinburgh	1	27	26	ERP	135 (87 additional markers on 4p)	Genome-wide	4p12–13 = 4.8
McMahon *et al.* (1997)	Clinic and inpatient from Baltimore and Iowa City	23	251	228	ASP; ERP	13	Chromosome18	18q23 = 2.8
Ginns *et al.* (1996)	Older-order Amish	5	207	202	ERP	551	Genome-wide	6p25 = 2.5; 13q13 = 1.4; 15q21 = 1.1
Adams *et al.* (1998)	Australian	11	224	213	ERP	214	Genome-wide	4q35 = 3.2
Ewald *et al.* (1998b)	Danish	2	89	87	ERP	16	Chromosome 12q22-q24	12q24 = 3.4
Ewald *et al.* (1998a)	Danish	2	89	87	ERP	16	Chromosome 4	4p16 = 2.0

Table 13.3 (*cont.*)

Study	Sample	Pedigrees	Affected subjects	Genotyped pairs	Pair type	Number of markers	Scanned what?	Locus = LOD
Ginns *et al.* (1998)	Older-order Amish	4	68	64	ERP	980	Genome-wide	4p12–13 = 4.1; 4q = 3.3
Detera-Wadleigh *et al.* (1999)	NIMH-CNG+ right extension of Amish	22	159	137	ERP	607	Genome-wide	13q32 = 3.5; 1q31–32 = 2.67; 18p11 = 2.32
Morissette *et al.* (1999)	Saguenay-Lac St. John	1	53	52	ERP	332	Genome-wide	12q23–24 = 1.3
Aita *et al.* (1999)	USA (57 pedigrees) and Israel (18 pedigrees)	40	373	333	ERP	31	Chromosome 21	21q22 = 3.4
Nöthen *et al.* (1999)	German	57	176	119	ASP	23	Chromosome 18	18p11.2 = 2.5; 18q22–23 = 2.1
Kelsoe *et al.* (2001)	San Diego/ Vancouver, British Columbia	20	76	56	ERP	443	Genome-wide	22q13 = 3.8
Cichon *et al.* (2001)	Germany/Israel /Italy	75	206	131	ASP	33	Chromosome 10	10q25 = 2.9
McMahon *et al.* (2001)	Clinic and inpatient from Baltimore and Iowa City	58	586	259	NRP	32	Chromosome 18	18q21–23 = 4.7

Liu, C. *et al.* (2001)	Caucasian + right branch of old-order Amish pedigree + 3 Ashkenazi Jewish families	22	371	349	ERP	16	Chromosome 13 (specific to area near 13q32)	13q32 = 3.3
Liu, J. *et al.* (2001)	USA and Israel	56	range 156–576	431	ERP	14	Chromosome 21 (specific to area near 21q22)	21q22 = 3.6

Adapted from Merikangas *et al.* (2002b).

ERP, extended pedigree; ASP, affected sib pairs; NIMH-CNG, National Institute of Mental Health, Collaborative genetics study.

Challenges to the identification of genes for mood disorders

The major problem in defining future strategies for identifying genes for mood disorders is the lack of consistent findings from existing studies, and uncertainty regarding appropriate designs and methods for detecting genes for complex disorders. Although there is a substantial degree of pessimism regarding the identification of genes underlying mood disorders, the lack of success in identifying major genes for psychiatric disorders in general and mood disorders specifically using approaches that had been successful for many single-gene disorders is not altogether unexpected in the light of the complexity of mood disorders.

The conclusion that the lack of consistency in the findings of linkage studies may be attributed in part to ascertainment and methodological differences across studies (Prathikanti and McMahon, 2001) suggests that standardization of definitions, analyses, and procedures may enhance the comparability across studies. To the extent that integration of previous studies is methodologically feasible, pooling of prior linkage studies of bipolar disorders would increase the power of the aggregate data to detect linkage.

Psychiatric disorder phenotypes

There is widespread agreement regarding the limitations in applying the current nomenclature for mental disorders to biologic studies. Psychiatric disorder phenotypes, based solely on clinical manifestations without pathogenomic markers, still lack conclusive evidence for validity of classification and reliability of measurement (Kendell, 1989). The lack of specificity of biologic and psychosocial risk factors and correlates, as well as the lack of longitudinal stability, still suggest etiologic and phenotypic heterogeneity.

Advances in neuroscience and genetics leading to enhanced understanding of the structure and function of the human brain, and the role of genetic and environmental factors involved in cognition, emotion, and behavior will likely have a major impact on classification. Likewise, advances in our ability to measure and observe the major components of behavior will also facilitate identification of etiologic mechanisms.

Lack of direct correspondence between the genotype and phenotype

Despite these advances in characterizing human genotypes, application of this knowledge to human diseases is still limited by the complexity of the process through which genes exert their influence. A lack of one-to-one correspondence between the genotype and phenotype is clearly the rule rather than the exception

for most human disorders. Phenomena such as penetrance (probability of phenotypic expression among individuals with susceptibility gene), variable expressivity (degree to which susceptible individuals express components of genotype), gene–environment interaction (expression of genotype only in the presence of particular environmental exposures), pleiotropy (capacity of a gene to manifest simultaneously several different phenotypes), and genetic heterogeneity (different genes leading to indistinguishable phenotypes) have been demonstrated for several human disorders for which susceptibility genes have been identified.

Two of these phenomena that have been of particular concern for genetic nosology are genetic heterogeneity, or one from many, and pleiotropy, or many from one. These two situations are reflected in the nosologic tension between lumping and splitting, as described by Victor McKusick in his review of historical developments in genetic nosology (1973). With increasing specialization in medicine, there has been a tendency to split categories excessively. The lumpers have corrected the oversplitting; but recent advances in genetics have led to a new wave of "better-founded splitting" based on an increased ability to detect subtler phenotypic similarity but genotypically heterogeneous conditions.

Gene–environment interaction

Gene–environment interaction characterizes a broad range of human diseases such as cancer and birth defects. Not only is the expression of genes modified by the environment, but there is now also substantial evidence to indicate that numerous environmental factors may actually alter the genotype. Francis and colleagues (1999) have shown that maternal behavior mediates stress reactivity in adulthood and is associated with future maternal behavior among offspring. Genes may also be involved in the response or resistance to purely environmental agents such as diet, stress, exercise, drugs, and nutritional deficiencies (Omenn and Motulsky, 1978). The methods of genetic epidemiology are designed specifically to identify gene–environment interactions (Ottman, 1995; Yang and Khoury, 1997).

The lack of validity of diagnostic categories is therefore by no means unique to psychiatry. Similar to other domains of complex disorders, the major impediments to the establishment of validity of the classification of psychiatric disorders are: the unreliability of measurement (of both diagnoses and markers); the lack of specificity of risk factors and biologic markers; and the lack of one-to-one correspondence between the phenotype and genotype likely attributable to both etiologic and phenotypic heterogeneity and gene–environment interaction. The well-known steps for validating phenotypes recently reiterated by Tsuang *et al.* (1993) include the following guidelines: specificity, state of independence, heritability, familial association, co-segregation, and biological and clinical plausibility.

Although there have been numerous controlled family studies of psychiatric disorders, there are very few that were designed to investigate the specificity of core components of the phenotypes. Those that have examined subtypes of psychiatric disorders have not provided sufficient evidence for familial specificity. The experienced investigators in this field tended to abandon this research because of the advent of opportunities to identify genes in the early 1990s. This was unfortunate because this was also the time when there had been numerous advances in methods and analyses for family studies (Weissman *et al.*, 1986b), including population-based ascertainment of common disorders and appropriate selection of controls (Kendler, 1990; Klein, 1993; Hill and Neiswanger, 1997) and random-effects regression models that incorporate familial clustering.

The recent shift in psychiatric genetics to identify endophenotypes, or underlying biologic factors, that explain familial recurrence is an important step in moving from broad phenotypes to specific components of disorders. Recent advances in neuroscience and the behavioral sciences, not available to the pioneers in family study research in psychiatry, will be important tools in enhancing this process. Substantial effort should be devoted to the application of genetic epidemiologic studies that are designed to define more homogeneous components of mood disorders and associated biologic markers that may yield higher familial relative risk than the heterogeneous category of major depression. Ironically, however, genetic mapping strategies may also assist in defining subtypes (Reus and Freimer, 1997). Nevertheless, lessons from other disorders have demonstrated that, even after the identification of the gene for single-gene disorders, the classification still requires additional testing to identify sources of heterogeneity in phenotypic expression. For example, despite the identification of the actual gene for Marfan's syndrome, the checklist criteria appear to be remarkably similar to those within the realm of DSM-IV. Likewise, recent studies of neurofibromatosis have examined familial specificity of diverse clinical manifestations of the same genetic mutations.

Two directions of research that are particularly promising for informing phenotypic validity include: (1) genetic epidemiologic strategies and prospective longitudinal studies for phenotype refinement; and (2) studies designed to identify endophenotypes of mood disorders, informed by advances in neuroscience.

Future directions

The tremendous progress in molecular biology, neuroscience, and related fields is likely to lead to new approaches to the genetics of psychiatric disorders of human diseases. Identification of all of the genes in the human genome and their functional variation will provide opportunities for studying the impact of those variants on phenotypic outcomes of interest. Studies of gene regulation,

microarray techniques that can detect tissue-specific expression, transgenic mice, expression arrays, and proteomics, allowing identification of gene function, will enhance our knowledge of the biologic significance of gene markers. Parallel research across numerous species will provide important information regarding gene expression, phenotypic models, and gene–environment interaction (Peltonen and McKusick, 2001). Knowledge of gene function and regulation is likely to lead to a shift from reverse-genetic approaches (linkage and linkage disequilibrium analysis) to forward-genetic approaches (Risch, 2000).

Similar progress in neuroscience, particularly developmental neuroscience, which investigates molecular, cellular, and integrative brain functions involved in the development of mental disorders, will advance our understanding of the complex biologic processes underlying mental disorders. The tools of neuroimaging, psychophysiology, and preclinical models of emotion are likely to provide information on etiologic pathways to mental disorders. Likewise, the impact of environmental exposures on modifying the development of cognition, emotion, and activity level will provide new opportunities to investigate mechanisms underlying gene–environment interactions involved in mental disorders. Greater understanding of the biologic and contextual factors from which mental disorders arise will dramatically improve the power of genetic studies to close the gap between the phenotype and genotype.

As we move from single-gene disorders to complex disorders, new tools will be necessary to reflect the multiple interacting factors. Increasingly, statistical methods will be based on the biological significance of markers, and new models will be employed to identify gene clusters, expression profiles, haplotype sharing, genetic attributable risk, and direct assessment of gene–environment interactions. The major focus on genetic studies will shift from a search for the gene, to which genes in which contexts lead to the development of mental disorders. The highly restricted sampling of the earlier generation of studies is likely to move into the general population where the concept of attributable risk will become salient.

Finally, the dramatic developments in molecular genetics and new approaches to sampling and gene detection will require substantial focus on ethical issues relevant to subject recruitment and interpretation of genetic data. Education of professionals involved in genetic research as well as those involved in the dissemination and interpretation of genetic marker data will be critical to ensure the ethical application of genetics to complex diseases in general and psychiatric disorders specifically. The assurance of truly informed consent will require comprehension of a risk-factor approach to genetics with respect to the concepts of absolute, relative, and attributable risk. Professional education should then be followed by public education in order for the public to gain an understanding of the meaning of genetic markers in disease prediction. Ironically, the public tends to attribute far greater significance to genetic markers than has been realized for

most of the complex human disorders. Because of the unique aspects of each disease, responsibility for assessing issues related to consent would be best maintained by local investigators and ethics boards, rather than regulations that apply across all diseases (Renegar *et al.* 2001).

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14

Biological aspects of rapid cycling and mixed states

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Introduction

Despite the fact that rapid cycling and mixed states are common manifestations of bipolar disorder (Kilzieh and Akiskal, 1999; Akiskal *et al.*, 2000; Grunze *et al.*, 2002a) they have very rarely been subjects of interest for clinical and basic research. As far as clinical research is concerned, rapid cycling and mixed state traditionally were exclusion criteria for controlled randomized phase III studies. This changed just recently, where antiepileptics such as lamotrigine (Calabrese *et al.*, 2000) were tested for their prophylactic efficacy in rapid-cycling patients. As far as mixed states are concerned, recent trials on modern antipsychotics (Keck *et al.*, 2003; Sachs *et al.*, 2002; Tohen *et al.*, 2002) also allowed mixed patients in these studies.

A major problem for including mixed states in studies is the lack of a generally excepted definition. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV) criteria (fulfillment of all criteria of mania and typical depression at the same time: American Psychiatric Association, 1994) are too narrow, as it has been shown in retrospective analysis of the valproate mania study (Bowden *et al.*, 1994) that one depressive syndrome predicts inferior responsiveness to lithium and better response to valproate (Swann *et al.*, 1997). A commonly used definition is the so-called Cincinnati criteria, which require at least three relevant depressive syndromes (McElroy *et al.*, 1992); however, again, a general consensus on how to define mixed states has not yet been achieved as other views may also have clinical advantages (Perugi *et al.*, 1997).

The same problem of heterogeneous definitions of mixed state is true for studies trying to characterize biological differences between mixed patients, manic patients, and healthy controls. This is also true for rapid-cycling patients. Rapid cycling has been defined by having four or more mood episodes within 1 year. This definition has been made according to a pivotal trial conducted by Dunner and

Fiève (1974) showing a rapid decline of lithium responsiveness with a cut-off at four episodes. Recent observations of large patient samples however question this "magic line" defined by four episodes. Data from the Stanley Foundation Bipolar Network (Kupka *et al.*, unpublished data) demonstrate that there is a continuous decline of treatment response with increasing number of episodes per year. Rapid cycling also includes some rare manifestations which appear to have a highly biological background, probably coupled to the circadian rhythm and Zeitgeber. However, these patients with 48-rapid cycling only represent a very narrow selection of rapid-cycling patients at large and conclusions from their biology may be not transferable to rapid-cycling patients with a chaotic and irregular course of illness.

The reason why it still makes sense to review the biology of rapid cycling and mixed states in one chapter is that some aspects of these manifestations may be in common. On a theoretical level, mixed states not following this strict definition of DSM-IV but the wider definition of the *Tenth Revision of International Classification of Diseases* (ICD-10: World Health Organization, 1992), which also allows timely separation of depressive and manic syndromes, may also be called ultradian rapid cycling. On the level of treatment, evidence from several open and some controlled trials points towards common principles in drug treatment. It appears to be general consensus that lithium is not very effective in both conditions, whereas antiepileptic drugs, especially valproate and lamotrigine, and also atypical antipsychotics such as olanzapine and risperidone may be more efficacious. To understand aspects of the biology of rapid cycling and mixed states, another possible approach would therefore be to look for mechanisms of action of these drugs which are not or only partially shared by lithium. We will use this approach in the second part of this chapter.

Implications of catecholamines on mixed states and rapid cycling

The first level to be considered is the cell membrane and the action of different neurotransmitters that may play a role in affective states. For bipolar disorder in general, results are still conflicting about changes in neurotransmission. Increased cortical norepinephrine (noradrenaline) and decreased 5-hydroxytryptamine and dopamine turnover has been described in bipolar patients (Manji and Potter, 1997). Within manic patients, the central nervous system levels of norepinephrine appear to increase with the degree of dysphoria, anger, and anxiety (Post *et al.*, 1989). Also a central serotonergic deficit, in both manic and depressed patients, has been suggested (Meltzer and Lowy, 1987) which may improve after treatment with valproate (Maes *et al.*, 1997). Tandon *et al.* (1988) compared selected cerebrospinal fluid (CSF) parameters from patients with bipolar disorder, mixed, to those with mania

and major depression. Fourteen patients in each category (DSM-III) were studied with regard to the dopamine metabolite homovanillic acid (HVA) and the serotonergic metabolite 5-hydroxyindoleacetic acid (5HIAA) in CSF under carefully controlled conditions. Both CSF HVA and 5HIAA were found to be significantly higher in manic than in major depressive patients. Discriminant analysis of the biochemical variables of the mixed affective group identified two biochemically distinct and clinically different subgroups of seven patients each, one resembling the manic group and the other the major depressive group. Tandon *et al.* conclude from these findings that mixed affective states do not exist as a separate entity, but are composed of two subgroups obtained from the manic and major depressive categories – a view that remains controversial (McElroy *et al.*, 2000).

However, other studies make a strong monoaminergic link to mixed states less likely, as they reported no change in either 5-HT2A or 1A receptor density (Dean *et al.*, 2001) and, as far as the noradrenergic action is concerned, no change in beta-receptor density (Werstiuk *et al.*, 1990).

As bipolar illness is quite heterogeneous, more precise results may be expected in a homologous group of patients. Therefore, several studies looked at a monoaminergic imbalance in 48-h rapid-cycling patients.

Characteristic and reproducible changes in norepinephrine and metanephrine excretion, closely related to mood swings, were described by Juckel *et al.* (2000). In general, the urinary excretion of norepinephrine and metanephrine was increased on both manic and depressed days, with higher values during mania, and was generally ameliorated after successful valproate treatment. As far as mixed states are concerned, Swann *et al.* (1994) reported on increased 3-methoxy-4-hydroxyphenylethyleneglycol excretion in mixed states. As especially tricyclic noradrenergic acting antidepressants are capable of inducing a switch from pure depression into mixed states or mania, and may also induce a rapid-cycling course, norepinephrine and its metabolites may play at least a strongly modulating role in these conditions.

Concerning an impact of the serotonergic system, a very high and, compared to bipolar disorder in general, increased comorbidity has been described between mixed states, obsessive-compulsive disorder, and anxiety disorders, which are generally considered as serotonergic disorders. Thus, for mixed states the serotonergic system may also play a role. From clinical observation, this appears less likely for rapid cycling, as selective serotonin reuptake inhibitors are considered a generally safe treatment for possible induction of switch or rapid cycling.

To our knowledge, mixed states and rapid cycling have not yet been explored with a special focus on the dopaminergic system, with the exception of the cited study of Tandon *et al.* (1988). In general, a dopamine hypothesis of mania has been proposed by several authors (Diehl and Gershon, 1992; Buki and Goodnick, 1998) and genetic aberrations of dopamine receptors and transporters have been demonstrated in

bipolar patients (Kelsoe *et al.*, 1996; Manki *et al.*, 1996; Waldman *et al.*, 1997). Recently, the D_2-receptor region came out as a candidate locus associated specifically with bipolar disorder (Massat *et al.*, 2002). Decreased presynaptic dopamine function in the basal ganglia after successful treatment of mania with valproate has been demonstrated in a recent positron emission tomography study (Yatham *et al.*, 2001). However, so far no study on the dopaminergic system seems to have a special focus on rapid cycling.

Taken together, data on aberrations of biogenic amines in rapid cycling and mixed states are sparse, with the best evidence so far existing for distinct abnormalities of the noradrenergic metabolism, at least in 48-h ultrarapid-cycling patients. Generalizing these results to rapid cycling at large and mixed states, however, would be premature.

Implications of hormonal aberrations on mixed states and rapid cycling

The case report of Juckel *et al.* (2000) not only looked into biogenic amines, but also into changes of the limbic–hypothalamic–pituitary–adrenocortical axis in this 48-h rapid-cycling patient. Changes of both human growth hormone and cortisol were quite dramatic, with peaks during mania and troughs during depression. Again, successful valproate treatment ameliorated this rollercoaster of the LHPA axis.

As far as mixed states are concerned, a small study of Cassidy *et al.* (1998) compared seven mixed patients with purely manic patients concerning their plasma dexamethasone concentration and cortisol response in the dexamethasone suppression test (DST) during manic episodes. Measuring these parameters at 3 and 10 p.m., there was a tendency to decreased dexamethasone and increased cortisol levels in the mixed group. Other studies, unfortunately not exceeding 10 patients, reconfirm a tendency for increased DST non-suppression (Evans and Nemeroff, 1983; Krishnan *et al.*, 1983).

Swann *et al.* (1992) investigated HPA function and its relationship to clinical state in 19 hospitalized manic patients meeting Schedule for Affective Disorders and Schizophrenia – Research Diagnostic Criteria for acute manic episodes, compared patients with and without a mixed presentation, and examined the correlation between HPA activity and behavior. In this study, data were available from 13–16 patients. Patients with mania had elevated CSF and urinary free cortisol excretion compared with healthy subjects, and did not differ from depressed patients in any cortisol measures. Mixed manic patients had significantly higher morning plasma cortisol, postdexamethasone plasma cortisol and CSF cortisol than pure manics. Five of seven mixed manics and three of nine pure manics were DST non-suppressors. Afternoon plasma cortisol and CSF cortisol correlated significantly with depressed mood; urinary free cortisol correlated with

anxiety. None of the cortisol measures correlated with mania or agitation scores. From these data, the authors suggest that increased cortisol secretion is a characteristic of the depressed state in mixed manics, although pure manics may also have increased DST non-suppression.

Thyroid dysfunction has been implicated by several authors in rapid-cycling patients. Sack *et al.* (1988) reported on decreased nocturnal thyroid-stimulating hormone (TSH) secretion in rapid-cycling patients. Hypothyroid metabolism has also been reported by several authors in rapid cyclers (for a review, see Joffe and Sokolov, 1997), and low basal TSH levels also appear to be associated with a higher switch risk when bipolar depressed patients are exposed to antidepressants (Bottlender *et al.*, 2000). Preliminary clinical data (Bauer and Whybrow, 1990) suggest that thyroxine addition may be a helpful augmentation strategy in refractory rapid-cycling patients. For mixed patients, however, a correlation to thyroid dysfunction has not been convincingly observed so far. Joffe *et al.* (1994) found no difference in the frequency of grade II subclinical hypothyroidsm or thyroid hormone level between mixed ($n = 10$) and non-mixed ($n = 57$) manic patients. However, a study of Zarate *et al.* (1997) in first-episode manic patients, 15 mixed and 57 pure, showed a greater likelihood for elevated TSH in mixed patients, and a small study of Chang points in the same direction of hypothyroidism in mixed patients (Chang *et al.*, 1998). In the largest trial looking for thyroid antibodies in different mood states in 226 bipolar patients (including 28 patients with mixed states), Kupka *et al.* (2002) found no difference in the number of thyroid antibody-positive patients between euthymic, depressed, and mixed patients.

Besides these cited studies, there also several case reports on changes of neuroendocrinological abnormalities in rapid-cycling bipolar patients and their amelioration with remission (e.g., Shimizu *et al.*, 1997). But all these reports and studies do not solve a general problem, and that is causality. Are aberrations of the metabolism of biogenic amines and hormonal changes the cause of mixed states and rapid cycling or are they simply effects of a different mood state? Or are they even completely independent from mood and represent a variable triggered by another unknown, underlying mechanism which also affects the mood state? Thus, not only the evidence but also the causality of the impact of neurotransmitters and hormones remains weak on the course of mixed state and rapid cycling.

The impact of transmembranous ion fluxes on rapid cycling and mixed states

Besides acting on different neurotransmitters (5-hydroxytryptamine, dopamine, gamma-aminobutyric acid, and glutamate: for the latter two no studies have so far been done for rapid cycling and mixed states), antiepileptic drugs mainly target transmembranous ion fluxes. For carbamazepine, valproate, and lamotrigine,

blockade of fast sodium inward currents may be a decisive mechanism of antiepileptic action. For bipolar disorder in general, calcium (and probably potassium) fluxes may be the more important target.

A potential role of calcium in bipolar disorder?

Mobilization of calcium is a key event in presynaptic and postsynaptic signalling and also in lasting neuronal changes, as long-term potentiation.

Increased intracellular calcium concentrations, under baseline conditions or after mobilization following specific stimulation paradigms, are a solid finding in platelets and lymphocytes of bipolar patients, in both manic and depressive episodes (cf. Grunze *et al.*, 1997; Hough *et al.*, 1999). If we allow the speculative assumption that these findings in peripheral cells also reflect the neuronal environment, we suggest the following simplified model: mild elevations of intracellular calcium activate metabolic processes, by activating adenylate cyclase. This increases, beside other cyclic adenosine monophosphate-activated protein kinase-dependent steps, the synthesis of catecholamines by phosphorylation of tyrosine hydroxylase, leading to increased neuronal excitability. Excitability may also be increased by a partial inhibition of the Na, K-ATPase activity (el Mallakh and Wyatt, 1995). The clinical counterpart may be a manic syndrome. Further increase of intracellular calcium, however, dampens the adenylate cyclase activity even below its normal level, decreasing catecholamine synthesis, and, hypothetically, may lead to a state of lasting neuronal depolarization by maximum inhibition of Na, K-ATPase. This state may manifest itself clinically as depression. If patients are now recovering from depression, the intracellular calcium declines on its way to normalization, passing a level that may again activate adenylate cyclase, causing the often-observed hypomanic state after depression. Calcium concentrations fluctuating around the threshold between the manic and depressed stage may be a hypothetical origin of mixed states or ultradian cycling.

In conclusion, this hypothesis combines special potential factors of vulnerability in bipolar patients, such as altered Na, K-ATPase (Antia *et al.*, 1995) and adenylate cyclase activity (Meltzer, 1986), with the potentiating effects of increased intracellular calcium mobilization or calcium influx into the cell.

How do antiepileptic drugs used in treating mixed states and rapid cycling potentially interfere with intracellular calcium signalling?

A well-known target of lithium action is the inositol phospholipid pathway which shows increased sensitivity in bipolar patients (Moscovich *et al.*, 1990). Inositol 1, 4, 5-triphosphate (IP_3) synthesis mobilizes intracellular calcium stores

in close proximity to their calcium-dependent effector proteins. Lithium inhibits IP_3 (Berridge and Irvine, 1989). Recently, it has been shown that valproate is also capable of inhibiting the synthesis of inositol monophosphate (Vaden *et al.*, 2001). This also means a reduction of the activation rate of Ca^{2+} calmodulin kinase II, a enzyme that is critically involved in long-term synaptic changes (Lisman, 1994) and of myristoylated alanine-rich C kinase substrate, implicated in synaptic neurotransmission and cytoskeletal restructuring (Lenox and Watson, 1994), thus inhibiting structural changes of neurons in the course of the disease.

Different mechanisms have been implied in the therapeutic action of carbamazepine (Grunze *et al.*, 1999). With respect to calcium, carbamazepine exerts strong calcium antagonistic properties *in vitro* by blocking L-type calcium channels (Walden *et al.*, 1992), whereas valproate inhibits another voltage-dependent calcium channel, the T channel (Altrup *et al.*, 1992). Lamotrigine also exerts part of its action by calcium antagonistic effects on L, N and P-type channels (Wegerer *et al.*, 1997; Xie and Hagan, 1998).

Another recently discovered effect of valproate is its action on the chaperones GRP 78, GRP 94, and calreticulin. These endoplasmatic reticulum stress proteins bind calcium and are protective against cell death. Chronic treatment with valproate increases the synthesis of all three chaperones in rat C6 glioma cells, thus contributing to calcium homeostasis in the endoplasmatic reticulum (Wang *et al.*, 2001).

In summary, all currently used effective mood stabilizers show somehow direct or indirect calcium antagonistic properties. Interestingly, a review by Hollister and Trevino (1999) listed 61 partially successful reports on trials of calcium antagonists in bipolar disorder.

Of special interest is the fact that a randomized study of the L-type calcium channel blocker nimodipine showed efficacy in thus far refractory rapid-cycling patients (Pazzaglia *et al.*, 1993, 1998).

As already indicated in the introduction, antiepileptic drugs, especially valproate and lamotrigine, are considered to be more efficacious than lithium in treating mixed states and rapid-cycling patients. Retrospective analysis of the pivotal trial of Bowden *et al.* (1994) by Swann *et al.* (1997) showed equal efficacy for valproate in pure manic and mixed patients, whereas lithium showed no benefit when mania was accompanied by depressive symptoms. The same appears true when analyzing other controlled trials for the efficacy of lithium in pure mania versus mixed states. In rapid-cycling patients, open data of 101 patients (Calabrese *et al.*, 1993) supported the clinical usefulness of valproate in patients with rapid cycling, both with pure mania and mixed states. Lamotrigine, on the other hand, is so far the only mood stabilizer whose efficacy for the prophylactic treatment of rapid cycling has been backed up by a large randomized, placebo-controlled study (Calabrese *et al.*, 2000). Lamotrigine appeared to be especially helpful in bipolar II rapid-cycling patients;

together with other controlled evidence (Calabrese *et al.*, 1999), this may suggest that its main benefit comes from treating and preventing depressive symptoms.

A recent review (Grunze *et al.*, 2002b) also highlighted effects of mood stabilizers on potassium channels. Unfortunately, aberrations of potassium currents or genes coding for potassium channels have not been explored so far with a special focus on mixed states and rapid cycling. But again, as valproate as well as lamotrigine and carbamazepine seems to act on potassium channels (which is not described for lithium), a key function of potassium channels in atypical manifestations of bipolar disorder can be hypothesized. Nevertheless, proof for this is still needed in both basic and clinical research.

Other mechanisms of mood stabilizers possibly related to rapid cycling and mixed states

The effects of antiepileptic drugs that are efficacious in mixed states and rapid cycling also include a variety of intracellular action targeting the protein kinase activity, the inositol phosphate metabolism, and finally the expression of early genes and cytoprotective proteins. These issues have also been reviewed extensively in a recent publication of the authors (Grunze *et al.*, 2002b). More than any transient effects on the cell surface, they may supply a key to remission and successful long-term prophylactic treatment with mood stabilizers in bipolar disorder. Data for valproate and lithium showing these effects are available, but are not yet available for the newer anticonvulsants or atypical antipsychotics. However, these data originate from the lab bench and are not reproduced even in animal models, not to mention rapid-cycling or mixed patients. Thus, relating any of these interesting activities of the drug to mixed states and rapid cycling is purely speculative. Additionally, as far as we know, lithium is at least as effective as valproate on this intracellular level. Thus, we may not find any specificity for influencing a rapid-cycling course or mixed state on this level.

Again speculative, but only little attention has so far been given to the effect of changes of the intracellular proton equilibrium (pH) in bipolar patients. Already very moderate changes in intracellular pH have a strong effect on both receptor sensitivity and second messenger systems. Even small fluctuations may have a strong impact on the expression of mood. Thus, looking for an easy trigger of rapid cycling and mixed states, changes in intracellular pH may qualify. As a matter of fact, a decrease in intracellular pH in the frontal lobe has been described in drug-free bipolar patients (Kato *et al.*, 1998), suggesting aberrations of the proton equilibrium in bipolar disorder. Controlled studies with magnetic resonance spectroscopy in mixed and rapid-cycling patients and correlation with mood states are therefore, in our opinion, urgently required.

Conclusions

There is a very obvious gap between our knowledge of biological courses of rapid cycling and mixed states and their clinical frequency and importance. There are some hints which imply a role of the noradrenergic system and a pronounced disturbance of the LHPA axis in well-characterized 48-h rapid-cycling patients where an underlying biological explanation appears very likely. However, generalization to rapid cycling and mixed states at large cannot be made with a reasonable level of confidence. As far as transmembranous ion fluxes and changes in intracellular metabolism are concerned, we can only extrapolate from the action of mood stabilizers, mainly antiepileptic drugs, which are useful in treating these clinical conditions. Thus, this field is still very open for new and innovative research which is urgently needed for a better understanding of these manifestations of bipolar disorder and for developing better drugs to treat these often highly refractory patients.

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15

The treatment of bipolar mixed states

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Mixed states pose particular problems in their classification, diagnosis, and treatment, because they may be conceptualized as arising in a variety of ways (Table 15.1).

Mixture of elements (mood, activity, thinking)

Mixed states may represent a mixture of different elements of depressed and manic conditions. For Kraepelin, the core pathology of clinical depression was expressed in separate areas of functioning: lowering of mood, and slowed or retarded mental and physical activity. The opposite applied in mania: euphoria, flight of ideas, and hyperactivity. Kraepelin (1913) recognized six mixed states, the most common being depressive or anxious mania, excited depression, and depression with flight of ideas. Others were manic stupor, mania with poverty of thought, and inhibited mania (without flight of ideas). Other combinations were theoretically possible but rarely recognized in practice. Kraepelin distinguished "autonomous" mixed episodes from those occurring during transitions from one mood phase to another (see transition state during a cycle, below) and thought them to be "the most unfavourable form of manic-depressive insanity."

Severe stage of mania

The mixed state may represent a qualitatively distinct presentation of mania, with classical manic symptoms accompanied by marked anxiety, depression, or anger. These symptoms tend to emerge in more severe stages of the illness and then to be correlated in severity; thus Carlson and Goodwin (1973) described three stages of mania through which an episode may develop, corresponding to mild, moderate, and severe levels of symptoms. At moderate severity, the euphoric mood is increasingly interrupted by periods of irritability and depression, and thinking becomes delusional. In the severe stage, there is frenzied overactivity, mood is

Table 15.1 Concepts of mixed states

Model	Authors
1. Mixture of elements (mood, activity, thinking)	Kraepelin
2. Severe stage of mania	Carlson and Goodwin
3. Dysphoric mania	Post
4. Depression as characterological response to mania	Akiskal, Bourgeois
5. Manic defense in depression	Klein, Winnicott
6. Transition state during a cycle (MDI/DMI)	Falret, Koukopoulos
7. Predominantly depressed (BP-II, Dm)	Dunner, Angst
8. Mania modified by substance misuse	Himmelhoch
9. Modified by organic brain disease	Himmelhoch and Garfinkel
10. Ultrarapid cycling	DSM-IV
11. With mood-incongruent psychotic features	Dell'Osso
12. Mixed schizoaffective disorder	Marneros

See text for definition of abbrevations.

experienced by the patients as unpleasant or even terrifying, delusional thinking becomes bizarre and they have hallucinations, and in some cases disorientation.

Dysphoric mania

The term "dysphoric mania" has been used to describe patients in whom classical manic symptoms are accompanied by marked anxiety, depression, or anger (Post *et al.*, 1989). Some patients present with these symptoms throughout an episode and might be described as having dysphoric, mixed, irritable–paranoid or even paranoid–destructive mania. Thus, Beigel and Murphy (1971) studied, prior to treatment, 12 consecutive patients admitted to the National Institute of Mental Health (NIMH). Eight were characterized as "elated–grandiose" and four as "paranoid–destructive," on the basis of their scores on the nurses' Manic State rating scales. Patients with repeated manic attacks tended to exhibit similar behavior and mood patterns during subsequent episodes and the pattern seemed to persist independently of the overall severity of mania. These authors found depressive symptoms in 11 of the 12 patients with mania. A similar division was found in a later factor analysis of 30 patients (Murphy and Beigel, 1974). The severity of dysphoria has been found to correlate with the level of norepinephrine (noradrenaline) in the lumbar cerebro-spinal fluid (CSF) (Post *et al.*, 1989). Likewise, levels of the norepinephrine metabolite methoxy-hydroxy phenylglycol were more elevated in mixed mania than in depression (Swann *et al.*, 1994).

Whether there is a sharp separation between pure and dysphoric mania is doubtful. Bauer *et al.* (1994b) assessed 37 outpatients with mania or hypomania (65% bipolar II and 92% rapid cycling) using five different definitions of dysphoric mania (all based upon the number of depressive symptoms). In this group no bimodality was found in the depression scores that would allow a separation into dysphoric and pure mania, and dysphoria was not found consistently in successive episodes.

Depression as characterological response to mania

The manic state may predominate while depressive elements are present to a lesser degree, perhaps fleetingly. The depressive symptoms may then be viewed as a characterological response to the occurrence of mania (Akiskal, *et al.*, 1998a). Treatment of mania would be predicted to improve the depressive symptoms.

The development of the concept of temperament in relation to bipolar disorder was reviewed by Angst (2000). There is as yet little direct evidence to link temperament and mixed presentation, or indeed any particular personality type with bipolar disorder. In the French national Epidemiology of Mania (EPIMAN) study, mixed manic patients had a higher rate of depressive temperamental traits compared with those with pure mania (Akiskal *et al.*, 1998a). Bourgeois (2002) reviewed the evidence that temperament, whether depressive or hyperthymic, may color the acute episode (Akiskal and Akiskal, 1992; Cassano *et al.*, 1992; Akiskal *et al.*, 1998b; Henry *et al.*, 1999; Perugi *et al.*, 2001). He also concluded that two subtypes of bipolar type I disorder may be differentiated: on the one hand, a subtype "with a predominance of manic psychopathology" and on the other a "preponderantly depressed" (Angst, 1978) or "depression-prone" type (Quitkin *et al.*, 1986) or a "poor prognosis subtype marked by a relative persistence of depressive symptoms" (Coryell *et al.*, 1998).

Manic defense in depression

The depressive state may predominate, but with elements of manic thinking, as implied in the concept of "manic defense" against depression, described by Donald Winnicott (1935) and Melanie Klein (1935), who had herself been psychoanalyzed by Karl Abraham, one of the first in 1924 to apply psychoanalytical ideas to manic-depressive illness. The manic defenses (omnipotent control, triumph, and contempt) protect the ego against despair, but interrupt the process of reparation, and produce a vicious circle by further attacks upon the "object." However, a manic form of reparation can occur and some of the identifications made in mania can be seen as potential advances in individual development. This psychoanalytically

derived formulation of manic or hypomanic responses can be helpful in understanding the personal and interpersonal dynamics or relationships in which the bipolar person may become involved. However their etiological significance is less clear, a fact recognized by Freud, who referred to the "economic problem" of the libido in mania and depression.

In Winston Churchill's case, Storr (1969) emphasized the creative use of words and ideas; his writing, painting, and oratory were "manic defenses" against the depressive tendencies which could be traced in the family to the first Duke of Marlborough. His daughter, however, has stated that her mother "very largely kennelled the black dog" of Churchill's melancholia except in his old age (Soames, 1993).

Specific issues to be addressed with manic patients are the alienation of family members, the progressive testing of limits by the patient, the over involvement with other patients, and the tendency to dominate the ward. Janowsky *et al.* (1974) described these tendencies as "the manic game" and implied that the manic patient demands care without having to admit a need for it. Staff need to understand these maneuvers in order to avoid becoming too personally involved, for instance in angry exchanges. Community meetings are helpful as they allow the responses of other patients to the manic's behavior to be recognized and guided.

Transition state during a cycle: MDI/DMI

Kraepelin (1899) suggested that a distinction should be made between "transitional forms" (mixed episodes representing a transitional point or interval during the switch from depression to mania or vice versa) and "autonomous forms" (mixed episodes as a separate disorder) of mixed episodes (Marneros and Angst, 2000). Thus the opposite affective state may emerge during recovery from the first state, as in postmanic depression, and the mixed state may occur during the transition. In some patients the "switch" occurs rapidly (in 24 h or overnight) but in others it is much slower (Sitaram *et al.*, 1978; Post *et al.*, 1981). Such cycles or periods of illness were first clearly recognized by Falret, in what he called *folie circulaire* (1854), and less clearly by Baillarger as *folie à double forme* (1854). Koukopoulos (2002) has emphasized the importance of these early ideas of Falret to contemporary clinical diagnosis and treatment.

The emergence of the second state may be due to adaptations occurring during the former. In this view the order of the sequence of mood states is important. Koukopoulos has used the sequence of mood changes to distinguish patients in whom an episode of mania is followed immediately by depression, followed by a well interval (MDI), from those with depression followed by mania or hypomania (DMI), those with a continuously circular (CC) pattern, and those with completely

separate affective swings. In an investigation of the course of manic-depressive cycles, involving 434 bipolar patients, Koukopoulos *et al.* (1980) found the following patterns. A total of 119 patients (28%) had a pattern of MDI and 106 (25%) of DMI; there were 87 (20%) with rapid cycling, 83 (19%) with a CC course, and 39 (9%) with irregular patterns. Thus 28% had a depressive phase immediately following a manic phase, and may therefore have experienced a transitional mixed stage.

Earlier intervention to treat or prevent the former state might prevent or reduce the subsequent severity of the later state. On the other hand, prompt treatment of the initial state might lead to earlier transition into the subsequent state than would occur without treatment, as in the apparent "triggering" of mania by treatment of bipolar depression with tricyclic antidepressant drugs. Thus, Kukopulos and Reginaldi (1973) proposed that such a mechanism might account for the finding that lithium reduces the frequency and severity of depressive episodes in the prophylaxis of MDI disorder. The same could be applied to the use of antipsychotic drugs in this condition. Drugs such as lithium and lamotrigine may have the advantage of treating or preventing the depressed phase of bipolar disorder with less risk of triggering secondary mania and may be particularly useful in DMI (bipolar: BP-II) disorder.

Faedda *et al.* (1991) analyzed the findings of five studies in which the response to lithium was considered in relation to clinical predictors of efficacy. They found that the MDI or hypomania with severe depression (mDI) pattern of episodes predicted better response to lithium than the other patterns. The sequence of declining responsiveness was from this MDI pattern to irregular through CC, DMI, or severe depression with hypomania (DmI) to rapid cycling, which was the least responsive pattern. The odds ratio for responding between MDI and DMI patterns was 4.4, with 95% confidence intervals of 2.8–7.0.

Mixed states in predominantly depressed bipolar patients (BP-II, Dm)

Patients with recurrent depression who have hypomanic episodes (not requiring hospitalization), especially on recovery from depression, were described as BP-II and those with a history of mania as BP-I (Dunner *et al.*, 1976). There is extensive overlap between patients with the DMI pattern and those with BP-II, and between those with the MDI pattern and BP-I. Koukopoulos (2002) reported that, of the 119 DMI bipolars described above, 101 (85%) were BP-I and represented almost half of the total of 207 patients with BP-I. On the other hand, 80 (75%) of the DMI patients could be classified as BP-II.

An average of 40% of BP-I patients develop a mixed state at some point during the course of their illness (Akiskal *et al.*, 2000). In two recent clinical trials, the

proportion of manic patients with mixed mania as defined by *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV: American Psychatric Association, 1994) was 17% (Tohen *et al.*, 1999) and 43% (Tohen *et al.*, 2000).

Another formulation of the predominantly depressed forms of bipolar disorder was proposed by Angst (1978). Because of the different combinations of severity of manic and depressive episodes, Angst proposed three categories of patients:

(1) MD (in whom both manic and depressive episodes are severe enough to require hospitalization)
(2) Md (recurrent mania with only mild depression)
(3) Dm (BP-II) (hypomania with severe depression)

To these might be added:

(1) md (cyclothymia)
(2) M (unipolar mania)

The phenomenon of switching from depression to mania has been studied extensively both in the era before antidepressant therapy (Angst, 1985) and recently (Wehr and Goodwin, 1987). The switch from mania to depression has been studied less. Angst (1978) examined the sequence of mood changes in 1176 separate episodes, in 95 consecutive bipolar admissions for the period 1959–1963. Ninety-nine percent of episodes entailed either one or two mood phases. Of 378 episodes that began with mania or hypomania, 123 (32%) were immediately followed by depressive states. In 27/378 (7%) cases the depression that followed was severe, and in 96/378 (25%) it was mild. Severe depression followed mania in 13/215 (6%) episodes, but followed hypomania in 14/67 (21%), indicating that the severity of subsequent depression is not related simply to the severity of the preceding mania. A recent trial in which switch rates into depression were high (27%), despite mood stabilizers, was that of Tohen *et al.* (2002a), in which outpatients with mild mania were recruited.

Severe agitated depression with associated hypomania was described by Himmelhoch *et al.* (1976) as a variant of bipolar mixed states. Koukopoulos and Koukopoulos (1999) have described intensely agitated depressions, which they consider as forms of not unipolar, but bipolar depressive mixed states. Perugi *et al.* (1997) also identified such a mixed depressive syndrome, with pressure of speech and flight of ideas. Likewise, mild mixed states have been described among BP-II patients, involving irritability, distractibility, and racing thoughts (Benazzi, 2000). Koukopoulos (2002) has argued that this form of agitated depression may require particular care in drug treatment.

Akiskal *et al.* (1998a) describe depressive mixed states related to BP-II disorder. These patients satisfy the criteria for a major depressive episode, but also show intense activation in the form of dramatic expressions of suffering; unrelenting dysphoria, irritability, and lability; psychomotor agitation; extreme fatigue with

racing thoughts; intense sexual excitement; free-floating anxiety, and panic attacks; as well as suicidal obsessions. In some cases these appear to be brought about by overzealous prescription of antidepressants (McElroy *et al.*, 2000).

Swann *et al.* (1993) compared the clinical characteristics of mixed manics with those of agitated depressed patients. The mixed manic patients had more severe agitation, hostility, and cognitive impairment (disorganization and lack of insight) than did the agitated depressed patients. However, they could not find sufficient evidence to classify agitated depression as a mixed state. The term "hyperthymic depression," has been suggested as a preferable name for these mixed states rather than "agitated depression," which has other connotations (Marneros and Angst, 2000).

Modified by substance misuse

The presentation of mania may be modified, leading to mixed forms, by the comorbid misuse of alcohol, sedatives, or stimulant drugs. The combination of mental illness and substance misuse is known as dual diagnosis or comorbidity. Bipolar disorder is associated with an increased risk of comorbid conditions, including personality disorder, alcohol or drug misuse, and anxiety states. Some patients increase and some decrease alcohol or drug abuse when manic compared to euthymic (Bernadt and Murray, 1986). Alcohol and stimulants such as amfetamines and cocaine are misused by patients to restore hypomania during a dysphoric phase or to heighten existing states of elation (Gawin and Kleber, 1986). These drugs can alter the course of bipolar disorder by triggering mania; they diminish impulse control and impair judgment and are serious risk factors for suicide. Therefore the recognition and treatment of alcohol or drug abuse in recurrent affective patients is a matter of urgency. Despite the earlier use of *Cannabis indica* for mania in the nineteenth century, for example, by Clouston (1896), current preparations of cannabis have been associated with an increase in psychotic symptoms in mania (Harding and Knight, 1973), and with the induction of mania (Rottanburg *et al.*, 1982).

A manic episode may be triggered by amfetamine in predisposed individuals (Gerner *et al.*, 1976). Dopamine agonists with preferential presynaptic effects are sedative and may improve mania, but dopamine agonists may also cause secondary mania, presumably by stimulating postsynaptic receptors. Paradoxically, single doses of amfetamine may improve mania in some cases (Chiarello and Cole, 1987).

The onset of the first symptoms of bipolar disorder is frequently in adolescence, with the emergence of subsyndromal mood swings or cyclothymia. The diagnosis of bipolar disorder is commonly delayed by as much as 10 years. Recognition of these prodromal features is particularly important in young people with a family

history of major affective disorder. Recently there have been more frequent reports of mania in children (Geller *et al.*, 2001), a phenomenon that has been suggested to be linked to the use of stimulant and antidepressant drugs in young people thought to have attention-deficit hyperactivity disorder or depression, respectively (Reichart *et al.*, 2000). The age at presentation with bipolar disorder is earlier in those who had previous exposure to methylphenidate than those who had not (Shulman *et al.*, 2002).

All psychiatrists should now be familiar with the problems of cannabis in their patients, and in future may be able to intervene more effectively if a cannabinoid antagonist becomes available. However the most serious immediate challenge is from "crack" cocaine, which is short-acting and highly addictive, and dramatically destabilizes both the illness and social structure. In urban areas with heavy trade in this substance, it is linked to violent gangs, and patients put their health and safety at risk. A "dual diagnosis service" led by a psychiatrist with a special interest in drug misuse may be needed to address the complex psychiatric, medical, and legal problems that arise; a specialized ward area must have sufficient security to exclude drug dealers and to treat the patients in a state free of harmful substances.

Keck *et al.* (1998) observed 134 consecutive manic patients for 12 months after discharge, 58 having had mixed episodes according to DSM-IIIR (American Psychiatric Association, 1987). They found no significant difference between the two groups in any outcome variable, including alcohol or drug misuse. Substance misuse was however associated with poor compliance with treatment.

Modified by organic brain disease

The presentation of mania may also be modified, leading to mixed forms, by the comorbid occurrence of organic brain disease (Himmelhoch and Garfinkel, 1986). A total of 31/37 patients with mixed mania had some indication of possible neuropsychiatric impairment (seizures, paroxysmal electroencephalogranus, migraine, a history of severe head injury or perinatal insults, or hyperactivity). These were postulated to be a correlate of both mixed mania and of non-response to lithium. By contrast, examination of children who became manic subsequently has revealed a superior level of motor development and intelligence than controls and no greater risk of obstetric complications (Cannon *et al.*, 2002). A recent addition to this controversy is the discovery on magnetic resonance imaging of deep white-matter lesions, particularly in the frontal and parietal brain areas of patients with major depression, including bipolar disorder, in excess of those seen in psychiatric controls. These lesions may be associated with vascular ischemic pathology (Thomas *et al.*, 2002), and their presence is associated with treatment resistance (Moore *et al.*, 2001). A possible association with cognitive impairment is

being investigated, but as yet no clear phenomenological association with mixed states has been reported.

It has been reported that mania occurring in later life (after the age of 65) is more likely to present in mixed episodes (Shulman and Post, 1980), but this has not been confirmed. The situation in people with a first presentation of mania in older age is being researched in detail. A study based on Danish national case registers found that the diagnosis of dementia was associated with an increased risk of both depression and mania over subsequent years compared with control groups with osteoarthritis or diabetes (Nilsson *et al.*, 2002).

Ultrarapid cycling

Operationally mixed states may be defined in terms of the coexistence of symptoms of both mania and depression in sufficient numbers or at sufficient levels of severity. It should be noted that DSM-IV and *Tenth Revision of International Classification of Disease* (ICD-10: World Health Organization, 1993) differ somewhat in their definitions of mixed states. ICD-10 includes patients showing a mixture or alternation of manic and depressive symptoms for 2 weeks. This would include people who might otherwise be classified as having rapid-cycling bipolar disorder. DSM-IV requires full mania and full depression for 1 week.

Rapid cycling is included as a course specifier of bipolar disorders in DSM-IV (American Psychiatric Association, 1994), and defined as "at least four episodes of a mood disturbance in the previous 12 months that meet criteria for manic episode, a hypomanic episode, or a major depressive episode." Episodes are demarcated by either partial or full remission for at least 2 months, or a switch to a mood state of opposite polarity.

Ultrarapid cycling describes four or more episodes a month. Recently, ultradian cycling has been described in otherwise typical bipolar patients; mood changes in such patients occur in a matter of minutes or hours (Kramlinger and Post, 1996).

Perugi *et al.* (2000), reporting on 320 bipolar patients, have shown that bipolar illness with depression at onset is significantly more likely than manic and mixed states onset to develop rapid cycling, suicidal behavior, and psychotic symptoms. This study confirmed that rapid cycling was distinct from mixed states. However, in ultrarapid cycling (≥ 4 episodes/month) there may be considerable overlap with mixed states.

Patients with ultradian cycling can also be found among those with a diagnosis of borderline personality disorder, but these also present with extensive difficulties in maintaining relationships. Their treatment poses unusual difficulties. Antidepressant response to valproate in rapid-cycling patients was associated with absence of borderline personality disorder (Calabrese *et al.*, 1993).

The treatment of rapid cycling is reviewed elsewhere (see Chapter 3) and will not be considered further here.

With mood-incongruent psychotic features

Patients with affective disorder in whom the content of psychotic symptoms is incongruent with the prevailing mood are sometimes diagnosed as having mixed (bipolar) states (Kraepelin, 1921). Mixed episodes of bipolar disorder are notorious for signs and symptoms of protracted psychotic disorganization. Confusion and psychotic features, including mood incongruence, are also common clinical presentations (Perugi *et al.*, 1997; Dell'Osso *et al.*, 1991, 1993).

Dell'Osso *et al.* (1991) found higher rates of mood incongruence in the psychotic features of mixed as opposed to pure manic patients using DSM-IIIR criteria. However the inclusion of such patients in the bipolar grouping rather than schizoaffective or schizophrenic broadens the diagnosis to an extent that may not be helpful when attempting to relate diagnosis to response to specific treatments. For example, Prien *et al.* (1972) found that antimanic response to lithium was less in mania accompanied by severe symptoms or psychotic features; this is discussed by Goodwin and Jamison (1990) and Goodnick and Meltzer (1984). Concurrent psychotic features are associated with a high rate of recurrence with lithium-based prophylaxis (Tohen *et al.*, 1992).

On the other hand catatonic symptoms are relatively common in severe mania; they were present in three of 60 patients with pure mania and 24 of 39 with mixed mania (Braunig *et al.*, 2002). Although regarded as "mood-incongruent" in DSM-III, they became a specifier in DSM-IV.

This form will not be discussed further here.

Schizoaffective mixed states

It might be more appropriate to define mood-incongruent psychotic features more clearly and to separate those with incongruent content into the schizoaffective class that has been described by Marneros and Angst (2000). The treatment of this form will not be discussed here. It should be noted that validity is given to the inclusion of such patients in the bipolar group by genetic and twin studies, showing the diagnosis in identical twins or triplets, where one member has typical mania (McGuffin *et al.*, 1982).

Clinical trials in mania and mixed states

Evidence about drug treatment of mixed states arising from clinical trials should recall the nature and limitations of such trials. These are summarized in Table 15.2.

Table 15.2 Limitations of clinical trials of drugs in mixed states

1. The studies are powered to achieve significance when all subtypes of mania are included
2. Most recent large-scale studies showed a particularly high placebo response
3. Active comparators are often used at a single dose that may not be optimal
4. Patients giving informed consent to placebo-controlled trials may not be representative
5. Inclusion of treatment-resistant patients may bias results
6. Acute studies have a short duration
7. Abrupt withdrawal from previous medication may affect the clinical condition

First, the recent trials have mainly been carried out in mania rather than depression. They are not intended to study subtypes of mania, and are not "powered" to do so. Subanalyses of groups with or without psychotic features or with depressive symptoms are generally underpowered to answer the questions in those subgroups. That is, they do not necessarily include sufficient numbers of patients in mixed states.

Most recent studies showed a high placebo response, as judged by 50% improvement in the baseline severity of the mania rating scale, for example, 25% (Bowden *et al.*, 1994), 24% (Tohen *et al.*, 1999) and 43% (Tohen *et al.*, 2000) in monotherapy studies. In adjunctive studies similar high rates have been found: 45% (Tohen *et al.*, 2002a), 42% (Yatham 2000) and 46% (Muller-Oerlinghausen *et al.*, 2000). The only exception was a placebo response rate of 9% in the trial of valproate in lithium-resistant mania with recruitment of inpatients (Pope *et al.*, 1991). These high placebo response rates may occur for a variety reasons, but they are not typical of what is expected in acute mania, a condition that is notorious for the difficulties it can pose in nursing management unless effective medication is given. This suggests that the findings may not be generalizable to typical patients encountered in routine clinical practice. The high placebo response rate also reduces the effect size that the active drug is able to achieve, and makes it more difficult to identify predictors of response.

Active comparators such as haloperidol tend to be used at a single dose that may not be optimal.

Patients able to give informed consent to placebo-controlled trials may not be representative of other patients with mania (Licht, 2002). In general, they are likely to be less severely ill and to have fewer psychotic features and less aggressive behavior (Licht *et al.*, 1997). People under compulsory detention and those using illicit drugs are also mostly excluded.

Patients available for trials may be more likely to be resistant to previously available treatments. In a trial of valproate in acute mania, 42% had a history of non-response to lithium (Bowden *et al.*, 1994). This would clearly bias the results in favor of valproate rather than lithium.

Table 15.3 Prediction of response to antimanic drug in models

Model	Prediction
1. Mixture of elements (mood, activity, thinking)	Partial response (in manic elements)
2. Severe stage of mania	Proportionately large response
3. Dysphoric mania	Different from response in pure mania
4. Depression as characterological response to mania	Depression improves as mania improves
5. Manic defense in depression	Depression worsened
6. Transition state during a cycle (MDI/DMI)	MDI: shortened mania; less severe depression; stabilize mood "from above "
7. Predominantly depressed (BP-II, Dm)	Depression persists or worsens
8. Mania modified by substance misuse	Resistance while comorbidity persists
9. Modified by organic brain disease	Resistance while comorbidity persists

See text for definition of abbrevations.

The relatively short duration of studies in acute mania (3–4 weeks) means that longer-term outcomes, and in particular the switch into depression, may not be explored in the duration of the trial.

Discontinuation of lithium over a period of less than 2 weeks can increase the likelihood of mania developing or worsening. Abrupt discontinuation can lead to the development of mania in as many as 50% of bipolar patients who have been stabilized on the drug (Mander and Loudon, 1988; see Cookson, 1997). Little is known of how the discontinuation of other drugs may affect the clinical picture and response to treatment.

Treatment responses in different models of mixed states

The different concepts or "models" of the nature of mixed states lead to different predictions as to how drugs are likely to affect the condition. The predictions with respect to treatment with a drug that has antimanic but not antidepressant properties are shown in Table 15.3.

In general, with the exception of model 2 (severe stage), the models predict that mixed states will respond less fully to antimanic drugs, such as antipsychotics. There is limited evidence that dysphoric mania (model 3) responds differently, and that in severe mania there is a proportionately greater response (model 1). Thus, in a double-blind placebo-controlled cross-over study of carbamazepine in

19 acutely manic patients, the 12 who responded to carbamazepine had higher scores of severity of mania and tended to be more dysphoric (Post *et al.*, 1987).

Antipsychotics in mania

The response to antipsychotic medication in mania has recently been subject to careful investigation in clinical trials of atypical antipsychotics, particularly olanzapine and risperidone. These studies are reviewed in detail in Chapter 16. Two studies included, as a comparator, the classical antipsychotic haloperidol which is the most widely used antipsychotic for mania (see Cookson, 2001). All three drugs (haloperidol, olanzapine, and risperidone) tended to produce as great an improvement in mania ratings in the more severe and psychotic groups of patients as in less severe non-psychotic patients (in keeping with model 2).

Cortisol levels during response to antipsychotics

Elevated serum cortisol levels are found in mania. This elevation is correlated significantly with the severity of mania (Cookson *et al.*, 1985a), but is particularly high in mixed states (Swann *et al.*, 1992). Evans and Nemeroff (1983) found that mixed manics showed more resistance of plasma cortisol to suppression by dexamethasone than pure manics, although Swann *et al.* (1992) found cortisol non-suppression in both pure and mixed mania. Krishnan *et al.* (1983) found non-suppression in all of 10 consecutive patients with mixed states.

During treatment with pimozide, cortisol levels gradually return towards normal, with a time course similar to that of clinical improvement (Cookson, 1985). By contrast, during treatment with haloperidol, there appears to be a dissociation between an early normalization of cortisol levels within 3 days and a more gradual clinical improvement during 2 weeks of treatment (Cookson *et al.*, 1985b). This apparent difference between haloperidol and pimozide might be related to the different pharmacology of the two drugs. Both drugs block dopamine receptors, but haloperidol in addition blocks norepinephrine alpha$_1$-receptors in humans (Szabadi *et al.*, 1981). Alpha$_1$-receptors are known to be involved in the control of cortisol secretion (Rees *et al.*, 1970). Alpha$_1$-receptor blockade is thought to contribute to the sedative effects of antipsychotics (Peroutka and Snyder, 1980). It may account for the early transient sedative effects seen in mania with haloperidol (Cookson *et al.*, 1983). Levels of norepinephrine in the CSF are raised in mania (Post *et al.*, 1978), and particularly in mixed mania (Swann *et al.*, 1987, 1994), and correlated with levels of dysphoria, anger, and anxiety in dysphoric mania (Post *et al.*, 1989). Blockade of norepinephrine receptors by haloperidol may be part of the mechanism of the drug's antimanic effect, and may be particularly important in dysphoric mania. Certain atypical antipsychotics such as olanzapine and risperidone

are also antagonists at 5-HT-2 receptors and norepinephrine alpha$_2$-receptors, actions that may endow them with antidepressant properties.

Antipsychotics, depression in mania, and switch into depression

The response to treatment of depressive symptoms in mania has two aspects. First, there is the response of depressive symptoms that occur during the presenting manic phase. Second, there are the depressive symptoms that emerge as the manic phase resolves; these may be regarded as postmanic depression or – especially if they appear suddenly – as resulting from a switch from mania to depression.

In placebo-controlled studies of olanzapine in mania, 27% of patients had high depression scores at the start (Hamilton-D > 20). Depressive symptoms improved along with the mania ratings within 1 week (Baker *et al.*, 2000). This improvement in moderately severe depressive symptoms in a large proportion of bipolar patients is compatible with model 4 (characterological response).

Olanzapine and haloperidol brought about similar degrees of improvement, not only in ratings of mania, but also of depressive symptoms in patients with high depression scores (Hamilton-D > 20) at the start (Tohen *et al.*, 2003). However the remission rates in patients with mixed mania ($n = 25$, with full DSM-IV syndromes) tended to be less than in pure mania ($n = 428$), whether to olanzapine (39% versus 53%) or haloperidol (17% versus 48%) (Tohen *et al.*, 2003). This is in keeping with model 1 (mixture of elements) applying to the small proportion of patients with more severe depressive symptoms accompanying mania.

In the placebo-controlled studies, worsening of depression was not more common on olanzapine (3/33) than with placebo (7/35) (Baker *et al.*, 2000). On the other hand, the risk of switching from mania to depression within 6 weeks was found to be less with olanzapine (6/128 or 4.7%) than with haloperidol (16/131 or 12.2%) (Tohen *et al.*, 2003; Baker *et al.*, 2004). This suggests that certain atypical antipsychotics may have an advantage over classical antipsychotics in preventing the development of mixed states and depression.

Combining olanzapine with lithium or valproate in manic patients (nearly all outpatients) who had already been on the mood stabilizer for at least 2 weeks led to greater improvement than mood stabilizer with placebo in the subset (48%) of mixed mania (Tohen *et al.*, 2002a). Depression scores also improved more with olanzapine combination, and the proportion of patients gaining 50% improvement in depression scores was greater for olanzapine (43.1%) than for mood stabilizer with placebo (9.5%).

"Manic defense," transitions, and treatment of mania

Thus there is little evidence that treatment of mania or mixed states with antimanic drugs worsens depressive symptoms as model 5 (manic defense) predicts. Another

prediction of this model is that more prolonged mania would lead to greater subsequent depression, as reparation has eventually to be made. This dynamic interpretation is in keeping with a biological view that compensatory changes occurring during mania might predispose to subsequent depression. In support of these views, the high switch rate into depression among outpatients recovering from mania on mood stabilizers in the study of Tohen *et al.* (2002a) was reduced by additional treatment with olanzapine, which hastened the recovery from mania. Evidence from prophylactic studies supports the view that intervening with a drug that treats one phase may prevent recurrences of that phase and also, to a lesser extent, the opposite phase.

Antipsychotics in prophylaxis of bipolar disorder

Antipsychotics are widely prescribed in the follow-up of patients after discharge from hospital for mania; the majority are on antipsychotics at the time of discharge, and a large proportion are still on antipsychotics 3–6 months later (Cookson, 2001). In the large clinics run by community psychiatric nurses for patients on depot medication, most patients have a diagnosis of schizophrenia or paranoid states; however, there is a proportion of patients with a bipolar disorder. Two retrospective studies, using a "mirror image" design, have examined the effects of depot treatment in bipolar patients in such clinics. One study reported an improvement in the frequency only of manic episodes (White *et al.*, 1993). The other study found an improvement in manic, depressive, and mixed episodes (Littlejohn *et al.*, 1994). Long-term treatment with antipsychotic drugs may enable a proportion of bipolar patients to experience periods of greater stability. The mechanisms involved may be primarily antimanic, but resulting in less subsequent depression, as is argued for lithium (Koukopoulos *et al.*, 1980). These drugs are mostly prescribed for those with frequently recurring episodes, who either do not benefit from or do not adhere to oral medication. For rapid-cycling bipolar patients, depot antipsychotics such as haloperidol decanoate stabilize mood swings (Lowe and Batchelor, 1990). Ketter and Calabrese (2002) have described such action as "stabilizing mood from above."

The atypical antipsychotic clozapine is generally reserved for treatment-resistant schizophrenia, because of its side-effects, which include agranulocytosis. However, it is also of value in some cases of resistant bipolar disorder, including patients with rapid-cycling and mixed states (Suppes *et al.*, 1999). An open randomized controlled trial of clozapine as an adjunct to previous medication versus continuing treatment as usual included 38 patients with BP-I or schizoaffective disorder. Ten had mixed bipolar states and 21 had a history of rapid cycling. With the criterion for improvement being a 30% reduction in scores on the Brief Psychiatric Rating Scale, by 6 months 82% on clozapine and 57% on treatment as usual had

responded, a 25% advantage for clozapine, corresponding to a "number needed to treat" of four.

Long-term studies of olanzapine are discussed in Chapter 16, and suggest that this atypical antipsychotic and antimanic drug may reduce not only manic but also a proportion of depressive recurrences.

Lamotrigine

Results from an open-label study of lamotrigine for treatment of BP-I disorder suggested that lamotrigine was effective in the treatment of depressive and manic symptoms (Calabrese *et al.*, 1999a). Subsequently, a 7-week double-blind, placebo-controlled study demonstrated that lamotrigine monotherapy was effective for depressive episodes in 159 patients with BP-I disorder as early as 3 weeks after initiating therapy (Calabrese *et al.*, 1999b). More recently, the efficacy and tolerability of lamotrigine monotherapy for BP-I disorder were established in two 18-month placebo-controlled maintenance studies (Bowden *et al.*, 2002; Calabrese *et al.*, 2002) and a meta-analysis of these two trials, where lamotrigine was found to reduce significantly mean Hamilton-D and Clinical Global Impression (70) scores across 76 weeks of treatment in 638 patients (Goodwin *et al.*, 2002). These results suggest that lamotrigine is effective for the acute treatment and long-term management of BP-I depression. Acute effectiveness has also been demonstrated in patients with treatment-refractory (Bowden *et al.*, 2000) and rapid-cycling BP-II disorder (Bowden *et al.*, 2001), as well as a cohort of recently manic patients with BP-I disorder (Frye *et al.*, 2000). It would appear important to examine further whether these responses were related to the patterns of mood cycles in the patients, using the classifications of Angst and of Koukopoulos.

Treatment of mixed states with antidepressants

The predictions of responses to antidepressants in different models of mixed states are shown in Table 15.4

Antidepressants in bipolar mixed states

The use of antidepressants in bipolar depression is controversial, because of the suspected risk of triggering mania; their use in mixed states is also controversial. Akiskal and Mallya (1987) described 25 patients referred for treatment-resistant depression who displayed subacute or chronic mixed states apparently induced by tricyclic antidepressants. They improved with discontinuation of antidepressants and treatment with lithium or carbamazepine, with or without antipsychotics. Akiskal (2002) has argued that failure to recognize such a depressive mixed state as being bipolar is a serious clinical lapse, as antidepressants are likely to aggravate it.

Table 15.4 Prediction of response to antidepressant drug in models

Model	Prediction
1. Mixture of elements (mood, activity, thinking)	Partial response (in depressive elements)
2. Severe stage of mania	No response
3. Dysphoric mania	No prediction
4. Depression as characterological response to mania	No response
5. Manic defense in depression	Improved
6. Transition state during a cycle (MDI/DMI)	DMI: shortened depression, mania or hypomania occur sooner; stabilize mood "from below"
7. Predominantly depressed (BP-II, Dm)	Depression improved, mania more evident
8. Mania modified by substance misuse	Resistance while comorbidity persists
9. Modified by organic brain disease	Resistance while comorbidity persists

See text for definition of abbrevations.

Similarly, Koukopoulos *et al.* (1992) reported 45 patients with bipolar disorder who experienced a mixed depressive syndrome, meeting DSM-IIIR criteria for major depression but not for mania, who deteriorated when treated with antidepressants, displaying increased agitation, insomnia, and, in some cases, suicidal impulses. The continuation of antidepressants may eventually result in rapid cycling (Koukopoulos *et al.*, 1983). On the other hand, a substantial proportion of depressed patients with mild bipolar features may show satisfactory and stable long-term outcome with antidepressants not necessarily combined with mood stabilizers (Cassano, 2002).

Monoamine oxidase inhibitors may be effective in bipolar depressed states. Himmelhoch *et al.*, (1991) conducted a double-blind randomized study comparing imipramine (100–300 mg/day) with the stimulant monoamine oxidase inhibitor tranylcypromine (20–60 mg/day) in 56 outpatients with anergic bipolar depression. Tranylcypromine was superior to imipramine with greater symptomatic improvement and a higher global response rate, with no greater risk of treatment-induced hypomania or mania (14% and 20%). The 12 non-responders to imipramine were then crossed over to tranylcypromine and nine responded (Thase *et al.*, 1992).

It is unclear whether mixed states are more or less likely to deteriorate than pure manias when exposed to antidepressants. For example, in a study by Altshuler *et al.* (1995) of 51 patients with BP-I and BP-II, 85% switched to mania while

on antidepressants, of which 35% were antidepressant-induced. However, in a randomized, double-blind, prospective trial (Altshuler *et al.*, 2003), the risk of depressive relapse was significantly lower in patients continuing the antidepressants compared to those discontinuing after remission, with no statistically significant difference for breakthrough manic episodes. Generally, clinical practice favors protecting the bipolar patient from manic switches and cycle acceleration by the preferred use of mood stabilizers over antidepressants, or their combination. This approach is not necessarily supported by the literature, but a recent review concluded that patients taking an antidepressant without a mood stabilizer are more likely to develop a manic or hypomanic episode than patients who are also taking a mood stabilizer (Ghaemi and Goodwin, 1999).

Resistance to treatment in mixed states

It has been thought that mixed states are less responsive to treatment than pure or classical manic states. Himmelhoch *et al.* (1976) identified mixed states in 26/84 (31%) of manics in 143 consecutive admissions in Yale and Pittsburgh. Alcohol and sedative misuse was more common in the mixed patients. Poor prognosis (strongly influenced by poor response to lithium) was more common in mixed patients, and this was only partially accounted for by the association with substance misuse. Paradoxically, 10/14 mixed patients with psychotic features showed a good response to lithium, whereas only 1/12 mixed patients without psychotic features did so. A total of 47/58 with pure mania responded well to treatment. This suggested to Himmelhoch and Garfinkel (1986) that the non-psychotic mixed patients had some other poor prognostic factor and, in a second series of 46 lithium-resistant bipolar patients, they identified a substantial frequency of features of organic brain disease (developmental disorders, and electroencephalographic abnormalities). In all, 37/46 of these patients had mixed states and 31 of these 37 had these neuropsychiatric factors (Himmelhoch and Garfinkel, 1986). However, 23 out of the group of 46 were in adolescence, suggesting that factors involved in the selection process may have produced a somewhat unrepresentative sample. In the combined groups of 63 mixed manic presentations, only 1/45 with additional neuropsychiatric or substance misuse factors responded to lithium–antidepressant combinations; by contrast, 10/18 with uncomplicated mixed mania responded to this combination. Only 11 of the 45 showed psychotic features. Perugi *et al.* (1997) found that mixed states took longer to recover.

Keller *et al.* (1986) also found mixed manic patients less responsive to lithium than other manic patients. Secunda *et al.* (1987b) found a good response to lithium in 10/11 patients with pure mania (91%) but in significantly fewer (2/7) who had mixed mania (29%). Himmelhoch and Garfinkel (1986) reported that

21/46 (46%) of lithium-resistant patients (80% had mixed mania) responded to anticonvulsant therapy, which usually involved carbamazepine.

In the placebo-controlled study of Pope *et al.* (1991) of valproate in 23 patients with lithium-resistant mania, the antimanic response was not associated with measures of dysphoria. Valproate differs in its mechanism of action from antipsychotic drugs, reducing presynaptic dopamine release as opposed to blocking postsynaptic receptors (Yatham *et al.*, 2002). Freeman *et al.* (1992) conducted a 3-week randomized controlled trial, comparing lithium and valproate in 27 patients with mania, of whom eight had mixed mania and 19 pure mania. The response rate on lithium (12/13) was non-significantly higher than on valproate (9/14), and non-responders to valproate had significantly lower depression scores than the responders.

Swann *et al.* (1997) had quite different findings. They investigated the relationship between depressive symptoms and response to treatment with lithium or valproate among 179 patients with mania in the trial of Bowden *et al.* (1994). Mixed states were associated with poor response to lithium, compared with pure mania. By contrast, the presence of depressive symptoms had no effect on the response to valproate. A limitation of this study is that a proportion of patients (75/179) admitted to the trial were already known to be non-responders to lithium. Thus, a bias against lithium was introduced at the start of the trial, and the validity of the concept of "lithium non-responder" was confirmed. Nevertheless, among patients with pure mania there were fewer drop-outs for lack of effect on lithium (29%) than on valproate (40%). Performing a multiple regression analysis to identify factors that might predict response to lithium or valproate, they found no correlation with gender, number of previous episodes, psychotic features, or history of substance abuse.

Two studies have compared valproate with olanzapine in mania. One of these has reported the response in mixed mania, which comprised 43% of the sample (Tohen *et al.*, 2002a, 2002b). Although the response to olanzapine was greater and more rapid than that to valproate, each drug was effective in mixed mania to only a slightly lesser extent than in pure mania. The improvement in depression scores was similar in the two treatment groups.

Electroconvulsive therapy is potentially a useful option in mania, especially in treatment-resistant cases (Okasha, 2002).

Combining lithium and antidepressants in prophylaxis of mixed mania

Prien *et al.* (1988) conducted a double-blind, prophylactic study of lithium, imipramine, and the combination in three subgroups, including 34 with pure mania, 46 with mixed mania with mild depression (Hamilton-D score 7–14), and 23 with mixed mania with moderate to severe depression (Hamilton-D score $\geq$15).

They confirmed the poor acute response to treatment of mixed as opposed to pure manics, and followed up patients treated for 2 years after recovery from mania. Those who had mixed episodes were also at higher risk of recurrence on treatment than the pure manics. Lithium alone or in combination with imipramine was highly effective in prevention for the pure group, but not for the mixed group. Only 1/17 pure manics on lithium had any recurrence, compared with six manic recurrences, five depressive recurrences, and one mixed recurrence in the 16 patients with mixed mania.

The prophylactic phase of the study involved 25 mixed bipolar states (16 with mild depression, nine with moderate to severe depression). A total of 5/8 on lithium, 7/7 on imipramine, and 9/10 on the combination experienced a recurrence. Imipramine treatment was thus associated with a greater risk of recurrence. The combination of lithium with imipramine provided no apparent advantage to lithium alone in prevention in this small group of patients after mixed mania.

Similarly, a double-blind study comparing the prophylactic use of lithium carbonate with and without imipramine for BP-I patients (Quitkin *et al.*, 1981) found that the use of antidepressants contributed to some instability of mood. This mood instability was only partially ameliorated by the concurrent use of mood stabilizer.

Suicide risk

Long-term treatment with lithium has been associated with a reduction in the risk of suicide. The mechanisms involved may be separate from the benefits of lithium in preventing depression or hypomania (Muller-Oerlinghausen *et al.*, 1992). Such findings are of particular interest considering the especially high suicidal ideation in people with mixed as opposed to pure mania (Dilsaver *et al.*, 1994; Strakowski *et al.*, 1996).

Conclusions

The diagnosis of mixed affective states can be applied to many different clinical presentations of bipolar disorder. Twelve different formulations of the condition are discussed here. The literature concerning prognosis and treatment of mixed states is controversial and inconsistent. Recent clinical trials using standard diagnostic criteria have clarified some of the issues about response to medication. The majority of patients with mania display some depressive symptoms and a substantial minority meets the more stringent criteria for a mixed state according to DSM-IV, having additional symptomatology of a major depressive episode. In most such patients depressive symptoms improve, along with manic symptoms during treatment. However a minority of patients respond less fully to drugs,

including antipsychotics and lithium. Some of these respond more fully to valproate and perhaps to carbamazepine than to lithium. Electroconvulsive treatment is also considered an effective option for such patients. Factors other than mixity that may contribute to treatment resistance in mania include substance misuse and organic brain pathology, but it has not been established that these factors increase the mixity of mania.

Predominantly depressed patients with mixed states are likely to require antidepressant medication, but most guidelines recommend that monoamine reuptake inhibitor or monoamine oxidase inhibitor treatment should be accompanied by a mood stabilizer, such as lithium or valproate, or by the antidepressant anticonvulsant lamotrigine, in order to reduce the risk of subsequent switch into mania and that the antidepressant should be stopped if manic symptoms appear or worsen (Hirschfeld *et al.*, 2002; Grunze *et al.*, 2003). The combination of an antidepressant with an antipsychotic is widely used and may also avoid worsening mania.

For long-term treatment it is important to consider not only the distinction between BP-I and BP-II mixed types, but also the history of sequences of mood transitions, including the MDI and Md concepts of classification. Lithium may be preferable for patients with primarily manic sequences (BP-I, MDI, or Md), while lamotrigine may be useful for those with initial or preponderant depressive phases (BP-II, DMI, Dm, and dM).

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16

The use of atypical antipsychotic agents in the treatment of diagnostic subgroups of bipolar disorder: mixed and pure states, psychotic and non-psychotic

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Introduction

There are many challenges in treating bipolar disorder, including confronting marked variability in symptoms between patients, as well as highly differing symptomatic presentations within an individual patient's course of illness. Diversity of presentation and course is potentially quite important to prognosis and treatment selection, though the relevance has not been consistently well defined in empirical research. This chapter reviews controlled findings regarding the impact of variant bipolar presentations to predicting treatment response with atypical antipsychotic agents.

Classic bipolar I disorder consists of euthymic periods punctuated by episodes of mania or major depression. Interindividual variability is manifest in differing severity, length, and frequency of manic and depressive episodes and the degree of symptom relief occurring between acute episodes. There are, of course, many variations on the classic pattern, such as the concurrent dysphoric and manic symptoms of mixed states, subsyndromal presentations, or the markedly frequent episodes of rapid cycling. Bipolar disorder is also commonly complicated by psychiatric comorbidity, such as psychosis, as well as substance abuse or physical disorders. Not surprisingly, patients with bipolar disorder have increased mortality from suicide, accidents, substance-abuse-related causes, and various medical diseases (Baldessarini, 2002).

Variant presentations may be more difficult to treat than classic bipolar depression or mania. First, these presentations often broaden the range of target symptoms

requiring treatment, including, for example, psychotic symptoms or the pivotal need to slow cycling in rapid cyclers. Such variant presentations may help to explain the polypharmacy that is typical of bipolar disorder treatment. Second, treatment for one symptom may aggravate others, such as dysphoria secondary to administration of some antipsychotic medications (Koukopoulos *et al.*, 1980; Krakowski *et al.*, 1997) or manic or hypomanic symptoms promoted by antidepressant treatment (Tohen *et al.*, 2002a). Third, variant course may be a marker for relatively treatment-resistant patients (e.g., rapid cycling) or for an independent complication such as substance abuse or dependence. Finally, variant illness presentations may respond differently to particular psychotropic treatments, such as apparent poor response of patients with dysphoric mania to lithium (Swann *et al.*, 1997). In fact, the clinical benefit of identifying bipolar subtypes is amplified when such identification can help to guide treatment decisions, such as evidence related to atypical antipsychotic agents, as discussed below.

An expanded repertoire of psychotropic treatments for bipolar disorder is needed, preferably accompanied by clinical trial data to guide clinicians in matching medications to individual patients. In the case of atypical antipsychotic medications, some findings are available regarding their use in patients with rapid-cycling bipolar disorder, as well as mania complicated by depression or psychosis. These findings are the principal focus of this chapter.

Controlled studies of atypical antipsychotic medications in bipolar disorder

For several decades, antipsychotic medications have been widely used for patients with bipolar disorder, especially in the manic phase of illness. Conventional agents, such as chlorpromazine, have a well-established efficacy for acute mania, but their usefulness is limited by other considerations. Antipsychotic agents may have unidirectional antimanic properties, tending to accelerate switch to depression or to cause dysphoria even in those without a primary mood disorder (Morgan, 1972; Garfinkel *et al.*, 1980; Koukopoulos *et al.*, 1980; Tohen and Zarate, 1998; Tohen *et al.*, 2002a). Moreover, antimanic properties may not be accompanied by prophylaxis against subsequent episodes (Goodwin and Jamison, 1990); chlorpromazine, for example, appeared inferior to lithium in double-blind relapse prevention studies (Goodwin and Jamison, 1990). Finally, extrapyramidal side-effects and risk of tardive dyskinesia are important limitations to the use of dopamine-antagonists in bipolar disorder, especially because patients with mood disorders appear to have heightened sensitivity to these side-effects (Nasrallah *et al.*, 1988; Khanna *et al.*, 1992; Brotman *et al.*, 2000), and because alternate treatments are available. Atypical antipsychotic agents may differ from each other in presence or degree of association with extrapyramidal side-effects,

but each appears to carry less overall risk of extrapyramidal side-effects than benchmark conventional antipsychotic agents such as haloperidol (Seeman and Tallerico, 1999; Glazer, 2000a, b, c; Stanniland and Taylor, 2000; Kapur and Seeman, 2001). Consequently, atypical antipsychotics may, as a group, offer some improvements over older agents for treating patients with bipolar disorder, just as they have for schizophrenia. The differences or similarities across the atypical agents remain unclear; certainly they are not homogeneous in several neuropharmacological actions of potential relevance to mood, such as effects on receptors or neurotransmitter release of catecholamines, acetylcholine, glutamate, or gamma-aminobutyric acid. Further, as discussed below, clinical evaluation for the other agents is lagging behind olanzapine. Therefore, it is too soon to determine whether the agents have similar efficacy to conventional neuroleptics and to each other for acute mania. Even less is known about relative impacts for diagnostic subgroups and whether, in addition to olanzapine, any will be useful across phases of bipolar disorder, or, like conventional neuroleptics, be relevant mostly to acute mania.

Starting in the late 1990s, a flurry of clinical trials have tested atypical antipsychotic agents for bipolar disorder. The authors of this chapter have contributed to the large portfolio of studies of olanzapine in bipolar disorder, several of which yield information on treatment response of rapid-cycling patients and those with psychotic or dysphoric mania. At this writing, data comparable in breadth or depth to those on olanzapine are not yet available for other atypical antipsychotic agents. However, research is ongoing and one or more controlled acute mania studies have been encouraged for risperidone (Hirschfeld *et al.*, 2004; Sachs *et al.*, 2002a, 2002b; Vieta *et al.*, 2002), ziprasidone (Keck *et al.*, 2003a), quetiapine (Sachs *et al.*, 2004), and aripiprazole (Keck *et al.*, 2003b). Data are not available for other potentially useful atypical agents currently under development, such as iloperidone.

Method

We briefly review available data on antipsychotic agents for the treatment of patients with bipolar disorder. The review is limited to controlled, double-blind clinical trials; these were identified through Medline search (as of March 2003); cross–referencing bibliographies of identified manuscripts; olanzapine trials conducted by us; and preliminary reports obtained at public scientific meetings through 2002. This fourth method offers up-to-date information in this fast-developing field, but carries significant limitations, such as less detailed presentation of methods and/or findings than is typical in manuscripts; incomplete peer review; and the likelihood that some relevant presentations or posters were not available to us.

Our primary focus is the relative response within diagnostic subgroups, especially psychotic versus non-psychotic, mixed versus manic, and rapid versus non-rapid cycling. When available, we report the group-by-treatment interaction, because a significant interaction would signal the potential usefulness of diagnostic categorization to treatment selection. Most data are from mania studies. In order to maintain consistent presentation across studies, we focus on improvement in the primary mania rating scale; response rates; and relative results for diagnostic subgroups. Further, as older antipsychotic agents are constrained in use for bipolar disorder by neurological and depressogenic side-effects, also reviewed are reports of: study completion rates; impact of treatment on depression ratings; and extrapyramidal adverse events. In the interest of comparison across studies, we generally convert raw change to percentage change. For example, percent improvement in mania is calculated by dividing mean within-treatment group improvement by the mean baseline mania rating score for that treatment group. *P*-values are not revised with the conversion to percentage change, but are those reported for mean change and interaction comparisons in the primary studies.

Clozapine

Clozapine was the first of the atypical antipsychotic agents, with clinical trials in schizophrenia starting over three decades ago. Nevertheless, there are no blinded studies of its use in bipolar disorder. Small, open trials are encouraging, including use adjunctive to other mood stabilizers for up to 1 year in a mixed group of schizoaffective and bipolar patients (Suppes *et al.*, 1999). A number of open reports (total $n = 42$) on its efficacy for treatment–refractory mania (Calabrese *et al.*, 1996; Green *et al.*, 2000) have been reported. Controlled double-blind studies in this subgroup would be welcome.

Risperidone

Two available double-blind trials of risperidone in patients with bipolar disorder explored its usefulness as an adjunct to mood stabilizers for treating acute mania. One of these studies was positive. Sachs and collaborators (2002ab) reported a double-blind 3-week study in patients with acute mania or mixed episodes being treated with divalproex or lithium, who were randomly assigned to adjunctive treatment with risperidone 1–6 mg/day ($n = 52$), haloperidol 2–12 mg/day ($n = 53$), or placebo ($n = 51$). Improvement from baseline to endpoint in Young Mania Rating Scale (YMRS) was superior among patients receiving risperidone (51%) or haloperidol (49%) compared to placebo (29%). Though group-by-treatment interaction analysis is not reported, the mania rating mean change results suggest consistent therapeutic effects across psychotic and non-psychotic subgroups for both haloperidol and risperidone as adjunctive treatment to mood

stabilizers. Interestingly, however, results were not consistent across mixed and manic episodes; both adjunctive antipsychotic treatments were effective for manic patients and neither was for mixed patients. In fact, among mixed patients, the group who had placebo added to lithium or divalproex had the greatest mean improvement. Depression ratings were not reported. Discontinuation rates during the 3-week study were 35% on risperidone, 53% on haloperidol, and 49% on placebo. Extrapyramidal symptom ratings worsened significantly in the haloperidol group, but not the risperidone group, compared to placebo. Adverse events of extrapyramidal disorder were reported in 28% of patients receiving adjunctive haloperidol compared to 13% of those receiving risperidone and 4% of those on placebo.

A second study enrolling 150 patients in acute manic or mixed episodes failed to confirm the superiority of risperidone over placebo as an adjunct to divalproex, lithium, or carbamazepine (Yatham, 2000). In this study, the contribution of risperidone was least apparent among those patients using carbamazepine as their primary mood stabilizer, raising the possibility that accelerated metabolism secondary to activation of cytochrome CYP-2D6 may have been an important contributor to the failure of risperidone to differentiate from placebo. Detailed information on efficacy within diagnostic subgroups is not yet available for this study.

A South African group (Segal *et al.*, 1998) published a double-blind, randomized monotherapy comparison of risperidone 6 mg/day and haloperidol 10 mg/day to lithium (mean level 0.53 mmol/l week 1, 0.62 mmol/l week 3, 0.72 mmol/l week 4) for hospitalized patients with acute mania, many with psychosis. Improvement from baseline YMRS was not statistically significantly different among the treatment groups, with 55% reduction on lithium, 43% on risperidone, and 41% on haloperidol. Depression ratings are not reported. However, extrapyramidal symptoms were similar in the risperidone and haloperidol groups, with both worsening substantially compared to the lithium group. Given dose-related extrapyramidal side-effects with risperidone, it is possible that lower doses would have been associated with lower neurological side-effects than haloperidol 10 mg; likewise the small sample size (15 patients per group) and absence of a placebo control necessitate caution in interpreting the lack of statistically significant difference in mania improvement across these groups.

Two placebo-controlled trials have shown promising efficacy of risperidone monotherapy for acute mania. In a USA-based study, Hirschfeld and collaborators (2004) evaluated risperidone 1–6 mg/day (mean modal dose 4.1 mg/day) for patients hospitalized with acute mania. Mean YMRS improvement after 3 weeks of treatment was superior on risperidone (38% improvement, $n = 134$) than on placebo (17% improvement, $n = 125$, $P<0.001$). Response rates, defined as at least

50% reduction in YMRS, were 43% on risperidone and 24% on placebo ($P<0.01$). Efficacy was significant for both psychotic and non-psychotic patients; though group-by-treatment interaction analysis is not provided, the efficacy of risperidone appears roughly comparable in both groups (advantage over placebo in mean YMRS change of 6.3 points in psychotic patients versus 5.3 points in non-psychotic patients). Unfortunately this trial does not address other subgroups: patients with a history of rapid cycling and/or current mixed episode were not enrolled. Changes in depression ratings were minimal in both groups and did not differ significantly between risperidone and placebo. Drop-out rates for the 3-week trial were 44% on risperidone and 58% on placebo (*P*-value not provided). Sixteen percent of risperidone-treated patients had adverse events of "hyperkinesia" versus 5% on placebo (*P*-value not provided).

Vieta and colleagues (2002) reported a 3-week inpatient study of risperidone versus placebo for acute manic or mixed episodes. At doses of 1–6 mg/day, risperidone ($n = 146$, mean modal dose 5.6 mg/day) was associated with superior YMRS improvement than placebo ($n = 144$). Treatment response, defined as 50% or more reduction in YMRS ratings, was achieved twice as frequently on risperidone (73%) as on placebo (36%, $P<0.001$). Changes in depression ratings are not reported, though the authors indicate that their findings do not suggest induction of depression with risperidone. Again, efficacy was significant in both psychotic (approximately 60% of the overall sample) and non-psychotic subgroups. Relative benefits to mixed versus classic manic episodes are not reported, and the impact for rapid-cycling patients cannot be addressed as they were excluded from the study. Three-week completion rates were relatively high – 89% and 71% in risperidone and placebo groups respectively (between-group *P*-value not provided). Use of anticholinergic medications and extrapyramidal symptom ratings are not described. The rates of adverse events of extrapyramidal disorder in this 3-week study were 35% among risperidone-treated patients and 6% on placebo; tremor was an adverse event for 10% of patients on risperidone versus 1% on placebo.

Olanzapine

Olanzapine is now among the best-studied agents for bipolar disorder, with over 1000 patients studied in double-blind mania studies, and recently reported, large double-blind studies in both acute bipolar depression and bipolar relapse prevention.

At least seven double-blind studies have explored the use of olanzapine for acute mania, with superior efficacy observed in all three placebo-controlled studies (Tohen *et al.*, 1999, 2000, 2002b) and a valproate-controlled study (Tohen *et al.*, 2002a); statistically significant differences in acute mania improvement were not found in three other active comparator-controlled studies (Berk *et al.*, 1999;

Zajecka *et al.*, 2002; Tohen *et al.*, 2003a). Olanzapine has proven relatively free of the depressive symptom worsening and extrapyramidal side-effects that limit the usefulness of conventional antipsychotic agents.

Two placebo-controlled studies of olanzapine monotherapy for acute mania have been published (Tohen *et al.*, 1999, 2000) and one for addition to treatment with valproate or lithium (Tohen *et al.*, 2002b).

A 3-week study compared olanzapine 5–20 mg/day ($n = 70$) to placebo ($n = 66$) for inpatients in acute manic or mixed episodes (Tohen *et al.*, 1999). Olanzapine-treated patients had 36% mean reduction in YMRS, superior to 18% mean improvement on placebo. Response rates, defined as 50% or greater YMRS improvement, were 48.6% for olanzapine-treated patients and 24.2% for placebo-treated patients. Efficacy was consistent across psychotic and non-psychotic subgroups: interaction $P = 0.880$. Interaction was also non-significant ($P = 0.998$) for manic versus mixed subgroups. In this case, the advantage of olanzapine over placebo was evident for the manic group (37% versus 16% YMRS improvement), but in the mixed group YMRS reduction on olanzapine averaged 28% versus 25% on placebo. Interaction was likely non-significant because so few mixed patients were enrolled in this study: there were only 12 per treatment group. Mean Hamilton Depression ratings improved similarly in olanzapine (23%) and placebo (21%) groups. The 39% discontinuation rate in the olanzapine group was significantly lower than the 65% discontinuation rate on placebo. Change in extrapyramidal symptom ratings (Simpson-Angus and Barnes Akathisia scales) did not differ between treatment groups.

A second trial (Tohen *et al.*, 2000), this time of 4 weeks' duration, compared olanzapine 5–20 mg/day ($n = 55$) to placebo ($n = 60$) for inpatients in acute manic or mixed episodes. The 51% mean reduction in YMRS during olanzapine treatment was superior to the 28% mean improvement on placebo. Response rates, defined as an individual's mania rating improvement of 50% or more, were 65% on olanzapine versus 43% on placebo ($P = 0.02$). In this study, olanzapine's advantage was particularly evident in psychotic patients (mean YMRS reduction of 52% versus 13% on placebo; in non-psychotic patients, mean improvements were 51% and 44%). The test of interaction was nearing significance ($P = 0.110$); this finding is discrepant from other available studies, which point to olanzapine efficacy as great or greater among non-psychotic than psychotic patients; it may reflect the particularly large improvement on placebo for non-psychotic individuals in this particular trial. In this study, the efficacy of olanzapine was consistent across mixed and manic episodes (interaction $P = 0.706$). Mean Hamilton Depression ratings trended to superior improvement on olanzapine (45%) compared to placebo (28%). The 32% discontinuation rate in the olanzapine group was significantly lower than the 58% discontinuation rate on placebo. Change in

extrapyramidal symptom ratings (Simpson-Angus and Barnes Akathisia scales) did not differ between treatment groups.

A 6-week trial (Tohen *et al.*, 2002b), predominantly in outpatients with at least moderate symptoms of a manic or mixed episode, compared double-blind addition of olanzapine 5–20 mg/day ($n = 229$) or placebo ($n = 115$) to open treatment with valproate or lithium that had been established for at least 2 weeks. Mean YMRS improvement at endpoint was superior in the olanzapine group (59% reduction) compared to the placebo group (40%). Response rates were 68% in the olanzapine co-therapy group, versus 45% in patients receiving lithium or divalproex monotherapy ($P<0.001$). Antimanic efficacy was consistent across diagnostic subgroups: psychotic versus non-psychotic (interaction $P = 0.440$) and mixed versus manic (interaction $P = 0.708$). Improvement in Hamilton Depression ratings was also superior on olanzapine (34% reduction) compared to placebo (7%). Interestingly, this significant antidepressant effect largely reflected an improvement in mixed patients with high baseline depression scores.

Controlled trials of mood stabilizers generally have not addressed the simultaneous improvement of manic and depressive features seen on olanzapine in this study. Thirty percent of the olanzapine group and 29% of the placebo group discontinued treatment during the 6-week study. Change in extrapyramidal symptom ratings (Simpson-Angus and Barnes Akathisia scales) did not differ between olanzapine and placebo groups, though treatment-emergent tremor was more common on olanzapine (23%) than placebo (13%).

A South African group (Berk *et al.*, 1999) conducted a 4-week double-blind comparison of olanzapine to lithium in small cohorts of hospitalized patients with acute mania ($n = 15$ for each group). Though olanzapine trended to superiority in global ratings, change in mania ratings and extrapyramidal symptoms did not differ between the groups, and depression ratings are not reported. As with their similar report (Segal *et al.*, 1998) comparing risperidone and lithium, the small sample sizes limit conclusions from these results.

Olanzapine 5–20 mg/day ($n = 234$) and haloperidol 3–15 mg/day ($n = 219$) were compared in a 12-week monotherapy study in patients with acute mania (Tohen *et al.*, 2003a). The primary outcome was remission from both mania and depression at week 6, which did not differ significantly between groups (57% of olanzapine-treated patients achieved remission, versus 46% on haloperidol). Importantly, however, an interaction was found ($P = 0.09$) between outcome and psychosis status, suggesting that haloperidol and olanzapine are similarly effective for the acute treatment of psychotic mania (remission rate of 49% in each group) whereas olanzapine was more effective for non-psychotic patients (remission rate of 57% versus 42% on haloperidol, $P = 0.04$). There was no interaction ($P = 0.33$) based on diagnosis of mixed versus manic episode. Mean YMRS improvement at 6 weeks did

not differ significantly between groups (69% on olanzapine and 77% on haloperidol), whereas Hamilton Depression rating improvement trended to superiority in the olanzapine group (35% reduction versus 23% in the haloperidol group). Discontinuation rates in the olanzapine group were 29% at week 6 and 40% by week 12, compared to 36% and 47% respectively, in the haloperidol group. This study is an interesting reminder that typical antipsychotic medications can be quite effective for acute mania, perhaps especially for psychotic mania. However, there was confirmation of the principal limitations of conventional agents, with switch to depression occurring significantly sooner and in more patients in the haloperidol group, and significantly greater extrapyramidal symptoms on haloperidol, as measured by Simpson-Angus and Barnes Akathisia, and Abnormal Involuntary Movement scales. Several treatment-emergent extrapyramidal adverse events were significantly more common on haloperidol than olanzapine, including akathisia (30% versus 6%), extrapyramidal syndrome (24% versus 2%), hypertonia (18% versus 5%), tremor (16% versus 6%), dystonia (7% versus 1%), dyskinesia (3% versus 0%), and tardive dyskinesia (3% versus 0%). Moreover, switch to depressive episodes trended to being more frequent among haloperidol-treated patients (17%) than olanzapine-treated patients (9%), $P = 0.098$, and time to switch to depression was earlier in the haloperidol group ($P = 0.04$).

Finally, two studies compared olanzapine to valproate monotherapy for inpatients with acute mania. A study conducted by Zajecka and collaborators compared olanzapine (starting dose 10 mg/day, maximum 20 mg/day, $n = 57$) to valproate (starting dose 20 mg/kg/per day, maximum increase 1000 mg/day, $n = 63$) for inpatients with acute mania (Zajecka *et al.*, 2002). Mean YMRS improvement at 3 weeks did not differ significantly between olanzapine (53%) and valproate (48%). Response rates and diagnostic subgroup results were not reported. Hamilton Depression ratings also improved similarly in the two groups: 46% on olanzapine and 42% on divalproex. Three-week completion rates were 68% on olanzapine, 62% on valproate, *P*-value was not provided. Extrapyramidal symptom ratings on the Simpson-Angus or Barnes Akathisia scales did not differ between groups. And no treatment-emergent extrapyramidal adverse events differed between treatment groups.

A larger, olanzapine–valproate double-blind comparison has been published (Tohen *et al.*, 2002a). In this trial, inpatients were randomized to olanzapine 5–20 mg/day (starting dose 15 mg, $n = 125$) or valproate 500–2500 mg/day (starting dose 750 mg/day, $n = 123$). YMRS improvement at 3 weeks was superior on olanzapine (49%) compared to valproate (37%) ($P < 0.03$). Response rates, defined as improvement of at least 50% on the YMRS, were 54% on olanzapine versus 42% for valproate ($P = 0.06$). This study found an interaction ($P = 0.06$) based on psychosis status. Among patients with psychotic mania, YMRS improvement was similar on olanzapine (44% reduction) and on valproate (41% reduction). However, among

Table 16.1 Improvement from baseline Young Mania Rating Scale in psychotic versus non-psychotic patients treated with olanzapine or a comparator

Duration	Group	Psychotic	Non-psychotic	Interaction
3 weeks	Olanzapine	34% ($n=38$)	39% ($n=32$)	$P=0.880$
	Placebo	19% ($n=33$)	17% ($n=33$)	
3 weeks	Olanzapine	44% ($n=62$)	54% ($n=63$)	$P=0.061$
	Divalproex	41% ($n=51$)	34% ($n=74$)	
4 weeks	Olanzapine	52% ($n=33$)	51% ($n=21$)	$P=0.110$
	Placebo	13% ($n=28$)	44% ($n=28$)	
6 weeks	Olanzapine + lithium or valproate	54% ($n=70$)	62% ($n=150$)	$P=0.440$
	Placebo + lithium or valproate	45% ($n=38$)	39% ($n=76$)	

non-psychotic individuals, mania rating improvement was superior on olanzapine (54%) than on valproate (34%, $P<0.001$). No interaction was found ($P=0.95$) based on manic versus mixed episode, suggesting the relative performance of olanzapine and divalproex is similar across this diagnostic dimension. Hamilton Depression rating scale reduction did not differ significantly between the groups (33% improvement on olanzapine and 26% on valproate). Discontinuation rates were 31% on olanzapine and 36% on divalproex. Though treatment-emergent tremor was more common on olanzapine (10% versus 3%), mean changes in extrapyramidal symptom ratings (Simpson-Angus and Barnes Akathisia scales) did not differ between groups. Tables 16.1 and 16.2 summarize improvement in manic symptoms seen in olanzapine- or comparator-treated patients with psychotic versus non-psychotic and manic versus mixed manic symptoms, respectively.

Given the question of worsening of depression with some antipsychotic agents, the findings of a recent trial of olanzapine for bipolar I depression are of interest (Tohen *et al.*, 2003b). To our knowledge no other study has been conducted of antipsychotic monotherapy for bipolar depression. In this 8-week, double-blind study, mean Montgomery-Asberg Depression symptom rating improvements were significantly greater among 370 patients treated with olanzapine 5–20 mg/day (39% improvement) than among 377 placebo-treated patients (30% improvement from baseline). Of note, this study also included a group treated with olanzapine 6 or 12 mg/day plus fluoxetine 25 or 50 mg/day; depressive symptoms improved significantly more in this group (55%) than in either of the other groups, while the rate of switch to mania was not increased. Eight-week completion rate was significantly higher on olanzapine (48%) than placebo (39%), and completion rate on the olanzapine–fluoxetine combination (64%) was significantly greater than in both other groups. Extrapyramidal side-effects, measured by Simpson-Angus and Abnormal Involuntary Movement scales, did not differ among the groups.

Table 16.2 Improvement from baseline Young Mania Rating Scale in manic versus mixed patients treated with olanzapine or a comparator

Duration	Group	Manic	Mixed	Interaction
3 weeks	Olanzapine	37% ($n = 58$)	28% ($n = 12$)	$P = 0.998$
	Placebo	16% ($n = 54$)	25% ($n = 12$)	
3 weeks	Olanzapine	49% ($n = 69$)	48% ($n = 56$)	$P = 0.950$
	Divalproex	36% ($n = 74$)	38% ($n = 52$)	
4 weeks	Olanzapine	53% ($n = 31$)	50% ($n = 23$)	$P = 0.706$
	Placebo	26% ($n = 33$)	30% ($n = 23$)	
6 weeks	Olanzapine + lithium or valproate	60% ($n = 99$)	58% ($n = 121$)	$P = 0.708$
	Placebo + lithium or valproate	45% ($n = 60$)	34% ($n = 54$)	

Finally, initial results are available of a 1-year comparison of olanzapine 5–20 mg/day and lithium (mean level 0.77 mmol/l) for relapse prevention among bipolar patients stabilized on an open combination of olanzapine and lithium and a 1-year comparison of olanzapine to placebo for relapse prevention among manic patients openly stabilized on olanzapine (Tohen *et al.*, 2004). The lithium comparison study however enrolled very few (<10%) rapid-cycling patients. On the other hand, rapid-cycling patients constituted roughly half of the placebo comparison study. Overall relapse rates were modestly higher among rapid-cycling patients, but olanzapine was significantly better than placebo in delaying relapse for both rapid and non-rapid cycling patients. To our knowledge, no controlled maintenance data or information on slowing the course of rapid cycling are available for the other agents reviewed in this chapter.

Quetiapine

Two double-blind studies have been reported demonstrating efficacy of quetiapine as adjunctive treatment for acute mania. The first (DelBello *et al.*, 2002) was a 6-week trial in adolescent (aged 12–18) inpatients in acute manic or mixed episodes, receiving open treatment with valproate 20 mg/kg per day. They were randomized to adjunctive treatment with valproate 450 mg/day ($n = 15$) or placebo ($n = 15$). Repeated measures of analysis of variance of completers only found greater improvement of YMRS in the quetiapine group at two of the seven ratings (days 21 and 42). Information available to date does not state whether the groups differed in intent-to-treat analysis of mania ratings. Forty percent of patients receiving quetiapine and 13% on placebo discontinued treatment during the 6-week study. Changes in extrapyramidal symptom ratings did not differ between treatment groups.

The second, larger trial (Sachs *et al.*, 2004) was conducted in adult inpatients with acute mania receiving open treatment with lithium or divalproex. It appears that the

initiation of mood-stabilizer treatment did not necessarily antedate starting quetiapine or placebo. Patients were randomized to 3 weeks of adjunctive treatment with quetiapine 200–800 mg/day ($n = 91$) or placebo ($n = 100$); significantly greater improvement in YMRS from baseline occurred in the adjunctive quetiapine group (44% reduction) than in the placebo group (32%) ($P = 0.021$). Response, defined as 50% or greater YMRS improvement, was more common in patients taking adjunctive quetiapine (54.9%) than placebo (32.6%, $P = 0.005$). Montgomery-Asberg depression ratings improved from baseline in both groups (25% reduction on quetiapine versus 20% on placebo, difference not significant) and the number of patients with treatment-emergent depression also did not differ significantly between groups (quetiapine 17%, placebo 14%). Unfortunately, the report does not shed light on subgroup efficacy; the authors do not mention whether improvement is consistent irrespective of presence of psychosis, and both rapid-cycling patients and those in current mixed episodes were excluded from the trial. Dropout rate did not differ significantly between placebo-treated (51%) and quetiapine-treated patients (39%) for this 3-week adjunctive-treatment study. Changes in extrapyramidal symptom ratings (Simpson-Angus and Barnes Akathisia scales) were modest and apparently did not differ between the groups.

Ziprasidone

At this writing, one double-blind trial of ziprasidone in bipolar disorder has been reported (Keck *et al.*, 2003a). This 3-week, placebo-controlled study in patients with acute manic or mixed episodes found superior YMRS improvement on ziprasidone 80–160 mg/day (46% reduction, $n = 131$) than on placebo (29%, $n = 64$) ($P<0.005$). Response rates, defined as 50% or greater improvement in YMRS scores, were 50% and 35% for ziprasidone and placebo groups, respectively ($P<0.05$). Raw improvement in mania ratings during ziprasidone treatment was similar among patients in classic manic ($n = 85$) or mixed episodes ($n = 46$). However, reports to date do not address whether effect size, or improvement relative to placebo, differs between manic and mixed subgroups. Similarly, relative efficacy for psychotic versus non-psychotic subjects and rapid versus non-rapid-cycling patients was not addressed in the first manuscript. Discontinuation rate in the ziprasidone group was 46% versus 56% for placebo, *P*-value not provided. Changes in depressive symptoms are not addressed and apparently were not assessed in this trial. Extrapyramidal side-effect ratings (Simpson-Angus and Barnes Akathisia Rating Scales, and Abnormal Involuntary Movement Scale) did not differ significantly between ziprasidone and placebo groups. However, treatment-emergent events reported more frequently on ziprasidone than on placebo included hypertonia (11% versus 3%) and akathisia (11% versus 6%). Tests of statistical significance were not reported for these adverse events.

Aripiprazole

Aripiprazole is the most recently introduced antipsychotic agent, and at least two controlled monotherapy trials have been conducted in acute mania. One of these had positive findings (Keck *et al.*, 2003b). Among hospitalized patients with acute mania, mean YMRS improved from baseline to the 3-week endpoint significantly more frequently among patients treated with aripiprazole (29% reduction, $n = 130$, mean dose 27.9 mg/day) compared to placebo (11%, $n = 132$). Depression ratings significantly improved in aripiprazole-treated patients versus depression (clinical global Impression-Bipolar severity of Depression). The authors do not address any of the potentially important response by subgroup interactions, that is, based on rapid cycling, psychosis, or mixed state status. Drop-out rates were high in this 3-week study (58% on aripiprazole and 79% on placebo). Measurements of extrapyramidal symptoms (Simpson–Angus and Barnes Akathisia scales) worsened significantly on aripiprazole compared to placebo. Extrapyramidal adverse events reported more commonly in the aripiprazole than placebo groups included akathisia (11% versus 2%), tremor (6% versus 3%), and increased salivation (6% versus 1%), but it is not reported whether any of these findings were statistically significant.

Use of atypical antipsychotic medications in mania: psychotic and non-psychotic patients

A diverse array of medications has evidence of usefulness in mania, including lithium, anticonvulsants, antipsychotics, atypical antipsychotics, benzodiazepines, and calcium channel blockers. There is little information on the relative effects of such treatments, including whether a specific medication differentially targets a subset of manic symptoms. Nevertheless, in the case of antipsychotic agents, clinical guidelines, unsurprisingly, are particularly supportive of their use for patients with psychotic mania (and in some cases for more agitated or severely ill patients)[a] (Sachs *et al.*, 2000, American Psychiatric Association, 2002; Baldessarini, 2002).

A secondary analysis was performed for the double-blind studies of olanzapine in acute mania to evaluate effectiveness for psychotic and non-psychotic subgroups, as

[a] There is some evidence that, at least in the case of olanzapine, usefulness extends beyond more severely ill patients. In a previously unpublished secondary analysis of a 3-week olanzapine–divalproex monotherapy comparison for acute mania (Tohen *et al.*, 2002a), treatment groups were divided into more and less severely ill groups by a median split of baseline YMRS. Among olanzapine-treated patients, baseline to endpoint improvement was similar in more and less severely ill patients. As compared to those receiving divalproex, improvement was similar in the more severely ill cohort, but superior on olanzapine among less ill patients. In that all patients in this study were hospitalized and had bipolar I disorder, the less severely ill patients probably still had relatively severe symptoms. Nevertheless, these data suggest that the usefulness of olanzapine, at least, extends beyond the sickest patients.

defined by baseline diagnosis confirmed by Structured Clinical Interview for *Diagnostic and Statistical Manual* IV using *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV): American Psychiatric Association (1994) criteria. These data are not available for two of the trials (Berk *et al.*, 1999; Zajecka *et al.*, 2002). The principal intent of these analyses was to seek an interaction between diagnostic subgroup and clinical outcome, that is, is efficacy better among psychotic patients, thereby suggesting that antimanic effects derive from antipsychotic properties? The answer appears to be no.

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17

Investigational strategies: treatment of rapid cycling, mixed episodes, and atypical bipolar mood disorder

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The psychiatric literature includes relatively few adequately powered controlled double-blind clinical trials reporting results for bipolar disorders. The majority of these randomized clinical trials report results for treatment of acute mania in hospitalized bipolar I (BP-I) patients. The majority of bipolar patients are, however, not BP-I and manic states are relatively infrequent. Why are there so few published controlled treatment studies dealing with common clinical problems like rapid cycling, mixed episodes, and atypical bipolar disorder?

Rapid cycling, mixed episodes, and atypical bipolar mood disorder each challenge clinical researchers in distinctly different ways. This chapter explores the issues as they relate to study design in general and offers suggestions for study methodology.

The first consideration is the conceptual dissimilarity of the terms rapid cycling, mixed episodes, and atypical bipolar disorder. These terms correspond to three distinct organizational levels used in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV) mood-disorder nosology and represent the concepts of course specifier, acute episode, and subtype of bipolar (American Psychiatric Association, 1994). Study designs for each require attention to sample selection, outcome measures, and an analysis plan matched to the appropriate level in the organizational hierarchy of the DSM-IV mood-disorder classification.

Difficulties in conducting clinical trials for atypical bipolar disorder

The DSM-IV bipolar mood disorder category is subtyped into BP-I, BP-II, cyclothymia, and bipolar disorder not otherwise specified. The latter encompasses all forms of "atypical bipolar disorder" which do not meet criteria for one of the three defined subtypes. There are, as yet, no treatments that are indicated for any of these disorders *per se*. Various regulatory authorities have granted indications

specifically for treatment of single acute manic episodes and prophylaxis, but there is neither treatment for bipolar disorder itself nor any of its subtypes. Several practical obstacles make it difficult to carry out clinical trials that aim at the disorder or its subtypes. The term "atypical bipolar disorder" could be defined in many ways, but little research has been done to validate any particular definition. Whether or not research focused on atypical bipolar disorder adopted a definition akin to that used by the DSM-IV, the variance implied by this term creates a statistical challenge. Heterogeneous diagnostic categories, like atypical bipolar disorder, are a disadvantageous target for clinical trials because combining dissimilar conditions under a single heading increases variance. Clinical trialists able to surmount this formidable obstacle confront a series of additional daunting dilemmas such as what outcome measure is appropriate in determining outcome for a longitudinal illness and what duration of study might be sufficient to measure such an outcome confidently.

There are other important problems related to subtyping bipolar disorder. The DSM-IV relies primarily on the characteristics and consequences of episodes of mood elevation to assign subtypes. For instance, the classification BP-I is given when the most extreme episode meets criteria for mania. Subtyping might, however, be based on other characteristics such as age of onset, course of illness, biological markers, and response to treatment.

Categorical approaches to subtyping are as yet not well validated and any lifetime diagnosis assigned to a living patient must be regarded as subject to change. Furthermore there is no evidence of sharp distinctions between subtypes. Figure 17.1, the bipolarity index under study in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), scores five dimensions of bipolarity and was developed to provide a continuous measure (0–100) where a score of 20 on each dimension is assigned for unambiguous characteristics considered most consistent with the classic form of BP-I illness. This scale offers a continuous measure of bipolarity that can be determined separately from formal diagnostic subtype.

Despite the difficulties in evaluating subtypes of bipolar illness, some notable successes suggest the potential value of subtyping bipolar disorders. Subtyping of bipolar illness by the sequence of phases or episode pattern has been shown to predict response to lithium (Koukopoulos *et al.*, 1980; Grof *et al.*, 1987; Haag *et al.*, 1987; Maj *et al.*, 1989). This promising technique may merit wide usage, if its reliability and validity can be formally established.

The 11-year follow-up carried out by Alda *et al.* (1998) for 559 subjects previously diagnosed with unipolar depression demonstrated differences in self-report measures of mood lability, energy activity, and daydreaming between the 3.9% of subjects who developed full manic episodes (BP-I) and the 8.6% who experienced hypomanias only (BP-II).

BIPOLARITY INDEX

For each of the items below, circle the score next to the characteristic that best describes the patient.
Characteristics' scores range from 0 (no evidence of bipolar disorder) to 20 (most convincing characteristic of bipolar disorder).

I. Episode Characteristics	
20	• Documented acute mania or mixed episode with prominent euphoria, grandiosity, or expansiveness and no significant general medical or known secondary etiology
15	• Clear-cut acute mixed episode or dysphoric or irritable mania with no significant general medical or known secondary etiology.
10	• Clear-cut hypomania with no significant general medical or known secondary etiology. • Clear-cut cyclothymia with no significant general medical or known secondary etiology. • Clear-cut mania secondary to antidepressant use.
5	• Clear-cut hypomania secondary to antidepressant use. • Episodes with characteristic sxs of hypomania, but sxs, duration, or intensity are subthreshold for hypomania or cyclothymia. • A single MDE with psychotic or atypical features (Atypical is 2 of the following sxs: hypersomnia, hyperphagia, leaden paralysis of limbs) • Any postpartum depression.
2	• Any recurrent typical unipolar major depressive disorder. • History of any kind of psychotic disorder (i.e., presence of delusions, hallucinations, ideas of reference, magical thinking).
0	• No history of significant mood elevation, recurrent depression, or psychosis.
II. Age of Onset (1st affective episode/syndrome)	
20	• 15 to 19 years
15	• before age 15 or between 20 and 30
10	• 30 to 45 years
5	• after age 45
0	• No history of affective illness (no episodes, cyclothymia, dysthymia, or BP NOS).
III. Course of Illness/Associated Features	
20	• Recurrent, distinct manic episodes separated by periods of full recovery.
15	• Recurrent, distinct manic episodes with incomplete inter-episode recovery. • Recurrent distinct hypomanic episodes with full inter-episode recovery.
10	• Comorbid substance abuse. • Psychotic features only during acute mood episodes. • Incarceration or repeated legal offenses related to manic behavior (e.g., shoplifting, reckless driving, bankruptcy).
5	• Recurrent unipolar MDD with 3 or more major depressive episodes. • Recurrent, distinct hypomanic episodes without full inter-episode recovery. • Recurrent medication non-compliance. • Comorbid borderline personality disorder, anxiety disorders, or eating disorders, or history of ADHD. • Engagement in risky behaviors that pose a problem for patient, family, or friends. • Behavioral evidence of perimenstrual exacerbation of mood symptoms.
2	• Baseline hyperthymic personality (when not manic or depressed). • Marriage 3 or more times (including remarriage to the same individual). • In two or more years, has started a new job and changed jobs after less than a year. • Has more than two advanced degrees.
0	• None of the above.
IV. Response to Treatment	
20	• Full recovery within 4 weeks of therapeutic treatment with mood stabilizing medication.
15	• Full recovery within 12 weeks of therapeutic treatment with mood stabilizing medication or relapse within 12 weeks of discontinuing tx. • Affective switch to mania (pure or mixed) within 12 weeks of starting a new antidepressant or increasing dose.
10	• Worsening dysphoria or mixed symptoms during antidepressant treatment subthreshold for mania. • Partial response to one or two mood stabilizers within 12 weeks of therapeutic treatment. • Antidepressant-induced new or worsening rapid-cycling course.
5	• Treatment resistance: lack of response to complete trials of 3 or more antidepressants. • Affective switch to mania or hypomania with antidepressant withdrawal.
2	• Immediate near complete response to antidepressant withdrawal.
0	• None of the above, or no treatment.
V. Family History	
20	• At least one first degree relative with documented bipolar illness.
15	• At least one second degree relative with documented bipolar illness. • At least one first degree relative with documented, recurrent unipolar MDD and behavioral evidence suggesting bipolar illness.
10	• First degree relative with documented, recurrent unipolar MDD or schizoaffective disorder. • Any relative with documented bipolar illness or recurrent unipolar MDD and behavioral evidence suggesting bipolar illness.
5	• First degree relative with documented substance abuse. • And relative with possible bipolar illness.
2	• First degree relative with possible recurrent unipolar MDD. • First degree relative with diagnosed related illness: anxiety disorders, eating disorders, ADD/ADHD.
0	• None of the above, or no family psychiatric illness.
_____	← **Total score (0–100)**

Fig. 17.1 Bipolarity index: a continuous measure sunmarizing five dimensions of mood disorder relative to classic characteristics of bipolar I disorder.

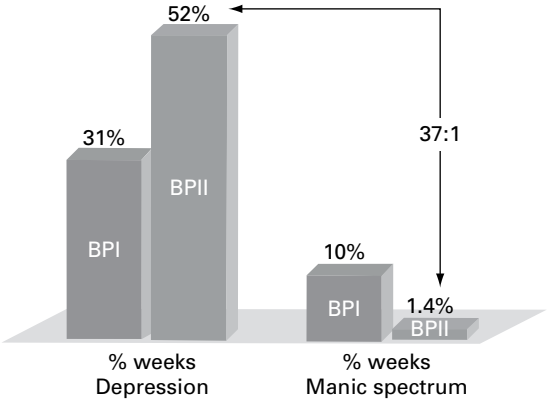


Fig. 17.2 Course over 15-year follow-up. Bipolar I (BPI), $n = 135$; bipolar II (BPII), $n = 71$. Adapted from Judd *et al.* (2002).

Robb *et al.* (1997) employed a self-report measure, the Illness Intrusiveness Rating Scale, and found that euthymic BP-II patients suffered greater impairment than BP-I subjects (Robb *et al.*, 1997).

Judd *et al.* (2002) compared the course of illness for BP-I ($n = 135$) and BP-II ($n = 71$) followed in the National Institute of Mental Health (NIMH) Collaborative Depression Study over 15 years of follow-up. Figure 17.2 shows outcomes from the Longitudinal Interval Follow-up Evaluation (LIFE: Keller *et al.*, 1987), one of the few measures that harvests systematic data over time periods sufficiently long enough to describe course of illness. The impressive differences in percentage of weeks depressed (BP-I = 31%; BP-II = 52%) and the ratio of weeks depressed to weeks with hypomania+mania (BP-I = 3:1; BP-II = 37:1) demonstrates the possibility for capturing long-term outcomes.

Difficulties in conducting clinical trials for mixed episodes

The DSM-IV definition of mixed episodes requires a period of at least 1 week during which a patient meets full criteria for mania and major depression. Few studies reporting results for mixed episodes, however, use the DSM-IV definition. Leaving aside the confusing array of "mixed states" described as fulfilling one or more criteria for "mixiety" (Akiskal and Pinto, 1999), many studies of mixed states are problematic. Within the limits of brevity permissible here, it is possible to highlight only two commonly underappreciated issues related to interpretation of studies reporting results for mixed states.

Some studies operationalize the term "mixed state" by using cut-off scores on formal rating scales, which are not validated as diagnostic instruments. For

instance, it is not possible to state with certainty that a patient meeting criteria for mania and also having a Hamilton Depression Rating Scale score > 20 meets the DSM criteria for a mixed episode.

Most treatment results published for mixed episodes are derived from clinical trials conducted primarily to gain regulatory approval for treatment of acute mania. Studies designed for this objective are subject to potentially serious distortions when outcomes are reported. In such studies response rates are operationally defined based on improvement on the mania rating scale without considering the persistence or worsening of depressive severity. Thus patients with moderate mania at study entry who become severely depressed during the study can meet the outcome criteria for treatment response. Furthermore, accession bias can have dramatic consequences. At the baseline study visit, clinically depressed bipolar patients with just one or two moderate manic symptoms, such as irritability, agitation, insomnia, and racing thoughts, may well meet rating scale criteria for a mixed episode. In light of longitudinal data indicating that mixed episodes are very likely to be chronic (Kupfer *et al.*, 2001), it is surprisingly common to observe that a substantial percentage of subjects in clinical trials with mixed episodes at baseline meet remission criteria at the week 1 follow-up assessment.

Addressing factors related to the specificity of diagnosis and treatment outcome has great potential to improve the prospects for research on mixed episodes. Standardizing criteria for accession of more uniform samples or at least clearly defining the condition is a critical need. Himmelhoch *et al.* (1976) recognized the importance of secondary factors such as comorbid conditions and psychoactive substance use in the phenomenology of mixed episodes. Kraepelin (1921) noted the occurrence of mixed states and distinguished transient mixed states which might arise in the course of cycling from a manic episode to a depression, from persistent states in which the symptoms of mania and depression co-occur chronically. Entry criteria for studies focusing in mixed states could promote more homogeneous samples by excluding subjects with known secondary factors and requiring a duration longer than 4 weeks to improve the homogeneity of their sample. Studies reporting outcomes for mixed episode should include composite outcome measures that employ concurrent assessment of mania and depression rather than reporting outcome measure related exclusively to mania (e.g., 50% improvement from baseline mania rating scale score).

Difficulties in conducting clinical trials for rapid cycling

What is rapid cycling? The term "rapid cycling" was coined by Dunner *et al.* (1977) based on the high frequency of four episodes or more per year among those patients with poor response to lithium. Since then, treatment for rapid cycling

has become recognized as an important area of unmet clinical need. The DSM-IV classifies rapid cycling as a course specifier rather than a subtype of bipolar disorder. Although rapid cycling is associated with relatively poor response to treatment and persistence of higher rates of cycling than non-rapid cycling (Bauer *et al.*, 1994; Baldessarini *et al.*, 2000), bipolar illness, indices such as family history, and age of onset do not separate rapid-cycling from non-rapid-cycling patients (Bauer *et al.*, 1994). Furthermore, prospective follow-up reveals rapid cycling is seldom persistent. Among subjects diagnosed as rapid cycling on entry into the NIMH Collaborative Depression study, Coryell *et al.* (1992) found only a third demonstrated four or more episodes through the first year of prospective follow-up and in only 3% did rapid cycling persist through 3 years.

The DSM-IV concept of rapid cycling retains Dunner and colleagues' definition of rapid cycling as four or more episodes in 1 year (Dunner *et al.*, 1977). Importantly, the DSM-IV concept of rapid cycling requires counting episodes; either as four episodes separated by periods of remission or a switch from an episode of one polarity to an episode of opposite polarity. Strict application of the DSM definitions can provide upper as well as lower boundaries for annual episode frequency consistent with the rapid-cycling concept. Notably, the DSM requires separate episodes be bounded by a period of full or partial remission lasting at least 8 weeks and the definition of mania requires the presence of symptoms for at least 1 week. Therefore, in the course of a year, patients following this 9-week pattern could have no more than six episodes. A pattern of continuous cycling in which a patient abruptly switches from a 1-week period meeting criteria for mania to a 2-week period of symptoms meeting criteria for depression could produce a higher cycle frequency. Even repetition of this 3-week pattern throughout a year could produce an annual cycle frequency only as high as 17 per year. Many patients and practitioners, however, report cycle frequencies greatly exceeding 17 per year. In fact, it has become common to hear descriptions of patients with multiple cycles within a single day. These various forms of so-called 'ultrarapid cycling' are characterized by "truncated episodes" (Bauer *et al.*, 1994). The concept of truncated episodes allows a phase to count toward the diagnosis of rapid cycling even when that phase is too short to qualify as a DSM-defined episode. The advantage of the truncated episode concept is obvious: it allows the rapid-cycling designation to be applied to patients such as those described with 48-h periods of depression alternating with 48-h periods of mood elevation. The problem, however, is that when we suspend the requirement to meet the definition for an episode we lack criteria to distinguish meaningfully mixed episodes from rapid cycling or even reliably distinguish a phase of illness from an emotion. Using the concept of truncated episodes in clinical trials, therefore, requires researchers to use great caution and standardized counting procedures.

What are the lessons from clinical trials for rapid cycling?

Perhaps the most striking lesson from trials that have focused on rapid cycling is how difficult it is to study this condition. To date the only published parallel-group double-blind controlled trial reporting results for rapid cycling found a significant advantage for lamotrigine over placebo. This trial is remarkable not only because it represents the best available evidence pertaining to the treatment of rapid cycling, but also because the results document a clearly consistent pattern of differential response across multiple outcome measures in which BP-II rapid cycling appears robustly responsive to lamotrigine and BP-I patients appear minimally, if at all, responsive to lamotrigine (Calabrese *et al.*, 2000).

Published reports of lithium treatment for rapid cycling suffer from the limitations of mirror design, but do suggest lithium can be a beneficial treatment for some rapid-cycling patients (Dunner *et al.*, 1977; Maj *et al.*, 1989). One small single-blind trial described benefit for thyroid hormone at hypermetabolic doses (Bauer and Whybrow, 1990). There are, however, no published studies that examine the use of valproate, carbamazepine, gabapentin, oxcarbazepine, conventional antipsychotics, or atypical antipsychotics under double-blind conditions.

Some recent clinical trials may create confusion when reporting results for rapid-cycling patients for outcomes other than rapid cycling. For example, *post hoc* analyses have been conducted to examine results for rapid-cycling patients enrolled in double-blind trials testing the efficacy of potential treatments for acute episodes of mania or depression. Such results, with appropriate caveats, can be perfectly acceptable, but confusion may arise for several reasons. First, the reported outcome measure for acute episodes is easily misinterpreted as an outcome for rapid cycling *per se*. Change in rating scale scores over a brief (usually 3–4-week) phase of blinded treatment does not speak to the issue most pertinent for rapid cycling – change in cycle frequency over time. Second, even interpretation of acute response rates should take into consideration whether the process of randomization balances treatment groups for the presence of rapid cycling. Third, published reports often fail to clarify whether results presented for rapid-cycling patients refer to current or lifetime rapid cycling, and fail to make clear that the diagnosis of rapid cycling relied on a single question asked during the baseline assessment of an acutely ill patient. Consistent with the DSM-IV classification, rapid cycling concurrent with study entry might represent a valid state designation. Bipolar individuals who are not currently cycling rapidly, but who have experienced a period of rapid cycling in the remote past, might define a clinically important trait. Bipolar patients shown to be prone to periods of cycle acceleration or affective switch may represent a distinct subgroup, perhaps at high risk of becoming manic during treatment with standard antidepressant medications. Consistent use of operationalized definitions and validated procedures for assessment

are needed to examine the state-versus-trait question. (See Definitions for characterizing rapid cycling, below.)

Post hoc analysis of results for patients with rapid cycling have been presented for the acute mania trials (Bowden and McElroy, 1995; Tohen *et al.*, 1999) and illustrate common problems related to assessment and interpretation. The acute mania trials conducted by Bowden and McElroy, and Tohen *et al.* relied on retrospective diagnosis of rapid cycling based on simply asking acutely manic patients how many episodes they had had. *Post hoc* analysis of the Bowden trial is sometimes cited as evidence of the superior efficacy of valproate over lithium. This interpretation cannot be correct. The randomization process in that acute mania study was not intended to balance the treatment groups for rapid cycling and for purely random reasons did not result in the assignment of any rapid-cycling patient to the lithium treatment group. Tohen *et al.* found a higher response rate in rapid-cycling patients treated with olanzapine than non-rapid-cycling patients. This outcome indicates that manic episodes in subjects with rapid cycling responded to olanzapine sooner than manic episodes in non-rapid-cycling bipolar patients, but does not address rapid cycling.

The problem of counting episodes is a serious obstacle to research on rapid cycling. Figure 17.3 depicts the course of a single hospitalized patient over a period of about 90 days. The graphed daily ratings, made by nursing staff using independent scales to rate separately the severity of mania and depression, reveal extreme variability of mood state. While this patient was described clinically as simply having a manic episode, an observer counting the peaks and valleys generated by the daily ratings could easily describe this patient's course as ultrarapid cycling, and a rater applying DSM-IV criteria would likely diagnose a mixed episode. This discrepancy, which is a serious impediment to research on rapid cycling, requires

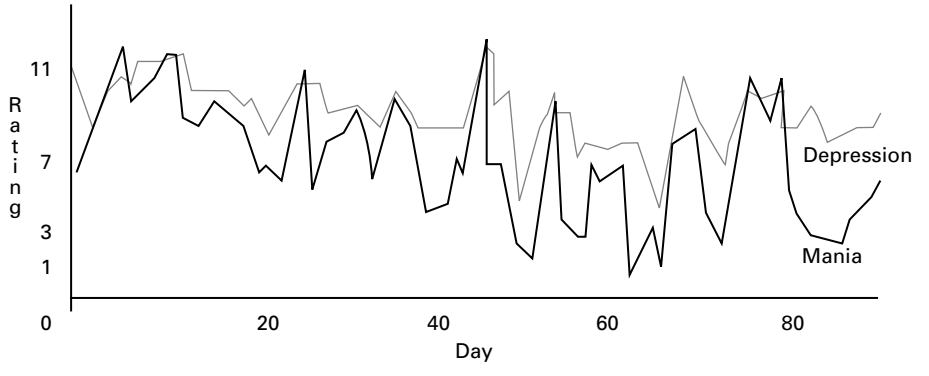


Fig. 17.3 Daily independent mania and depression ratings. Depression is the most common chief complaint during mania. Adapted from Goodwin and Jamison (1990).

Table 17.1 Counting phase shifts

	Previous assigned mood state			
Current mood state	Depression	Hypomania	Mania	Mixed
Depression	No phase shift	Yes	Yes	No phase shift
Hypomania	Yes	No phase shift	No phase shift	No phase shift
Mania	Yes	No phase shift	No phase shift	No phase shift
Mixed	Yes	Yes	Yes	No phase shift

investigators to develop clear operational procedures that can be applied consistently by raters at multiple sites.

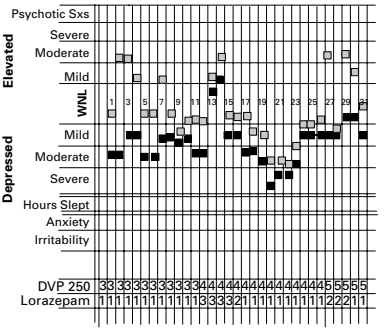
Standardized assessment tools for prospective longitudinal follow-up may offer advantages over retrospective assessments like LIFE. The advantages of prospective rating may be particularly important when attempting to track multiple brief fluctuations in mood state.

Defining a phase of illness is a key research need. Kramlinger and Post (1996) defined an alternative to the DSM episode definitions of ultrarapid cycling to account for phase shifts that occur within a 24-h period. The 15-point Bunney-Hamburg Rating Scale, administered twice daily by nurses, was used to identify a phase shift. Subjects also marked 100-mm visual analogue lines, where the left side was anchored by "best ever" (manic) and the right side by "worst ever" (depressed). A new depressive episode was defined as a sudden increase of three points in the assessment score or at least 7 days with a depression rating greater than 7. The end of the depressive episode was determined by a sudden decrease of 3–6 points, a sustained period of at least 7 days with a score less than five, or a switch in polarity from depression to mania.

There are some obvious problems with this technique: a patient who was already in a major depressive episode could experience several brief depressions due to transient three-point fluctuations in the course of a single day. Perhaps more important than the technical issues is the fact that patients are typically not observed in inpatient units while undergoing treatment for rapid cycling. In order for a trial to target rapid cycling effectively, it would need to take place over a period of 6 months or more. Outcome measures that rely on trained observer ratings are impractical, because subjects are not likely to remain hospitalized for the long periods required to assess multiple episodes.

Methods developed in our clinic for counting phases can be more readily applied to outpatient studies. Phase changes are defined as the appearance of a new mood state with duration of 48 h (Table 17.1). If the new mood state is not sustained for 48 h, it must meet the DSM-IV criteria for an episode. This

Month 1 Mood chart

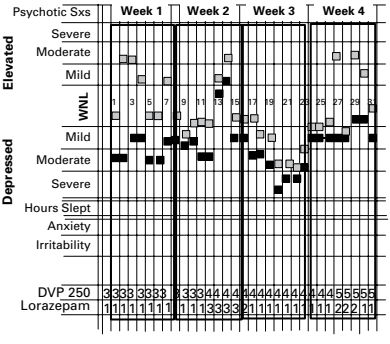


Daily mood ratings indicate highest and lowest mood state for each date.

Baseline assessment: a 31-year-old female previously diagnosed as rapid cycling begins the month with a hypomanic phase.

In light of labs indicating valproate levels of 62 mmol/mg, treatment commenced with increasing dose of valproic acid and assessed weekly.

Month 1 with 7-day assessment intervals

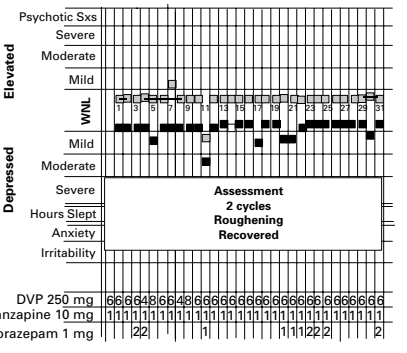


Diagnostic impressions made serially based on careful assessment of the preceding 7 days leaves much room for subjectivity.

Potential diagnoses:
Week 1: Depression, mania, mixed
Week 2: Depression, mania, recovering
Week 3: Depression, recovering
Week 4: Depression, mania, recovering

Entire month = rapid cycling 1–2 phases
CGI-I = 4 (no change)

Month 12 mood chart



Month 12 diagnostic assessments on based serial weekly assessments made during include:

-2 cycles
-Roughening
-Recovered

Entire monthly: recovered (0 cycles)
CGI-I = 1 (very much improved)

Fig 17.4 Challenges in assessment of phases during course of rapid cycling. CGI-I, Clinical Global Impression of Improvement.

phase-counting technique allows both continuous and categorical outcome definitions for rapid cycling. As a continuous measure, the 48-h rule limits the range of phase changes per month to between zero and 15. Even so, it can be problematic to reach consensus on the total number of phase changes. Consensus is much easier to reach when the number of phases is collapsed to one of three categories: none, one, or more than one. Thus, in the example shown in Figure 17.4, the last month would be

categorized as zero phase changes, because no episode lasted longer than 24 h. This approach simplifies the measurement of treatment outcome and decreases the variance attributable to individual raters by not requiring fine distinctions.

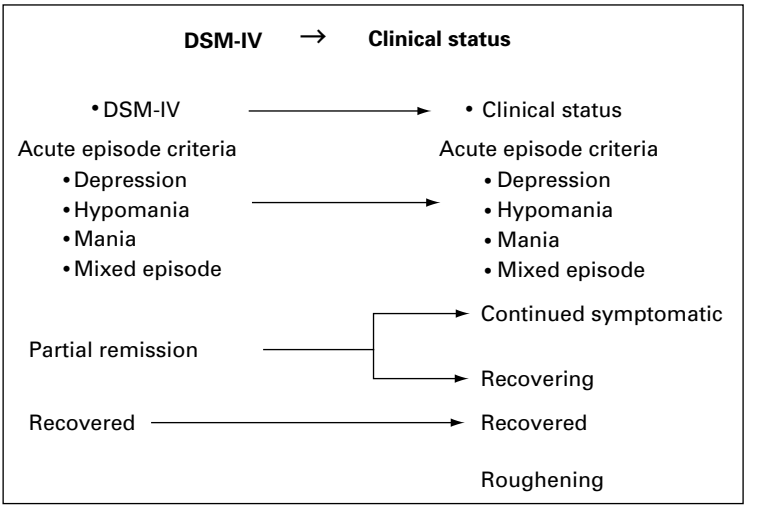
STEP-BD assesses clinical states prospectively using the Clinical Monitoring Form (CMF), which also serves as the progress note in the patient's medical record. The CMF is a one-page assessment tool (available from www.manicdepressive.org; Sachs *et al.*, 2002a) consisting of nine parts, including modified versions of the Structured Clinical Interview for DSM-IV (SCID) current mood modules; associated symptoms, stressors, medical problems, and comorbid conditions; selected mental status items; current medication compliance and adverse effects; laboratory data; summary scores (i.e., clinical status, Clinical Global Impressions Severity of Illness and Global Assessment of Functioning) narrative, and treatment plan.

The CMF's operational conventions for concise clinical record-keeping allow it to serve as the source document as well as a key outcome measure in STEP-BD (Sachs *et al.*, 2002b). Central to the tracking of outcome is designation of the current clinical status. Course of illness over time can be determined prospectively by using the CMF clinical status designations made at every follow-up visit. The eight mutually exclusive clinical states are outlined in Figure 17.5. This clinician-rated technique makes use of, but does not rely on, self-report measures such as the STEP-BD waiting-room self-report form and daily mood-charting. The CMF, its companion waiting-room self-report form, daily mood charts, and full instructions for their use are available at www.manicdepressive.org. These methods do not eliminate the problems encountered in tracking treatment response in patients with rapid cycling. Figure 17.4 depicts the disparate assessments made by raters for a rapid-cycling bipolar patient subject during the 1st and 12th month of valproic acid treatment. As noted above, using the 48-h rule and simplifying the outcome criteria helps to avoid potential discrepant ratings.

Rapid cycling: clinical trial design issues

Research on rapid cycling need not wait until perfect solutions are found for the many daunting problems noted here. Considerable progress can be made by first testing simple approaches to the easiest questions.

Sample selection and outcome measures are perhaps the most important aspects of any trial. Although retrospective assessment of rapid cycling at study entry does appear to give an indication of the propensity to cycle (Baldessarini *et al.*, 2000), studies are disadvantaged when subjects likely to remain well are randomized. Limiting randomization to only those subjects with active cycling during a prospective assessment period can help reduce this problem. We recommend entering retrospectively diagnosed subjects into a stabilization phase lasting 2–3 months



If DSM criteria for current episode are positive		
	Associated symptoms of mania or depression	**Assigned status**
Major depression	≥ 5 moderate	Depression
Mania	≥ 3 moderate	Mania
Hypomania	≥ 3 moderate	Hypomania
Major depression and mania	≥ 3 moderate for mania and ≥ 5 moderate for depression	Mixed

If DSM criteria for current episode are negative		
"Recovered" from last acute episode	Associated symptoms of mania or depression	Assigned status
No	≥ 3 moderate symptoms	Continued symptomatic
No	≤ 2 moderate symptoms	Recovering
Yes, if "recovering" ≥ 8 consecutive weeks	≤ 2 moderate symptoms	Recovered
Yes	≥ 3 moderate symptoms	Roughening

Fig. 17.5 Mapping DSM-IV to eight operationally defined clinical states. DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders,* 4th edn.

and randomizing only those subjects who have at least one prospectively observed phase change during any month. Subjects should be excluded who meet criteria for secondary rapid cycling (see definitions and Table. 17.2).

The difficulties in determination of mood state and cycle rate are magnified as the time period being assessed becomes briefer. This problem may be better managed by avoiding fine but unreliable measurement of brief changes in mood. It is likely that

Table 17.2 Causes of rapid cycling

- Brain injury
  - Mental retardation
  - Head trauma
  - Multiple sclerosis
- Neuroendocrine
  - Hypothyroidism
  - Reproductive hormones
- Psychotropic drugs
  - Alcohol
  - Stimulants
  - Antidepressant drugs
- Circadian rhythm abnormality

retrospective measures like the LIFE can make more meaningful assessments when applied over short intervals. Standard operating procedures for assigning a clinical status for each week using the CMF appear to offer a reasonably reliable means of prospective assessment. Outpatient studies could employ either of these techniques to establish episode pattern as well as measure phase changes.

Treatment efficacy outcome criteria specifically for rapid cycling are not well established. Calabrese *et al.* (2000) reported results for several efficacy measures used on the double-blind trial comparing the outcome for rapid-cycling patients maintained on placebo or lamotrigine. Interestingly, time to intervention for a new mood episode proved relatively insensitive, but percentage remaining stable without relapse through the 6-month follow-up period, time to drop-out, change from baseline severity, and change from baseline Global Assessment Scale score were useful in distinguishing between lamotrigine and placebo.

The most compelling of these measures, percentage remaining stable without relapse, becomes highly relevant to course of illness, in large part because the follow-up was carried out for 6 months. Beyond the sense of clinical relevance, it is noteworthy that survival curves for both active and placebo-treated subjects in most maintenance studies nearly always begin with an initial period of sharp decline lasting 6–18 weeks. Therefore, study designs with follow-up of duration shorter than 6 months are statistically disadvantageous.

Outcome criteria, such as percentage minimally symptomatic (meeting CMF criteria for recovered or recovering), correspond to "stable without relapse," but may be insensitive to the beneficial effects of treatments that reduce the frequency but do not eliminate cycling.

Demonstration of decreased cycle rates might be possible using the continuous-phase counting strategy above or using the categorical determination of zero, one, or more than one phase change to compare the percentage of months with zero phase changes. The duration of longest well period and quality-of-life measures may also be promising efficacy measures. Each of these represents in itself a composite outcome assessment, which avoids the problem of misinterpretation of improvement on a mania or depression scale as improvement when it actually represents affective switch. Whenever mood-rating scales are used, concurrent measurement should be made for both depression and mood elevation.

Conclusion

The complexity of bipolar disorder and its subtypes need not discourage clinical trials. Simple investigational strategies can facilitate the conduct of clinical trials for mixed episodes and rapid cycling. Recommendations for studies of treatment for mixed episodes include constructing a trial design for mixed episode subject only, requiring the presence of mixed features for at least 4 weeks prior to randomization, and use of composite outcome measures. For rapid cycling, the development of standard operating procedures and definitions for prospective assessment can reduce the complex problem of phase counting to a reliable categorical determination (0, 1, >1). Recommendations offered include randomizing subjects on the basis of prospectively assessed active cycling and determining response to treatment over periods of at least 6 months.

Definitions

Current rapid cycling

1. Patient meets the criteria for bipolar disorder and has had four episodes or more in the preceding 12 months
2. Patient has experienced four episodes or two complete cycles within the preceding 12 months. Longest remission over the past 6 months does not exceed 12 weeks

History of rapid cycling

1. Patient meets criteria for bipolar disorder
2. Patient has had at least four episodes or two complete cycles in any 12-month period

Secondary rapid cycling

1. Patient meets criteria for bipolar disorder

2. The 12-month period during which the patient satisfied the definition for rapid cycling includes episodes attributable to secondary factors such as antidepressant medication, substance abuse, travel across time zones, and sleep apnea
3. The subject would no longer meet criteria for rapid cycling if those phases attributable to secondary factors were no longer counted

Primary rapid cycling

1. Patient meets criteria for bipolar disorder
2. Patient has experienced a period of rapid cycling characterized by at least four episodes or two complete cycles within a 12-month period
3. At least two or more episodes were phases having occurred 6 months or more after discontinuing the exposure to all identifiable cycle-promoting factors

Defining a phase shift

1. Phase change: the appearance of a new mood state with duration of 48 h or that meets the DSM-IV criteria for an episode
2. As a continuous measure, the 48-h rule limits the range of phase changes per month to between zero and 15. Even so, it can be problematic to reach consensus on the total number of phase changes. Consensus is much easier to reach when the number of phases is collapsed to one of three categories: none, one, or more than one

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