Essentials of Menopause Management

A Case-Based Approach

Lubna Pal
Raja A. Sayegh
Editors

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Editors
Lubna Pal
Department of Obstetrics, Gynecology
and Reproductive Sciences, Division of
Reproductive Endocrinology and Infertility
Yale School of Medicine
New Haven
Connecticut
USA

Raja A. Sayegh
Department of Obstetrics and Gynecology
Boston University School of Medicine
Boston
Massachusetts
USA

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Foreword

The collection of essays *Essentials of Menopause Management: A Case-Based Approach* could not be appearing at a more opportune time. In its comprehensive, knowledgeable, lucidly written treatment of the subject, it is an all the more welcome contribution to the current literature. Our understanding of the phenomenon of menopause has undergone dramatic changes over the past 40 years. It is likewise with the medical responses to the condition, and hence the importance of keeping up to date with the latest twists and turns. Having been involved in both the clinical and research areas of menopause, let me take you back through those seesaw years characterized by erratic fluctuations, one day's *ever*, another day's *never*.

A good place to start would be the widely heralded (at first!) book *Feminine Forever*, by Robert A. Wilson, M.D., published in 1966, in the aftermath of the discovery of available synthetic estrogens. *Feminine Forever* loudly trumpeted the case for estrogens embodying a panacea, a veritable fountain of youth for menopausal women. The book went on to suggest that since women rarely suffer heart attacks until they pass through menopause – that is, when their ovaries stop producing estrogens – it must surely be the lack of hormone that increases the risk of atherosclerosis and heart disease. In the late 1960's, male physicians, all powerful in their domination of academic medicine, reached the "obvious" conclusion that estrogen replacement therapy could prevent recurrent heart attacks in men likely to suffer another event. Thus the first reliable study of estrogens and heart disease, the so-called Coronary Drug Project, was performed on men. The study was designed in an excellent manner in that a number of different agents such as placebo, thyroxin, and low dose and high dose estrogen were used. The unexpected result of the experiment, however, was that the men with heart disease who were treated with high dose estrogens experienced a *higher* rate of pulmonary emboli and *more* heart attacks than the men not treated. In that same spirit it was thought that if a little bit of estrogen made one feel better, then a lot would provide extraordinary benefits. That line of reasoning was also subsequently shown to be incorrect. And so it was already known, by the late 1960's and early 1970's, that estrogens did not lessen recurrent cardiac events in men.

Along with the new disappointing perspective, physicians in the early 1970s began to observe heart attacks among young women, occurring with a frequency never seen before. In an unfortunate *give and take*, it was soon noted that the afflicted women had been given and were taking the birth control pill. The dose of estrogens

in the oral contraceptives of the early 1970's was more than five times the amount that is currently generally prescribed. The deleterious effects of smoking on the heart were also observed at about the same time. The clear empirical evidence was that added estrogens were as unsafe for women as they were for men.

Fast forward to the mid-1980's, by which time a number of clinical retrospective and observational studies had surprisingly begun to suggest that estrogens did indeed prevent heart disease. So now, in those 20 years, we'd come full circle. Was the concatenation real, or was it the broken clock that, without moving, announces the correct time twice every day? In the 1960's estrogen was the miracle substance; in the 1970's, it was no longer. In the 1980's, the pendulum – the clock has a pendulum, now swinging – swung to very positive. But now there appeared to be a biological basis for the swing. A series of physiological studies suggested that estrogens were beneficial for the cardiovascular system because they improved the HDL/LDL ratios; moreover they might be coronary artery dilators as well.

On further reflection, the women who were selected for the observational studies and subsequently showed beneficial effects may have been selected to receive hormones because, in the light of the contradictory outcomes with hormones, physicians would be giving them to their healthiest patients only. Still, the observational trials weren't able to take into account the healthy user effect. In the 1970's, we were concerned about estrogens and heart disease; in the 1980's, health care providers may have avoided prescribing estrogens to women at risk. We are starting to appreciate the fact that some drugs are never as bad as we think they are, and some are not as good as we expected. Nor can the role of emotion be excluded.

For the 1990's, the resonant metaphor is a runaway train. Gynecologists for the most part now felt that since a large number of observational trials showed estrogens to be beneficial, hormones were now again prescribed for even the treatment of heart disease. In order to solidly confirm the premise, the HERS trial was undertaken among women who had already experienced a heart event. It was randomized and prospective, and patients received either estrogen and progesterone or placebo (similar to the coronary drug project protocol in men). The major finding turned out to be that at the end of 5 years, there was no statistical difference between the hormone group and the placebo group. What was also interesting was that at the completion of the first two years, the group that received estrogen and progesterone had actually an increased risk compared with the placebo group. But by the fourth year, the placebo group had more events, and so no discernible "between group" difference was evident after five years. The investigators, nevertheless, were so convinced that if allowed to proceed for a few more years, they would find clear evidence of the benefits of estrogens. However, after a few more years, the data did not show that. Thus once again, estrogen was found not to prevent recurrent cardiac events in women, even as the coronary drug project had found to be the case with men.

The healthy user effect was a common theme in the late 1980's, as an explanation for the known benefits of estrogens. In order to remove this bias once and for all, a comprehensive study known as the Women's Health Initiative, or WHI, was undertaken. It would be a double blind randomized *trial* where women would *receive*

hormones or placebo. The trial protocols would rule out as well physician bias and self-selection by patients.

I have the deepest respect for the investigators who designed the WHI and carried it out. However, for the hormone group, the WHI decided on estrogen in unopposed fashion for the women who had undergone a hysterectomy, and continuous combined estrogens and progesterone for women possessing a uterus. But we never had collected any retrospective data that showed that continuous combined estrogens and progesterone could prevent heart disease. Moreover, by introducing this new treatment, another parameter had been changed. That would make the interpretation of the data much more difficult. Now why would you be so short sighted as to use a drug that had never been involved in a retrospective trial and spend hundreds of millions of dollars in a randomized study, only to confirm what can't be known? I'm curious as to why the researchers who designed the study would not have asked that question. But of course, I'm engaging in *Monday morning quarterbacking*. Now what if the group that received continuous combined estrogens overall had a reduced risk for heart disease? Does that mean the administered drug would have been the only agent to get a citation from the FDA as a palliative for heart disease, while other preparations would be left out in the cold? I'd have hoped that the WHI investigators would have been able to anticipate the various scenarios their procedures had opened without resolving and to avoid such problems. This is not rocket science. If you want to confirm the findings of a retrospective trial by doing a prospective randomized one, why would you also switch the drugs? You should randomize only in order to answer the question of the healthy user effect. When in July 2002 the WHI continuous combined hormone trial results became available, many physicians were troubled. It was as though a bomb had dropped, and the clinical and the scientific worlds reverberated with shock and awe. Clinicians were upset because it went against many of their instincts as to the positive effects of estrogens. In addition, many clinicians had been sharing information with their patients, with the best of intentions, touting how many diseases estrogens prevented. At the same time, one can imagine how upset patients felt after having been promised all the unique benefits of estrogen therapy. Not only were patients feeling betrayed, so were the physicians caring for them. Everyone shares some responsibility for what ensued – from the pharmaceutical houses that studied the beneficial effects to the consultants and lecturers who had oversold the benefits. The NIH also played a negative role, since it had declined to support estrogen studies, counting as it did on the pharmaceutical houses to do it all. And of course, if a pharmaceutical house designs a study, it'll attempt to show the product they're promoting in the best possible light.

It has taken a number of years to explain the divergence between the observational studies that suggest that estrogens prevent heart disease and the Women's Health Initiative, which suggested a risk with the continuous combined hormones. The retrospective data derived from patients who were symptomatic. Also, the patients were in early menopause, and so hormones were prescribed. The WHI not only changed the medication but the indications for its use. The women studied were an average age of around 60 when hormones were first prescribed. That age was 10 years later than the usual start date for the women who were studied

retrospectively. It turns out – it took some time to recognize – that the age factor is critical. When there's a significant delay in beginning hormones, the hormones may turn out to be harmful or a nonevent. Thus we learned it is not safe to prescribe hormones for the first time after age 60.

In summary, it is a fascinating conundrum that the same hormone prescribed for the treatment of menopause for the past 40 years has had such a checkered career. At first it was seen as beneficial, then risky, then beneficial, then risky again. At times, the pendulum swung too far to the benefit side, and now too far to the harmful. For that reason among others, *Essentials of Menopause Management* is important, indeed crucial reading, for persons in the field. The book takes a frequently misunderstood subject and distills its complexities and ambiguities into readily discernible principles that should greatly help the investigator and clinician alike seeking the best treatments with our present state of knowledge. Physicians and researchers widely recognized as leaders in their respective specializations have contributed the various chapters. The ensemble of essays is remarkably up-to-date, given the time lapse it takes for a work of this order to be put together. With this volume in hand, the now well-informed clinician makes the case for the science of medicine, in the doctor/patient encounter that all the strands of theory and experiment discussed above ultimately lead to.

Professor of Obstetrics and Gynecology, Isaac Schiff, MD
Massachusetts General Hospital,
Harvard Medical School, Boston, Massachusets, USA

Preface

More than a decade since the findings of the WHI hormonal trials, the field of menopause stands transformed, with patient centeredness as the principal driver of current menopause management. Today's patients are better served by sensitization of diverse providers to the needs of the menopausal populations, by increased access to an expanding pharmacopeia for varied symptomatology, and by pursuit of systematic inquiry and data quality analysis before existing and emerging evidence is allowed to translate into clinical practice.

In *Essentials of Menopause Management*, our goal is to demystify the practice of menopausal medicine for the health care provider catering to reproductively aging females. Beyond familiarizing our readers with the journey traversed by the field over the past half century (Sayegh and Awwad), and the spectrum of both overt and covert concerns faced by aging females (Kuokkanen and Pal), a collection of chapters in Part I offer an in-depth overview of the gamut of interventions that have proven efficacious against common menopausal symptoms including nonhormonal (Reed), hormonal (Pinkerton), and complementary and alternative (Gergen-Barnett et al.) treatment strategies. In Part II, management of common symptoms is approached in an iterative manner with choice of treatment being guided by the symptom spectrum and severity as well as by patient's unique health profile. Through use of clinical vignettes and case based discussions, we hope to familiarize clinicians with an inferential and individualized approach to menopausal management, and to highlight concepts that are critical to arriving at individualized management strategies for common and familiar clinical scenarios. These range from disturbed sleep (Mathews et al), to genitourinary symptoms (Lukas et al), to sexual dysfunction (Minkin, Basaria and Huang), to scalp hair loss (Goldberg), to hirsutism (Kurani et al), and skeletal fragility (Holick). Chapters by Santoro, Kuohung, and Michelis provide a comprehensive coverage of the topics of premature ovarian insufficiency and surgical menopause, and the chapter by Stuenkel offers valuable insights into challenges and considerations for patients with underlying medical conditions. In Part III, we have charged ourselves with the goal of enhancing awareness regarding the unique concerns and the disproportionate burden of menopausal symptoms in women diagnosed with breast and other common gynecological cancers. A succession of chapters provide a comprehensive review of the existing data on therapeutic options available to breast cancer survivors for the management of vasomotor symptoms (Bonnett et al), osteoporosis (Jiang et al), and sexual

wellbeing (Overton et al). Lastly, a chapter by Durfee places in perspective the place of hormone therapy for survivors of gynecological cancers.

The absolute strength of our effort lies in the experience and expertise of the physicians and scientists who joined hands with us to systematically review the bother and the burden and negotiate the evidence to guide readers in optimally addressing the health needs of menopausal women. *Essentials of Menopause Management* is a collaborative effort that draws on the knowledge and skills of diverse practitioners in several fields: gynecologists, primary care and family physicians, endocrinologists, reproductive endocrinologists, oncologists, psychiatrists, and dermatologists. It reflects our firm belief in the value of multidisciplinary collaborations as the best path forward towards optimized clinical and research outcomes in the field of menopausal medicine. We dedicate this effort to women worldwide who deserve no less than our most informed, sincere, and personalized efforts to guide them not only through turbulent transitions, but also help them ward off the ravages of advancing age through judicious application of the available tools in our armamentarium.

We are greatly indebted to each one of our authors for volunteering their time and expertise and enduring the rigorous editorial process with its many demands and deadlines. Our appreciation to the publisher for the enthusiastic support that has sustained this venture from concept to proof, and to the development editor Ms. R. Balachandran for the administrative support. Our appreciation to the many teachers, mentors, trainees, and above all, our patients who have all helped shape our perspective on the preciousness of life quality. Lastly, this endeavor would not have been possible without the unequivocal support of our families.

It is our hope that this collection, by breaching boundaries between and across specialties and disciplines, will serve as a meaningful resource for all engaged in and committed to improving women's health and will help empower women in taking charge of their own wellbeing.

New Haven, CT, USA — Lubna Pal, MD
Boston, MA, USA — Raja Sayegh, MD

Contents

Part I

An Overview of the Epidemiology and Symptomatology, and an Update on Existing Strategies to Improve the Quality of Life of Menopausal Women

Reproductive Aging: Epidemiology, Symptomatology, and Nomenclature

1

Satu Kuokkanen and Lubna Pal

Epidemiology

The hallmark of menopause is a permanent loss of ovarian function due to depletion of ovarian reserve, i.e., ovarian complement of oocyte-granulosa cells. Menopause is defined retrospectively as the cessation of spontaneous menstrual cycles for 12 months. The average age of natural menopause varies slightly across races and ethnicities; however, in Caucasian women, it has remained relatively fixed at 51 years [1]. With advances in health care and reduction in maternal mortality in the Western world, women are expected to live long enough and spend roughly 40 % of their lives in a postmenopausal state. Accordingly, the burden of menopausal symptoms for individual women as well as the population cannot be trivialized.

Symptomatology

Vasomotor Symptoms (VMS)

Vasomotor symptoms (VMS), including hot flashes, night sweats, and less often "cold shivers," are common with a reported prevalence of 60–80 % among women experiencing natural menopause [2]. Hot flashes are commonly described as a sudden onset warm sensation starting in the face, neck, and chest and gradually

S. Kuokkanen, MD, PhD (✉)
Montefiore Medical Center/Albert Einstein College of Medicine,
1300 Morris Park Avenue, Block building 6th Floor, Room 627, Bronx, NY 10461, USA
e-mail: skuokkanen@verizon.net

L. Pal, MBBS, FRCOG, MS, FACOG
Yale School of Medicine,
33 Cedar Street, P.O. Box 208063, New Haven, CT 06510, USA
e-mail: lubna.pal@yale.edu

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spreading to the entire body (predominantly upper body) followed by perspiration and sense of chill. Frequent vasomotor symptoms as defined ≥6 days during a period of 2 weeks are reported as the most bothersome [3]. Night sweats are often considered intense hot flashes; however, it remains to be investigated if their etiology is different from classical hot flashes.

Significant ethnic and racial differences in the menopause experience are recognized with the highest VMS burden reporting among African-American and the least symptomatology rates among Asian women residing in the USA, with symptomatology among women of Hispanic and Caucasian racial backgrounds falling in the intermediary range [2]. Women who have increased body mass, are smokers, and suffer from premenstrual symptoms are at increased risk for experiencing bothersome VMS during menopausal transition and postmenopause [2]. Psychological factors, including perceived stress, anxiety, depressive symptoms, and high symptom sensitivity, are associated with increased prevalence and persistence of VMS [2, 4–7]. On the other hand, physical activity and alcohol and caffeine consumption appear not to be related to VMS [2]. Identification of modifiable risk factors of VMS, such as smoking, increased body mass, and psychological factors, will provide an opportunity for physicians to counsel women and recommend intervention.

A recent longitudinal study investigated the total duration of VMS across menopausal transition among 1,449 American women of multiethnic and multiracial representation [4]. More than half of the women experienced frequent VMS over more than 7 years during the period of menopausal transition with persistence of symptoms up to 4.5 years after the final menstrual period. The duration of the VMS was found to vary depending on the stage of menopausal transition (the stages of menopause are described below in the section of nomenclature). Women who were premenopausal or perimenopausal when they first experienced VMS were affected the longest (up to a decade) from these bothersome symptoms. In contrast, for those who first became symptomatic after menopause, the duration of symptoms was the shortest with a median total duration of 3.4 years. Similar to the severity of VMS, symptom duration has been reported to vary by race and ethnicity [4]. Compared to other races, African-American women experienced particularly persistent VMS that lasted up to a decade, whereas Chinese and Japanese women had the shortest duration of VMS. Given the high prevalence and duration of VMS among midlife women, it is important for providers to query their patients about these symptoms and understand the extent to which these can impair quality of life in aging women.

Genitourinary Syndrome of Menopause (GUSM)

Genitourinary Syndrome of Menopause (GUSM). Similar to VMS, menopause-related genitourinary symptoms are highly prevalent among reproductively aging women. Based on a large online survey, conducted in six different countries (Vaginal Health: Insights, Views, & Attitudes (VIVA)), a wide variety of genitourinary symptoms were acknowledged by postmenopausal women, including vaginal dryness

(83 %), dyspareunia (42 %), involuntary urination (30 %), soreness (27 %), itching (26 %), burning (14 %), and pain (11 %) [8]. In a longitudinal, population-based study of over 400 women in Australia, the prevalence of vaginal dryness was 4 % in the early perimenopause, rising to 25 % 1 year after menopause and to 47 % 3 years after menopause [9]. Despite the high prevalence of vulvovaginal symptoms and their adverse impact on sexual health and quality of life [8, 10, 11], only ~30 % of affected women seek medical assistance [12]. This reality is concerning given that these symptoms can last long into postmenopausal life, regardless of the status of sexual activity [13]. The term vulvovaginal atrophy (VVA) that describes tissue effects of hypoestrogenism fails to convey the uroepithelial burden consequent to hypoestrogenism, as reflected in common menopausal complaints of urinary frequency, urgency, nocturia, dysuria, and recurrent urinary tract infections (UTI). Recurrent UTIs can affect 5–17 % of postmenopausal women [14]. The changes associated with menopause with the decrease in the diversity of vaginal microbiota and the increase in coliform species may predispose to infection and urogenital problems [15]. The terminology GUSM, a recently introduced comprehensive term, describes the spectrum of symptoms attributed to lack of estrogen including genital dryness, burning, irritation, sexual symptoms of lack of lubrication, discomfort or pain, as well as urinary symptoms of urgency, dysuria, and recurrent UTIs [16]. Recognizing and treating the underlying mechanism (i.e., estrogen insufficiency at target tissue level) with either systemic or local vaginal estrogen or with the recently introduced oral selective estrogen receptor modulator, ospemifene [17], can help resolve the vaginal symptoms and reduce the risk of recurrent UTIs for those at risk.

Sleep Quality

Sleep quality declines with age, but the studies have suggested that the menopausal transition, independent of age, may contribute to this decline in midlife women [18]. According to a community-based survey. Perceived poor sleep was reported by as many as 38 % of women who underwent menopausal transition in the longitudinal observational Study of Women Across the Nation (SWAN) [18]. While several studies have reported a subjective association between VMS and poor sleep [19–22], such an association remains controversial as it was not found when hot flashes and sleep parameters were measured physiologically [23, 24]. Interestingly, many midlife women report poor sleep without a significant complaint of VMS [18] suggesting that sleep difficulties at this age may be partially due to aging, certain drug use, and the disorders of obstructive sleep apnea (OSA), periodic limb movement syndrome, and restless legs syndrome (RLS) that all can interfere with sleep. The state of psychological well-being is intimately tied to both quantity and quality of sleep, and sleep disturbances in menopausal women are frequently associated with depression and anxiety [25].

The prevalence of intrinsic sleep disorders, in particular OSA and RLS, increases as women transverse into menopause. Obstructive sleep apnea in midlife women may not present with the typical male-type OSA symptom, “classical” snoring, but rather may manifest as insomnia, depression, and fatigue. In the Wisconsin Cohort

Study, the prevalence of moderate-to-severe OSA was found to be 3 % among premenopausal women (30–49 years) compared to 9 % among postmenopausal women (50–70 years) [26]. Restless legs syndrome is poorly recognized clinical condition with uncomfortable sensation in the legs associated with an urge to move, and this symptom often occurs in the evening and at bedtime. Restless legs syndrome affects 7–11 % of the populations in Western countries [27, 28] and is almost twice as prevalent in women than men [27–29]. Women previously affected with RLS report a worsening symptomatology after menopause, regardless of the use of HT [30]. Obstructive sleep apnea and RLS not only interfere with sleep but also impair quality of life. Additionally, untreated OSA has severe health-related consequences.

Therefore, when evaluating women with sleep disturbances, it is important to consider a wide range of clinical problems and to exclude other medical and psychiatric conditions as well as medications that can contribute to poor sleep [31].

Depression

Depression is an important public health concern worldwide (WHO mental health and older adults, September 2015), and it seriously affects health, cognition, and quality of life. Based on epidemiological studies, women have double the lifetime risk of major depressive disorder compared with men [32, 33], suggesting that female hormonal fluctuations during reproductive years (premenstrual and postpartum phase) and beyond (perimenopausal phase) confer vulnerability to depressive mood. Whether depression is included in the core symptoms of the menopause remains controversial. Most studies have reported greater increase in depressive symptoms among women during menopausal transition compared to premenopausal or postmenopausal years [34–39]. Clinically, it is important to note that women with a history of depression prior to menopausal transition are most vulnerable to a reoccurrence of depressive symptoms during the years leading to final menstrul period (FMP) and thereafter [34]. A recent meta-analysis indicated a link between later menopause and decreased risk of depression after menopause compared to women who experienced earlier menopause [40]. This observation suggests protective effect of increasing duration of exposure to endogenous estrogens; however, further research is needed to formalize this new concept.

Joint and Muscle Pain

Musculoskeletal pain is common in general population and its prevalence appears to increase in women with menopausal transition. Several cross-sectional studies have reported high prevalence of muscle and joint aches among midlife women (between ages 40 and 60 years), especially in Asian (Chinese [41] and Nepalese [42]), Latin American [43], and Middle Eastern [44] populations, with over 60 % mid-aged women suffering from these symptoms. Moreover, muscle and joint pains

are the most prevalent menopausal symptom reported by Omani and Nigerian women [44, 45]. While an association between muscle/joint aches and menopausal symptoms, especially vasomotor symptoms [41], has been reported, it is unknown whether female hormonal changes, in particular estrogen deprivation, during menopausal transition are the culprit to joint aches. Nevertheless, some evidence suggests that estrogen replacement therapy in postmenopausal women reduces the frequency of muscle and joint aches [46]. Clearly, more research is needed to better understand the role of estrogen in menopausal musculoskeletal pain.

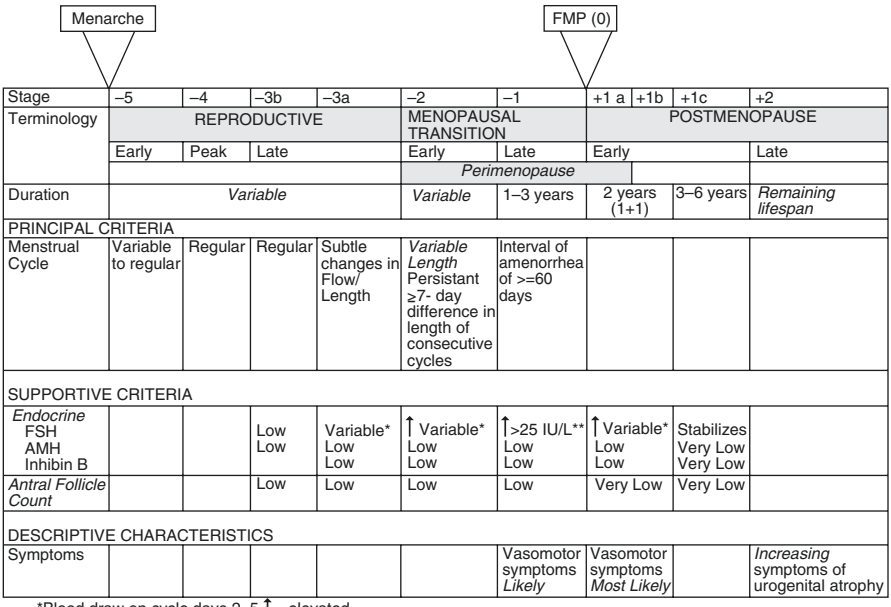
Nomenclature/Definitions

Reproductive Aging Is a Continuum In females, decline in ovarian function to a point of senescence occurs over a wide age range, between 42 and 58 years. By definition, *menopause* occurs 12 months after the final menstrual period (FMP), in the absence of any pathological or other physiological causes of amenorrhea. The *menopausal transition* is the time period in the continuum of reproductive aging, prior to the FMP, when symptomatic manifestations of ovarian aging and hormonal fluctuations become manifest, including new-onset menstrual cycle irregularity, onset of VMS, sleep disturbances, and early symptoms of GUSM. Although the changing hormonal milieu of menopause transition is well characterized, features of hormonal fluctuations also prevail.

The Stages of Reproductive Aging Workshop (STRAW) has attempted to promote uniformity in assessment and categorization of reproductive aging primarily to facilitate research and secondarily to provide tools for clinical settings. In its latest update, STRAW + 10 identifies seven distinct stages in the continuum of reproductive aging, from reproductive years to the menopausal transition phase, to menopause, and then beyond into the postmenopausal phase (Fig. 1.1.) [47–50]. The FMP stage is notated as stage 0; five of the seven stages of aging occur before the FMP with *reproductive aging years* denoted as stages −5 to −3, *menopause transition* as stages −2 to −1, and *postmenopausal period* as stages +1 to +2.

As evident in Fig. 1.1, the period of menopausal transition is itself divided into early and late stages based on the pattern and magnitude of symptoms. In the early transition (stage −2), women are likely to experience increasing variability in their menstrual cycle length (defined as persistent difference of 7 days or more in the length of consecutive cycles). In late menopausal transition (stage −1), menstrual cycles become more variable with extreme fluctuations in the hormonal milieu. The hallmark of late menopausal transition is the occurrence of amenorrhea of 60 days or longer, and this stage is estimated to last, on average, 1–3 years, culminating in the FMP. Classical vasomotor symptoms are common in the period of menopausal transition.

The span beyond menopause onset (as defined by 12 months after FMP) is subdivided into early (+1) and late (+2) periods, reflecting heterogeneity in the endocrinology and accompanying clinical manifestations. To add to this complexity, the



Menarche					FMP (0)					
Stage	–5	–4	–3b	–3a	–2	–1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*Variable*				*Variable*	1–3 years	2 years (1+1)		3–6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistant ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑>25 IU/L** Low Low	↑ Variable* Low Low		Stabilizes Very Low Very Low	
Antral Follicle Count			Low	Low	Low	Low	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

*Blood draw on cycle days 2–5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard

Fig. 1.1 Stages of reproductive aging: STRAW + 10 staging system [47–50]. *FMP* final menstrual period, *FSH* follicle-stimulating hormone, *AMH* anti-Müllerian hormone (Reprinted with permission from Taylor & Francis (www.tandfonline.com))

early postmenopause is further classified into three substages (stages +1a, +1b, and 1c), each lasting approximately 1 year. The last stage of STRAW classification is that of late postmenopause (stage +2) which is characterized by eventual attainment of a stable state of hypergonadotropic hypogonadism (persistently elevated FSH and suppressed estradiol levels).

Relevance of Symptoms to Stages of Reproductive Aging

Figure 1.2 presents some commonly acknowledged symptoms enquired of midlife women over the course of a 7-year longitudinal study that assessed the symptom spectrum, prevalence, and relationship to the various stages of reproductive aging.

Vasomotor Symptoms Hot flashes are reported nearly as often in the late stages of reproductive years and transition phase as in early postmenopause [2]. The precise pathophysiology of hot flashes remains puzzling, but they are thought to be associated with low estradiol levels and narrowing of the thermoregulatory zone system that resides in the hypothalamus [51]. The racial and ethnic variation in prevalence, severity, and total duration of VMS is interesting and suggests multifactorial etiology with contributing environmental and genetic factors.

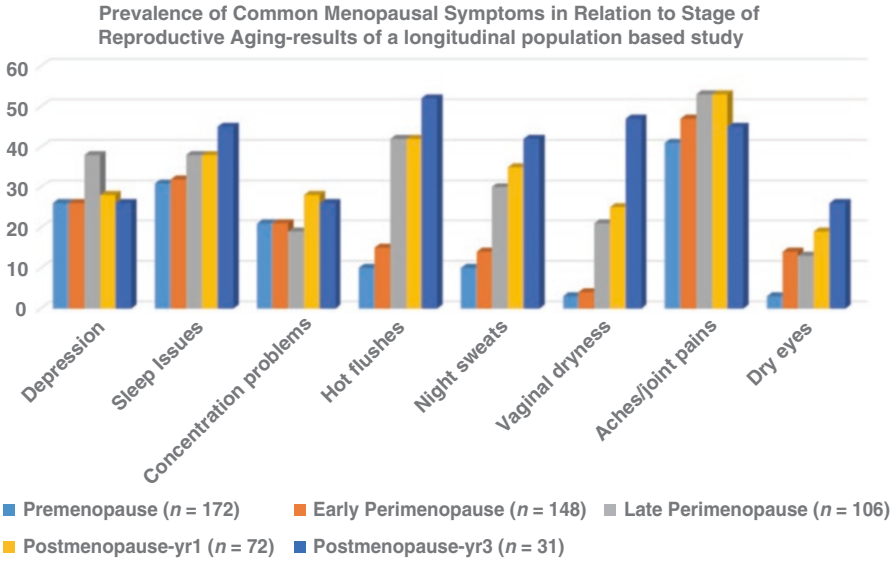


Fig. 1.2 Caption (Adapted from Dennerstein et al. [9]) Percentage of women reporting common menopausal symptoms in previous 2 weeks.

Symptoms of Genitourinary Syndrome of Menopause While these symptoms may occur in the early stage of the menopausal transition, symptoms of GUSM dominate the late stage of postmenopausal years and once apparent can become progressive and chronic over time if left untreated [52, 53]. A large survey of women 55–65 years of age found that only 30% of women with vaginal discomfort had spoken to their providers about their symptoms [54], emphasizing the importance for providers to prompt discussion and question their postmenopausal patients about vulvovaginal and urinary symptoms. In the VIVA study, 50% of women identified their primary care doctor as a primary source they had or would use for information on vulvovaginal symptoms, whereas 46% of women had or would consults their gynecologist about these symptoms [8]. These survey findings indicate that both primary care physicians and gynecologists are central in providing diagnostic and therapeutic assistance in the care of menopausal women suffering from genitourinary symptoms.

Sexuality Although the association of sexual function, aging, and menopausal changes is complex, the Menopause Epidemiology Study found that women with VVA were at fourfold increased risk of experiencing sexual dysfunction [55]. Decreased vaginal lubrication and symptoms of vaginal dryness become manifest for many in years predating the menopause transition and worsen in the years postmenopause.

Sleep Disturbances Severity and prevalence of sleep disturbances appear to peak during the late menopausal transition when women are undergoing prolonged amenorrhea [18]. Self-reported measures of sleep quality including sleep latency,

sleep duration, and wakefulness all worsen as women traverse the menopause [18]. In a longitudinal study of midlife that followed women over a 16-year period, the annualized prevalence of moderate-to-severe poor sleep ranged between 25 and 38 % and did not vary significantly by menopausal status [19]. Notably in this study premenopausal sleep pattern strongly predicted the likelihood for sleep disturbances around the time of the final menstrual period. Those reporting moderate/severe poor sleep premenopausally were at a threefold higher risk of experiencing poor sleep of similar severity during the menopausal transition and in menopause, whereas women without sleep-related issues in the premenopausal phase of life generally continued to sleep well as they negotiated the menopausal transition into postmenopausal period. While the relationship between poor sleep, aging, and menopausal symptoms is complex and currently not completely understood, sleep quality and quantity are nonetheless influenced by both frequency and severity of vasomotor symptoms [19].

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Five Decades of Hormone Therapy Research: The Long, the Short, and the Inconclusive

2

Raja Sayegh and Johnny T. Awwad

Introduction

The symptom burden of midlife ovarian senescence and its impact on physical, emotional, and sexual well-being has long been perceived as disruptive to the personal, social, and professional aspirations of postmenopausal women. Low serum estrogen levels prevailing after menopause have also been associated with accelerated aging of tissues and organs, particularly the skeletal and cardiovascular systems [1, 2]. With the triumphant development of the oral contraceptive pill in 1960 [3], hope grew that biological challenges unique to the female post-reproductive years can too be conquered with the use of synthetic sex steroids. This hope was stoked as well by Wilson's negative portrayal of the menopause as an "estrogen deficiency state" which "must be replaced" to avoid the "tragedy" and "decay" of menopause [4, 5]. Within a decade of Wilson's influential assertions, the number of menopausal women who had taken up long-term estrogen therapy had soared [6]. Few years later, a significant body of observational data would demonstrate that such menopausal hormone therapy (MHT) is not only effective for control of troublesome symptoms but may also have benefits for the prevention of chronic diseases commonly associated with female aging [7–9]. The promise that a pill may improve life's quality, and possibly its quantity, by increasing the odds of avoiding a heart attack or a hip fracture captured the attention of tens of millions of menopausal women whose ranks in the USA were growing rapidly as the baby boom generation

R. Sayegh, MD (✉)
Department of Obstetrics and Gynecology, Boston University Medical Center, Boston, MA, USA
e-mail: raja.sayegh@bmc.org

J.T. Awwad, MD
Department of Obstetrics and Gynecology, American University of Beirut Medical Center, Beirut, Lebanon
e-mail: jawwad@aub.edu.lb

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matured. The promise of MHT also captured the attention of employers and the insurance industry who have a perennial interest in workforce wellness and of the pharmaceutical industry who saw a tremendous opportunity for growth. In 1991, the 102nd US Congress got involved as well, passing the Women's Health Equity Act of 1991 [10]. While this act failed to become law, significant portions of it were ultimately included in the NIH Revitalization Act of 1993 which did become law, appropriating significant resources for women's health research [11]. This confluence of public and private interests set the stage for accelerated investigation in menopausal medicine, including federally funded research developed and coordinated by the newly minted Office of Women's Health at the National Institutes of Health (NIH). With cancer, heart disease, and osteoporosis as the leading causes of death, disability, and impaired quality of life in older women, the NIH launched in 1993 a landmark 15-year effort, the Women's Health Initiative (WHI), to study these matters with scientific rigor. The role of MHT figured prominently in this effort with the inclusion of two long-term prospective randomized controlled trials (RCTs) – the WHI estrogen and progesterone (WHI-EP) and the WHI estrogen (WHI-E)-alone hormone trials. The publication of results in 2002 and 2004 of these WHI hormone trials formed a watershed event with worldwide changes in clinical practice and social attitudes toward acceptance of MHT. The WHI results inspired not only new and innovative MHT research but also a second look at existing MHT data that had predated WHI. This chapter summarizes five decades of MHT research in chronological order and highlights trends in clinical practice which swayed the research agenda and in turn were influenced by the results.

Pre-WHI

The Early Years of Estrogen Use

An isolate from the urine of pregnant mares, conjugated equine estrogen (CE) at an oral dose of 1.25 mg, had been approved for relief of menopausal symptoms by the Food and Drug Administration (FDA) in 1942, when proof of safety was the only requirement for approval [12]. CE's efficacy had been widely accepted at the time but was only formally acknowledged by the FDA decades later in compliance with 1962 legislation after the thalidomide tragedy [13]. In high doses, estrogen therapy then had also found use in "androgen deprivation therapy" for men with metastatic prostate cancer and for the "endocrine priming" before chemotherapy in women with metastatic breast cancer [14, 15]. Interestingly, men on these high doses of estrogen were noted to have a lower burden of coronary atherosclerosis at autopsy [16, 17]. Animal studies in chicken and rabbits had also revealed that estrogen can reverse atherosclerosis and exert a favorable influence on serum levels of atherogenic cholesterol and lipoproteins [18]. Those observations offered a biological explanation for the known gender gap in heart disease incidence [19] and suggested the possibility that this leading cause of mortality in

men can be prevented and treated with high doses of oral estrogen [20]. To investigate this possibility, middle-aged men with coronary artery disease (CAD) were enrolled in an estrogen arm of the "coronary drug project," but excess mortality from thromboembolic incidents led to the abandonment of this effort [21–23]. The use of high-dose estrogen in metastatic prostate and breast cancer patients was similarly abandoned when newer therapeutic alternatives became available for these conditions in the 1970s.

Coronary Benefits and Stroke Risks of Postmenopausal Estrogen

The concept of cardioprotection by estrogen was revived in the 1970s in postmenopausal women, many of whom had started taking CE a decade earlier to combat not only the symptoms but also the social and cultural stigma of menopause propagated by the influential New York Times best seller, "Feminine Forever" [5]. At that time, few small observational studies had suggested a 30–50 % reduction in risk of CAD, lower death rates from stroke and heart attacks, and reductions in all-cause mortality among postmenopausal estrogen users compared to nonusers [24–27]. Concurrent serum lipid studies had also revealed significant estrogen-induced reductions in total cholesterol levels and increases in high-density cholesterol levels [28, 29]. These desirable effects of estrogen on serum lipids were advanced as an important, but not singular, mechanism for the observed cardioprotective effects of estrogen that purportedly required sustained intake of estrogen to maintain. These impressions would later be confirmed by one of the largest and longest running observational studies of that era, the Nurses' Health Study (NHS), which in 1976 had started collecting detailed information on a cohort of 121,700 nurses to determine risk factors for major chronic diseases. In their first report on MHT in 1985, 32,317 postmenopausal women had been followed for an average 3.5 years, and those on estrogen had a 50 % lower risk of CAD [8]. One third of the estrogen users in this cohort were taking 1.25 mg CE daily, while others were using lower doses of estrogen. In 1991, a second NHS report affirmed this finding in a larger cohort of 48,470 postmenopausal women that had accrued an average follow-up period of 10 years [30]. In addition to a decreased incidence of CAD, this second NHS report had also found a trend toward reduction in all-cause mortality with current postmenopausal estrogen use. The cardioprotective benefits of oral estrogen were observed even in older women and in women with established CAD [31] bolstering the preponderance of evidence from many earlier and smaller observational studies which had come to a similar conclusion [32]. The one notable exception of that era was the Framingham study which, contrary to the bulk of the existing data, had found an increased coronary risk associated with menopausal estrogen therapy [33].

In contradistinction to the coronary benefits of estrogen, the Nurses' Health and Framingham studies both found trends toward increased risk of ischemic stroke among estrogen users, which in the case of the NHS cohort did not reach statistical significance [32]. As to the Framingham study, the cohort of postmenopausal women was much smaller than the NHS cohort, with a higher percentage

of older women, smokers, and 1.25-mg CE users [33]. The then controversial issue of an increased stroke risk with estrogen use was compounded by observational reports starting in 1996 of increased venous thromboembolism (VTE) risk in association with MHT use [34]. However, these concerns were inconsistent with other observational studies and meta-analyses which demonstrated either no increase [35, 36] or even a decrease in stroke risk with estrogen use [37–40]. Furthermore, the promise of neuroprotection by estrogen gained impetus with the reporting of a 30 % reduction in risk of cognitive impairment and Alzheimer's disease (AD) with MHT [41, 42]. Given that stroke was (and remains) a leading cause of mortality in aging women and given that nonfatal stroke is a major risk factor for cognitive decline in postmenopausal women, the idea of using estrogen for secondary prevention of stroke and cognitive decline emerged in the late 1990s and was tested in two NIH-sponsored RCTs: Women's Estrogen for Stroke Trial (WEST) and the cognitive substudy of the Heart and Estrogen/Progestin Replacement Study (HERS-Cog).

The WEST was a multicenter secondary prevention stroke trial that randomized 664 women (mean age 71), within 3 months of an incident stroke or ischemic attack, to receive either placebo or MHT [43]. The hormone regimen consisted of 1 mg oral estradiol daily along with cyclic medroxyprogesterone acetate (MPA) for non-hysterectomized women. Overall, there was no significant reduction in the incidence of recurrent stroke with MHT use after a mean follow-up duration of 2.8 years. Concerningly and unexpectedly, the estrogen users had a higher incidence of a fatal second stroke; furthermore, neurologic and functional deficits were worse among estrogen users who experienced a recurrent nonfatal stroke. There was a tendency toward more recurrent events in the first 6 months after randomization among estrogen users, although statistical significance was not reached for all these outcomes. As to those estrogen users who did not have a recurrent stroke during the course of this trial, cognitive scores were no better (or worse) than for those on placebo [44]. In the HERS-Cog trial (a substudy of the larger HERS trial to be discussed later), 1000 cognitively intact older postmenopausal women with established CAD (a known risk factor for stroke) were randomized to receive either placebo or continuous combined 0.625 mg CE with 5 mg MPA for 4 years. Those on MHT did not score any better or worse on cognitive tests after 4 years of therapy compared to women assigned to placebo [45]. Finally, in a randomized trial of estrogen in 120 postmenopausal women with established early AD, neither 0.625 mg CE nor 1.25 mg CE proved any better than placebo in halting or slowing disease progression, and in some instances the condition even got worse on estrogen [46]. What became clear after these trials was that conventional oral MHT is not beneficial for secondary prevention of stroke and cognitive decline in older postmenopausal women. However, the biological plausibility of neuroprotection by estrogen suggested by in vitro and animal studies [47] continued to fuel a hope that MHT will prove beneficial for neurocognitive processes. The scientific world and community looked forward to the results of the primary prevention trials which were already under way, including the WHI Memory Study (WHIMS), which will be discussed later.

The Postmenopausal Estrogen/Progestin Intervention (PEPI) Trial

Five decades after the introduction of CE in clinical practice, the widely acknowledged need for comprehensive RCTs to resolve lingering controversies and uncertainties materialized with the launch of the NIH-sponsored PEPI trial in 1991. One of those leading controversies of the time was the association between unopposed CE use and increased endometrial cancer risk which had emerged in 1975 [48]. While small-scale European and US studies had shown that this risk can be eliminated with the adjuvant use of a progestin [49, 50], such use remained controversial and unpopular in the USA due to the physical side effects of added progestin use (breast tenderness and resumption of periods) and concerns about progestin's lipid attenuation benefits [51]. This fact is reflected in the reality that only 12% of MHT users in the 1991 NHS report were using progestins! This changed significantly after PEPI.

In the PEPI trial, 800 and 75 newly menopausal women with and without a uterus were recruited to participate in a 3-year RCT of MHT. The mean age of participants was 56 years and none was more than 10 years postmenopausal. The study had a placebo arm and four MHT arms that utilized an identical standard 0.625 CE dose, reflecting the US market dominance of this product, but differed in progesterone type and regimens. The four MHT regimens included CE alone, CE plus oral micronized progesterone for 10 days every month, CE plus oral MPA taken continuously at a dose of 2.5 mg daily, and CE plus oral MPA taken cyclically at a dose of 5 mg for 10 days each month. All the study medications were donated by the manufacturing pharmaceutical companies. One of the limitations of the PEPI trial which emerged after the fact was that blinding was suboptimal due to estrogen's obvious physical effects. Adherence rates to assigned therapy were also suboptimal because symptomatic women who received placebo could not tolerate staying on for 3 years knowing that effective therapy was available. High dropout rates also occurred in some treatment arms due to bleeding and concerns about endometrial cancer risk. Adherent analyses were used to adjust for these limitations, raising concerns about introducing a selection bias [52]. Those limitations notwithstanding, the PEPI trial results remain groundbreaking and influential, confirming the efficacy of CE for menopausal symptoms, the effectiveness of progestins for endometrial protection, and the beneficial effects of standard dose hormones on preserving BMD [53, 54]. In addition, hope for cognitive protections was raised based on self-reported improvements in memory and cognition among estrogen users [55]. Most importantly the benefits of CE and to a lesser extent CE and progestin regimen on serum lipids, fibrinogen levels, and carbohydrate metabolism were now firmly established in a RCT [56]. While cyclic natural progesterone was found to be the least attenuating to CE effects on serum lipids, the use of continuous daily MPA with CE eventually promoted amenorrhea, a major advantage in the effort to enhance long-term compliance with MHT [57]. This so-called continuous combined estrogen/progestin (CCEP) regimen gained FDA approval for treatment of menopausal symptoms and osteoporosis prevention in 1995 and became the dominant form of MHT for non-hysterectomized women in the USA. It was also the regimen of choice which would be tested subsequently in landmark RCTs for primary and secondary prevention of CAD.

Postmenopausal Estrogen Use and Public Health

With CAD as the leading cause of death and disability among postmenopausal women, the near-consistent and biologically plausible evidence of significant cardioprotection by postmenopausal estrogen overshadowed other concerns. Ultimately, the argument for a public health benefit of long-term estrogen was so compelling that the second report of the Adult Treatment Panel of the National Cholesterol Education Program (ATP-NCEP) stated that estrogen can be considered as a first-line therapy for postmenopausal women with elevated cholesterol levels [58, 59]. In addition, a major physician group, the American College of Physicians (ACP), stated in 1992 that "women who have CAD or who are at increased risk for CAD are likely to benefit from hormone therapy" [60]. This recommendation was strong for women who have had a hysterectomy and were therefore able to use unopposed estrogen without concern for endometrial cancer risk. As to MHT use for non-hysterectomized women, ACP's recommendation was cautious given progestin's known attenuating effects on estrogen's lipid benefits and possibly its cardioprotective benefits. With the supportive PEPI trial findings coming shortly thereafter, the emphasis of postmenopausal hormonal therapy had clearly moved beyond quality-of-life issues (hot flash control, preservation of sexual function, relief of vulvovaginal atrophy, and improved sense of well-being). The focus in 1995 was on preventing heart attacks and reducing cardiovascular mortality for an entire population of postmenopausal women. An editorial by the first female director of NIH accompanying the PEPI publication expressed optimism that perhaps the "opportunity to halt womankind's vulnerability to heart disease after menopause may be at hand" [61]. Yet, as with the ACP recommendation 3 years earlier, there was careful acknowledgment by the author that the final answer regarding the efficacy of hormones for primary and secondary prevention of heart disease would have to await the results of much larger and longer RCTs in which hard clinical end points were being assessed. This left the door open to the possibility that recommendations may evolve accordingly.

National surveys conducted in the early to mid-1990s showed peaking prevalence of MHT use among middle-aged women, yet they also showed a persistently low prevalence of sustained long-term use believed necessary for the maintenance of cardiovascular and skeletal benefits. In one of these surveys conducted in 1995, 38 % of 50–74 years old women were using MHT, but only 20 % had used it for 5 years or more [62]. Another 1995 survey found MHT use to be rising among postmenopausal physicians, including older physicians, which presaged well for a continuing rise in MHT acceptability among the general public [63]. Other surveys revealed a significant regional variability in prevalence of MHT use which was highest among women in the South and West and lowest in the Northeast of the USA [64, 65]. Additional determinants of the prevalence of MHT use included hysterectomy status [66], the nature of counseling, and the specialty of those counseling menopausal women [67]. Perhaps most revealingly however were surveys that showed that more than half of the women who started MHT stopped it within 2 years of initiation either because of

undesirable side effects or concerns regarding increased risk of stroke, breast cancer, and endometrial cancer [68, 69].

Skeletal Benefits of Postmenopausal Estrogen and the Push for Lower Doses

By the early 1980s, a number of observational and randomized trials had shown postmenopausal estrogen use to be associated with preservation of bone mineral density (BMD) and skeletal protections against osteoporotic fractures, a major contributor to disability and morbidity in the aging populations [9, 70]. Furthermore, 0.625 mg of CE was found to be equally effective as higher CE doses for menopausal symptom relief and for BMD preservation [71]. In 1986, CE became the first FDA-approved antiresorptive therapy for the prevention of postmenopausal osteoporosis [13, 72]. Recognizing the tremendous marketplace potential of this development, rival pharmaceutical companies launched efforts to introduce synthetic equivalents to the marketed CE, but those efforts failed as the chemical complexity of CE was revealed [73]. While 0.625 mg CE became the standard MHT dose and maintained its market dominance in the USA, compliance with long-term use believed necessary for the realization of its presumed skeletal and cardioprotective benefits remained suboptimal for reasons discussed earlier. In an effort to overcome barriers against wider utilization and long-term compliance, industry-sponsored randomized trials were launched, demonstrating that CE doses under 0.625 mg remained efficacious for relief of hot flash and vulvovaginal atrophy, preserved BMD, and induced favorable serum lipid changes, albeit less robustly than 0.625 mg of CE [74, 75]. In lower doses, oral estrogen had a lesser impact on the triglyceride (TG) level, which was found to be an independent marker of cardiovascular risk in women in the Framingham study [76]. Around the same time, natural estradiol and the means to deliver it transdermally via patch were also introduced, and short-term trials with the transdermal estradiol (TDE) found it comparable to oral CE for symptom relief and BMD preservation [77, 78]. While TDE was less effective in comparison to oral estrogen as far as cholesterol benefits were concerned, it had the advantage of promoting a more physiologic estrogenic milieu and avoided the "first-pass" liver effects implicated in much of estrogen's undesired prothrombotic effects and stroke risk [79].

While TDE use was becoming increasingly popular in Europe, greater than 80 % of estrogen users in the USA continued to use oral conventional doses of CE due to its perceived benefits on hard clinical end points (fractures and heart attacks) and not just on surrogate markers of risk (BMD and serum lipid levels). This clinical reality would play an important role in the design of the NIH-sponsored randomized MHT trials that launched in the early 1990s. No transdermal or low-dose estrogen products were tested neither in the PEPI nor the WHI trials. These low-dose oral and transdermal products which had gained FDA approval for menopausal symptom relief and osteoporosis prevention in

this era would however play important clinical and research roles in the aftermath of WHI.

Postmenopausal Estrogen Use and the Secondary Prevention Trials

Contemporaneously with the PEPI trial, a sizable industry-sponsored multicenter RCT was launched to test the hypothesis generated by earlier observational studies that CE therapy was beneficial not just for primary prevention but also for secondary prevention in women who already have CAD. The Heart and Estrogen/Progestin Replacement Study (HERS) recruited 2700 older non-hysterectomized women (average age 67 years) with established CAD, randomized them to CCEP or placebo, followed them for over 6 years, and measured well-defined clinical end points as well as surrogate markers of cardiovascular risk. The hormone therapy regimen which was chosen for HERS had already been proven to protect the endometrium and promote amenorrhea, factors that would help maximize long-term compliance with assigned therapy. The results of HERS published in 1998 contradicted the observational evidence, finding an increase in risk of cardiovascular events in the first year of therapy, a decrease in events in subsequent years, and no net overall cardiovascular benefit over the 6.8 year duration of the study [80–82].

In addition to HERS, the secondary prevention of CAD and stroke was investigated in a number of NIH-sponsored angiographic RCTs [83–85]. Women recruited for these 2–3-year trials were comparable in age and cardiac history to those in HERS, and many of them were on lipid-lowering therapies. Conventional oral doses of CE and natural estradiol with and without progestins neither slowed the progression of coronary artery stenosis nor reversed it, despite inducing desirable and expected changes in serum lipids. These findings were consistent with the HERS clinical findings, but unlike HERS there was no evidence of excess risk in the early months of hormone use in the angiographic trials. While this may be due to lack of study power, the concurrent statin use by the majority of women in those trials may have protected against early events. This theory was tested in a subgroup reanalysis of the HERS data, finding no increased risk of early adverse events among the subgroup of CCEP users who were taking statins [86].

Taken collectively, the clinical and angiographic secondary prevention trials indicated that commonly prescribed oral estrogen doses with or without progestins are not helpful in women with established CAD in the sixth and seventh decade of life. While the hope for secondary prevention of CAD by estrogen faded, hope persisted that estrogen might be proven beneficial for primary prevention of CAD. This hope was kept alive by the results of the Estrogen in the Prevention of Atherosclerosis Trial (EPAT), a 2-year randomized prospective trial which found that standard dose oral estradiol slowed the progression of subclinical carotid atherosclerosis in younger postmenopausal women with high cholesterol levels, particularly those of them who were not on statins [87]. This however was a surrogate end point study, and it would be few more years before a number of RCTs with hard clinical end

points could weigh in on the subject matter. In the USA, the WHI hormonal trials had been underway since 1998. Overseas, the Women's International Study of long Duration Oestrogen after Menopause (WISDOM) was also afoot, with plans to test the effects of CE and CCEP on multiple primary and secondary outcomes in a younger cohort of menopausal women in the UK, Australia, and New Zealand. The Danish Osteoporosis Prevention Study (DOPS), a-20 year effort to test the fracture reduction benefits of natural oral estradiol in newly menopausal women, had been in progress as well since 1990, with plans to report on cardiovascular disease as a secondary outcome.

The Women's Health Initiative (WHI)

Summary of the Trial Design

The WHI, a large and multifaceted NIH effort, was launched the same year as PEPI, to evaluate the most common causes of death, disability, and poor quality of life in postmenopausal women, namely, cardiovascular disease, cancer, and osteoporosis. The effort consisted of an observational cohort and two hormone trials, which altogether involved 161,808 generally healthy postmenopausal women [88]. The hormone trials of the WHI were designed to test the effects of MHT on heart disease, fractures, and colorectal and breast cancer. Based on existing knowledge, hormones were expected to decrease CAD risk and increase breast cancer risk, and those were the two primary outcomes for which the trials were designed and powered. Skeletal fractures, other cancers, and total mortality were secondary outcome measures in the WHI. Over 27000 women age 50–79 were enrolled at 40 clinical centers nationwide in the two WHI hormone RCTs, one for hysterectomized women (WHI-E trial that compared 0.625 oral CE against placebo) and the other for women with an intact uterus (WHI-EP trial in which CCEP was tested against placebo). Wyeth-Ayerst Research Laboratories (Philadelphia, PA), the maker of both hormonal products, agreed to donate the active and placebo pills for the effort. It is noteworthy that these were the first large-scale menopause trials to enroll significant proportions of nonwhite minority women in an effort to ensure that results would be generalizable to the population at large.

Just like PEPI and HERS, the choice of hormonal regimen utilized in the WHI hormone trials reflected prevalent prescribing practices in the USA at the time. Unlike PEPI however, WHI participants were older with a mean age of 64, and only a third of them were within 10 years of menopause. A mere 3.5 % of WHI participants were between 50 and 54 years, the age at which women often decide whether to initiate HT or not for symptom management. The choice of mostly asymptomatic postmenopausal women would help ensure better blinding and reduce dropout rates which had plagued PEPI. Most participants in WHI (70 %) were also overweight or obese with a mean BMI of 30 kg/m2, and nearly 40 % were former smokers. The inclusion of many women with these CAD risk factors was justifiable for trials whose intent was to evaluate estrogen's role in primary prevention of CAD and in

light of existing favorable observational and biomarker studies [31, 56]. One should remember here that the HERS and the angiographic trial findings discussed earlier had not been known yet when design and recruitment for the WHI clinical trials got under way.

Placing WHI Core Findings in Perspective

WHI-EP trial was planned to run until 2005, but the findings of an overall increase in risks of coronary heart disease, stroke, pulmonary embolism, and breast cancer relating to hormone use led to its premature termination in 2002 after an average follow-up period of 5.2 years [89]. While CCEP users experienced fewer hip fractures and colon cancers (secondary outcomes), the monitoring agency felt that the net risk of harm of MHT was larger than the net benefit and stopped the study. However, longitudinal follow-up of the WHI-EP cohort continued until 2010 yielding important information which will be discussed later. WHI-E kept going for another 2 years when it too was stopped prematurely. After an average 6.8 years of oral CE use, the only benefit was a reduced risk of hip and other fractures [90], a secondary outcome for the study. While reassuringly, there was no increased risk of breast cancer or coronary heart disease with the use of CE alone; no obvious cardioprotective benefit was apparent either. Similar to the WHI-EP trial, an increased risk of stroke and deep vein thrombosis (secondary outcomes) was evident in the hormone, compared to placebo users.

The 30 % increase risk of ischemic stroke (50 % increase after adjusting for non-adherence) found in association with HT use in both WHI-EP and WHI-E would soon be compounded by negative cognitive findings from the WHI Memory Study, or WHIMS [91, 92]. This substudy of WHI involved over 7000 cognitively intact subjects aged 65–79 years from both WHI trials who were followed for approximately 5 years. A 76 % increase in risk of cognitive decline and dementia was found among HT users in WHIMS, but it was not clear to what extent this increased risk of cognitive decline was mediated by stroke. However, it became clear after WHI and WHIMS, and the earlier WEST and HERS-Cog trials, that the use of conventional oral HT for primary or secondary prevention of cognitive decline in older postmenopausal women is in the least ineffective and possibly associated with increased stroke risk and accelerated cognitive decline. While these findings were somewhat disappointing, they were not unique to conventional oral MHT. Increasingly, popular alternatives for skeletal protection and menopause management, e.g., selective estrogen receptor modulators (SERMs) and tibolone, would soon be tested in industry-sponsored RCTs and would also be found to be associated with increased stroke and thromboembolism risks [93, 94].

Revelations from the WHI's hormonal trials and its substudies would have profound, lasting, and far-reaching influence on social attitudes toward MHT and on governmental oversight of existing and new women's health products. This transpired despite the many shortcomings of those trials which became apparent only in hindsight, including the older age and advanced menopausal state of the enrollees, the low adherence and high dropout rates, the inadequate power for the stroke

outcomes, and the fact that only a single type and dose of oral estrogen and one oral progestin were tested (compared to the wide variety of hormonal products and regimen in existence at the time in the USA and worldwide). The WHI trial findings would also trigger a massive revisionist effort to try to understand the reason behind the discordance between WHI and observational studies regarding cardioprotection. In the process, clinical practice would change, new hypothesis would be generated and tested, and the quest for optimal post-reproductive female health and well-being would march on.

In contrast to the discordance on coronary artery disease, the WHI results were concordant with earlier observational and randomized trial evidence regarding estrogen's osteoporosis prevention and fracture reduction benefits. WHI-E and WHI-EP were indeed the first primary prevention trials in menopause research to demonstrate that skeletal protection extended to black women and that race/ethnicity did not modify the treatment effect [89, 90, 95]. Prior to WHI, the HERS secondary prevention trial did observe BMD improvements with estrogen use in older women not selected for osteoporosis but could not demonstrate a fracture reduction efficacy, possibly because of its much smaller cohort size [96]. From a public health point of view, this demonstration of success in primary prevention of osteoporotic fractures in a randomized trial with hard clinical end points was remarkable. Yet the requisite sustained intake of conventional MHT for fracture prevention had, by virtue of the same trials, become less palatable due to the increased CAD and breast cancer risks among WHI-EP subjects and the increased stroke risk among WHI-E and WHI-EP participants. Furthermore, the increasing focus on treatment-related risk/benefit calculus had also extended well beyond the realm of hormone therapy. Contemporaneously, national guidelines for osteoporosis prevention and fracture reduction had evolved since the 1980s, emphasizing calcium, vitamin D, and smoking cessation for primary prevention [97]. Pharmacotherapy was no longer advisable except in women where the calculated 10-year hip fracture risk exceeded 3% or the 10-year all-site fracture risk exceeded 20% [97]. Although estrogen remained FDA approved for osteoporosis prevention, bisphosphonates which had been approved in 1995 had now replaced estrogen as first-line agents for fracture prevention in at-risk women in both the USA, Europe and most of the world [98, 99]. An important exception to this paradigm shift is women experiencing premature menopause, be it natural or iatrogenic, where WHI findings are not relevant. In these women there is evidence and consensus that, barring any contraindications, conventional dose MHT is advisable until the usual age of menopause, to help preempt the negative skeletal and cardiovascular impact of premature loss of ovarian endocrine function [100].

Post WHI

A Changed and Changing Landscape

With the release of the WHI findings and the consequent mandate by the FDA for a black box warning on all E and EP products sold in the USA [101], a new day had dawned on the field with dramatic decline in HT use in the USA and worldwide

[102–106]. A case in point is the drop in number of CE and CCEP prescriptions in the USA from 61 million in 2001 to 21 million in 2004 [102, 105]. Additional dramatic effects were manifest with the abrupt termination of several long-term randomized controlled MHT trials. One of the notable casualties was the WISDOM trial which was halted before any meaningful accrual had occurred [107]. Had WISDOM been allowed to continue, it could have provided invaluable information about the coronary risks and benefits of the same hormones used in WHI trials, but in a cohort of younger women. Clinically, the doubts raised by WHI about cardioprotection by estrogen and the possibility of increased coronary risk with EP further undermined the main public health argument for the cardioprotective benefits of long-term MHT. This argument had in fact been steadily eroding with a 50% decline in CAD mortality between 1980 and 2000, mostly attributed to improved diagnostic and therapeutic interventions for CAD and to widespread societal change in attitudes and behavior toward modifiable risk factors, e.g., smoking, hypertension, and dietary cholesterol [108, 109]. With this as a backdrop, the revelations from WHI drove a large number of women and their providers to abandon MHT not only for prevention of chronic disease but also for symptom relief, despite their superior efficacy and continued FDA approval for management of menopausal symptoms. This flight away from HT after WHI was facilitated as well by the availability of alternative less stigmatized pharmacologic options for symptom management and for the prevention of chronic diseases (e.g., statins, bisphosphonates, SERMs, and SSRIs), although these too were later proven not to be without risk [93, 110–112].

In this changing landscape, a new emphasis emerged post WHI that focused on individualized therapy to improve the quality of life for symptomatic menopausal women [113]. If the old paradigm of postmenopausal MHT use was “more is better,” the mantra after WHI became “less is more.” But the questions begging for answers persisted; are those low-dose, short-term, FDA-approved hormones absolutely safe? Yes, they are effective hot flash therapies and they might improve sleep [75, 114, 115], but women who use them do not want to lose sleep worrying about their long-term risk of stroke, heart attack, cognitive decline, and breast cancer; similarly, prescribing providers need not lose sleep either, worrying about potential for litigation. The clinical agenda after WHI thus focused on developing evidence-based guidelines to better define and quantify the magnitude of MHT risks for the real-life users (i.e., symptomatic young perimenopausal and early menopausal women) and to aid in the individualized assessment, counseling, and treatment of the symptomatic menopausal woman. The research agenda post WHI was similarly dominated by clinical concerns and fell into four main categories: (1) efforts to reconcile the discordance between randomized trials and observational studies, (2) mining of new data from ongoing observational studies both in the USA and internationally, (3) randomized controlled trials to test hypothesis generated from 1 to 2 using low-dose HT doses and non-WHI regimen, and (4) novel basic and clinical research seeking to find effective safe alternatives for management of symptomatic menopausal women. What follows is a summary of these research efforts as they relate to these main clinical concerns.

Menopausal Hormone Therapy and Coronary Risk

Reconciling the Discordance Between Observational and Experimental Studies

Understanding the root cause of discordance regarding cardioprotection between WHI hormone trial data and results of earlier observational studies required a revisit of the methodologies and reevaluation of the participants in these studies. Upon review and application of new statistical tools and reanalyses, two factors emerged as important contributors to the inadvertent exaggeration of estrogen's benefits in the observational trials. These were (1) a "healthy user" selection bias (80% of estrogen users in NHS were newly menopausal symptomatic women) and (2) a selection bias caused by the inefficient accounting for early postexposure risk [116–118]. In this latter situation, an adverse event shortly after exposure to MHT often reduces the likelihood that those afflicted are available and counted at the time of the biennial questionnaire. A case in point is WHI's own observational study (WHI-OS) which had in fact initially found decreased coronary risk among current EP users, but on reanalysis and inclusion of those who had suffered early postexposure coronary events, no cardioprotective benefit was found among current EP users [118]. As to the "healthy user" effect, a stratified subset reanalysis of the WHI-E and WHI-EP cohorts revealed menopausal age at initiation of HT to be an important determinant of coronary risk. Women who were less than 10 years postmenopausal at randomization actually demonstrated decreased CAD risk with MHT use. In contrast, those who were more than 20 years postmenopausal at randomization demonstrated an increased risk of CAD with hormone use [119]. This impression was also corroborated by WHI-OS which found similar risk patterns based on menopausal age at initiation of MHT [120]. Given the small number of subjects under 60 in the WHI, statistical power for the age-stratified analysis was lacking, and controversy persisted whether initiation of hormones at a younger menopausal age is associated with a real protective benefit, or just no risk [121]. Nevertheless, the "timing hypothesis" emerged as a new concept in coronary protection by estrogen.

Emergence of the "Timing Hypothesis"

The timing hypothesis stipulates that initiation of estrogens closer to the time of onset of menopause may protect the coronaries not only via reductions in serum lipids but also thru direct vascular effects that require a healthy coronary endothelium. By the same argument, older postmenopausal women who are more than 10 years postmenopausal are more likely to have coronary endothelium that is compromised by unstable atherosclerotic plaques. As such, older women will either derive no coronary benefits from estrogen or may even accrue an early risk due to acute thrombosis and rupture of unstable atherosclerotic plaques promoted by prothrombotic and pro-inflammatory effects of oral estrogen. The theory is supported by strong evidence from primate research [122] and by the results of the EPAT trial mentioned earlier where oral 17-beta estradiol intake for 2 years did slow the progression of subclinical carotid atherosclerosis in a cohort of young and healthy postmenopausal women with elevated cholesterol levels [87]. The timing hypothesis would also explain the HERS trial results and many of the angiographic studies

discussed earlier that identified no benefits and possibly an increase in early post-exposure risk; notably, all of these studies recruited predominantly older women who were more than 10 years postmenopausal.

Experimental Testing of the Timing Hypothesis

The timing hypothesis would be tested prospectively in two new RCTs after the WHI. The Kronos Early Estrogen and Progesterone Study (KEEPS) was a privately funded multicenter placebo-controlled RCT of 727 non-hysterectomized women [123, 124]. The average age of the cohort was 52.7 years, and all were within 3 years of the onset of menopause. Study subjects were randomized to a placebo arm, or one of two low-dose estrogen arms: oral CE 0.45 mg and 50 μg/day TDE. Uterine protection in the hormone users was achieved with cyclic oral natural progesterone, 100 mg/day for 10 days each month. The trial was not large or long enough to allow reliable use of clinical outcomes; surrogate markers of cardiovascular risk (coronary artery calcium [CAC] and carotid intimal-medial thickness [CIMT]) were measured instead as primary outcomes of interest over the 4-year study duration. Following 4 years of hormone intervention, there was no difference between hormone therapy groups and placebo in the progression of subclinical atherosclerosis reflected by CAC score and CIMT [123]. Predictably, low-dose oral CE was associated with reduced LDL-C and increased HDL-C and TG levels, while low-dose TDE was neutral on lipids. Both hormonal treatment regimens were effective for vasomotor symptom relief. Thus, while KEEPS did not support the timing hypothesis, the minimal progression of subclinical atherosclerosis observed in all three study arms provided a measure of reassurance to newly menopausal short-term users of low-dose HT formulations.

The Early vs. Late Intervention Trial with Estrogen, or ELITE, was the second trial that explored the timing hypothesis, again with a focus on CIMT as a surrogate measure of cardiovascular risk. A longer 6-year RCT compared to KEEPS, conventional dose oral estradiol therapy was utilized in ELITE that recruited 643 women who were either less than 6 years postmenopausal (mean age 55) or more than 10 years postmenopausal (mean age 65). Each subgroup was randomized to placebo vs. 1 mg of oral estradiol; cyclic vaginal micronized progesterone gel was utilized for endometrial protection for the hormone users [125]. In a recent preliminary report from ELITE, oral estradiol therapy in the younger subgroup of women appeared to be associated with a slower progression of subclinical atherosclerosis as reflected by CIMT, compared to placebo; notably, no such difference was seen among the older cohort of estradiol users [126].

Additional support for the timing hypothesis has come from post hoc analysis of the long-running Danish Osteoporosis Prevention Study (DOPS) which had been terminated in the wake of WHI. By then, the cohort of nearly 1006 newly menopausal women enrolled within 2 years of their last period had completed 10 years of randomized treatment. 504 subjects received no active hormonal therapy and 502 subjects received 2 mg daily oral estradiol. Those taking estradiol who had an intact uterus also received oral 1 mg norethisterone acetate for 10 days each month. After 10 years of randomized treatment and an additional 6-year post cessation follow-up of the cohort, a 50 % lower risk of mortality, heart failure, and myocardial infarctions was reported among subjects randomized to hormone therapy compared to those on placebo [127].

Menopausal Hormone Therapy and Breast Cancer Risk

The Origins and Evolution of the Association

With serious doubts cast by WHI over the cardioprotective benefits of estrogen, the perennial and decades-old debate about the association between HT and breast cancer was rekindled, along with a sharpened focus on the role of progestins in this association. Starting in the 1970s, various observational studies, including the NHS, had reported an increased risk of breast cancer among long-term MHT users, but the nature and strength of this association had remained controversial [128]. Some felt the risk to be overstated due to increased utilization of screening mammography in women on HT (screening bias) resulting in discovery of occult, low-grade, node-negative, estrogen receptor-positive tumors with no increase in breast cancer-related mortality [129, 130]. Others felt the risk to be understated due to a selection bias whereby women with early onset surgical menopause, known to have a lower baseline risk of breast cancer, were overrepresented in the MHT cohorts [131].

The argument for a causative association between MHT and breast cancer received a boost from the PEPI randomized controlled trial where an increase in mammographic density was noted in some subjects on combination EP regimen [132]. This also generated concern about reduced sensitivity of screening mammography in women on HT [133]. Biological plausibility of an association between estrogen and breast cancer was further supported by trials demonstrating decreased breast cancer risk among users of the SERMs: tamoxifen and raloxifene [134, 135]. The case for causation was further strengthened with the release of WHI-EP findings showing a 30 % higher breast cancer risk among CCEP users [89]. Given the screening mandates of the WHI, the "screening bias" argument could no longer be invoked for WHI-EP. The average time to harm in this trial was 5.6 years, and the breast cancers were more advanced with more lymph node involvement and associated with higher mortality rates than the breast cancers occurring in women on placebo. This increased risk of, and mortality from, breast cancer would be later confirmed among CCEP users in WHI-OS [136], corroborating the randomized trial findings. It is not entirely clear however if the more advanced breast cancers in CCEP users were due to biologically more aggressive higher-grade tumors, or consequent to a delayed diagnosis attributable to reduced sensitivity of screening mammography, or both. It also remains a matter of debate whether the higher mortality from breast cancer in CCEP users was due to a higher incidence or higher case fatality rate or both. It is interesting to note that the extended follow-up of the WHI-EP cohort after the trial ended found that the MHT-related breast cancer risk persisted for many years after cessation of therapy [137]. This was discordant with the results of the majority of older and newer observational studies and meta-analyses which had shown declining breast cancer risk among past users of hormone therapy and vanishing risk after 5 years of MHT cessation [138]. It is also at odds with population data showing a worldwide decline in incidence of breast cancer with the global decline in MHT use in the early years after WHI [139–143].

Estrogen, the "Gap Theory," and Breast Cancer

In contrast to WHI-EP, the WHI-E trial found no increase in breast cancer risk after 6 years of unopposed CE use and an actual decrease in the incidence and mortality from breast cancer in the 5-year post study follow-up of the cohort [144, 145]. These findings are at first glance discordant with most of the older observational studies, including NHS where unopposed CE was similarly the predominant form of MHT used. On stratified reanalysis of the NHS cohort however, an increased risk of breast cancer was only noted after 15–20 years of estrogen-alone use [146], reconciling it to some degree with findings of the much shorter WHI-E trial. WHI-E findings remain discordant however with those of two very large observational studies which commenced in the 1990s. The Million Women Study (MWS) undertaken in the UK and the French *Etude Epidemiologique aupres de femmes de l'Education National* (E3N) study had both found increased breast cancer risk to be associated not only with EP use but also, and to a lesser degree, with unopposed estrogen use as well [147, 148]. Important methodological differences between these newer observational studies and the WHI-E study may account at least in part for this discordance. This includes higher obesity rates in the WHI trial cohorts, higher prevalence of natural transdermal estrogen use in Europe, higher prevalence of MHT use prior to study enrollment in the observational trials, and a younger age at initiation of MHT in the observational studies. Regarding the latter, it is noteworthy that all three newer observational studies (E3N, MWS, and WHI-OS) found the risk of breast cancer associated with MHT use to be lower among women whose menopausal age was greater than 5 years when they initiated MHT [149–151]. This so-called gap theory may have a biological basis and suggests that a longer lag time between onset of menopause and initiation of hormones may be protective against carcinogenic effects of estrogen on the breast tissue [152]. The current clinical utility of the "gap theory" however is minimal given that symptom burden, and hence benefit from the use of MHT is the highest within the first few years of menopause.

The Role of Progestins in Breast Cancer Risk

Prior to WHI, the role of progestins in the association between MHT and breast cancer had been a subject of significant controversy; conflicting observational studies suggested a protective effect, no effect, and even adverse effects of progestins on risk for breast cancer [153–156]. Up until the early 1990s, progestin use as a component of MHT was relatively infrequent, estimated at around 12% of MHT prescriptions in a large meta-analysis of epidemiologic studies worldwide [138]. This reality hindered the ability of observational studies, including the very large NHS, to provide conclusive evidence about the impact of progestins on the magnitude and direction of breast cancer risk in postmenopausal MHT users [154, 156]. In subsequent years, the revelation that the highest risk of breast cancer was associated with EP regimen, both in WHI-EP and in the newer observational studies (MWS, WHI-OS, and E3N), sharpened the focus on the role of progestins in breast carcinogenesis, a role initially suspected in the PEPI trial based on increases in mammographic breast density associated with CCEP use [132]. Adding to the complexity of the matter, evidence emerged from the E3N study cohort that progestins may not all

be equal as far as the risk of invasive breast cancer associated with MHT. Upon stratification by the type of progestin used in this cohort of half a million women aged 40–65 who were followed for 12 years, natural progesterone and dydrogesterone were found not to add to the risk of unopposed estrogen when compared to 17-hydroxyprogesterone- and 19-nortestosterone-derived progestins whose use was associated with a 60 % increase in relative risk of invasive breast cancer [148]. This suggested that in addition to the type of estrogen, its timing, and its duration of use, the type of progestin might be another determinant of the risk of breast cancer associated with long-term EP regimen. It should be noted however that in this analyses from E3N stratified by progestin type, the number of subjects in each subgroup was small and the power to draw solid conclusions was insufficient. As regards lower than conventional doses of progestins and estrogens, there is not enough quality data at this time to judge whether they are associated with reduced breast cancer risk; yet findings from the KEEPS study indicating no increase in breast tenderness in women on low-dose oral and transdermal combination MHT regimen offer some reassurance as regards breast tissue effects of low-dose MHT regimens [157].

In a manner reminiscent of the late 1980s when resistance to progestin use was encountered for fear of its attenuating effects on estrogen's lipid and coronary benefits [158], aversion to progestin use rose again after WHI due to fears of breast cancer related to inclusion of progestin in MHT regimen [159]. While oral micronized progesterone and dydrogesterone appeared in some observational studies to be less risky on the breast, those same studies revealed them inferior to other progestins for endometrial protection [160]. The need for a new therapeutic class became obvious and led to intense basic and clinical research efforts to find alternatives to progestins for the non-hysterectomized woman taking estrogen. The discovery that a new SERM, bazedoxifene, serves that purpose when combined with CE led to the development and testing of a new class of hormonal therapies for menopausal women, namely, the tissue-selective estrogen complex, or TSEC [161]. In addition to endometrial protection, short-term industry-sponsored clinical trials have found this TSEC to be effective for relief of vasomotor and atrophic vaginal symptoms, protective of BMD, and not associated with the increased breast density seen in women on EP regimen [162–165]. While longer-term studies with hard clinical data, including cardiovascular and cancer end points, will ultimately be needed, the first TSEC product was approved by the FDA and European Medicines Agency for MHT with the same warnings currently mandated on E and EP products sold in the USA [166, 167].

Menopausal Hormone Therapy, Stroke, Thromboembolism, and Cognition

Stroke

While hopes that conventional MHT can offer protections against stroke and accelerated cognitive decline in aging women were dashed by the findings of several RCTs and a reanalysis of the NHS data, younger symptomatic postmenopausal women on

low-dose HT needed to know whether they too are at increased risk. This was also of particular concern given that the increased risk of stroke in the WHI trials and also in HERS and NHS appeared within 1–2 years after initiation of therapy, a duration which falls within the definition of "short-term" therapy currently endorsed by most professional societies. The answers to these important questions would come from reanalyses of existing data and additionally from newer observational and smaller-scale randomized trial data. Reanalysis of the WHI stroke data stratified by age identified a higher incidence of stroke in the youngest age category of MHT users (age 50–59); notably, although this relationship lacked statistical significance, the study was deemed to lack in power for this end point given the very low number of strokes in this age group [119]. In a combined analysis which included over 90,000 women enrolled in the observational study of WHI (WHI-OS), increased stroke risk was similarly noted among younger healthy postmenopausal women within 10 years of menopause, even among those taking less than conventional CE doses [168]. Similarly, on reanalysis of NHS data, an increase stroke risk persisted in younger women on conventional dose E and EP regimen [169]. While the absolute risk of stroke in this age group is very small and estimated at one additional stroke in one thousand women taking MHT for 5 years [170], these findings suggest that the "timing hypothesis" that was proposed for MHT-related CAD risk does not apply to MHT-related stroke risk. Two additional interesting findings emerged from these reanalyses; in the NHS there was no increased stroke risk among users of the 0.3 mg CE who had no baseline comorbidities [169], and in the WHI-OS, there was a trend toward lower stroke risk among oral estradiol users compared with CE users [168]. It is also worth mentioning here that in a post hoc analysis from the DOPS trial, those who were randomized to conventional oral doses of estradiol for 10 years did not show an increased risk of stroke compared to placebo, yet here again the number of observations was very small and power was limited [127].

Clinically important information post WHI was also gleaned from European observational studies where transdermal estrogen use had been for decades much more prevalent than in the USA. These studies have shown a lower risk of stroke associated with transdermal estrogens, with some albeit limited evidence that low-dose TDE (0.05 mg/day or less) may not confer increased stroke risk [171]. This purported safety of TDE is biologically plausible by virtue of avoidance of the obligatory "first-pass" effects of oral estrogens on hepatic synthesis of various clotting and pro-inflammatory factors [172]. Taken collectively, the findings since WHI from both the USA and Europe identify the risk of stroke to be higher with MHT use; notably however, the absolute attributable risk is quite low and can be minimized by modifications in the type, dose, and route of estrogen and by limiting therapy to newly menopausal and otherwise healthy women under age 60. For those who chose to accept this small risk of stroke after a careful risk/benefit analysis, it is reassuring for them to know that this increased risk dissipates quickly within a year of cessation of therapy, as demonstrated in the extended follow-up of the WHI trial cohorts [137].

Venous Thromboembolism (VTE)

Regarding VTE, an important risk factor for stroke, the observational studies MWS and the French Estrogen and Thromboembolism Risk (ESTHER) study have confirmed an increased risk among women on conventional dose MHT [173, 174]. A two to almost fourfold increase in VTE risk with conventional MHT had been known from earlier observational reports starting in 1996 as well as several randomized trials discussed earlier (PEPI, HERS, and WHI) and was also confirmed in an updated analysis from NHS [34, 175–177]. While the DOPS trial did not show a statistically significant increase in VTE risk with conventional oral estradiol use, there was nevertheless a doubling of risk based on one observation in the placebo arm and two in the treatment arm [127]. Contrary to the earlier studies dominated by conventional doses and oral routes of unopposed estrogen, ESTHER and MWS had enrolled many women on low doses and transdermal routes of estrogen and also on various estrogen/progestin combination therapies. The evidence from these studies, albeit limited, indicates that micronized progesterone (MP) and norethindrone acetate (NET) are less thrombogenic than MPA [173, 174]. It also suggests that in addition to the use of TDE, the risk of VTE can be further mitigated with the use of non-MPA progestins in MHT. As in the case of stroke, MWS also showed that the increased VTE risk with MHT appears to occur early in the first 2 years of therapy [174].

Taken collectively, existing data indicate that age, years since menopause, type, dose, and route of E and P can all influence the risk of VTE. It is important to state however that when these risks are displayed in absolute rather than relative terms, even those newly menopausal women in the highest risk category have a 1 in 250 chance of a VTE as opposed to 1 in 750 among nonusers of HT [174]. In addition, 50–79 years old hyperlipidemic women considering MHT may find it reassuring that the risk of thromboembolic events in the first year of MHT use was not increased among those who were already on statins in a nested case-control study from the UK General Practice Research Database, although here again statistical power was suboptimal [178].

Cognition and Memory

The question of whether the process of cognitive decline and memory loss is accelerated with the use of hormones in newly postmenopausal women has been addressed in two post WHI randomized trials. The ELITE trial discussed earlier had a cognitive arm and recently reported in an abstract form that conventional dose oral estradiol taken early or late after menopause, and for 5 years, provided no cognitive benefit nor caused any cognitive harm [179]. This, to date, is the only study designed and powered to test the critical window hypothesis as far as cognitive function is concerned. As to low-dose HT, data from the KEEPS trial showed no negative impact on cognitive function after 3 years of low-dose oral CE or transdermal estradiol [180], providing a measure of comfort to newly menopausal healthy women choosing to use one of these two regimens for symptom relief.

Menopausal Hormone Therapy, Osteoporosis, and Fracture Risk Reduction

As discussed earlier the fracture reduction benefits of conventional dose MHT had been suspected since 1986 and affirmed in subsequent cohort studies [181, 182], in meta-analyses of randomized trials prior to WHI [183], as well as in the WHI hormone trials which demonstrated reduction in hip fracture risk with MHT [89, 90, 95]. Although a few reports have suggested a possible lasting skeletal benefit after stopping MHT [137, 184], the plurality of evidence since the WHI indicates a rapid dissipation of benefits with a return to baseline fracture risk within few years of cessation of MHT [185, 186]. Whether MHT-related skeletal benefit observed in an era dominated by conventional dose MHT use is applicable to current low-dose MHT users is unclear. What is currently known is that low-dose MHT regimens, including those utilizing ultralow doses of estrogen, have proven comparable to standard MHT on BMD preservation, at least in short-term trials [187]. Many of these low-dose hormone therapies remain FDA approved for osteoporosis prevention, allowing their use in women at increased fracture risk who are deemed eligible for MHT use. As observational studies continue to enroll women on low-dose MHT, it is hoped that fracture data will be forthcoming in the years ahead. At this time however, the level of certainty regarding fracture reduction efficacy of low-dose MHT regimens is low, and fracture reduction benefit from the use of low-dose MHT formulations may not be assumed for those deemed at an innately enhanced risk for fracture.

Summary and Future Directions

Menopausal hormone therapy-related research has maintained a pioneering translational quality since its early beginnings dating almost five decades and has resulted in a remarkable output of clinical products, policies, and educational tools intended to improve health, well-being, and quality of life for individual post-reproductive women and the community at large. The WHI hormone trials have helped shape the course of menopause management over the past decade; the debate and the introspection of the past 10 years have helped carve the current climate where focus is on an individualized approach to menopause management with the goal of maximizing benefit while mitigating any potential for harm. This fact is reflected in the consensus guidelines for MHT use by many professional societies which get updated regularly as new research evidence emerges [188–193]. The common thread in most current guidelines is that the risk/benefit equation is more favorable for unopposed E than for EP products and that low doses of MHT and transdermal estrogens are associated with less side effects and safer as far as stroke risk is concerned. Regarding breast cancer risk, EP use for 3–5 years and unopposed E use for 7 years are considered relatively safe for symptomatic women with no past history of MHT use. As to coronary risk, E and EP products are relatively safe for the heart when taken by symptomatic menopausal women who are under 65 years, with no cardiovascular risk factors, and who are within 10 years of menopause. For women

65 years and over, systemic estrogen and EP products remain since 2003 on the Beers' list of potentially inappropriate medications [194]. Notably however, recent evidence of prolonged symptom persistence in some women [195, 196] has prompted a position statement from the North American Menopause Society (NAMS) supporting judicious continuation of HT use beyond age 65 [197]. Despite the biological plausibility of the timing hypothesis and the promise of MHT-related cardioprotection suggested by data from ELITE, and the established antifracture efficacy of conventional dose MHT, professional societies and experts recommend against the use of MHT for prevention of chronic diseases, a stance that is supported by the FDA and USPSTF [101, 198].

While current professional guidelines have discouraged the use of existing MHT regimen for anything but short-term symptom management, the final chapter on the role of long-term MHT for chronic disease prevention has yet to be written. The post WHI research output has nevertheless generated significant ideas, concepts, and hypothesis that are likely to propel the field into new horizons, help meet the currently unmet needs of a large segment of post-reproductive women all over the world, and write a new chapter in the storied history of MHT.

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Nonhormonal Pharmacotherapies for Menopause Management

3

Susan D. Reed

Hot Flash Physiology: Targeting Nonhormonal Therapies

The neuroendocrine factors that trigger hot flashes are not well understood, but estrogen-sensitive circuits in the brain, anatomically juxtaposed to the thermoregulatory center, are the primary targets of investigation [1]. Research in the late 1970s suggested that hot flashes temporally correlate with pulses of luteinizing hormone (LH) and it was hypothesized that the same mechanism that drives hot flashes also triggers episodic LH secretion [2]. Pulsatile LH secretion from the pituitary is driven by intermittent secretion of gonadotropin-releasing hormone (GnRH) from the brain [3, 4]. However, hot flashes do not appear to be solely dependent on pulsatile LH since they occur even in the absence of LH pulses [5]. Rather, the same upstream afferent input responsible for driving GnRH neurons is more likely to be responsible for triggering hot flashes. It is hypothesized that hot flashes and LH pulses have the same estrogen-regulated source generator, but they are not causally linked to one another [6].

Pulsatile GnRH secretion is governed by a network of estrogen-sensitive neurons in the hypothalamic arcuate (infundibular) nucleus, which express kisspeptin (*K*iss1), neurokinin B (*N*KB), and dynorphin (*Dy*) [7, 8]. These *KNDy* neurons also express the key isoform of the estrogen receptor, ERα [9], and KNDy neurons are the primary targets for the estrogen-dependent regulation of GnRH and gonadotropin secretion [10]. Moreover, it appears likely that KNDy neurons drive the pulsatile secretion of GnRH and LH – as evidenced by the fact that blockade of kisspeptin signaling in the brain inhibits GnRH pulses [11]. If bursts of KNDy neuronal activity evoke the

S.D. Reed, MD, MPH
Department of Obstetrics and Gynecology, Epidemiology, Women's Reproductive Health Research Program, University of Washington School of Medicine, Box 359865, Seattle, WA 98195, USA

Obstetrics and Gynecology, Harborview Medical Center, Seattle, WA, USA
e-mail: reeds@uw.edu

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pulsatile release of GnRH and LH, it is plausible that they also drive hot flashes [6, 12]. If Kiss1 neurons trigger hot flashes, it is conceivable that hot flashes could be inhibited pharmacologically by molecules that inhibit the neuronal activity of KNDy neurons [6, 13]. To date, there are no Food and Drug Administration (FDA)-approved products that affect the KNDy neuron complex, but drugs first developed for pain control and for mood disorders are under investigation in the USA and Europe.

It is unknown whether serotonin, norepinephrine, or gamma-aminobutyric acid (GABA)ergic compounds interact directly with the KNDy neuron complex (Fig. 3.1). It is hypothesized that the physiologic effect of serotonergic agents on VMS is due to an increase in serotonergic tone that then interacts with estrogen and/or norepinephrine receptors in the brain, a mechanism different from that for mood regulation. Elevated central noradrenergic activation appears to narrow the thermoneutral zone [14]. It has also been proposed that gabapentin affects

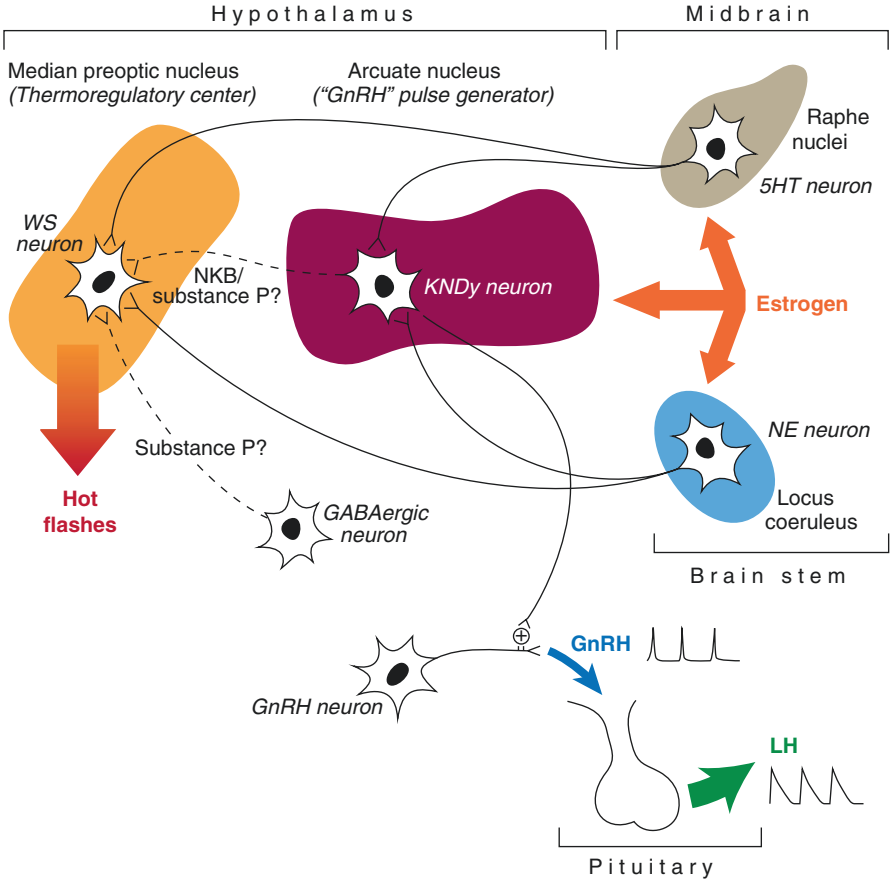

Fig. 3.1 Menopausal hot flash etiology – proposed model (*WS* warm sensing; *NKB* neurokinin B; *KNDy* kisspeptin, neurokinin B, dynorphin; *GnRH* gonadotropin-releasing hormone; *5HT* serotonin; *NE* norepinephrine; *GABAergic* gamma-aminobutyric acidergic)

thermoregulation via hypothalamic calcium channel activity regulated by extensive substance P projection to the medial preoptic nucleus [15]. Moreover, it is highly likely that at least some actions of nonhormonal pharmacotherapies that affect serotonin (selective serotonin reuptake inhibitors or SSRIs) and norepinephrine (selective norepinephrine reuptake inhibitors or SNRIs) and clonidine act peripherally by controlling either vasodilation or vasoconstriction, a downstream physiologic mechanism driven by the CNS thermoregulatory center.

The clinical use of SSRIs, SNRIs, and gabapentin precedes our understanding of their mechanism of action. This chapter will concentrate on the clinical evidence for the efficacy of nonhormonal pharmacotherapies for VMS and their effect on the management of other menopausal symptoms (sleep, sexual function, mood, and quality of life). Nuances of prescribing and tailoring the approach to the individual patient will be highlighted.

History of Serotonergic Medications for Hot Flash Management

In the 1990s, oncologists first noted anecdotal evidence that SSRIs provided hot flash benefit in men and women with cancer [16, 17]. The first randomized controlled trial (RCT) to investigate an SSRI for hot flashes was published in 2000; venlafaxine showed modest benefit for VMS after 4 weeks in breast cancer survivors or women at high risk for breast cancer [18]. It was not until 2015 that an SSRI was approved by the FDA for the treatment of hot flashes (paroxetine mesylate 7.5 mg daily). Studies show benefit of approximately one hot flash per day with this product [19]. Some oncologists continue to have concern about the theoretical risk of paroxetine use in women taking tamoxifen (potential decrease in effectiveness due to CYP2D6 polymorphism) [20], but clinical evidence to support this risk is lacking [21, 22]. All of the other nonhormonal pharmacotherapy products discussed in this chapter are not FDA approved, and their utilization for menopausal symptom management represents an "off-label" use.

Evidence for Serotonergic Medications for Management of Vasomotor Symptoms: RCTs

A multitude of reviews are available that describe the efficacy of SSRIs for menopause management [20], but on detailed inspection, only a handful of studies include requisite criteria that allow inter-study comparisons and provide sufficient data to judge efficacy. These criteria include (1) an adequate control group; (2) participants were midlife women with hot flashes (not depressed populations); (3) follow-up was at least 6–8 weeks duration; (4) there was at least 1 week of baseline hot flash data, preferably 2–3 weeks; (5) the population studied had sufficient hot flashes at baseline to evaluate change (at least 6 hot flashes per day); (6) there was data on frequency and severity of hot flashes; and (7) the outcomes were described as change in frequency from baseline compared with placebo.

Using these criteria, both SSRIs and SNRIs decreased hot flashes by approximately 1–3 hot flashes per day above the decreases demonstrated with placebo (Table 3.1). Serotonergic medications with efficacy greater than placebo in RCTs include the SSRIs fluoxetine, escitalopram, and paroxetine and the SNRIs venlafaxine and desvenlafaxine. One study included in Table 3.1 was only 4 weeks in duration, and was an outlier at an improvement of 3.9 hot flashes per day above placebo, but is included in the table because of its size and historical significance [18].

Studies evaluating serotonergic medications for VMS that did not meet the comparison criteria outlined above, and that were not included in Table 3.1, are discussed below. Paroxetine studies not included had either a crossover design [23] or low baseline VMS and limited power [24]. A single study evaluating citalopram lacked baseline measures [25] as did a single study of venlafaxine [26]. Other studies evaluating venlafaxine included a crossover design [27] and an open-label design [28]. Two studies of sertraline incorporated crossover designs [29, 30].

One study of sertraline for VMS met criteria as listed above, but did not find benefit [31]. With approximately 50 women per group, this study had limited power to detect small differences. Notably, there were group differences at baseline. Women taking placebo were older, more likely to be Caucasian, and were of higher

Table 3.1 Serotonergic therapies for vasomotor symptoms

SSRI or SNRI (italicized = preferred daily dose for hot flash amelioration)	*N* Completed, randomized [reference]	Trial duration (weeks)	Frequency ↓ from baseline HF/day Active vs placebo	Frequency HF/day at baseline	Overall ↓ # HF/day	Inclusion criteria only severe hot flashes
** † *Paroxetine* *7.5*, *12.5CR*, 25CR mg	160, 165 [57] 599, 614* [19]	6 12	3.3 vs 2.2 6.2 vs 5.3	6.7 11.7*	~0.9 ~1.1*	+
Escitalopram *10*, 20 mg	200, 205 [60]	8	4.6 vs 3.2	9.8	~1.4	+
Citalopram *10*, 20,30 mg	196, 254 [15]	6	3.6 vs 1.4	8	~2.2	+
Venlafaxine 37.5, *75*, 150 mg	191, 221 [18] 292, 339 [48]	4 8	6.6 vs 2.7 3.9 vs 2.2	8 8	~1.7–3.9	+
***Desvenlafaxine* 50, *100*, 150, 200 mg	519, 620* [48] 436, 452* [61] 541, 567* [62] 319, 365* [63]	12 12 26 (n = 368) 52	7.4 vs 5.9 7.1 vs 5.8 7.6 vs 6.0 7.7 vs 4.8	10.9* 10.8* 10.6* 11.8*	~1.3–2.9*	+

↓ decrease, *HF/d* hot flashes per day, * moderate to severe HF, ** industry sponsored, † 7.5 paroxetine mesylate, FDA approved

socioeconomic status (SES) compared to women in the sertraline group, who were younger, more likely to be African American, and were of lower SES. These differences, in addition to small numbers, may have confounded the null study findings.

There were no trials of fluoxetine that fit inclusion criteria for review. One study lacked baseline measures [25], and another was a crossover design [32]. No RCTs of duloxetine, fluvoxamine, or quetiapine XR exist.

Serotonergic medications are FDA approved for depression and anxiety and are also commonly used to treat post-traumatic stress disorder (PTSD), eating disorders, and obsessive-compulsive disorder [33, 34]. They are known to bind to serotonin receptors in the brain, vascular endothelium, gut, and bone. Adverse effects of serotonergic medications observed in populations for FDA-approved usages (e.g., anxiety and depression) vary, but in general include nausea, insomnia, dizziness, headache, dry mouth, diarrhea, bloating, constipation, insomnia, and sexual dysfunction. Other associations include increased risk of fractures, akathisia, and photosensitivity. In general, these medications are extremely well tolerated and safe in the doses recommended here.

If an SSRI or an SNRI is stopped abruptly, *SSRI withdrawal symptoms* can occur (dizziness, nausea, diarrhea, sweating, anxiety, irritability), but these symptoms are uncommon in women using SSRIs/SNRIs for hot flashes because of the low doses used. SSRI withdrawal symptoms do not occur with fluoxetine because of its long half-life. When stopping venlafaxine, the recommendation is to reduce the dose by no more than 50% every 3–4 days until discontinued (personal opinion). For desvenlafaxine, the recommendation is to give a full daily dose (50 mg) less frequently, e.g., alternate days for 1 week. This approach of every-other-day dosing can be used for all SSRIs and SNRIs once you have reached the lowest available dose. In all cases, if withdrawal symptoms emerge during discontinuation, raise the dose to stop the symptoms and then restart withdrawal more slowly. SSRI withdrawal symptoms occur from *lowering doses of serotonin* and are in contradistinction to the *serotonin syndrome* (agitation, confusion, dilated pupils, increased heart rate, elevated blood pressure, clonus, diarrhea, sweating, shivering, headache) that is due to an *increase in blood serotonin levels* [34]. Serotonin syndrome is unlikely to occur with any of the SSRI/SNRI doses recommended for the management of menopausal VMS but can occur with high doses of SSRIs or with combinations of medications (e.g., monoamine oxidase inhibitors [MAOIs] and SSRIs, SSRIs and SNRIs, SSRIs and triptans) [34].

Evidence for γ-Aminobutyric Acid (GABA)ergic Medications for Management of VMS: RCTs

Similar criteria were applied to examine existing data on GABAergic pharmacotherapies for VMS:

- Adequate control group
- At least 1 week baseline hot flash data (preferably 2–3 week), >6 hot flashes per day at baseline
- No crossover designs

- Midlife women, not selected for depression
- At least 6 weeks, preferably 8-week duration
- Data on hot flash frequency, severity provided
- Outcome – change from baseline compared with placebo

Using these inclusion criteria, studies evaluating gabapentin immediate release (IR), gabapentin gradual release (GR), and pregabalin have shown benefit for reducing VMS, similar to SSRIs and SNRIs – a reduction of approximately 1–3 hot flashes per day above placebo (Table 3.2). A single study of gabapentin IR of 4-week duration is included in Table 3.1 because of the number of women in the study and its otherwise strong design, but we acknowledge it did not strictly meet the criteria outlined above [35]. Studies evaluating gabapentin IR and not included in Table 3.2 either did not have a control group and were not blinded [36] or did not display outcomes as hot flash frequency, so they could not be compared with other studies [37].

Gabapentin is FDA approved as an adjuvant for seizures and for the treatment of postherpetic neuralgia. It is commonly used to relieve other types of neuropathic pain (diabetic neuropathy and central neuropathic pain) and restless legs syndrome. It is also commonly prescribed for off-label use to treat anxiety, insomnia, and mood disorders. Pregabalin, like gabapentin, is commonly used for seizure disorders and neuropathic pain. It is used off label for anxiety and is FDA approved for use in fibromyalgia. Gabapentin and pregabalin are structural analogues of the inhibitory neurotransmitter γ-aminobutyric acid (GABA).

The most common side effects of gabapentin and pregabalin, observed in over 10 % of individuals when used for FDA-approved indications, are dizziness and drowsiness. Both drugs may also produce sexual dysfunction in a smaller percentage of patients (loss of libido and inability to orgasm) [38]. Additional potential side effects are ataxia, blurred vision, headache, diplopia, euphoria, confusion, vivid dreams,

Table 3.2 GABAergic therapies for vasomotor symptoms

GABA derivative (italicized = preferred daily dose for hot flash amelioration)	*N* Completed, randomized [reference]	Trial duration (weeks)	Frequency ↓ from baseline HF/day Active vs placebo	Frequency HF/day at baseline	Overall ↓ # HF/day	Inclusion criteria only severe hot flashes
Gabapentin immediate release 300, *900* mg	347, 420 [64] 59 [65] 193, 197 [35]	8 12 4	4.2 vs 2.2 5.8 vs 3.2 6.5 vs 4.5	8.7 10.6 8.5	~2.0–2.6	+
*Gabapentin gradual release** 600, 1200, *1800* mg	593, 600 [51]	12	7.6 vs 6.5	11.9 >7 **	~1.1	+
Pregabalin 150, 300 mg	163, 207 [59]	6	4.6 vs 2.9	>6	~1.5	+

↓ decrease, *HF/d* hot flashes per day, * moderate to severe HF, ** industry sponsored

irritability, memory impairment, tremors, dysarthria, paresthesias, vertigo, dry mouth, GI side effects, weight gain, and peripheral edema. Notably, pregabalin can increase creatine kinase and decrease platelets (package insert [http://labeling.pfizer.com/ShowLabeling.aspx?id=561]).

It is important to titrate doses to balance benefit with side effects. This is most effectively done by increasing doses slowly and to dose GABAergic medications predominantly before bed to take advantage of potential sleep benefit of the drowsiness side effect.

Evidence for the Use of Clonidine in the Management of VMS: RCTs

Similar criteria that were applied to serotonerigic and gabaergic medications were used to examine clonidine for the treatment of VMS.

Clonidine may have modest benefit in decreasing VMS. A single study met criteria established here for efficacy evaluation. Clonidine decreased VMS by approximately one hot flash per day in a single 12-week RCT of 194 postmenopausal women with breast cancer [39]. Although findings were described as percent change in frequency of hot flashes, the baseline hot flash number was provided; at 12 weeks there were 1.9 fewer hot flashes than the 8.0 at baseline in the clonidine group, and there were 0.9 fewer hot flashes than the 6.3 at baseline in the placebo group. This difference was not statistically significant ($p=0.09$), but decreases at 4 and 8 weeks were significant ($p=0.001$ and $p=0.006$, respectively).

Other studies evaluating clonidine include a crossover design that did not describe the 1-week baseline VMS frequency [40] and a second study with only 17 women in the placebo group and in which the VMS outcome was recorded as a score rather than VMS frequency [41]. Thus data are limited, and benefit described in the single adequate study [39] seems insufficient to fully embrace clonidine as a viable therapy for VMS.

Clonidine is FDA approved for the management of hypertension. However, off-label uses include smoking cessation and management of opioid and alcohol withdrawal, attention-deficit hyperactivity disorder (ADHD), Tourette's syndrome, insomnia, and restless legs syndrome [42, 43]. Clonidine appears to act through a central mechanism and is classified as an alpha-2 adrenergic agonist and acts as a sympatholytic medication. It inhibits the presynaptic release of norepinephrine and decreases sympathetic tone. It appears to improve anxiety, palpitations, tachycardia, sweating, restlessness, and tremor.

The common side effects among populations using clonidine for FDA-approved indications include constipation, dizziness, drowsiness, dry mouth, headache, fainting, nausea, nervousness, reduced sexual ability, fatigue, vomiting, and weakness. Older people and those who weigh less than average or have kidney problems may experience confusion. Lower doses have fewer side effects,

0.01 mg transdermal or 0.1 mg oral daily. The use for VMS can be limited as orthostatic hypotension is often an intolerable side effect. If used, however, tapering to avoid rebound is recommended.

How Do Nonhormonal Pharmacotherapies Compare with Hormonal Therapies for Management of Menopausal Symptoms?

SSRIs for VMS have not been compared head-to-head with "standard-dose" hormonal therapies. A single trial included venlafaxine and low-dose oral estrogen and showed similar benefit [44] (Fig. 3.2). A single study of gabapentin and standard-dose estrogen showed similar benefit, but there were only 20 women in each arm, and the gabapentin dosing was quite high, often a dose not tolerated by many women (placebo, gabapentin 2400 mg, and conjugated equine estrogen 0.625 mg) [37] (Fig. 3.2).

Effective Dosing

Estrogen benefits for VMS follow dose-response curves (Fig. 3.3). This does not appear to be so for serotonergic or GABAergic medications. Rather, there seems to be a threshold dose at which serotonergic and GABAergic medications become effective and higher doses do not have added benefit for VMS (unlike mood and pain disorders). Whether choosing an SSRI, SNRI, GABAergic medications, or clonidine, the "rule of thumb" is to use low-dose therapies. Almost across the board, low-dose formulations appear just as effective as the higher-dose formulations used for mood, pain, or hypertensive disorders, and lower doses afford a lower-risk side effect profile (Fig. 3.4). Benefit from serotonergic and GABAergic medications may plateau by 4 weeks, whereas improvement with estrogen may plateau by 8 weeks and is dose dependent [45]. Optimal doses of serotonergic and GABAergic medications are listed in bold type in Tables 3.1 and 3.2.

Other Benefits of Nonhormonal Pharmacotherapies Beyond VMS Benefit: Effects on Mood, Sleep, Sexual Function, Weight Gain, and Quality of Life

Mood, sleep, sexual function, weight gain, and quality of life are important considerations when choosing a nonhormonal pharmacotherapy, just as when considering hormonal options. Very few RCTs have evaluated serotonergic or GABAergic medication effects beyond those described for VMS benefit, and head-to-head comparisons with hormone therapy are limited. RCT findings are summarized in Table 3.3. Additional details are provided below.

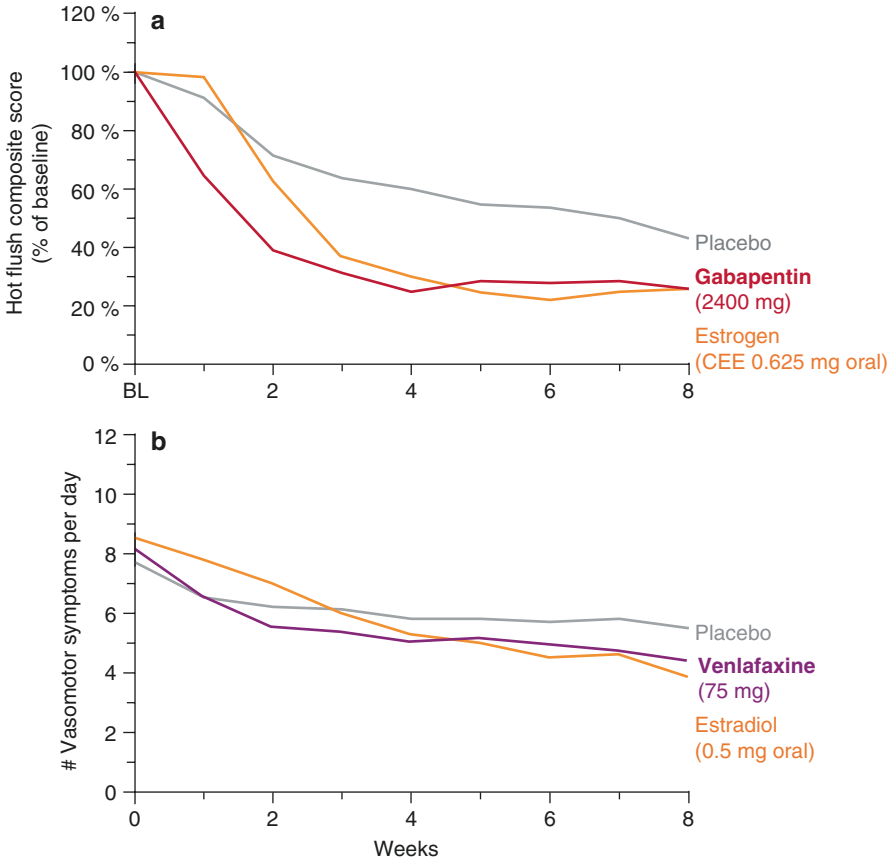

Fig. 3.2 Nonhormonal pharmacotherapies vs estrogen for the management of vasomotor symptoms. (*Panel* **a**) 8-week randomized controlled trial of gabapentin 2400 mg, oral conjugated equine estrogen (CEE) 0.625 mg vs placebo, *Y-axis* hot flash composite score, *X-axis* time in weeks [37]. (*Panel* **b**) 8-week randomized controlled trial of venlafaxine 75 mg, oral estradiol 0.5 mg, and placebo [44], *Y-axis* hot flash frequency, *X-axis* time in weeks, *#* number

Mood

To date, RCTs evaluating nonhormonal pharmacotherapies for VMS have not shown benefit or disbenefit for mood disorders, but the prevalence of mood disorders in the populations being studied is low. Clearly, antidepressants are beneficial for treatment of women with depressive symptoms or with a diagnosis of major depression during and after the menopause transition. SSRI/SNRI doses used for VMS are often insufficient to properly manage significant mood disorders, and doses should be titrated up to achieve benefit for both mood symptoms and VMS, although increased side effects can be expected. Gabapentin and pregabalin are used off label for anxiety and mood, but trial data are lacking.

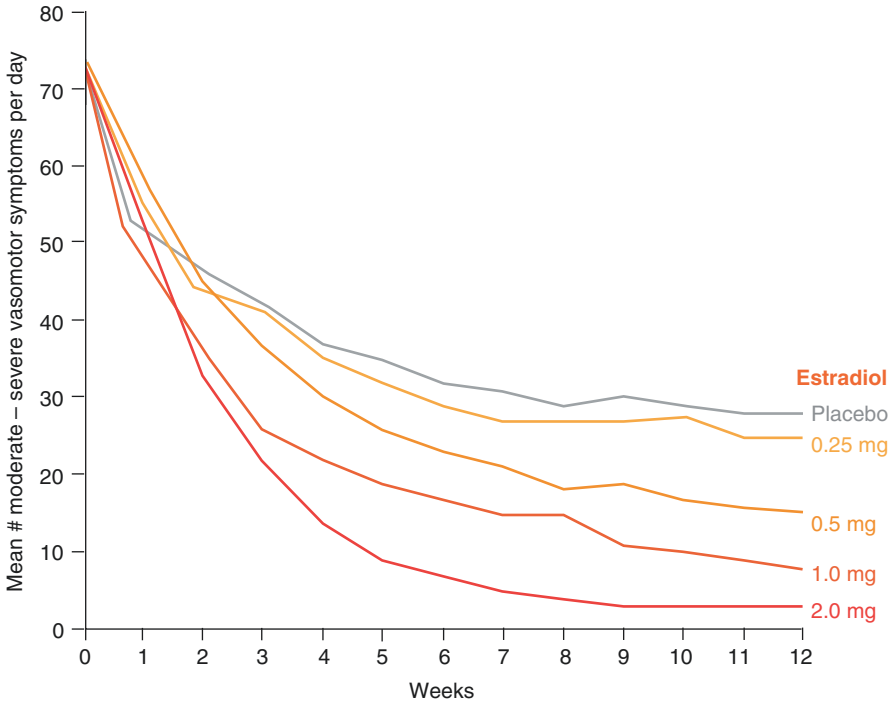

Fig. 3.3 Oral estradiol vs placebo – dose response for vasomotor symptom treatment. Hot flash diminution (*Y-axis*) with increasing estradiol dose as compared with placebo, over 12 weeks (*X-axis*), # number [45]

Sleep

Individuals taking serotonergic medications for depression can have worsened sleep [47–49]. In contrast, several placebo-controlled trials have evaluated sleep in women taking SSRIs, gabapentin, or pregabalin for VMS. Benefit was noted with escitalopram [46], paroxetine [47], desvenlafaxine [48], and venlafaxine [49]. As compared with placebo, both low-dose estrogen and low-dose venlafaxine modestly reduced insomnia symptoms and improved subjective sleep quality [49].

Not surprisingly, with drowsiness being its most common side effect, gabapentin is of benefit for women with sleep disturbance [50, 51].

Sexual Function

Sexual dysfunction has been described in up to 5 % of midlife women taking SSRIs, SNRIs, gabapentin, or pregabalin for VMS [52–54]. However, the overall impact of these nonhormonal pharmacotherapies on sexual function appears much lower than that reported for depressed populations and may even be improved in some circumstances, e.g., venlafaxine was associated with decreased dyspareunia and increased

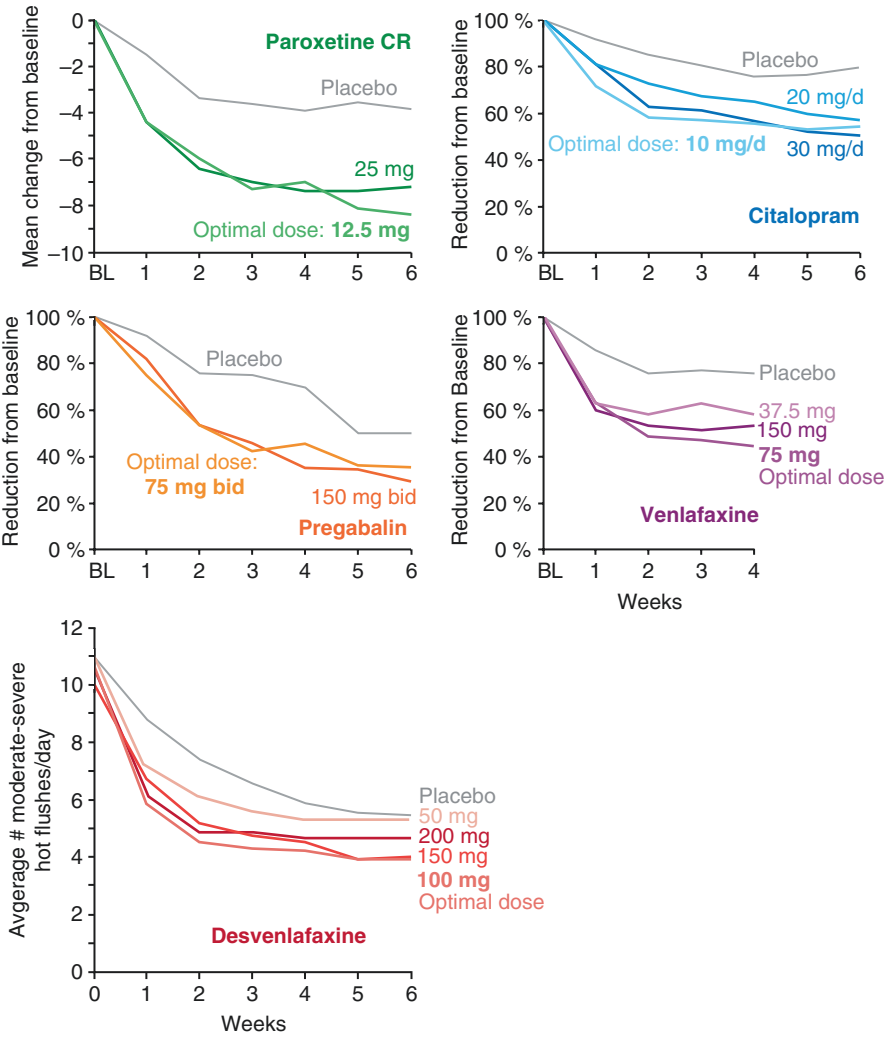

Fig. 3.4 Nonhormonal pharmacotherapies vs placebo – dose response for vasomotor symptom treatment. Paroxetine [57], citalopram [15], pregabalin [60], venlafaxine [18], and desvenlafaxine [18, 48, 59] dose-response curves. *Y-axis* vasomotor symptom frequency (paroxetine CR, desvenlafaxine) or % reduction (citalopram, pregabalin, venlafaxine), *X-axis* time in weeks (venlafaxine 4 weeks, all others 6-week data although some trials show data through 12 weeks)

lubrication in a single trial [52]. Most trials to date have evaluated libido and or pain as a single item in a checklist or as a component of a menopause quality-of-life scale [15, 35, 48]. Specifically, citalopram-treated women reported worsening scores for sexual relations and difficulty with orgasm and vaginal lubrication compared with placebo in a 6-week trial [15]. Among women taking desvenlafaxine, 5.3 % reported decreased libido as an adverse event compared with 1.3 % of women given placebo at 12 weeks [48]. Conversely, women taking gabapentin had greater improvement

Table 3.3 Nonhormonal pharmacotherapies: effects on sleep, sexual function, and quality of life

	Sleep	Sexual function	Quality of life
Paroxetine [52, 53, 57]	↑ [53]	– ASEX [53]	– Green climacteric [57]
Escitalopram [46, 49, 54]	↑ [46]	– FSFI [54]	↑ MENQOL [49]
Citalopram [15]	– [15]	↓ orgasm	↑ HFRDIS
Venlafaxine [49, 50, 55]	↑	– FSFI [50]	↑ MENQOL
Desvenlafaxine [48]	↑	–	↑ Green climacteric
Gabapentin [35, 51]	↑ [51]	↑* [35]	↑ MENQOL [35]

↑ improvement, ↓ worsened, – no change, * menopause-specific quality of life (MENQOL) sexual function domain

ASEX Arizona Sexual Experience Scale, *FSFI* Female Sexual Function Index, *HFRDIS* Hot Flash-Related Daily Interference Scale

in menopause-specific quality of life (MENQOL) sexual function domain scores than did women taking placebo [35].

Only three RCTs in midlife women with hot flashes have used validated sexual function measures, stronger data than single items from MENQOL, or adverse event reporting. Using the Arizona Sexual Experience Scale, sexual function in women taking paroxetine mesylate 7.5 mg was no different than sexual function in women taking placebo over 12 and 24 weeks [53]. There were no differences in the Female Sexual Function Index (FSFI) in a single RCT of women taking escitalopram compared with placebo [54]. Among women who reported being sexually active at baseline and who completed orgasm-related questions, changes in rates of anorgasmia were not observed. However, orgasmic function domain scores were reduced by at least one point, out of six points, in 33% of escitalopram-treated vs 15% of placebo-treated women (P=0.02) and by at least two points in 15% of escitalopram-treated vs 10% of placebo-treated women (P=0.39) at week 8. Scores in the lubrication domains differed after 8 weeks (p=0.02), but this statistical difference may have been driven by an increase in lubrication among women taking placebo. Among women given venlafaxine for VMS, decreased pain and increased lubrication were observed as compared with placebo, whereas women taking estrogen had a subtle increase in desire [52].

In summary, venlafaxine may be a good SNRI choice for women with mild to moderate hot flashes and dyspareunia, although additional studies are warranted before this recommendation can be fully endorsed. Similarly, paroxetine mesylate 7.5 mg, escitalopram, and gabapentin have not shown adverse effects on sexual function and may be excellent options for sexually active women unable to take hormonal therapy with mild to moderate VMS frequency and bother.

Weight Gain

Some SSRIs and GABAergic medications have been associated with weight gain when used for FDA-approved indications [53]. Relatively little data on long-term use of these medications for VMS exists, therefore potential weight gain is poorly studied in menopausal populations. However, weight gain in women taking paroxetine mesylate 7.5 mg was no different than weight gain in women taking placebo

over 24 weeks [53]. In a 12-week RCT of 707 postmenopausal women, weight gain was reported as an adverse event in up to 7.6 % of women who were treated with desvenlafaxine compared with 3.9 % of women who were given placebo [48]. The effect of gabapentin GR on weight over 24 weeks was not reported [51]. Pregabalin in other populations has a clear association with weight gain.

Quality of Life (QOL)

Only three RCTs evaluated nonhormonal pharmacotherapies for menopausal VMS and measured QOL with a validated instrument [35, 46, 51]. Escitalopram, venlafaxine, and gabapentin IR showed modest QOL improvements as measured by the MENQOL [35]. Escitalopram improved overall QOL score and was also significantly different from the placebo group in the vasomotor, psychosocial, and physical domains [46]. In the second RCT, low-dose oral estrogen improved all MENQOL domains except the psychosocial domain, whereas venlafaxine improved only the psychosocial domain, both estrogen and venlafaxine had overall MENQOL scores that were significantly different from placebo. Using the MENQOL, gabapentin demonstrated improved quality of life as compared with placebo at week 4 in the total score and in all domains, with the exception of the psychosocial domain [35].

Nonhormonal Therapy versus Hormonal Therapy Benefits

Relatively little data on long-term use of these medications for VMS exists. In general, the following conclusions regarding the use of nonhormonal pharmacotherapies for VMS, as compared with estrogen, can be made based on the existing limited evidence:

- Time to efficacy plateau for VMS with SSRI and gabapentin appears sooner than with estrogen.
- VMS efficacy appears lower than that observed for standard-dose estrogen formulations.
- Side effects of nonhormonal pharmacotherapy do not appear greater than those with hormonal therapy based on evidence of RCTs among midlife women with hot flashes.

Considerations and Special Warnings When Using Nonhoromonal Pharmacotherapy Considerations: Minimizing Side Effects and Special Warnings

Side effects from SSRIs/SNRIs and gabapentin for VMS are intolerable in only a very small group of women (<5 %).

Benefits must be balanced with potential side effects (Table 3.4). The following summary statements can guide therapeutic considerations.

Table 3.4 Effective nonhormonal therapies, doses, FDA-approved indications, and common side effects

	Dose (mg)	FDA-approved benefits, usually at higher doses	Common distinguishing side effect
Citalopram	10	Anxiety, depression	Drowsy, sweating, dizzy, sexual function
Clonidine	0.01 transdermal	Hypertension	Dizzy, drowsy, dry mouth, fainting
Desvenlafaxine	75–100	Anxiety, depression	Nausea, vomiting
Escitalopram	10–20	Anxiety, depression	Nausea, sweating, dizzy
Gabapentin IR	Up to 900/day, usually taken at night	Pain	Drowsy, unsteady, dizzy
Gabapentin GR	1800	Pain	Drowsy, unsteady, dizzy
Paroxetine	7.5 (mesylate), 12.5 (HCl)	Anxiety, depression	Nausea, fatigue, dizzy
Pregabalin	150	Fibromyalgia	Dizzy, cognition, drowsy, blurry vision, weight gain
Venlafaxine	75	Anxiety, depression	Headache, jittery, nausea, hypertension

Serotonergic Medications

- Majority of side effects are self-limiting and resolve in first 2–4 weeks.
- Higher rate of side effects are observed in depressed populations.
- Side effects vary from woman to woman.
- Timing of dosing may be relevant for some. If somnolence is experienced, dosing is better tolerated if taken at night; conversely, if activating, it is best to take in the morning.
- Close follow-up and encouragement are critical for ongoing adherence.
- A small percentage of women do not tolerate.
- Taper when discontinuing, especially venlafaxine and desvenlafaxine to avoid *serotonin withdrawal*.
- At the doses used for VMS, *serotonin syndrome*, due to elevated serotonin concentrations, is highly unlikely unless the patient is also taking a MAOI, another SSRI/SNRI, or a triptan.

GABAergic Medications

- Drowsiness and dizziness are noted in over 10 % of women.
- Side effects are dose related and vary woman to woman.
- Begin treatment with gabapentin IR at 300 mg nightly, slowly titrate up to 900–1200 nightly, and use lower doses during the day to minimize side effects.

- Pregabalin may cause weight gain.

Clonidine

- Orthostatic hypotension is often prohibitive.
- Evidence for efficacy is somewhat limited.

Comparable Cost Considerations

Nonhormonal therapies vary widely in their cost differences, and the cost for some nonhormonal pharmacotherapies is less than some hormonal preparations (Table 3.5) [55]. Newer nonhormonal pharmacotherapies for VMS, such as the FDA-approved paroxetine mesylate, are more expensive. Similar efficacy is suggested between the lower- and higher-cost medications. Choosing a higher-cost formulation at the outset of treatment is not recommended.

Tailoring Nonhormonal Pharmacotherapy to Your Patient's Needs

Hormonally Sensitive Cancer

Effective nonhormonal therapies are most important for women that cannot take hormones. Studies have shown equal efficacy of SSRIs and SNRIs in women with and without breast cancer [56]. Concern has been raised that women who are high metabolizers of CYP2D6 due to genetic polymorphisms should not take paroxetine or fluoxetine with tamoxifen (Table 3.6). Some SSRIs, like paroxetine and fluoxetine, are strong inhibitors of CYP2D6, the enzyme in the cytochrome p450 system responsible for tamoxifen metabolism. The pharmacologic action of tamoxifen may be due to its

Table 3.5 Cost (in USD) for nonhormonal pharmacotherapies

	Price per month[a]
Paroxetine mesylate	$165
Paroxetine HCl	$25
Escitalopram	$49
Citalopram	$34
Venlafaxine	$40
Desvenlafaxine	$180
Gabapentin IR	$29
Gabapentin GR	$443
Pregabalin	$336

[a]http://www.goodrx.com/ accessed Sept 1, 2014

Table 3.6 CYP2D6, SSRIs, tamoxifen, and *cytochrome p450 inhibition*

	No/low	Moderate	High
Paroxetine mesylate			X
Paroxetine HCl			X
Escitalopram		X	
Citalopram		X	
Venlafaxine	X		
Desvenlafaxine	X		

conversion to active metabolites that are more potent than tamoxifen itself, e.g., endotoxifen. Coadministration of paroxetine 10 mg/d with tamoxifen decreased plasma concentrations of endotoxifen by 64 % [57]. But it appears that despite this concern, CYP2D6 genotype does not predict clinical benefit with adjuvant tamoxifen therapy in postmenopausal breast cancer patients, in conjunction with or without SSRIs [21, 22]. Thus, in women who are already taking paroxetine and have benefit for VMS, sleep, mood, or quality of life, concomitant use of tamoxifen should be considered relatively safe [21, 22]. For women not already taking paroxetine and who are taking tamoxifen, there is a theoretical benefit of choosing gabapentin, venlafaxine, or escitalopram for VMS, sleep, mood, or quality of life, rather than an SSRI associated with the inhibition of tamoxifen metabolism in the setting of CYP2D6 polymorphism.

Genetic Risk for VTE

There are no specific guidelines for choosing one nonhormonal pharmacotherapy over another for women at genetic risk for venous thromboembolism. Clearly nonhormonal pharmacotherapies are safer choice than hormonal therapies for this group of women.

Osteoporosis

Studies in depressed populations have suggested that SSRIs may worsen osteoporosis and increase fractures [58]. Information is conflicting and study methodologies are variable. Controlling for confounding is challenging. For women with osteoporosis, consideration of a bisphosphonate with a nonhormonal VMS therapy is appropriate. Alternatively, recommending gabapentin as a first choice for treatment of VMS, sleep, or quality of life in women with osteoporosis may be an option, but fall risk must be considered.

Pain

Considerable benefit from gabapentin, pregabalin, and some SSRIs (e.g., venlafaxine) for pain has been well described in other populations. For women with fibromyalgia and pain syndromes, these nonhormonal pharmacotherapies can be of

considerable benefit and should be considered as first line in women with mild to moderate VMS. Caution should be used, however, as RCTs specifically evaluating their benefit among women with pain and VMS do not exist.

Hypertension, ADHD, Restless Legs Syndrome, and Opioid Dependence

For menopausal women with VMS and hypertension, ADHD, restless legs syndrome, or opioid dependence with dominant symptoms of anxiety, tremors, sweating, and increased heart rate, clonidine may be a good choice, but careful monitoring for orthostatic hypotension should occur. Trial data specific to women with VMS, hypertension, ADHD, restless legs syndrome, or opioid dependence are not available.

Summary

Counseling women regarding menopausal therapies should be evidence based and include information on nonhormonal pharmacotherapy options. It is important to stress that effective SSRI, SNRI, and GABAergic medication doses for VMS are typically lower than doses used for depression, anxiety, and pain; thus, tolerability among women with VMS appears greater than in populations with pain or mood disorders. Tailoring the medication to treat the totality of the menopausal symptom complex while simultaneously considering the medication risk profile may result in the choice of an SSRI, an SNRI, a gabapentin, a pregabalin, or a clonidine over traditional hormonal therapies:

- Paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, gabapentin, pregabalin, and clonidine are effective for decreasing hot flashes and, in many cases, improve quality of life and other menopausal symptoms in midlife women.
- The effect is modest, 50–60 % decrease from baseline or a decrease of approximately 1–3 hot flashes per day above placebo.
- SSRIs, SNRIs, and gabapentin are effective in women with and without breast cancer.
- The effect of SSRIs and SNRIs may be similar to low-dose oral estrogen (0.5 mg oral estradiol).
- Side effects of nonhormonal pharmacotherapies in some menopausal women will preclude their use, though in general these treatments are relatively well tolerated at low doses, particularly the SSRIs and SNRIs.
- SSRIs, SNRIs, and gabapentin can be associated with nausea, dizziness, headache, dry mouth, nervousness, constipation, somnolence, and sweating, but side effects are rare.
- Prior evidence suggested that women taking tamoxifen for the prevention of breast cancer recurrence should avoid potent CYP2D6 inhibitors such as paroxetine, but

this recommendation no longer appears valid; nonetheless, if an SSRI is being considered for a patient on tamoxifen, it would be safest to consider a low-potency SNRI (Table 3.6).

- Nonhormonal pharmacotherapy medication costs vary considerably.
- Tailor therapy – consider mood, sleep, pain, sexual function, weight gain, and individual quality-of-life goals.
- Nonhormonal pharmacotherapy studies for VMS have been conducted predominantly in white women, with the exception of escitalopram which demonstrated similar efficacy among white and black women.

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Pharmacotherapies for Menopause Management: Hormonal Options

4

JoAnn V. Pinkerton

Overview

Prior to the release of the initial findings of the Women's Health Initiative (WHI) in 2002, menopausal hormone therapy (MHT) was not only used to relieve hot flashes and night sweats but had widespread acceptance for the prevention of heart disease, osteoporosis, and Alzheimer's disease. Following the release of the initial results [1] from the estrogen/progestin arm of the trial (EPT-conjugated estrogen 0.625 mg/medroxyprogesterone 2.5 mg), sales of MHT products dropped precipitously, and women and providers were frightened to start or continue hormone therapy. Although the estrogen-only arm of the WHI trial (ET) released in 2004 [2] showed a reduction in breast cancer cases with conjugated estrogen 0.625 when used in hysterectomized women, fear of cardiovascular events remained a predominant deterrent against resurgent use of hormonal therapies. In 2007, *Rossouw* et al. [3] published the evaluation of the WHI with findings that MHT had differing effects depending on age and timing of initiation. Today, MHT remains the most effective treatment for vasomotor symptoms (VMS) [4] and other symptoms of the climacteric for postmenopausal women without contraindications (Table 4.1) [5]. We know now that benefits may exceed risks for the majority of symptomatic postmenopausal women who at the time of initiation of MHT are less than age 60 or less than 10 years since the onset of menopause and at low baseline risk for cardiovascular events [6]. In addition to timing and duration of therapy, there also appears to be differences in the risk/benefit profiles between different types of hormonal regimens, including formulation, dose, and route of administration [7–9]. Prior to initiating MHT, women should be screened

J.V. Pinkerton, MD, NCMP
Division Director Midlife Health, University of Virginia Health System,
PO Box 801104, Charlottesville, VA 22908, USA

The North American Menopause Society, Mayfield Heights, OH, USA
e-mail: jvp9u@virginia.edu

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Table 4.1 Relative contraindications to systemic menopausal hormone therapy [5]

Estrogen-sensitive cancer such as prior or current breast or endometrial cancer
Active liver disease or liver impairment
Active gallbladder disease for oral HT
Elevated risk of heart disease including hypertriglyceridemia
Venous thromboembolic disorders or thrombophilic disorders
Prior stroke or myocardial infarction
Undiagnosed vaginal bleeding
Untreated endometriosis
Enlarging leiomyomatous uterus
Pregnancy
Porphyria
Prior anaphylactic reaction or angioedema to ingredients in the product
Migraine with aura (oral)
Large liver cysts
Adverse effects and risks
Nausea
Bloating, fluid retention, possible weight gain
Mood changes – more common with progestogenic component
Breakthrough bleeding
Breast tenderness, increased breast density, breast cystic activity

for cardiovascular and breast cancer risk, and the most appropriate therapy should be recommended depending on benefit/risk profile, indications, and goals of therapy. Therapy should be individualized based on clinical issues including risk factors, treatment goals, and patient preference [7–9].

Approved Indications for Hormone Therapy

In the USA, MHT is approved by the Food and Drug Administration (FDA) for four indications for postmenopausal women: relief of moderate to severe menopausal vasomotor symptoms; hypoestrogenism due to hypogonadism, castration, or premature ovarian insufficiency; prevention of osteoporosis; and relief of vulvovaginal atrophy [10, 11].

Vasomotor Symptoms

Menopausal hormone therapy, whether estrogen alone in women with prior hysterectomy, estrogen combined with progestogen for women with a uterus, or the novel hormone therapy of conjugated estrogen combined with bazedoxifene (CEE/BZA),

has been shown in randomized clinical trials (RCTs) to provide relief of moderate to severe hot flashes associated with menopause, usually defined at more than seven hot flashes per day or 50 per week to meet FDA criteria. A meta-analysis [12] of VMS studies shows that hormone therapy on average provides relief 75% of the time compared to 50% for placebo, although this degree of improvement may depend on dose and route of administration. Very low doses of systemic MHT may not be as effective or may take longer for effectiveness to be realized [13].

Prevention of Osteoporosis

Menopausal hormone therapy has been shown to lower the risk of vertebral and hip fractures in postmenopausal women [14] and has been shown to prevent fractures in women without prior fracture [15]. Due to the options of nonhormonal therapies for bone loss, MHT is not commonly used as primary prevention of bone loss due to concerns of risks associated with long-term use of MHT. Women with premature or early surgical or natural menopause will in particular benefit from the bone-protective benefit of MHT [16]. Absolute risks based on results from the WHI trials indicate that 5 years of conventional or standard dose combined MHT reduced the incidence of hip fractures by about one case per 1000 women younger than 70 years and by about eight cases per 1000 women aged 70–79 years [1]. However, anti-fracture efficacy of MHT lasts only for the duration of treatment, and this protection is rapidly lost following discontinuation of MHT [17, 18].

Relief of Vulvovaginal Atrophy (VVA) (Part of Genitourinary Syndrome of Menopause (GSM))

Both topical and systemic MHT have been shown to improve the menopausal symptoms of vaginal dryness, superficial dyspareunia, and urinary frequency and urgency [19]. In the absence of other menopausal symptoms, topical/local estrogen therapy is the preferred approach for VVA if the symptoms are not relieved by nonhormonal, nonprescription remedies, e.g., lubricants and moisturizers, that are widely available over the counter. For those who can't tolerate vaginal products, there is now an oral selective estrogen receptor modulator (SERM), ospemifene, which is FDA-approved in the USA to treat moderate to severe vaginal atrophy due to menopause and improves other symptoms of VVA including vaginal dryness and urinary urgency [20].

Nontraditional MHT and Novel Hormone Therapies

Tibolone

Tibolone is considered a STEAR (selective tissue estrogenic activity regulator). Although widely used outside of the USA, including Europe, Asia, and Australasia, it has not been approved in the USA. It received a non-approvable letter from the US

Food and Drug Administration (FDA) in June 2006 for menopausal women, possibly due to the need for additional endometrial safety data. The metabolites of orally ingested tibolone have estrogenic, androgenic, and progestogenic effects [21]. Tibolone has been shown to prevent hot flashes, prevent bone loss, and prevent vaginal atrophy. The progesterone-like effects prevent endometrial thickening and bleeding, and thus there is no need for a progestogen. Tibolone has effects on lipids with lowered total LDL and HDL cholesterol and triglyceride levels but should not be used as primary prevention of heart disease. Tibolone has shown testosterone-like activity that appears to improve mood and libido, with variable sexual response [21, 22]. Tibolone has been shown to prevent bone loss and reduce spinal fractures [23] but has not been shown to prevent hip fractures. The Million Women Study [23] found an increased risk of breast cancer with tibolone, but other RTCs have not shown increases in breast cancer rates, and breast density is not increased [24, 25]. Tibolone is contraindicated in women with breast cancer. An increased risk of stroke [23] has been found in women over 60 years of age (four extra cases/1000 women under 60 and 13 extra cases/1000 women among women in 60s.

Tissue-Selective Estrogen Complex or TSEC

The only TSEC which is government approved in the USA consists of conjugated equine estrogen (CEE) combined with the selective estrogen receptor modulator, bazedoxifene (BZA). In the selective estrogen, menopause, and response to therapy (SMART) [26–34] randomized controlled trials, CEE/BZA showed fewer hot flashes (74 % compared to 51 % for placebo); prevention of bone loss, with improvement in night sweats, sleep disruptions, and total cholesterol; signs of VVA, with a neutral effect on the breast and uterus, specifically rates of breast tenderness, breast density changes, and breast cancer; and amenorrhea similar to placebo. The major benefit for women with a uterus is the lack of significant breast tenderness or vaginal bleeding.

General Principles Guiding Systemic Menopausal Hormone Therapies

Systemic MHT can be prescribed as oral pills, transdermal patches, gels and lotions, and a vaginal ring. The following are some general principles that guide systemic MHT prescribing and utilization. Estrogen can be used unopposed for women who have had a hysterectomy.

- In women with an intact uterus who are taking estrogen, a progestogen (synthetic progestins or micronized progesterone) is necessary to reduce the risk of endometrial cancer [35]. Progestogens can be added sequentially for 10–14 days each month or used daily in a continuous combined regimen with estrogen [35]. Novel methods include use of intermittent progestogen therapy or use of levonorgestrel intrauterine device [36].

- Few hormonal therapies, e.g., tibolone and the novel TSEC-conjugated estrogen combined with the BZA, do not require adjuvant progestogen use in the non-hysterectomized women.
- Transdermal estrogen therapies are preferred for women with mild cardiovascular risk (e.g., those who are overweight to obese, have existing hypertension, have hyperlipidemia, and are diabetic) [37].
- Low doses of oral and transdermal MHT are effective against VMS and are associated with lower risks of venous thromboembolism (VTE) and stroke compared with conventional doses [38–40].

Effect of Menopausal Hormone Therapy on Other Target Organs

Coronary Heart Disease (CHD) and Stroke

RCTs, observational data, and meta-analyses suggest that estrogen-alone MHT may decrease the risk of myocardial infarction and all-cause mortality when initiated in women who are less than age 60 or under 10 years from menopause. This had led to a timing hypothesis, wherein MHT has benefits on the heart when given close to menopause but risks when initiated further from menopause.

In the WHI hormone trials which evaluated MHT for its role in prevention of chronic disease, women who have had a hysterectomy and were under age 60 and/or within 10 years of menopause, reduced incidences of myocardial infarction, composite CHD end points, coronary artery calcification, and all-cause mortality were seen in ET (CEE 0.625) (ref). However, RCTs of EPT (CEE 0.625 mg/MPA 0.25 mg) for women less than 60 years of age or within 10 years of menopause show less consistent results for CHD risk than the ET trials [6].

A recent, randomized, controlled clinical trial – the Kronos Early Estrogen Prevention Study (KEEPS) [41] – evaluated effects of estrogen use (oral CEE 0.45 and transdermal estradiol 0.5) compared to placebo on surrogate markers for cardiovascular disease in younger postmenopausal women within 3 years of onset of menopause and again found no significant association between MHT and cardiovascular benefit.

In keeping with the postulated timing hypothesis, for women in WHI who initiated MHT when aged 60 years and older or more than 10 years from menopause, both ET and EPT increased CHD risk. In the ELITE trial, oral estradiol therapy was associated with less progression of subclinical atherosclerosis (CIMT) than was placebo when therapy was initiated within 6 years after menopause but not with initiation 10 or more years from menopause [42].

In the WHI, the risk of stroke increased significantly with both EPT and ET for increases in ischemic but not hemorrhagic stroke, but the attributable risk for women who initiated HT under age 60 within 10 years of menopause was rare (5 out of 10,000 women per year for EPT and minus one for ET) [Manson 2013]. In Nurses' health study conventional dose HT was associated with an increased risk of stroke, again with a lower risk in younger women [43].

Diabetes Mellitus Type 2 diabetes is reduced in postmenopausal women who receive MHT compared with placebo. Insulin sensitivity is a key determinant of diabetes risk and cardiometabolic health. Studies suggest that estradiol directly impacts insulin action with reduction in new onset type 2 diabetes mellitus when given close to menopause [44].

Venous Thromboembolic Risk (VTE)

RCTs and observational studies have shown that postmenopausal hormone therapy use increases the risk of VTE [45], particularly within the first year of use with a doubling of the risk. For healthy menopausal women under 60 and within 10 years of menopause, however, the absolute risk of VTE is low even with oral hormone therapy. Risk is increased (Table 4.2) as women age or if they have other risk factors such as obesity, bedridden, having major surgery or prolonged air travel [45]. Thus discontinuation of HT in advance of major surgery and staying hydrated, moving around, and potentially taking an aspirin during long travel may be suggested to potentially decrease risk.

Oral HT (ET and EPT) increases risk of DVT and PE in women initiating HT regardless of age or time since menopause. The increase in VTE risk in WHI was demonstrated early (highest risks during first 2 years for ET and during 1 year in the EPT trial) [6].

Across studies in the literature, observational and meta-analysis suggest that transdermal preparations, whether estrogen alone or estrogen combined with a progestogen, have substantially lower risk of VTE and possibly stroke than oral, but there are no RCTs of head-to-head comparisons. Evidence from the French E3N study and the Million Women Study [46] suggests that progestogens may play a role in VTE risk [47] although lacking RCT or head-to-head trials.

Cognition and Mood

The memory sub-study of the WHI [48, 49] showed that older women (over age 65) taking combination hormone therapy (CEE 0.625/MPA 2.5 mg) had twice the rate of dementia, including Alzheimer's disease, compared with women who did not.

Table 4.2 Risk factors for venous thromboembolism

Increasing age
Obesity (body mass index >30)
Previous VTE
Post-thrombotic syndrome
Varicose veins with phlebitis
First-degree family history of VTE
Immobility for more than 3 days
Surgical procedures (anesthesia and surgical time >60 min)
Other disorders, e.g., malignancy, myeloproliferative disorders, cardiac disease, paralysis of lower limbs, systemic infection, inflammatory bowel disease, nephritic syndrome, sickle cell disease

This risk was increased in women who already had relatively low cognitive function at the start of treatment, a finding also seen in the WEST trial of women with prior stroke. There is no definite evidence that supports the use of HT to prevent or improve cognitive deterioration although observational studies such as CASHE provide suggestive evidence of a protective effect when HT is begun close to menopause when neurons are healthy.

HT has been shown to improve mood in early postmenopausal women with depression or anxiety and possibly may improve mood in perimenopausal depressed women. However, HT is not a treatment for depression, and antidepressant therapy is recommended when treatment for depression is needed [9].

Premature Menopause

Observational data suggests that women with natural, surgical, or induced menopause before age 40–45 may have increased risk for CHD, osteoporosis, mood changes, dementia, and Parkinson's disease. HT has been shown to reduce VMS and maintain bone density, and the use of HT until the average age of menopause may reduce these risks [50].

Breast Cancer

Decreased risk was seen in the WHI for estrogen alone (CEE 0.625) with possible increased rare risk with EPT (CEE 0.625/MPA 2.5 mg) which may be related in part to the use of the progestin (MPA in WHI) and may be related to duration of use. The risk of breast cancer with EPT in WHI was considered rare, with an incidence of <1.0 per 1000 women per year of use which is similar to the risks seen with being sedentary and obese or with alcohol consumption [6].

Endometrial Cancer

Progestogen therapy is needed for women with a uterus taking systemic ET to protect against endometrial neoplasm [9]. The exception is that the combination of CEE/BZA provides uterine protection without the need for a progestogen, and tibolone has progestational activity such that it does not require a progestogen.

Other Benefits

Sleep, quality of life, sexual function, and joint and muscle pains [9] may improve with systemic hormone therapy although type of hormone, formulation, and dose may affect these.

MHT reduces new onset type 2 diabetes mellitus (T2DM) but is not approved to prevent diabetes [51]. Both aging and menopause have been tied to the increasing incidence of type 2 diabetes mellitus, but the use of hormone therapy has been shown in WHI to have a decreased incidence of type 2 diabetes.

Duration of Hormonal Therapy

Longer duration of use appears more favorable for ET than EPT, with fewer breast cancers seen at 7 years compared to placebo in the estrogen-only arm of the WHI. Extended duration beyond age 60 or 65 may be considered [52] for persistent recurrent VMS or prevention of bone loss and fracture in selected women after appropriate and ongoing counseling about unclear risk and benefits of extended use.

Unregulated Compounded Bioidentical Menopausal Hormone Formulations and Their Uses

The ACOG, Endocrine Society, NAMS, EMAS, and IMS do *not* recommend custom-compounded bioidentical HT (CBHT). Unique concerns of compounding include the lack of approval by any regulatory agency; the lack of safety and efficacy data; no formal testing; the absence of regulatory oversight in manufacturing; concerns about quality, purity, and batch-to-batch consistency; and, oftentimes, a false sense of an improved safety profile [53].

Patient-Tailored Management: Examples of Application of an Evidence-Based Approach

Case 1: Surgical Menopause

A 40-year-old Caucasian female with surgical menopause with hysterectomy and bilateral salpingo-oophorectomy due to family history of ovarian cancer and large leiomyomatous uterus. She initially did not want to take MHT and began a low-dose selective serotonin reuptake inhibitor (SSRI) but has continued to have bothersome hot flashes at a frequency of 7–10 per day, as well as frequent awakening with night sweats.

Best option for her at this time based on literature of risks of early surgical menopause includes:

(a) Add gabapentin at night to her low-dose antidepressant.
(b) Raise the dose of her antidepressant to conventional dosing for depression.
(c) Start her on estrogen only therapy.

(d) Recommend tibolone.
(e) Start her on a conventional dose estrogen and progestogen therapy.

Correct answer is c.

Discussion
Early surgical or natural menopause has been associated with increased health risks in observational studies including increased risk of heart disease, bone loss, depression, Parkinson's, and cognitive change [50] with some evidence that hormone therapy continued to age of menopause will provide protection against these increased health risks. Based on her lack of a uterus, she has no need of a progestogen to provide endometrial protection. She is a great candidate for estrogen-only hormone therapy with dosing adjusted to provide relief of her menopausal symptoms and provide protection against bone loss.

Case 2: Symptomatic at Menopause

A 53-year-old Caucasian female, LMP 12 months ago, with frequent bothersome night sweats and difficulty concentrating who is otherwise healthy and a nonsmoker, BMI 28kg/m2. She exercises regularly. There is no family history of breast cancer but her mother fractured her hip at age 74. She is a candidate for all of the following *except*:

(a) Estrogen therapy combined with a progestogen
(b) Estrogen alone
(c) Tibolone
(d) Conjugated estrogen combined with bazedoxifene
(e) Systemic vaginal estrogen ring combined with a progesterone

Correct answer is b.

Discussion
This is a symptomatic menopausal woman who meets the criteria for FDA-approved indication of hormone therapy to relieve hot flashes and prevent bone loss. She is recently menopausal, under age 60, and within 10 years of menopause. Thus the reanalysis of data from the WHI suggests she can use the estrogen treatments suggested above except for estrogen alone as she has a uterus and requires endometrial protection when taking estrogen. The options above which could be discussed, depending on availability, include systemic estrogen (oral, transdermal, or vaginal dosing) combined with progestogen therapy, conjugated estrogen combined with bazedoxifene, and tibolone, with benefits and risks discussed and with annual reevaluation. In addition to different types of estrogen,

there are differences between synthetic progestins and micronized progesterone with less negative effects on lipids, breast density, and mood seen with micronized progesterone. Daily continuous therapy or intermittent therapy with progestogens is recommended with limited long-term safety data on long-cycle use of intermittent progestogen therapy. The levonorgestrel intrauterine device has been shown to provide endometrial protection with less systemic effects [36].

Case 3: Symptomatic, Further from Menopause

A 58-year-old Asian female who underwent a hysterectomy for fibroids started estrogen-only therapy for bothersome VMS 5 years ago. She has had improvement but not complete resolution of her hot flashes, night sweats, and sleep disruption. Bone mineral density shows evidence of osteopenia with BMD T-scores of −1.5 at her lumbar spine and −1.2 at her hips. She comes in for discussion about whether to continue MHT.

(a) She has been on MHT for 5 years; therefore, she should discontinue it due to increased risks seen in WHI.
(b) She has been on estrogen-only hormone therapy for 5 years and has evidence-based reasons to continue her HT including persistent VMS and osteopenia.
(c) She has been on hormone therapy for 5 years and should have a progestogen added to her regimen to protect against breast cancer.
(d) She should switch to a low-dose antidepressant therapy to treat her persistent VMS.
(e) She should switch to an oral bisphosphonate to prevent further bone loss.

Correct answer is b.

Discussion
There is no time limit for appropriate duration of MHT. Although 3–5 years has been suggested for the use of EPT following the initial release of the WHI, this particular woman has had a hysterectomy, and estrogen-alone therapy has been shown to be safer for longer duration including the reduction of breast cancer seen at 7 years of use in WHI ET arm [6]. She is using MHT (ET) for relief of VMS and prevention of bone loss, both indicated reasons for MHT, and she is under age 60 and within 10 years of menopause. Thus, she could continue her estrogen therapy, potentially at a lower dose, or switch to transdermal therapy over time. Although low-dose antidepressants may treat hot flashes and oral bisphosphonates are approved to prevent bone loss, there is no need to add these to her estrogen therapy or switch at this point.

Case 4: Request to Initiate MHT over Age 60 and More Than 10 Years from Menopause

A 65-year-old African-American female, menopausal since age 52, presents with persistent VMS that began about 2 years ago, which disturb her sleep. She has tried nonhormonal over-the-counter formulations without much effect and requests to start systemic hormone therapy for relief of her VMS. She has never taken HT. Her BMI is 32kg/m2; her waist circumference is 90 cm. She takes medication to treat her hypertension. Family history is remarkable for a mother with a stroke at age 63 and a brother with type 2 diabetes. You:

(a) After discussing benefits and risks, start her on systemic standard dose MHT to relieve her VMS and sleep disturbance.
(b) Counsel her that she may be at higher risk of CHD and stroke if she begins hormone therapy due to her risk factors, age of over 60 and more than 10 years since menopause.
(c) Recommend that she avoid nonhormonal pharmaceutical options such as low-dose antidepressants or gabapentin due to her need for treatment of her hypertension.
(d) After discussing benefits and risks, start her on standard dose vaginal estrogen ring to avoid liver effects and add an oral progestogen to protect the endometrial lining.

Correct answer is b.

Discussion
In the SWAN study [54], ethnic differences were identified and included shorter duration of VMS for Asian women of 5 years on average and Caucasian women with 7 years on average, but African-Americans continued to have VMS on an average of 10 years. However, the WHI showed increased risk of heart disease, dementia, stroke, and blood clots, and overall mortality for women as they aged [6]. For this patient to initiate MHT therapy over age 60 and more than 10 years from menopause may increase those risks regardless of type of therapy. Although non-oral therapies might be safer, there are no RCT data confirming this. She would be a candidate to try nonhormonal therapies such as low-dose antidepressant therapy or gabapentin (used off-label).

Case 5: Symptomatic VMS with Breast and Bleeding Concerns

A 53-year-old Hispanic female comes to see you for bothersome menopausal symptoms including hot flashes, night sweats, and sleep disruption. Her mother had a fractured hip at 82, and her sister has just been diagnosed at 70 with an early estrogen-sensitive breast cancer. She had problems during the perimenopause with

heavy bleeding and significant premenstrual breast tenderness. She is interested in hormone therapy but concerned about risks and side effects of bleeding and breast tenderness. Which might be the best option for her?

(a) Systemic hormone therapy with oral estrogen and progestogen will relieve her symptoms but is associated with both bleeding and breast tenderness.
(b) TSEC CEE/BZA will relieve her menopausal symptoms and prevent bone loss without increased bleeding or breast tenderness.
(c) Systemic transdermal hormone therapy at lower doses appears to have less risk of VTE than standard dose oral hormone therapy.
(d) Systemic hormone therapy will not only relieve her hot flashes but also prevent bone loss and improve vaginal dryness.

Correct answer is b.

Discussion
Although systemic oral or transdermal MHT will relieve her symptoms, prevent bone loss, and improve vaginal dryness, she might be an excellent candidate for the combination of conjugated estrogen and bazedoxifene since that product has shown that it relieves hot flashes and prevents bone loss with bleeding and breast tenderness effects similar to placebo unlike traditional convention dose EPT therapy which is associated with both bleeding and breast tenderness [29].

Case 6: Unregulated Compounded Bioidentical Hormone Therapy (CBHT)

A 65-year-old WF requests a second opinion on her current treatment with compounded non government approved hormone therapy. She provides limited information on the product being used but tells you she had breast cancer treated 10 years ago. Two years after her breast cancer, her homeopathic doctor started her on Triest (CBHT cream with estradiol, estrone, and estriol) and told her that this combination of "natural hormones" will prevent recurrent breast cancer. Which of the following would be helpful in her case?

(a) Obtain the pathology from her original breast cancer to determine stage, size, presence of lymph nodes, and whether it was estrogen sensitive.
(b) Confirm that Triest is safer and more effective for her than FDA-approved therapy.
(c) Discuss nonhormonal pharmaceutical and alternative therapies to hormone therapy.

(d) Discuss the lack of scientific evidence regarding safety and efficacy of CBHT and the unique risks of compounded HT including over- or under-dosing, the presence of contaminants, and lack of label-detailing risks.
(e) Recommend continuing systemic HT since she is doing well, but switch her to a standard dose FDA-approved systemic therapy.

a, c, and d are correct answers.

Discussion

This case raises many issues. The first is the concern that she is using systemic HT after breast cancer which is generally not recommended. Obtaining pathology from her original breast cancer in this case was helpful because she had a 4-cm, estrogen-sensitive, node-positive breast cancer which would be considered a contraindication to systemic HT, regardless of whether it was government-approved MHT or CBHT.

If she had bothersome menopausal symptoms after discontinuing her CBHT, consideration could be given to use of low-dose antidepressants or gabapentin.

Vaginal estrogen therapy might be considered, in consultation with her oncologist, if over-the-counter moisturizers and lubricants were unsuccessful at treating vaginal atrophy symptoms or painful intercourse as low-dose vaginal estrogens provide physiologic levels within postmenopausal hormone levels.

For women other than this particular case who request bioidentical MHT (BHT), the recommendation would be for a regulated and government-approved MHT formulation. She has a uterus, so this would include an estrogen (oral or transdermal estradiol) as well as protection against endometrial cancer with a systemic progestogen (such as bioidentical micronized progesterone). Dosing often starts with lowest effective dose, which might be a 0.025 estradiol patch with 100 mg of oral micronized progesterone taken continuously or cyclically on the last 14 days of cycle. Salivary testing is not recommended as there is both intra- and inter-patient variability and lack of correlation with tissue target levels [53]. Patient preference should not drive the decision to use unregulated CBHT. Instead the discussion should include concerns about the lack of government approval or monitoring, potential for over- or under-dosing, potential for contaminants, and lack of scientific data about efficacy or side effects.

Summary

An ideal MHT regimen for a woman with moderate or severe VMS should offer symptom relief (hot flashes, night sweats, and sleep disruption), prevent bone loss associated with declining estrogen levels, and improve symptoms related to

vulvovaginal atrophy while being neutral on the breast and protective against risk of endometrial cancer. Additional benefits could include prevention of heart disease, prevention of cognitive decline, and improvement in mood and quality of life while avoiding an increased risk of VTE and stroke. To date, this ideal therapy has not been found, although with the novel TSEC wherein CEE is paired with bazedoxifene, perhaps we are one step closer to the "ideal" hormonal formulation for menopause management.

Clinical Pearls: Which Women Should Use Hormone Therapy and Which Women Should Not Use HT

- Hormone therapy should be offered to women for an evidence-based indication, particularly relief of hot flashes and night sweats in the context of discussing menopausal hormonal changes and in conjunction with appropriate lifestyle modifications. Discussion should include shared decision-making and cover the spectrum of MHT-related benefits as well as risks individualized to the patient's unique profile [9].
- Hormone therapy should NOT be offered to asymptomatic menopausal women solely for the prevention of chronic diseases such as CHD or Alzheimer's disease [6].
- Best available evidence should be used to make treatment decision as the risks of MHT differ depending on the type, dose, duration, and route of administration of MHT, on the timing of initiation relative to age and the last menstrual period and whether a progestogen is needed for endometrial protection, and on the patient's unique risk profile (based on her personal, medical, and family histories). The choice of MHT regimen should be tailored to an individual woman's needs as well as her unique risk profile to ensure that the potential for benefit outweighs that for harm [56].
- Women with early menopause whether surgical or natural are considered candidates for treatment to at least the average age of menopause (age 51) to prevent the increased risks seen in observational studies of heart disease, bone loss, dementia, Parkinson's, and mood changes [50].
- In women with a hysterectomy who are started on estrogen only, there is a null or reduced risk of breast cancer up to 7 years [6], although longer durations of 20 years have shown increased risk.
- In women with a uterus who are started on estrogen and progestogen, a rare increased risk of breast cancer was seen in the WHI with CEE 0.625/MPA 2.5 mg continuous daily use [6].
- For women with a uterus started on conjugated estrogen 0.45 mg/20 mg of bazedoxifene, bleeding, breast tenderness, and breast density were similar to placebo at 2 years with relief of hot flashes and prevention of bone loss [29].
- Compounded, nonregulated bioidentical HT is not recommended due to concerns about over- or under-dosing, the lack of rigorous scientific efficacy and safety studies, and the lack of appropriate labeling about risks [53].

- Hormone therapy does not increase the risk of cardiovascular disease when initiated in younger women under 60 years or within 10 years of menopause [6].
- Longer duration of use appears more favorable for ET than EPT with fewer breast cancers seen at 7 years compared to placebo in the estrogen-only arm of the WHI [6].
- The benefit/risk ratio appears less favorable for women who initiate HT more than 10 years from menopause or after age 60 where increased absolute risks are seen for CHD, VTE, stroke, and dementia [6].
- Women who start HT should be educated about the risk of VTE signs and symptoms (painful swollen leg, difficulty breathing if clot goes to the lung). Women with prior VTE or at high risk should consider alternatives to HT. The absolute risk of VTE and stroke is lower in women under age 60 and may be lower with lower-dose transdermal products, but RCT data are lacking.
- For women on HT, continued surveillance with periodic reevaluation and discussion about benefits and risks of continuing or discontinuing MHT should be part of an annual visit.
- Extended duration beyond age 60 or 65 may be considered for persistent recurrent VMS or prevention of bone loss and fracture in selected women after appropriate and ongoing counseling about unclear risk and benefits of extended use [52].
- For bothersome vulvovaginal atrophy (GSM) that is not relieved with OTC therapies, low-dose vaginal ET is recommended as first-line therapy. Ospemifene, a SERM, is an oral alternative that is approved to relieve moderate to severe VVA.
- For those interested in using an algorithm to help determine appropriate candidates for HT and for whom HT is not recommended, please see the NAMS MenoPro mobile app [55], available to be downloaded for free to a mobile phone or tablet with two modes, one for clinicians and one for patients. This app was developed to help personalize decision-making about HT and includes risk stratification and the woman's personal preferences.

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5 Management of Menopause and Perimenopause: Integrative Medicine in Support of Wellness

Katherine Gergen Barnett, Marcia Klein-Patel, and Judith Balk

Introduction

Since antiquity, menopause has been a marker of transition in a woman's life. Despite all of the changes that have occurred in modernity, the age that menopause occurs has shifted very little. The median age at menopause among women from industrialized countries ranges between 50 and 52 years [27], and while there is slight evidence of increasing age at menopause over time and global variations [17], our mothers, grandmothers, and great grandmothers generally hit menopause at this same time in their lives. What is different today, however, is that women are often living another 30 years (greater than one-third of their lives) after they transition to menopause. While it is well known that there are many bothersome symptoms that women may experience during the perimenopausal and menopausal stages of their lives, this time can also be an enormous opportunity and invitation to wellness for women.

Integrative medicine offers some options for women to both mitigate the bothersome symptoms of menopause and support their wellness as they journey through this phase of life. Integrative medicine, as defined by *The Academic Consortium for Integrative Medicine and Health*, "reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic and lifestyle approaches, healthcare professionals and disciplines to achieve optimal health and healing." Though

K.G. Barnett, MD (✉)
Department of Family Medicine, Boston University Medical Center, Boston, MA, USA
e-mail: Katherine.Gergen-Barnett@bmc.org

M. Klein-Patel, MD, PhD
Department of OB/GYN, Allegheny Health Network, Pittsburgh, PA, USA

J. Balk, MD, MPH
Temple University School of Medicine, Philadelphia, PA, USA

Allegheny Health Network, Pittsburgh, PA, USA

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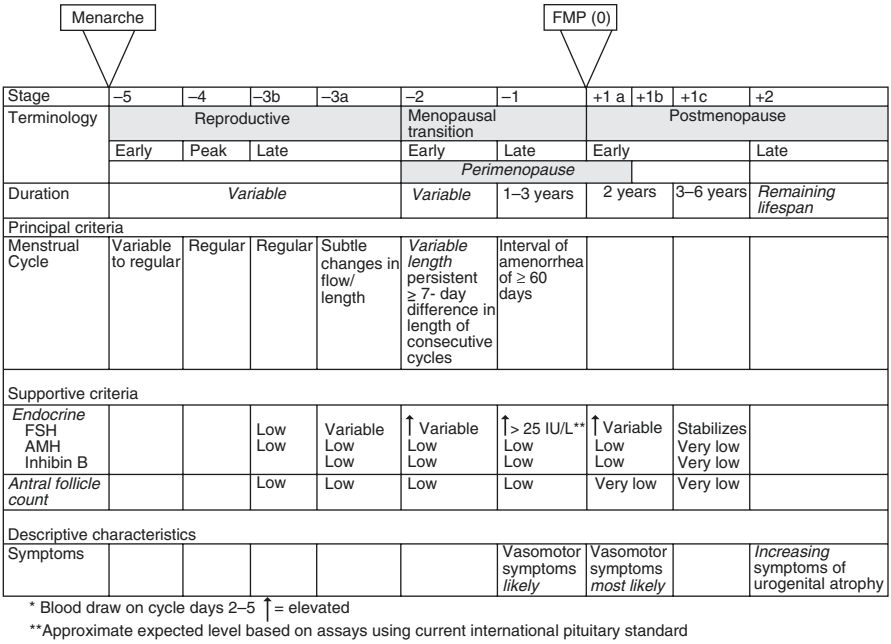
rooted in ancient healing practices such as traditional Chinese medicine (TCM), the field of integrative medicine also incorporates evidence-based approaches from modern medicine and is recognized by academic health institutes and large research bodies, nationally and internationally. The aim of integrative medicine is not always to fix, but rather to heal, and though it will use pharmaceutical intervention when needed, practitioners of integrative medicine also look toward lifestyle interventions, such as nutrition and stress reduction, to bring wellness to an individual. This chapter will focus mostly on integrative medicine modalities to ameliorate vasomotor (VMS) and other menopausal symptoms and on the basic strategies for supporting women's wellness during this rich, reflective time in their lives. At the risk of being repetitive, this chapter also includes a brief overview of female reproductive aging, the pathophysiology and impact of hot flushes, and select nonhormonal pharmacotherapies used in the management of VMS. Hormonal therapies have been addressed at length in other chapters and will not be discussed.

The Hormonal Shifts in Perimenopause and Menopause

While there has long been nomenclature to define a woman's transition from regular menstruation to the more irregular (perimenopause) and ultimately cessation of menstruation (menopause), there has been much study over the last decade to clarify the exact physiology in each of these stages as well as work on further characterizing each of these transitions. In 2001, the first group of scientists came together to apply some of this knowledge toward menopause and created a set of standards called Stages of Reproductive Aging Workshop (STRAW), and this had been considered the gold standard for the characterization of reproductive aging through menopause. In 2011, scientists from five different countries and a variety of backgrounds gathered to review data from a cohort of midlife women and evaluated changes in menstrual, endocrine, and ovarian markers of reproductive aging including anti-Mullerian hormone (AMH), inhibin B, follicle-stimulating hormone (FSH), and antral follicle count (AFC) [18]. STRAW-10, as this summit was called, was important as it helped stratify perimenopause and menopause into seven discrete categories. The STRAW-10 staging, though granular in its definition of each stage, was developed to promote the ability of future researchers and clinicians to determine exactly where a woman may be in her menstrual arc, as well as the sequelae at each stage. The hormonal shifts in each of these stages also bear clinical significance for the rest of the health and wellness of a woman (Fig. 5.1).

Vasomotor Symptoms and Other Impactful Issues Related to Menopause

Declining and variable production of estrogen during the menopausal transition (stages −2 to +1 in STRAW-10) is associated with many of the first, most bothersome, and most frequent symptoms of the menopausal transition: hot flushes and



Stage	–5	–4	–3b	–3a	–2	–1	+1 a	+1b	+1c	+2
Terminology	Reproductive				Menopausal transition		Postmenopause			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*Variable*				*Variable*	1–3 years	2 years		3–6 years	*Remaining lifespan*
Principal criteria										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in flow/ length	*Variable length* persistent ≥ 7- day difference in length of consecutive cycles	Interval of amenorrhea of ≥ 60 days				
Supportive criteria										
Endocrine FSH AMH Inhibin B			Low Low	Variable Low Low	↑ Variable Low Low	↑> 25 IU/L** Low Low	↑ Variable Low Low	Stabilizes Very low Very low		
Antral follicle count			Low	Low	Low	Low	Very low	Very low		
Descriptive characteristics										
Symptoms						Vasomotor symptoms *likely*	Vasomotor symptoms *most likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2–5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard

Fig. 5.1 STRAW stages of reproduction

night sweats. These symptoms are a consequence of unexpected, episodic, and sudden peripheral vasodilation with increased blood flow to the chest, face, and neck resulting in profuse sweating, heart palpitations, anxiety, and flushing. These symptoms can last anywhere from 1 to 5 min and can occur at night. Such symptoms, when frequent, may disrupt sleep patterns, which if sustained can lead to downstream consequences such as chronic fatigue, sexual dysfunction, and even depression [11]. According to findings from the Study of Women's Health Across the Nation (SWAN), which assessed menopausal symptoms in 14,906 ethnically diverse women aged 40–55 years residing in the United States, while vasomotor menopausal symptoms (VMS) vary greatly in their frequency and intensity among menopausal women, symptoms typically are most debilitating for 1–2 years, but for some women symptoms may persist for as long as 14 years [18]. Risk factors for VMS include obesity, smoking, depression/anxiety, and low socioeconomic status, in addition to ethnic and genetic factors [31]. Additionally, there is research to show variations of VMS among women of different ethnicities and race: African American women were most likely to report vasomotor symptoms, while Asian women (Japanese and Chinese) were the least likely to report them [31].

With the sustained hypoestrogenic state that characterizes menopause, the severity and frequency of vasomotor symptom will relent in most women, but additional symptoms may develop. These include vaginal dryness, vaginal atrophy, and recurrent urinary tract infections that cause physical discomfort. In addition, weight gain, skin dryness, and facial wrinkles may accelerate and impair one's self image.

Finally, accelerated bone loss and progression of subclinical atherosclerosis associated with hypoestrogenic states can increase the risk of osteoporotic fractures and heart disease with even greater impact on life's quality and quantity.

Reducing Symptoms: Treatment Options for Women

Supporting a woman's journey through perimenopause and menopause and working to mitigate the bothersome symptoms are integral to our role as medical providers. Equally important is our ability to discern patterns when symptoms are most troublesome and determine whether any other disease process could be causing or amplifying her symptoms. It is also our role to know about and provide patients with the full spectrum of treatment options, including hormonal and nonhormonal pharmacotherapies, and integrative approaches. Each encounter should thus be viewed as an opportunity to gain insight and knowledge into a woman's menopausal transition, evaluate her symptom burden and their impact on well-being and quality of life, and assess the personal psychosocial circumstances in which those symptoms are occurring. Understanding her desire for a particular therapy along with her expectations, reservations, and fears about such therapy is also crucial to the optimal selection of an appropriate intervention.

Nonhormonal Pharmacotherapies for Menopausal Hot Flushes

Although they are generally considered less effective than hormonal therapies, a number of nonhormonal therapies for vasomotor symptoms have been in clinical use for some time now. While their efficacy has been proven in clinical trials, it is important to note some of the important limitations of hot flush trials. The most significant is the high placebo response rate in hot flush therapy, with placebo improvement rates reported to be as high as 50 % (Boekhout). Large clinical trials are therefore needed to obtain adequate study power, yet most of the trials on nonhormonal therapies have been relatively small. Secondly, the hot flush diary commonly used to assess hot flushes in clinical trials is mostly subjective and influenced by recall bias, which limits accurate and reliable data capture [28].

One should never forget as well that all pharmacotherapies, including vitamins and supplements, have risks and side effects. It is important therefore for a woman to decide which of those are acceptable in return for a reduction of her vasomotor symptoms. Once a therapy is chosen after a careful, mindful, and individualized analysis, we find it useful to see patients every 6–8 weeks to confirm that treatment goals are being met, to rule out adverse effects, and to make sure the patient is content with her choice of therapy. For all therapies, we discuss the expected 2–3 year duration of treatment and recommend drug-free "holidays" every 6 months to determine whether continued therapy is necessary. We empower women to decide for themselves on the timing of the weaning trials and inform them of the 50 % chance

of recurrent symptoms. For some this would necessitate a return to therapy, while for others the symptoms may have become more manageable, and they may consider other approaches. Some of the most commonly used nonhormonal therapies for hot flushes are discussed next.

Selective Serotonin Reuptake Inhibitors/Selective Norepinephrine Reuptake Inhibitors

For those patients troubled by hot flushes in whom estrogen-containing therapy is not an option, either because of a contraindication, unjustifiable risk, or personal preference, consideration should be given to selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs). While their mechanism of action is not completely understood, they are believed to exert their beneficial effects centrally by restoring the balance of neurotransmitters which regulate the hypothalamic thermoregulatory zone, a balance that is often disrupted by declining estrogen levels [25]. Given that SSRIs and SNRIs are useful for management of anxiety and depressive disorders, they are particularly useful in the patient with VMS who also endorses mood changes during the transition. SSRIs that have been studied for VMS management include paroxetine, fluoxetine, citalopram, and sertraline, and they are all generally well tolerated though with some known possible side effects including weight gain and decreased libido, difficulty reaching orgasm, decreased energy, and headaches (http://www.drugwatch.com/ssri/). Table 5.1 shows the effect and dose of various SSRIs and SNRIs that have been studied for minimizing hot flushes [34]. For patients with a history of breast cancer who are on tamoxifen, SNRIs are preferred, as they do not increase the CYP2D6 system [4, 10]. Both venlafaxine (35.5–75 mg/day) and desvenlafaxine (100 mg/day) have been proven useful [10, 25, 32, 36].

Currently, however, the only FDA-approved SSRI for mitigation of hot flush symptoms is low-dose (7.5 mg) paroxetine.

Gabapentin

Gabapentin, a medication used primarily as an anticonvulsant, has also been shown to decrease vasomotor symptoms. Its mechanism is also not entirely known but believed to involve central and peripheral GABA neurotransmission. While less effective than hormone therapy, gabapentin at doses up to 300 mg three times a day is well tolerated [25]. Its major side effects are sedation, headache, and edema. While others have expressed increase concern of suicide on gabapentin, pharmacoepidemiologic studies have shown no drug effect was detected in the nonpsychiatric populations, while significant reductions in suicide attempt rates were seen for bipolar disorder, major depressive disorder, and other psychiatric disorders [16]. In our experience, this medication is most useful in patients who wish to avoid estrogen therapy and whose primary bothersome symptom is night sweats. A randomized trial found nonsuperiority of gabapentin 2400 mg compared with conjugated equine estrogens (0.625 mg/day), but at this dosage the side effects can become limiting [33].

Table 5.1 Results of the efficacy of escitalopram, paroxetine, sertraline, citalopram, and fluoxetine, conducted using the random-effect Bayesian method (total residual deviance = 18.87)

Comparison	Mean effect	95 % CI	Probability treatment is best	Rank
Placebo	Reference	–	0	–
Escitalopram	−2.05	−4.82 to 0.62	61 %	1
Paroxetine	−1.23	−2.39 to −0.12	18 %	2
Sertraline	−0.83	−3.44 to 1.64	16 %	3
Citalopram	−0.54	−2.00 to 0.83	3.4 %	4
Fluoxetine	−0.14	−1.55 to 1.30	0.9 %	5

Results of mixed treatment comparison comparing the efficacy of escitalopram, paroxetine, sertraline, citalopram, and fluoxetine, conducted using the random-effect Bayesian method (total residual deviance = 18.87)

Comparison	Mean effect	95 % CI	Probability treatment is best	Rank
Placebo	Reference	–	0	–
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Citalopram	−0.54	−2.00 to 0.83	3.4 %	4
Fluoxetine	−0.14	−1.55 to 1.30	0.9 %	5
Escitalopram vs. citalopram	1.511	−1.55 to 4.58	–	–
Escitalopram vs. fluoxetine	1.914	−1.11 to5.06	–	–
Escitalopram vs. sertraline	1.225	−2.44 to 4.89	–	–
Escitalopram vs. paroxetine	0.82	−2.06 to 3.82	–	–
Citalopram vs. fluoxetine	0.4	−1.02 to 1.92	–	–
Citalopram vs. sertraline	−0.29	−3.32 to 2.57	–	–
Citalopram vs. paroxetine	−0.69	−2.47 to 1.14	–	–
Fluoxetine vs. sertraline	−0.69	−3.64 to 2.12	–	–
Fluoxetine vs. paroxetine	−1.09	−2.94 to 0.70	–	–
Sertraline vs. paroxetine	−0.40	−3.11 to 2.46	–	–

Adapted from(Shams et al [34])

Clonidine

Clonidine (0.1 mg/day) is an antihypertensive, which had been used for VMS management in the 1970s for patients with breast cancer [25, 32]. It is a centrally acting α-2 adrenergic agonist, which has been theorized to exert its beneficial anti-VMS effects by reducing norepinephrine release and restoring homeostatic function in the thermoregulatory zone of the hypothalamus. Clonidine causes modest improvements in hot flush symptoms although the side effects of large symptom burden including mouth dryness, constipation, itchiness, drowsiness, and difficulty in sleeping can be

limiting in its use. This can be a good agent of choice for women who have a preexisting condition of hypertension and contraindications to taking other medications.

Integrative Approaches for Treating Menopausal Hot Flushes

Acupuncture

Acupuncture studies are ongoing in the treatment of hot flushes; however there is promising evidence for its efficacy. Part of the efficacy of acupuncture in improving hot flushes is based on the changes in levels of β-endorphins and other neurotransmitters during acupuncture, potentially affecting the thermoregulatory center in the hypothalamus [2]. A recent meta-analysis of 12 studies with 869 patients using acupuncture therapy for VMS showed significant reductions in both severity and frequency of hot flushes, with effects lasting up to 3 months. Acupuncture also resulted in lasting improvements in psychological, somatic, and urogenital subscale scores [8]. In our clinical practice, the points we most commonly use are St-36, Sp-6, CV-4, LI4, PC-6, GV-20, Lr-3, and Ht-6, although some variability does occur as we individualize each session. In our practice, acupuncture sessions are typically scheduled weekly or bi-weekly, and patients start noticing the benefits after 2–3 sessions, with hot flush intensity improving before hot flush frequency. Sessions last roughly 30 min.

Randomized, placebo-controlled trials on mind-body interventions such as acupuncture for hot flush management are challenging to conduct for a number of reasons. The first obvious reason is the lack of a valid placebo since the skin puncture itself is what induces the therapeutic effect. Secondly, acupuncture treatments are typically individualized, which renders research on a standard approach not generalizable or representative of the spectrum of clinical care. This may be one cause of the variation in effectiveness seen in these trials.

One study compared sham acupuncture to usual care in a pilot trial involving 56 perimenopausal and postmenopausal women. Patients received a standard true acupuncture regimen including the points CV-4, Ki-3, Sp-6, Bl-23, Ht-6, and Ki-7. Additional points were also needled depending on clinical judgment. The intervention occurred twice weekly for 8 weeks. The primary outcome variable was a hot flush score calculated from a daily diary. True and sham acupuncture were not statistically different from each other, and both were superior to usual care [2].

The ACUFLUSH study [4] was also a randomized controlled trial. This was a multicenter, pragmatic trial including postmenopausal women with at least seven hot flushes per day. Pragmatic trials are designed to test whether an intervention works in a real-life setting. The intervention group received up to ten acupuncture sessions over a 12-week period, and the treatments were individualized. The intervention group also received advice on self-care, and the control group received only advice on self-care. In the 134 women in the acupuncture group, hot flush frequency decreased by almost 6 per day and almost 4 per day in the 133 women in the control group. This difference of 2.1 per day was statistically significant. Hot flush intensity was also statistically significantly better in the acupuncture group. The acupuncture group also had statistically significant improvements in the vasomotor, sleep, and somatic symptoms.

Yoga

Yoga is an ancient Indian practice that includes postures, breathing, and meditation, among other practices. Similar to acupuncture, yoga is difficult to adequately control because it is impossible to mask the treatment arm to the subject, although the hypothesis could be kept from the patient, and the researcher conducting the outcome measures could be masked to treatment group.

Heightened sympathetic nervous system may play a role in hot flushes, and yoga appears to decrease sympathetic output, based on findings of increased heart rate variability and decreased oxygen consumption. Yoga also reduces blood pressure and insulin resistance.

In a randomized controlled trial, Joshi and colleagues randomized 200 women to either a daily yoga group or to a non-yoga control group for 90 days. The non-yoga group was asked not to perform yoga practices or take medication for menopausal symptoms during the study period. The Menopause Rating Scale (a validated instrument used in menopause research to assess impact of symptoms on health-related quality of life in various domains: psychological, somatic, and urogenital) was the primary outcome studied. The groups were similar at baseline, but only the yoga group significantly improved by the end of the study period, and the improvement was in the total score and each of the subscales. Yoga occurred daily in this study, which might be difficult to replicate in the United States.

Another significant trial was an 8-week trial comparing yoga therapy (physical movement in the form of sun salutations, breathing, and meditation) to simple physical exercise under supervision in 120 participants. Outcomes were assessed by the Greene Climacteric Scale, the Perceived Stress Scale, and the Eysenck's Personality Inventory before and after the interventions. Vasomotor symptoms statistically significantly improved in the yoga group, as did perceived stress scores and neuroticism. Other changes were not statistically significant [7]. Thus, it may not be merely physical exercise that helps women with hot flushes, as the control group was doing physical exercise. Yoga's effect on perceived stress, thus lowering sympathetic output, may be responsible for effects on hot flushes. Paced respiration, as studied by Freedman and Woodward, significantly reduces hot flush frequency. Breathing techniques are common in yoga.

In 2012, a meta-analysis of randomized controlled trials found moderate evidence for short-term effectiveness of yoga for psychological symptoms but not for somatic symptoms, vasomotor symptoms, or urogenital symptoms [9]. Improving psychological symptoms is important, and we do recommend yoga for our patients. Hot yoga variants may be enjoyable and may have other health benefits but cannot be recommended for hot flush management because there is no supporting evidence. Additionally, from anecdotal evidence, where yoga is done in a hot room, we do know that high ambient temperatures increase hot flushes. We suggest avoiding "hot" yoga.

Mind-Body Medicine

Mind-body techniques include stress reduction, relaxation, hypnosis, mindfulness, and cognitive behavior therapy. The early research on the use of mind-body medicine included case studies and case series. Similar to yoga and acupuncture, this research is challenging to blind, as study participants know if they are meditating or having hypnosis. However, participants can be hypothesis blind, and good evidence is possible. Stress triggers hot flushes, and stress reduction may reduce hot flushes. The mechanisms of action for mind-body approaches are likely similar to those of yoga and acupuncture, with decreasing sympathetic output playing a role.

In 1990, Swartzman, Edelberg, and Kemmann studied the impact of stress on objectively recorded hot flushes and on flush report bias, asking if women under stress were more likely to report hot flushes than women not under stress. The findings were consistent with what many women experiencing hot flushes know: significantly more flushes occur during the stress session compared to the nonstress session, and there was not a bias to reporting more hot flushes. We counsel patients that this study showed that lab stress increases hot flushes. We can predict that the effects of "real-life" stress may be even more substantial than lab stressors, and anecdotally, patients certainly report stress as a trigger for hot flushes.

One of the first controlled studies that investigated relaxation training on menopausal symptoms was conducted by Irvin et al. in 1996 and randomized women to relaxation response training, reading, or a control group. Participants listened to a 20-min relaxation audiotape daily, and the reading group read for 20 min daily. Hot flush intensity, tension-anxiety, and depression were significantly reduced in the relaxation-training group, whereas trait-anxiety and confusion-bewilderment were decreased in the reading group. The control group had no changes. The relaxation-training group showed a trend toward a decrease in all scores, but the sample size was small and may be underpowered. The authors postulate that the reading group may have chosen to take action and get control over their symptoms and may have read about menopause. This is possible, but it is also possible that relaxing for 20 min while reading leisure material is also a form of relaxation training.

Hypnosis now has a solid research backing, thanks to a research team at Baylor University. They studied a hypnosis intervention first in breast cancer survivors and then in women without breast cancer. In breast cancer survivors, hypnosis decreased hot flush scores 68% from baseline, with significant improvements in anxiety, depression, interference of hot flushes on daily activities, and sleep, compared to the no-treatment control group [13]. The subjects received a standardized hypnosis intervention. In 2012, Elkins et al. published a large study that included 187 postmenopausal women with severe VMS as defined by seven or more hot flushes per day at baseline. The hypnosis intervention included specific suggestions for mental imagery for coolness, safe place imagery, and relaxation. They had 5 weekly sessions, with a home self-hypnosis practice. The control group was a structured attention control, which matched the hypnosis intervention in all ways except the actual hypnosis, and also met weekly for 5 weeks, with the therapist discussing symptoms

and encouraging the subject. No specific cooling suggestions were made. Hot flush frequency reduced 74 % in the hypnosis group compared to 17 % in the control group. Hot flush score decreased 80 %, compared with 15 % for the control group. Hot flush interference, sleep quality, and treatment satisfaction all improved in the hypnosis group. There is no "licensure" for hypnosis although many states require that hypnotherapists have a state license for counseling in order to be certified to conduct hypnosis. Finding a local hypnotherapist is helpful for patients, and reaching out to mental health colleagues may be a good way to find a trusted professional to provide hypnosis for hot flushes.

Mindfulness-based stress reduction (MBSR) may reduce the bothersomeness and distress from hot flushes. MBSR is an approach that allows a nonreactive awareness to an experience. For instance, some women may react to a hot flush with a sense of despair and concern that the hot flushes will never stop and that they will never get a good night's sleep again. The mindfulness approach would halt that thought process and allow a woman to label the hot flush just as a hot flush, something temporary, and while it may be uncomfortable, it will go away. It would make sense then for the mindfulness training to reduce the distress and bothersomeness of hot flushes. In one randomized trial, 110 women with hot flushes were randomized to either an MBSR intervention or to a wait list control. The MBSR intervention was the standardized MBSR intervention, including a sitting meditation, mindful movement, and body awareness. The intervention included 8 weekly 2.5 h sessions as well as one all-day class. Significant improvements in hot flushes, quality of life, sleep quality, anxiety, and perceived stress were observed in the MBSR arm. Improvements in quality of life were maintained at 3 months post-intervention, and the hot flush score continues to improve post-intervention [6].

Cognitive behavior therapy (CBT) is not traditionally considered an integrative modality; however, it is a well-known therapeutic technique that again brings in the power of the mind-body connection. Much like MBSR it can reduce the burden of hot flushes by decreasing the reaction to the hot flush, CBT can decrease symptomatology by moderating the emotional reactions, negative beliefs, and catastrophic thoughts that can occur with hot flushes. In one study, CBT, delivered as a group intervention or through a self-help manual, improved hot flush severity, mood, quality of life, and emotional and physical functioning, compared with nonintervention. Learning a different way to think about and react to hot flushes may allow women to gain control over the symptoms. A self-help CBT for menopause workbook is commercially available [26], and parts of this book may be helpful for both patients and providers to help reframe the menopause experience.

Botanical Treatments

Many different botanical regimens have been recommended for management of hot flushes, such as black cohosh, isoflavones, and multibotanical preparations. One overall concern that we have with botanicals is the lack of oversight and quality control on the products in the United States (other countries such as Australia have

a strict regulation of supplements through the equivalent of the Food and Drug Administration). Therefore, when recommending supplements of any type, we recommend specific brands that have rigorous quality standards; however, patients are free to choose other brands and may choose ones that are not of high quality despite their high cost. One website that is helpful for finding supplements with rigorous quality standards is *consumerlabs.com*.

One important study of botanical supplements compared black cohosh alone to four parallel arms: a multibotanical including black cohosh and nine other ingredients, a multibotanical plus dietary soy counseling, hormone therapy with estrogen/progestogen, and placebo [29]. The botanical regimens did not differ from placebo with one exception, where the botanical was worse than placebo. As expected, hormone therapy improved symptoms. The authors note that differences between treatment groups smaller than 1.5 vasomotor symptoms per day cannot be ruled out. As mentioned earlier, and due to the variable nature of hot flushes, studies may be underpowered to show a difference. Other studies have also failed to show improvement compared with placebo for black cohosh, red clover, the Chinese herbal preparation Dang Gui Buxue Tang, or in any combinations of these therapies. In our experience, herbal remedies with black cohosh appear to help with mild symptoms for short periods of time; the appearance of improvement may be due to placebo, to the natural course of hot flushes, or to a true effect. However, it is important to be mindful that it remains unclear if botanicals interact with estrogen receptors and that long-term usage should be discouraged.

Another botanical studied for hot flushes is the special extract ERr 731 from the roots of *Rheum rhaponticum* that has been recently studied for the treatment of vasomotor symptoms [19]. In a prospective multicenter, double-blind, placebo-controlled study of perimenopausal women with climacteric complaints over the course of 12 weeks, menopausal symptoms significantly decreased in the ERr 731 group compared to the placebo group. They also showed an increase in quality of life. From this limited data, it appears to be safe and well tolerated.

Lastly, St. John's wort can be used in menopause. As discussed above, antidepressants, such as selective serotonin reuptake inhibitors, can reduce hot flushes. It is postulated that if St. John's wort has a similar mechanism, it is possible that it could help with hot flushes too. However, we tend not to recommend this due to the number of drug interactions that St. John's wort has, including drug-herb interactions and concern over a serotonin effect.

Journeying into Wellness

Despite the clear physiologic changes of perimenopause and menopause, many writers and thinkers throughout time have known this time of transition to be one that is ripe for reflection, growth, and increasing wisdom. Carl Jung characterized the later years of one's life as a time of "individuation," a time to bring the "consciousness into a working relationship with our inner terra incognita or our unknown

inner terrain," in other words, a time to integrate the experiences of their lives into a well-functioning whole.

Though a woman has many different options at hand for reducing symptomatology of perimenopause and menopause, perhaps none of these are as effective in isolation as they are when girded in a strong foundation of wellness of the body, mind, and spirit.

Feeding the Body

Calcium As the concentration of the protective hormone of estrogen declines, a woman's bones are more at risk for decreased bone density – making a diet rich in calcium perhaps more important than ever. Calcium is found in abundance in dark leafy greens such as spinach, broccoli, kale, brussel sprouts, and dandelion greens, to name a few. These greens are also high in vitamins A, C, and K, which further serve to strengthen the body and bones. Other traditional sources of calcium such as dairy (milk, cheese, ice cream) can be continued during this time but search for dairy that has no added hormones. We recommend that a woman lean on vegetable sources or fish such as sardines to supply her with most of her food-derived calcium.

Fiber A woman's chance for cardiac disease starts to rise after she goes through menopause. Fiber has been well studied in its role in lowering "bad cholesterol" (LDL), improving insulin resistance, decreasing inflammation, and protecting against heart disease. The Institute of Medicine recommends that women over age 50 get 21 g or more of fiber a day. Excellent fiber sources are vegetables, fruits, beans (all kinds), nuts, bran, bulgur, whole wheat flour, prunes, peas, barley, and potato skins.

Healthy Fats To further improve cardiac health, decrease inflammation, and potentially improve mood, foods rich in omega-3s are highly recommended. Foods such as almonds, walnuts, flaxseeds, chia seeds, cold-water fish such as mackerel, wild coho or Alaskan salmon, sardines, and herring are all excellent sources of omega-3 fatty acids. Food sources are a more reliable source of nutrients, but if needed, a supplement of fish or flaxseed oil can be taken.

Fluids As the body is moving through shifts in temperature and fluid regulations, it is best to treat the body kindly with decreased caffeine intake, moderate alcohol, teas, and plenty of room-temperature water. Alcohol, though known to protect against heart disease in moderate amounts, has been studied less in women and, when used at amounts of larger than one drink per day, has been shown to increase the risk of breast cancer. Coffee often increases symptoms of hot flushes in menopausal women. Black tea, however, is linked to a decreased risk of osteoporosis, and green tea, with its antioxidants and vitamin K, can help protect against breast cancer. We advise patients that hot beverages can exacerbate hot flushes, so drink when cooled.

Movement Regular and vigorous exercises such as walking, jogging, biking, and swimming are all highly encouraged. The benefits of regular cardiac exercise (at least 30 min 5 days per week) and weight-bearing exercises two to three times a week can help protect against heart disease, osteoporosis, insulin resistance, breast cancer, and memory impairment as well as keep women feeling more alert and well in the day. Movement can bring them back to their bodies and help them feel more at home in their changing bodies.

Mind and Spirit

As a woman is no longer riding the waves of hormone cycles and likely is no longer responsible for the continuous needs of children, she may find that she has more space to start focusing on her mind and the larger things that give her meaning. As Dr. Gaudet so beautifully illustrates in her "Consciously Female" guide for women, this is a time to start asking questions, such as "What are my expectations; Who are my role models; What do I love; What have I accomplished so far with my life, personally as well as professionally; and What have I not been able to accomplish yet?" She urges women to dream big, zero in on ideas, take action, and reflect. These questions can be answered alone, explored with communities, or brought to a place of worship. It is noted that while having an opportunity to ask these questions may connote a place of privilege, it is our strong belief that all women have been granted the opportunity to mark this time of profound change and use it as grist for their future wisdom.

We tell patients: this time is an invitation. Go forth and flourish.

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Part II

An Inferential and Individualized Approach to Management of Common Menopausal Concerns Through Clinical Vignettes

Clinical Management of Menopause-Related Sleep Disturbance

6

Sarah B. Mathews and C. Neill Epperson

Sleep Disturbances and Menopause

As with every medical condition, the diagnosis and treatment of insomnia begins with the medical history. We present here two cases drawn from our experience with sleep issues unmasked during assessment of psychiatric symptoms. Notably, sleep disorders are prevalent in many peri- and postmenopausal women who are seeking evaluation for changes in their quality of life occurring in the context of the menstrual cycle irregularity that characterizes the menopause transition and who do not meet criteria for a DSM-5 psychiatric disorder.

S.B. Mathews, MD
Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Penn Center for Women's Behavioral Wellness, Perelman School of Medicine at the University of Pennsylvania, 3535 Market Street, 3rd Floor, Philadelphia, PA 19104, USA; http://www.med.upenn.edu/womenswellness/

C.N. Epperson, MD (✉)
Departments of Psychiatry and Obstetrics and Gynecology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Penn PROMOTES Research on Sex and Gender in Health, University of Pennsylvania, Philadelphia, PA, USA

Penn Center for Women's Behavioral Wellness, Perelman School of Medicine at the University of Pennsylvania, 3535 Market Street, 3rd Floor, Philadelphia, PA 19104, USA
e-mail: cepp@mail.med.upenn.edu

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Case 1

Ms. A is a 48-year-old perimenopausal, full-time, working professional who presents with concerns relating to interrupted nocturnal sleep, daytime fatigue, and somnolence. She reports new onset menstrual infrequency over the past 4 months and acknowledges 3–4 hot flashes daily and one or two night sweats several times a week. In addition to be awakened by night sweats, her sleep difficulties are characterized by problems initiating sleep at the beginning of the night, middle of the night awakenings for 30–45 min, and waking 60–90 min before the set alarm. She describes intermittent low mood and is concerned that her symptoms are affecting her quality of life.

Case 2

Ms. B is a 55-year-old, obese, diabetic early postmenopausal woman with insomnia characterized primarily by interrupted nocturnal sleep. She wakes 2–4 times during the night, falls back to sleep after 15–20 min, and awakes with her alarm clock. She is no longer experiencing frequent hot flashes, but does report fatigue and joint pains. She denies significant mood symptoms. She feels like she is not getting a full night's rest despite being in bed for 8 h or longer every night and has tried several sleep aids without benefit.

Physiology of Sleep: *Restful Versus Restless*

Although sleep is clearly a requirement for the maintenance of health, its exact function remains a mystery. Sleep has been thought to have restorative properties, allowing the body and brain to repair and rejuvenate in preparation for another day's activities; however, evidence is still needed to confirm this idea. The two different types of sleep are rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep, which is further broken down into stages 1, 2, 3, and 4 [1]. Brain wave patterns, eye movements, and muscle tone vary with each stage of sleep, and therefore each may serve its own unique purpose. Stages 3 and 4, encompassing the slow-wave sleep (SWS), involve the least brain activity. REM sleep is the brain's most active stage, when dreaming occurs, even though the body is otherwise in a state of paralysis. The lighter sleep of stages 1 and 2 is present with the initiation of sleep, but does recur, allowing for periods of easier arousal from sleep. Individuals cycle through each stage of sleep in typical patterns several times throughout the night, as seen in Fig. 6.1. The changes to sleep patterns that occur throughout the lifespan are depicted in Fig. 6.2. The most typical changes to this sleep cycle that occur that with older age include a shift to a "phase-advanced" cycle, with earlier wake time, an increased sleep latency, an increase in nighttime arousals, a reduction in rapid eye movement (REM) sleep, and a decrease in slow-wave sleep [5].

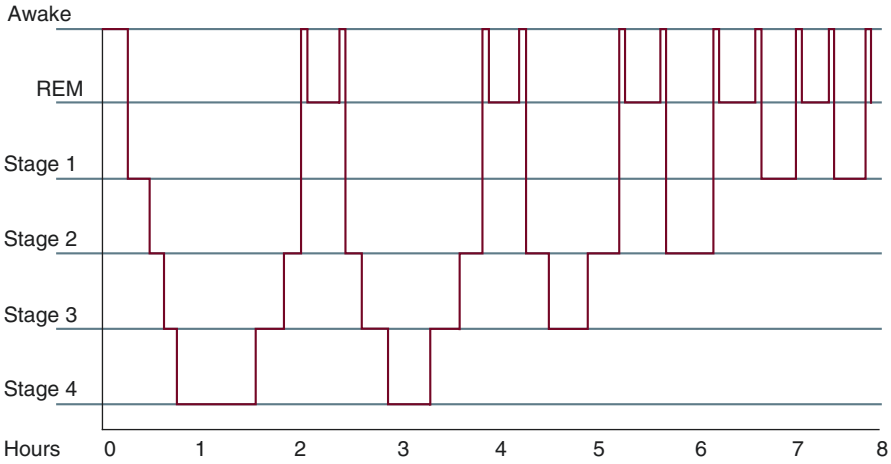
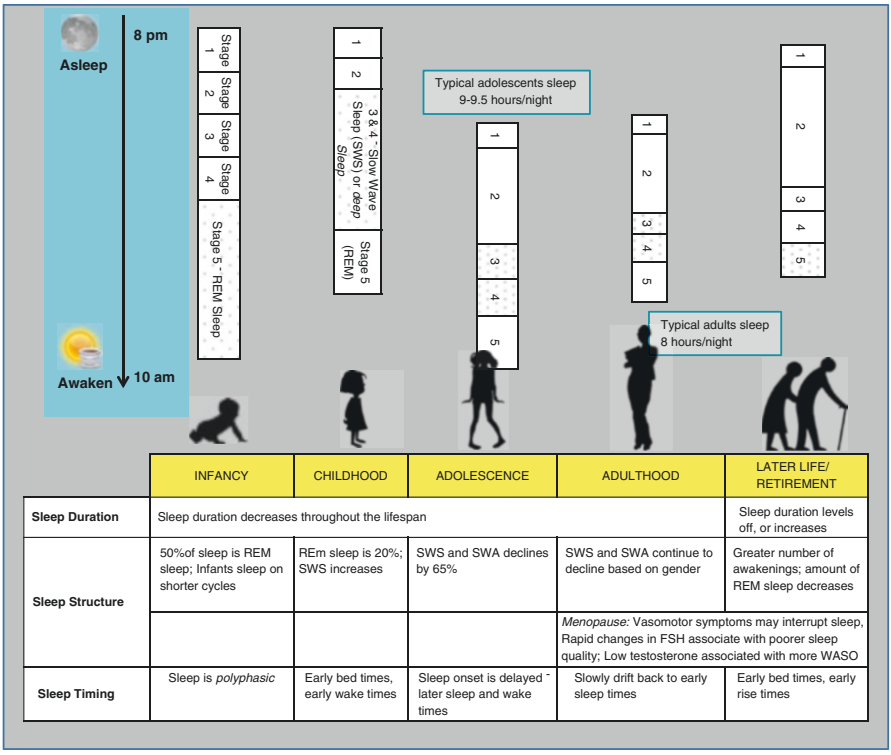


Fig. 6.1 A hypnogram showing cycling of stages of sleep throughout sleep duration

The most common sleep disturbances are disorders related to initiating and maintaining sleep, the insomnias. Some people experience most difficulty falling asleep and can take up to several hours to accomplish this. Others complain of waking during the night, with interruptions in sleep that may or may not be explained by external factors, such as a snoring partner or a night sweat. They also may or may not have difficulty in returning to sleep. If waking occurs frequently, patients often describe their sleep as restless. Still others are bothered by early morning awakening, with the inability to fall back to sleep. Many times these sleep issues co-occur.

A more comprehensive definition of insomnia, according to the DSM-V, the diagnostic manual for psychiatric disorders, is the dissatisfaction with sleep quantity or quality, with one or more of the following symptoms: difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening. The sleep disturbance causes significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning. Sleep difficulty occurs at least three nights per week and is present for at least 3 months, despite adequate opportunity for sleep. The insomnia does not co-occur with another sleep disorder. The insomnia is not explained by coexisting mental disorders or medical conditions [6]. Using this definition, sleep disturbance that is isolated to the menopause transition and is not due to one of the sleep disorders described below would be considered insomnia due to a general medical condition, rather than a primary insomnia disorder.

Stages of reproductive aging including menopause transition and distinction between early and late stages of menopause have been discussed in Chap. 1 of this text and are summarized in Fig. 6.3 [7]. From the perspective of psychological well-being, the late premenopause stage is of clinical importance, as studies have shown that risk for depression [8] and cognitive decline [9, 10] during the transition to menopause begins to increase at these earliest stages of declining reproductive



	INFANCY	CHILDHOOD	ADOLESCENCE	ADULTHOOD	LATER LIFE/ RETIREMENT
Sleep Duration	Sleep duration decreases throughout the lifespan				Sleep duration levels off, or increases
Sleep Structure	50%of sleep is REM sleep; Infants sleep on shorter cycles	REm sleep is 20%; SWS increases	SWS and SWA declines by 65%	SWS and SWA continue to decline based on gender	Greater number of awakenings; amount of REM sleep decreases
				Menopause: Vasomotor symptoms may interrupt sleep, Rapid changes in FSH associate with poorer sleep quality; Low testosterone associated with more WASO	
Sleep Timing	Sleep is *polyphasic*	Early bed times, early wake times	Sleep onset is delayed - later sleep and wake times	Slowly drift back to early sleep times	Early bed times, early rise times

Fig. 6.2 Sleep across the lifespan. The figure depicts typical sleep patterns with respect to sleep duration, structure, and timing across the lifespan [2]. The proportions of time spent in each type of sleep each night at each life stage are shown, and these cycles repeat throughout the night. During infancy, 50 % of the time sleeping is in the stage of rapid eye movement (REM). By primary school age, REM sleep has decreased to roughly 20 %, and slow-wave sleep (SWS, stages 3 and 4) also referred to as "deep sleep" increases. If adolescents are allowed to sleep the amount they prefer, they would go to sleep later and stay in bed longer. Sleep would increase to roughly 9.5 h/nightly with a decline in SWS and slow-wave activity (SWA) on polysomnography (PSG). This decline in SWS/SWA continues into adulthood, but is modulated by alterations in estradiol and testosterone [3]. Recent findings from the Study of Women's Health Across the Nation (SWAN) suggest that rapid increases in FSH are associated with reports of poorer sleep quality [4]. Sleep duration decreases across adulthood until the seventh decade and levels off or increases after retirement [5]

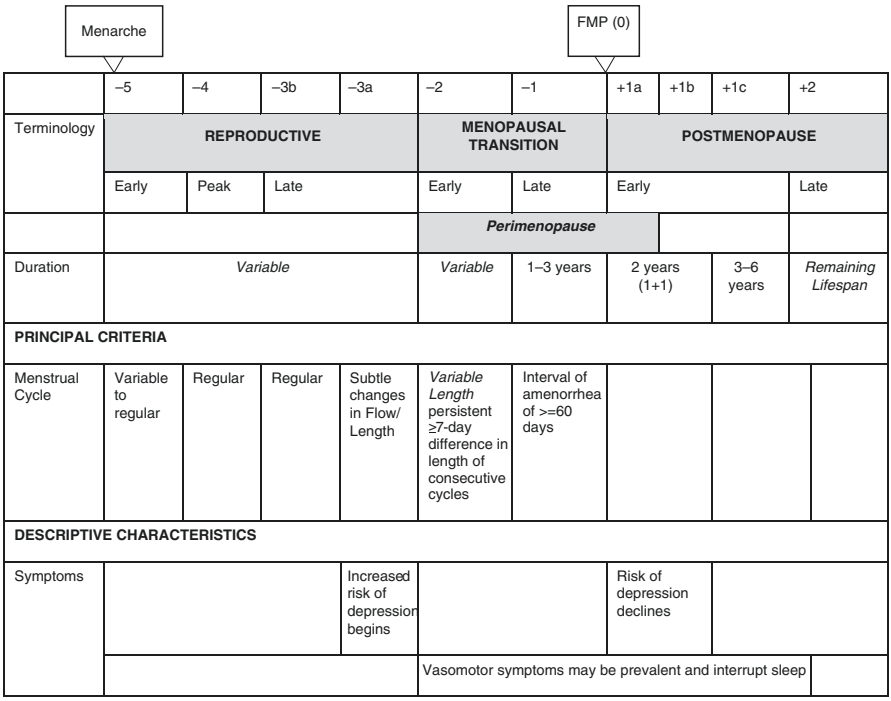


Fig. 6.3 Adaptation of STRAW – stages of menopause

physiology. Sleep disturbances can be seen as early as the late reproductive years and continue into the postmenopause [11].

Sleep-Related Burden and Risk Factors

Sleep disturbance can be one of the most troubling symptoms experienced by a woman during the menopause transition. Although changes in sleep are typical as one ages, the menopause transition represents a period of both an exaggerated magnitude and increased bother from sleep alterations. The prevalence for self-reported difficulty with sleeping during the early stage of the menopause transition is up to 40 % [11] and could increase to 46 % in women in the late menopause transition when frequency of menstrual cycles can be decreased to once or twice in a 12-month period [12]. Polysomnography (PSG)-based studies have demonstrated objective evidence of changes in sleep during the menopause transition, with decreased sleep efficiency in the perimenopausal, compared to premenopausal women [13]. Others however have found no significant differences in sleep patterns on PSG, nor has PSG data consistently coincided with subjective sleep disturbance in perimenopausal women [14].

Sleep difficulty during perimenopause can contribute significantly to poor quality of life and is often associated with fatigue, depressive symptoms, and anxiety, just as is demonstrated in both case examples [15, 16]. Women who report more sleep difficulties tend to have higher perceived stress and a lower perceived overall health status. The hormone cortisol is involved in regulating the stress response and may also play a role in maintaining the circadian rhythm, as it typically rises throughout the night, peaking in the morning hours [17]. Lower morning cortisol levels are reported in the setting of poor nocturnal sleep, suggesting a possible dysregulation in this hormone's circadian rhythm [3]. Many middle-aged women lead busy, demanding lifestyles, and poor quality of nocturnal sleep can lead to poorer functioning, just as noticed by Ms. A in Case 1. One study of perimenopausal women comparing women with insomnia to those without trouble falling asleep identified significantly more emergency department visits, greater activity impairment, and more occupational impairment (for those who were working) in the insomniac group [18]. Women with poor sleep report more fatigue and musculoskeletal discomfort seen with Ms. B in Case 2 [19]. There may even be a subset of women who experience insomnia, but actually exhibit normal sleep efficiencies on PSG; this subset is more likely to report greater psychological distress compared to those with objective PSG abnormalities [20].

Sleep disturbances are deemed as contributory to clinical depression and to depressed mood during and after the menopause transition [21]. Chronic sleep deprivation can alter the mood state; alternatively, sleep disturbance could be a symptom of depression instead (as discussed later). The relationship between depression, sleep, and vasomotor symptoms in actuality can be quite complex, as each may exacerbate the other. In one study, depressed women with vasomotor symptoms spent less time in bed and had shorter total sleep time, longer sleep-onset latency, and lower sleep efficiency compared with nondepressed women with vasomotor symptoms [22]. Reverse causality is also recognized as when depression is present, it can have an additive effect on sleep disturbance occurring with the menopause transition.

Although perimenopausal women may experience difficulty initiating sleep, frequent nighttime awakening, and early morning awakening, the nighttime awakening might be the most specific type of sleep issue common to the menopause transition [23]. Nighttime awakening, present in both cases described above, is most often associated with the late menopause transition or early postmenopause stage, presence of hot flashes, depressed mood, anxiety, and joint pain [3, 23]. Early morning awakening can also be common and tends to increase with age, even following the menopause transition [3]. PSG testing has also linked sleep symptoms with hot flashes, with lower sleep efficiencies and longer REM latency [19, 20, 24]. Nighttime vasomotor symptoms may also more directly lead to nighttime awakenings and poor sleep. Alternatively, women with more vasomotor symptoms are more likely to be depressed, which could lead to the sleep changes. Even if associated with vasomotor symptoms, it is not necessarily the case that the hot flash causes awakening, as one interesting study showed the arousal from sleep actually preceded a hot flash more often when the two were associated [25, 26]. Instead, a more generalized

state of hyperarousal could lead to both. This may be the case for Ms. A, who is experiencing this complex symptom triad, as she has multiple sleep complaints. It is important to consider how the relationship between these symptoms could be different for each individual.

Reproductive Hormones and Sleep

Changes in reproductive hormones during the menopause transition such as the decreases in estrogen, progesterone, and testosterone could contribute to sleep disturbances [27]. Younger women experiencing an unnatural menopause, following oophorectomy or premature ovarian failure due to chemotherapy, can have abrupt, drastic decreases in ovarian hormones and tend to have high risk for insomnia [28]. The association seen between vasomotor symptoms and reported sleep disturbance in perimenopausal women has been demonstrated repeatedly [3, 26, 29], and this relationship could certainly be explained by a shared causal factor such as estrogen withdrawal. Rapidly rising serum follicle-stimulating hormone (FSH), possibly indicating a rapid shift in hormone levels and transition through menopause, has been associated with more slow-wave sleep and longer sleep duration, but poor overall sleep quality [27]. In studies of perimenopausal women, lower serum estradiol levels have been associated with poor subjective sleep quality [27], and lower testosterone levels have been associated with difficulties with initiating and maintaining sleep [3]. It has also been proposed that decreases in progesterone, which is considered a respiratory stimulant, may be an important factor for risk of sleep-disordered breathing in menopause [30].

Other Sequelae to Disturbed Sleep

Insomnia can have many serious health consequences, including an increased risk for obesity [31], cardiovascular disease [32, 33], and all-cause mortality [34, 35]. Studies of individuals undergoing sleep deprivation have demonstrated an increase in levels of inflammatory markers that could play a role in the risk for various types of disease [36]. In a longitudinal cohort of younger adults, each additional hour of sleep at baseline was negatively associated with change in body mass index over the follow-up period of 10 years [31]. Possibly changes in insulin sensitivity or levels of hormones important for appetite and weight, such as leptin or ghrelin, occur with fewer hours of sleep. Interestingly, in a large population of older adults followed for 14 years, higher mortality was associated with both too few and too many hours of sleep, with least risk at 7 h per night of sleep [32]. Risk for death due to cardiovascular disease significantly associated with fewer hours of sleep only in the women in this study. Clearly adequate sleep is tremendously important for maintenance of vital functions, and sleep disturbances in menopause leading to consistently fewer hours of sleep per night would be expected to pose similar risks.

Differential Diagnoses

Before assuming that a sleep disorder is due to menopause, other medical conditions that contribute to disturbed sleep should be considered. See Table 6.1.

Obstructive sleep apnea (OSA) defined as an apnea hypopnea index of 5, indicating at least five complete or partial obstructions of the airway per hour, usually resulting in an awakening is quite common among menopause-aged women. OSA often involves symptoms of loud snoring, daytime sleepiness, shortness of breath, witnessed apnea episodes, dry mouth, and morning headaches. Of early postmenopausal women showing 68% experienced decreased sleep efficiency, 50% had apnea, 7.8% had periodic leg movements, and 2.6% had bruxism (involuntary gnashing and grinding of the teeth during sleep) on PSG [37]. These postmenopausal women had 3.5 times the risk of OSA compared to premenopausal women. Even among patients with similar sleep-related complaints, postmenopausal women have been found using PSG to have significantly more sleep-disordered breathing than premenopausal women [38]. Other risk factors for OSA include obesity, wider neck circumference, narrow airway, and cigarette smoking. Therefore, a clinician assessing Ms. B in Case 2 should strongly consider a diagnosis of OSA and order a sleep study given her obesity, nighttime awakenings, and daytime fatigue.

Restless legs syndrome (RLS) can also lead to sleep disruption in older women [39]. The disorder is thought to be caused by dysregulation in iron metabolism and dopaminergic function [40]. However, diabetes mellitus, obesity, thyroid disease, certain medications, and sleep deprivation can contribute to symptoms of RLS [40]. RLS involves uncomfortable sensations in the legs, especially when sitting or lying

Table 6.1 Common disorders in menopausal women causing sleep disturbance

Disorders	Sleep symptoms
Medical disorders	
Obstructive sleep apnea	Nighttime awakening due to interrupted breathing, snoring
Restless legs syndrome	Sensation of needing to move legs at bedtime, during sleep
Periodic limb movement disorder Urinary disturbances	Involuntary movement of limbs during sleep causing awakening Urinary frequency interfering with falling asleep, staying asleep; episodes of incontinence causing awakening
Psychiatric disorders	
Major depressive disorder Bipolar disorder	Difficulty falling asleep, nighttime awakenings, and often early morning awakening Decrease in need for sleep when manic; sleep symptoms seen in depressive episodes similar to above
Generalized anxiety disorder	Difficulty with falling asleep initially or after nighttime awakening due to anxiety
Panic disorder	Panic attacks occur during night, causing awakening
Post-traumatic stress disorder	Hyperarousal may cause difficulty falling asleep, nightmares

down, accompanied by an irresistible urge to move the affected limb. These symptoms, which occur more often at night, can interfere with sleep. Being twice as common in women than men, prevalence of RLS increases with age and parity, during pregnancy, and in the presence of vasomotor symptoms during menopause [39, 41]. Hormone therapy does not seem to change risk for the development of RLS, however [41].

Periodic limb movement disorder (PLMD) is another movement disorder, with jerking movements and cramping of limbs throughout the night leading to disruptive sleep. Movements of arms and legs are involuntary in contrast to RLS which involves the sensation of needing to move legs, with voluntary movement. The prevalence of PLMD is more common in women than men and more common during pregnancy. Risk also increases with age, but its prevalence during the menopause transition, and hormone therapy's effect on its symptoms, is not clear [42]. PLMD is often secondary to multiple other disorders and factors common in this population, including OSA, diabetes, anemia, and antidepressant use. If PLMD is suspected, a thorough medical investigation is needed. The presence of both RLS and PLMD should both be considered in the case of Ms. B even though she does not identify these issues, as her diagnosis of diabetes mellitus and her obesity and possible OSA increases her risk.

Urinary disturbances can often lead to sleep disruption. This issue has been thought to be a more common problem in the postmenopause due to the effects of the loss of estrogen on the urethral tissue, with increasing episodes of urinary incontinence. A recent study demonstrated, however, that women in the late reproductive stage and early perimenopause had problematic urinary symptoms, with 72 % reporting nocturia at least once per night and 50 % experiencing urinary incontinence at least once per week [43]. There are various types of incontinence, including stress incontinence, urge incontinence, overactive bladder, and overflow incontinence, so as each type could involve nighttime symptoms, causing awakening; the presence of urinary symptoms and effects on sleep should be considered. Either Ms. A or Ms. B could be struggling with these symptoms, but may not link them with their sleep disturbance. As many women also find bladder issues embarrassing to discuss [44], the clinician may have to ask specific questions about toileting behavior to determine whether the presence of lower urinary tract symptoms is contributing to disrupted sleep.

Psychiatric Well-Being and Sleep

Although it is possible that insomnia can contribute to depression as previously discussed, disrupted sleep is a very common symptom of depression and other psychiatric disorders. *Major depressive disorder* (*MDD*), *generalized anxiety disorder* (*GAD*), *post-traumatic stress disorder* (*PTSD*), and *panic disorder* are 2–3 times more common among women than men and should be considered in the

differential when women present with difficulty sleeping and daytime fatigue [45]. MDD involves symptoms of low mood, loss of interest in activities, lower energy, changing appetite, possibly suicidal ideation, and changes in sleep, often with insomnia [6]. After puberty and prior to the onset of menopause, women are twice as likely to be affected by depression as men, but this sex difference decreases once women reach the postmenopausal years [46]. In contrast, the perimenopause represents a time of increased vulnerability for depression for women during the process of aging. Perimenopausal women are 3–5 times at greater risk for the development of a major depressive episode during perimenopause compared to premenopause [8, 47].

Bipolar disorder involves the cycling between episodes of depression and episodes of mania, when patients experience a decreased in sleep, heightened energy, irritability, expansive mood, and delusions or engage in risk-taking behaviors [6]. Less is known regarding the risk for bipolar disorder in older female populations, but in younger populations, women with bipolar disorder have more risk for depressive and mixed episodes than men [47–49]. Retrospective studies of women with bipolar disorder during the menopause transition show that half of women with bipolar disorder report intense mood symptoms during the menopause transition, and depression occurs more often than mania [50, 51]. It is unclear whether hormone therapy is protective for these women.

The anxiety disorders that are most likely to affect sleep in older women are *GAD*, with excessive worry, muscle tension, fatigue, irritability, and insomnia, and *panic disorder*, with panic attacks, accompanied by fear of having panic attacks [6]. *PTSD* occurs less frequently, with anxiety symptoms following a traumatic event [6]. The incidence of anxiety disorders peaks in the fourth decade, but, as seen with depression, may increase in frequency during the midlife for women [45]. The majority of studies demonstrate an increase in anxiety symptoms during the menopause transition, especially in women with pre-existing anxiety [52, 53]. Risk for anxiety was elevated during perimenopause even for women with low levels of anxiety at baseline as well.

Sleep symptoms may vary with each psychiatric disorder. Early morning awakening is often experienced by depressed patients, although middle of night awakenings and difficulty initiating sleep can also occur [6]. Bipolar disorder is associated with a *decreased need* for sleep for periods of time, but the individual usually presents with other symptoms of mania, as described above [6], making it less likely that a clinician would misdiagnose bipolar disorder for a primary sleep disturbance. Patients with GAD often complain of their anxiety interfering with their ability to relax when attempting to fall asleep initially or during the night if they do wake [6]. Panic attacks involve intense fear, often with shortness of breath and rapid heartbeat, and can occur during the night waking a woman out of her sleep and are a common symptom among menopausal women [54]. Vasomotor symptoms have also been consistently associated with increased risk of anxiety during the menopause transition, and some women will even note a surge of panic-like anxiety immediately prior to onset of a hot flash [55, 56]. A core symptom of PTSD is hyperarousal, which frequently presents with difficulty sleeping with or without

nightmares [6]. Determining whether the individual has experienced an event that was associated with intense fear, helplessness, or horror can help the clinician rule out the presence of PTSD.

Psychiatric disorders are also often comorbid with medical conditions such as the metabolic syndrome or obesity [6], which are known risk factors for OSA. Psychiatric treatments, such as antidepressants, can also contribute to symptoms of RLS and PLMD. Little is known regarding substance use disorders in menopausal women. However, the use of substances, even when a primary substance use disorder is not present, can also affect sleep, with caffeine intake impairing the ability to fall asleep, particularly if used later in the day, and alcohol use often leads to interrupted sleep or early morning awakening [57]. Misuse of sleep aids and alcohol should be considered in an individual with long-standing sleep disturbance as they may have been trying to self-medicate.

With respect to the cases presented, a psychiatric disorder should be carefully considered as a primary factor leading to sleep disruption for Ms. A in Case 1 with her complaints of depressed mood and anxiety.

Assessment

A full evaluation for sleep disturbances among reproductively aging (transitioning and menopausal) women should include a detailed history regarding sleep changes and physical examination. Specifically, the interview should involve assessing comorbid medical and psychiatric symptoms and conditions, social history, as well as spectrum of menopausal symptoms. A psychiatric disorder is not likely to present with sleep disturbance alone, although substance misuse is still quite possible. A history of caffeine and alcohol intake and use of over-the-counter sleep aids is critical. See Table 6.2 for suggestions for assessment tools.

Self-report questionnaires can be used in the clinical setting to assess for depression and anxiety as well as nature and severity of sleep disruption. For depression, the Center for Epidemiologic Studies Depression [58] is a straightforward scale to complete; notably, this does not include a question regarding suicidal ideation, which may be a concern in a nonpsychiatric clinical setting. Anxiety rating scale such as the Spielberger State-Trait Anxiety Scale [59] is also self-administered and has clear cutoffs for mild, moderate, and severe anxiety. The Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index, or Epworth Sleepiness Scale can be useful for diagnosis and determination of severity of disturbed sleep [60].

When a sleep-related disorder such as OSA, RLS, and PLMD is suspected, a sleep study will be meaningful to establish diagnosis to inform definitive treatment. A sleep study, comprised of PSG, with nighttime electroencephalography (EEG), electromyography, and electrooculography to detect brain wave, movement, and eye rhythm changes during sleep cycles, can detect breathing disturbances and periodic limb movements as seen in Fig. 6.4. Wrist actigraphy, using a portable watch-like device, can also provide objective measurements of nighttime sleep patterns and movements [61]. While we may only require a basic history from Ms. A prior

Table 6.2 Assessment for sleep disturbance

Type of study		
Self-assessment tools		
Center for Epidemiologic Studies Depression (CESD)	Assesses risk for major depressive disorder	10-item scale; does not assess suicidality
Spielberger State-Trait Anxiety Scale	Assesses risk for anxiety disorders	20-item; distinguishes anxiety from depression, but not specific anxiety disorders
The Insomnia Severity Index (ISI)	Assesses severity of sleep impairment, effects on functioning, quality of life	7-item; does not assess type of sleep disturbance
Pittsburgh Sleep Quality Index	Assesses type of sleep disturbance as well as effects on quality of life	19-item; more comprehensive
Epworth Sleepiness Scale	Assesses level of sleepiness and risk for OSA	8-item; excessive sleepiness may be due to other sleep disorders as well
Objective sleep measures		
Sleep study	Assesses for sleep disorders such as OSA, RLS, PLMD	Utilizes electroencephalography (EEG), electromyography, and electrooculography
Wrist actigraphy	Assesses for sleep interruptions, movements during sleep	Measures sleep duration and movement during sleep

to initiating treatment as we suspect a primary psychiatric disorder, a sleep study will be important for Ms. B to rule out diagnoses such as OSA, RLS, and PLMD, in order to choose the most appropriate treatment options.

Disordered Sleep: Treatment

Non-pharmacological Treatments

Behavioral conditioning and maladaptive thinking patterns can exacerbate symptoms of insomnia. Increasing distress about poor sleep can lead to dysfunctional efforts to induce sleep and can cause conditioned arousal during bedtime [62]. Cognitive behavioral therapy for insomnia (CBT-I) is a form of psychotherapy which involves changing maladaptive thinking and behaviors that are contributing to insomnia, has been shown to be highly effective in various populations, and would be an appropriate choice for menopausal women experiencing sleep problems [62].

One component of CBT-I that may be effective on its own is the education piece about appropriate habits that can improve sleep, referred to as sleep hygiene. Sleep hygiene targets modifiable factors affecting sleep, such as factors regarding the

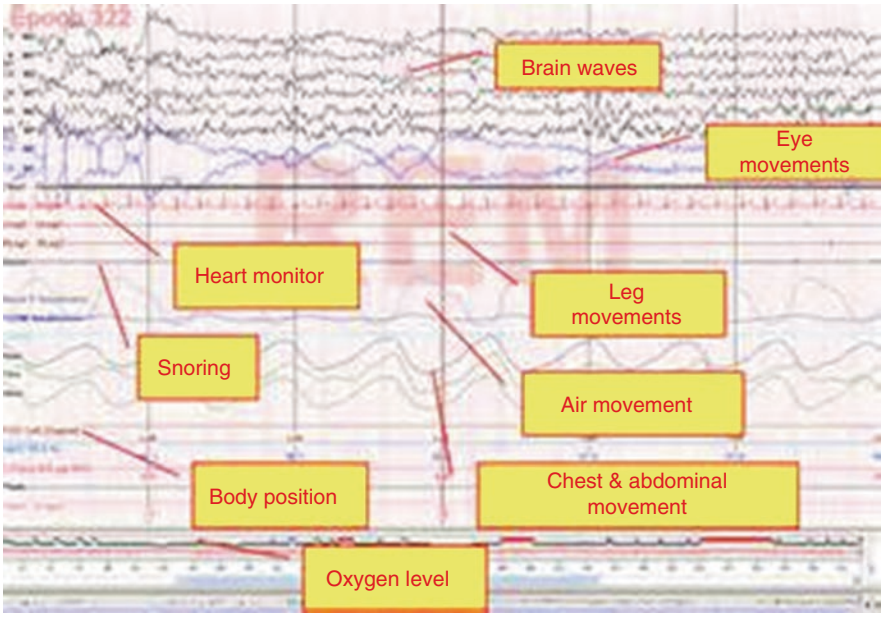


Fig. 6.4 A sample sleep study

chosen sleep environment, sleep schedule chosen, and avoidance of activating behaviors and substances near to bedtime. Recommendations for sleep hygiene, particularly for the perimenopausal woman, include: wearing lighter pajamas to bed and keeping a second pair of nightwear at hand, using lighter bedding and layering, keeping the ambient room temperature cool and keeping a fan nearby and a cool beverage near the bed, avoiding television and computer work in bed, attempting to have similar times for bedtime and morning wake-ups, limiting caffeine products throughout the day, avoiding alcohol and smoking, and avoiding exercise within 4 h of bedtime [63]. A regular bedtime that is not disrupted by environmental distractors, such as outdoor noises or a snoring partner, is critical to good sleep. In the case of disruption due to intermittent environmental noises, a constant sound machine or earplugs may offer some benefit [63].

A protocol of CBT for the treatment of climacteric symptoms (CBT-C) has also been developed [64, 65] and can be tailored more specifically to address sleep disturbances for the woman with moderate to severe vasomotor symptoms. CBT-C involves more focus on physical changes occurring with menopause and cognitive and behavioral strategies to challenge maladaptive thinking patterns regarding these changes – relaxation, exercise, and monitoring of vasomotor symptoms are key components of CBT-C. So far, research has demonstrated positive results of as few as ten sessions of weekly group CBT-C on reported sleep quality in peri- and postmenopausal women, in addition to benefits for mood, anxiety, and quality of life [64, 65]. Individual or group formats of CBT can be utilized.

Mindfulness-based stress reduction (MBSR), also often used in treatment of depression and anxiety, has been identified as an applicable treatment for vasomotor symptoms and insomnia in the peri- and postmenopause as well [66].

Options such as yoga, therapeutic massage, acupuncture, and acupressure have also shown benefits for treating insomnia during the menopause transition in small studies and can be considered given the low side-effect profile of these treatments [67–70]. Regular exercise has been shown to improve insomnia [71], but evidence in menopausal women is limited, showing small, but nonsignificant improvements in sleep with exercise [72]. More information regarding alternative treatments for menopausal symptoms in another chapter of this textbook is dedicated to this topic.

The option of CBT or MBSR would be helpful adjuncts to either in Cases 1 and 2, for both Ms. A and Ms. B, but is limited by availability of trained providers and the motivation of the patient, as both require individual or group sessions as well as daily homework practice. As long as there is no contraindication to regular exercise, massage, or acupressure/acupuncture, these alternatives are reasonable adjunctive interventions for most women including Ms. A and Ms. B.

Pharmacological Options

Menopausal Hormone Therapy (MHT) and Sleep

MHT remains the gold standard for vasomotor symptoms among the symptomatic peri- and early postmenopausal women. The North American Menopause Society (NAMS) supports the initiation of MHT around the time of menopause to treat menopause-related symptoms when the balance of potential benefits and risks is favorable for the individual woman [73]. While hysterectomized women can use unopposed estrogen therapy (ET), MHT regimen in non-hysterectomized women must in addition include a progestin or progesterone (EPT) to thwart endometrial hyperplasia and diminish the risk of uterine cancer [74]. MHT-prescribing practices vary from practitioner to practitioner and must be individualized, and a full review of these regimens is beyond the scope of this discussion, but is covered elsewhere in this textbook. If insomnia is a dominating complaint in a woman deemed to be in perimenopause, or in early menopause and poor sleep is due, at least in part, to night sweats, MHT is likely to improve consistency of sleep.

The efficacy of MHT for other types of sleep difficulties such as difficulty falling asleep and early morning awakening remains unclear, however, with mixed results in recent research. Some studies have evaluated the effects of ET alone, finding significant improvements in subjective sleep disturbance, increased REM sleep, and shorter sleep latencies compared to placebo [75, 76]. Improvements in subjective sleep quality have also been shown with progesterone and estrogen combinations over short- and longer-term protocols [77, 78]. Studies have not, however, demonstrated significant changes in sleep efficiency on objective testing with PSG [79–81]. Treatment with progesterone alone has shown significant reductions in time spent awake during the night, but given the lack of benefit for other menopausal symptoms, progesterone therapy alone is of limited value in menopause

management [82]. The inconclusive nature of the bulk of existing data and the potential risks of MHT, including blood clots, stroke, and breast cancer, particularly with EPT [83, 84], suggests that the role of MHT as a first-line treatment of sleep disorders in perimenopausal women must be individualized. For Ms. A, given the presence of bothersome vasomotor symptoms that are believed to be interfering with sleep in a relatively young perimenopausal woman, a trial of MHT should be a consideration. We would tailor the treatment of choice to her preference, but if MHT is initiated, it would be important to use a dosage of E that achieves effective control of the night sweats as otherwise, Ms. A is accepting the potential risks of MHT, without receiving sufficient benefit.

Sedative Hypnotics and Sleep

Often, the short-term use of a non-benzodiazepine hypnotic is warranted to achieve relief from acute, initial insomnia. Both zolpidem and eszopiclone, both gamma-aminobutyric acid (GABA)-A receptor agonists, have been shown to be more effective than placebo in the treatment of insomnia in peri- and early postmenopausal women, including in women with nighttime vasomotor symptoms [85–87]. Concerns regarding these medications include following possible tolerance, withdrawal, dependence, and rebound insomnia with discontinuation.

Benzodiazepines, such as clonazepam and lorazepam, are sometimes utilized to aid sleep difficulty as well, particularly in the setting of coexisting anxiety. It is important to appreciate that there is little evidence to support their use for insomnia in the peri- and postmenopausal population, and these agents can be considered for short-term use, given their risks of tolerance, withdrawal, dependence, and rebound insomnia.

Selective melatonin receptor agonist, ramelteon, has shown promise in menopausal women with insomnia, with improvements in sleep latency, total sleep times, and subjective sleep quality [88].

Although a brief use of a sedative-hypnotic can be considered in the case of Ms. A, it would be preferable to do so in conjunction with MHT. However, potential benefits may not outweigh risks for the use of these agents with Ms. B, given her comorbid medical issues.

Antidepressants, Anxiolytics, and Sleep

Antidepressants and anxiolytics can be of benefit when sleep issues are accompanied by symptoms of depression and/or anxiety. In addition to documented positive effects on mood, the selective serotonin reuptake inhibitor (SSRI) and serotonin and norepinephrine reuptake inhibitor (SNRI) classes of antidepressants have shown benefit against vasomotor symptoms in perimenopausal and early menopausal women [89, 90]. Among the many available formulations, escitalopram and venlafaxine's effects on sleep have been studied in peri- and postmenopausal populations, demonstrating decrease in nighttime awakenings and improved sleep quality [91, 92]. In treatment of mood and anxiety disorders, these medications may take time to have a positive effect on sleep as they gradually improve the underlying affective disorder, and patients should be appropriately counseled in this regard.

Caution is advised when initiating the SSRIs and SNRI as they can at temporarily exacerbate symptoms of anxiety when first started, typically causing physical symptoms, such as jitteriness or even more difficulty with sleep. Starting at a low dose, providing reassurance to the patient that these side effects will resolve, usually within several days, and combination with a benzodiazepine, such as clonazepam, briefly is often beneficial. Women should be counseled that positive effects are not immediate and may occur up to 4–6 weeks following initiation. Weight gain is not typically a significant concern with SSRIs/SNRIs, but many women experience changes in sexual function such as low libido or difficulty with orgasm, which can be frustrating [93].

Gabapentin, another agonist at the neurotransmitter GABA's receptors, is a medication often used to treat neuropathic pain and anxiety [94, 95]. As it has low risk for abuse and dependence, gabapentin is often preferred as a safe option for managing anxiety, particularly if comorbid substance abuse is present [96]. This medication also has been shown to be beneficial against vasomotor symptoms during the menopause transition [97, 98] and can lead to improved sleep quality in these women [99]. Gabapentin therefore may be helpful for a patient experiencing both night sweats and anxiety, like Ms. A in Case 1.

The sedating antidepressant, mirtazapine, has also demonstrated efficacy for insomnia related to menopause transition [100]. This is an effective serotonergic antidepressant, but its utility is limited by the associated weight gain [101]. Trazodone, another antidepressant, has shown benefits for sleep in postmenopausal women and, given its safety profile and low risk for side effect, can be a good option for the older aging women [102]. Tricyclic antidepressants can also have sedating effects; given their anticholinergic properties, they may be useful in patients with comorbid incontinence with insomnia, although bothersome side effects such as dry mouth and sedation are common with his class of agents, thus limiting their utility.

An antidepressant, most likely an SSRI or SNRI, should certainly be discussed with Ms. A if her full assessment leads to a diagnosis of a depressive or anxiety disorder. Table 6.3 summarizes the use of medications for sleep, depression, and anxiety.

Other Options

Patients often ask about herbal medication and supplements for menopausal symptoms. Given their unclear benefit and lack of monitoring through standardized regulatory boards, over-the-counter herbal medications and supplements are not currently recommended as first-line treatment for menopausal symptoms [103].

Targeted interventions for sleep-related disorder such as OSA or RLS include continuous positive airway pressure (CPAP) for obstructive sleep apnea, and medications such as ropinirole for RLS, to be prescribed by sleep specialists. However, women may benefit from a combination with other treatments discussed, particularly as the nature of their insomnia can be complex. For Ms. B, we should initiate CPAP if she does indeed have OSA, but she may also benefit from non-pharmacologic strategies targeting weight loss and blood glucose management.

Table 6.3 Common medications used for sleep, depression, and anxiety

Medication	Starting dose	Uses	Side effects/concerns
Non-benzodiazepine sedative hypnotics			
Zolpidem	5 mg	Sleep initiation	Tolerance, dependence, rebound insomnia; sedation
Eszopiclone	1–2 mg	Sleep initiation	Tolerance, dependence, rebound insomnia; sedation
Ramelteon	8 mg	Sleep initiation with delayed sleep phase	Sedation
Benzodiazepines			
Lorazepam	0.5–1 mg	Sleep initiation, when anxiety present; short acting	Tolerance, dependence
Clonazepam	0.25–0.5 mg	Sleep initiation, when anxiety present; longer acting	Tolerance, dependence
Antidepressants			
Trazodone	50–100 mg	Sleep initiation and preventing nighttime awakenings	Sedation
Mirtazapine	7.5–15 mg	Sleep initiation and preventing nighttime awakenings	Weight gain, sedation
Escitalopram	5–10 mg	MDD and anxiety disorders; vasomotor symptoms	Sexual dysfunction, gastrointestinal upset; increased anxiety or insomnia with starting
Venlafaxine	75–150 mg	MDD and anxiety disorders; vasomotor symptoms	Sexual dysfunction; increased anxiety or insomnia with starting
Other medications			
Gabapentin	300–600 mg	Pain, anxiety, vasomotor symptoms	Sedation, possible tolerance, withdrawal

Summary

Sleep disturbances are common during the menopause transition and early postmenopause. The hormonal fluctuations are frequently associated with bothersome vasomotor symptoms which disrupt sleep. However, for many women, sleep disruption is multifactorial. While hormonal fluctuations are a given during the perimenopause, factors that must be considered among menopausal women with sleep complaints include poor sleep hygiene, maladaptive psychological responses to insomnia, psychiatric disorders, lower urinary tract issues, sleep disorders (OSA, RLS, PLMD), and misuse of sleep aids and/or alcohol. Once the etiology and contributing factors for an individual are determined, appropriate, effective treatments

are available, and often regimens need to be tailored to patient characteristics and individualized preferences.

Now we can return to summarize our management of our cases of Ms. A and Ms. B. As Ms. A has vasomotor symptoms, a trial of MHT can be considered. If, however, we determine that her sleep difficulties are associated with a depressive episode or anxiety disorder, then a trial of an SSRI or SNRI is appropriate. This alternative could be considered to address her vasomotor symptoms as well, especially if she is averse to starting MHT. Additionally, education regarding sleep hygiene, particularly avoidance of alcohol and caffeine, wearing light clothes to bed, and keeping regular sleep schedules, would be recommended. A trial CBT-C may be helpful for her as well. For Ms. B, it seems very likely that ordering a sleep study may reveal a primary sleep disorder, most likely OSA. If this is the case, then CPAP is likely to offer benefit. Similar recommendations for sleep hygiene will remain important for her in addition to this.

Clinical Pearls

- Sleep disturbances are common in the menopause transition and can include difficulty with falling asleep, nighttime awakenings, and early morning awakening. Vasomotor symptoms may be associated with the nighttime awakenings.
- Medical illnesses, such as OSA, PLS, and PLMD, are common in menopausal women and can be associated with sleep disturbance. Appropriate questioning regarding their symptoms and evaluation with a sleep study will be helpful for diagnosis.
- Psychiatric disorders are also common in menopausal women and can contribute to sleep disturbances. Evaluation involving a clinical interview and self-assessment tools are helpful for screening and for diagnosis.
- Treatment with MHT may be appropriate for some menopausal women, especially when sleep disturbance may be associated with vasomotor symptoms.
- Brief use of sedative hypnotics or sedating antidepressants may also help with sleep when used in conjunction with recommendations for sleep hygiene.
- Cognitive behavioral therapy or mindfulness-based treatments are helpful as well.

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Management of Genitourinary Syndrome of Menopause (GSM)

7

Vanessa A. Lukas and James A. Simon

Case 1

A 55-year-old, married, nulliparous, Caucasian woman who is 5 years postmenopausal presented to the clinic with worsening vaginal dryness and sexual pain. She stated that her symptoms were initially intermittent and mild beginning at age 52 and consisting of a sensation of dryness or vulvar irritation from long-distance walking or after toilet tissue use. At that time, increased foreplay prior to vaginal penetration and over-the-counter vaginal lubricants provided adequate symptom relief. More recently, however, the dryness could no longer be remedied despite profuse lubricant use. Sexual pain, both superficial and deep, has increased to a point that sexual activity had ceased. For someone who has had an average of two satisfactory sexual encounters weekly and continues to enjoy a good libido, this has caused great distress and has impacted her relationship with her 55-year-old husband whose erectile dysfunction had been successfully managed for over a decade with a daily maintenance of 2.5 mg dose of tadalafil. She is hoping that similar relief can be afforded to her as she remains otherwise healthy, nonobese, and without chronic diseases, vasomotor symptoms, sleep disorders, or depression. She takes daily calcium and vitamin D supplements and has no known history of cancer, liver disease, or blood clots. Additionally, the patient has a history of negative screening mammograms. On pelvic exam, inspection revealed no evidence of gross deformity or visible lesions except for evidence of moderate introital and vaginal stenosis. On palpation, there was no focal point tenderness on cotton swab testing (Q-tip test) of the introital tissue. An attempt at bimanual examination was limited as the patient

V.A. Lukas, BA
Clinical Research, Women's Health and Research Consultants®,
1850 M St. NW, Suite 450, Washington, DC 20036, USA
e-mail: vlukas@jamesasimonmd.com

J.A. Simon, MD, CCD, NCMP, IF, FACOG (✉)
Obstetrics and Gynecology, George Washington University, School of Medicine, Women's Health and Research Consultants®, 1850 M St. NW, Suite 450, Washington, DC 20036, USA
e-mail: JSimon@JamesASimonMD.com

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could tolerate only a single finger being introduced into the vagina before acknowledging severe discomfort. The vaginal mucosae were thin, dry, pale, and without rugae. There was no evidence of vaginal infection or discharge. The vaginal pH was 6.2 and vaginal cytology was normal with a maturation index consistent with postmenopausal vaginal atrophy (2 % superficial cells, 78 % intermediate cells, and 20 % parabasal cells). No uterovaginal prolapse or pelvic floor musculature tenderness or nodularity was appreciated on exam.

Case 2

A 60-year-old multiparous, Caucasian, nonobese woman who has been postmenopausal since age 53 complained of experiencing 3 years of generalized vulvar discomfort described as near constant "burning and rawness" in both the vulvar and perineal areas, with intermittent aggravation of symptoms after urination, bowel movements, or following intercourse. In addition, she reports a history of recurrent urinary tract infections treated with antibiotics and intermittent urgency incontinence requiring the use of absorbent sanitary products. She further reports a longstanding history of vaginal dryness and dyspareunia for which she has been using over-the-counter moisturizers and lubricants with some relief. The degree of bother related to these symptoms has rendered her asexual over the past year, although she denies any resulting marital discord with her 69-year-old husband, who has developed a decreased desire over the years. However, she hopes to return to her former baseline average of two acts of intercourse monthly once her symptoms of vulvar and perineal pain resolve. On inquiry, the patient acknowledged a history of a prolonged second stage of labor in her last pregnancy requiring an episiotomy to achieve vaginal delivery, with a subsequent postpartum perineal infection that took weeks to heal. She also acknowledges some degree of stress urinary incontinence dating back to her last delivery. The patient reported negative screening mammograms and no history to contraindicate the use of menopausal hormone therapy. Visual inspection revealed significant vulvar atrophy with a prominent, erythematous urethral meatus, moderate regression of the labia minora and clitoral phimosis. The surrounding labial tissue was sparsely covered with pubic hair; the skin appeared pale, dry, and thin. There was no evidence of any vulvar or vaginal lesions, papules, plaques, or of abnormal pigmentation. The perineal tissue demonstrated a prominent midline healed episiotomy scar. On cotton swab testing (Q-tip test), the patient verbalized moderate pain, and petechiae were noticeable on areas of contact where the skin appeared especially thin. The vaginal mucosa was atrophic, pale, and dry without evidence of erythema or discharge; introital elasticity was limited, and severe "stabbing and tearing pain" was elicited on attempts at introducing the smallest vaginal speculum. The vaginal pH was 7, and vaginal cytology confirmed atrophy with 95 % parabasal cells; there was no evidence of bacterial or yeast vaginitis. There was no evidence of pelvic mass or any anatomical variant of genital prolapse (uterovaginal prolapse, cystocele, or rectocele). Minimal dribbling of urine was noted from the urethral meatus when the patient was asked to cough while in modified lithotomy position. Urinalysis was positive for protein and white and red blood cells, and a urine culture revealed heavy growth of *E. coli*.

What is the most effective and appropriate first step in management of case 1?

A. More moisturizers/lubricants
B. Low-dose vaginal estrogen (answer)
C. Oral ospemifene
D. Pelvic floor physical therapy
E. Systemic conventional-dose hormone therapy (oral or transdermal)

What is the most effective and appropriate first step in management of case 2?

A. Oral anticholinergics
B. Low-dose vaginal estrogen and a course of antibiotics to treat the urinary infection (answer)
C. Extended suppressive therapy with oral fluconazole
D. Topical vulvar lidocaine
E. Low-dose oral tricyclic antidepressants

Overview of the Evaluation and Management of GSM

General Considerations

Vulvar and vaginal symptoms of menopause are experienced by approximately 50 % of postmenopausal women although this prevalence is likely underestimated [1]. Clinically, symptoms of vulvovaginal atrophy (VVA) can be identified within 4–5 years of the last menstrual period, with a fivefold increase in prevalence as women progress through menopause; the highest incidence of VVA occurs in late menopause (STRAW stage +2) [2–5]. VVA is chronic and, without hormonal intervention, progressive [2]. While a number of retrospective studies have attempted to quantify the magnitude of prevalent VVA, consensus is lacking, and the prevalence of VVA symptoms by race and age cohorts remains unclear [6]. Surveys of postmenopausal women show a distinct lack of awareness among both providers and the general population regarding vaginal changes consequent to menopause [1, 7]. Unfortunately, VVA is rarely screened for without the patient initiating the conversation regarding bothersome and distressing symptoms [2].

Recently, the terminology VVA has been replaced with genitourinary syndrome of menopause (GSM) to be more inclusive of all the genitourinary symptoms experienced by postmenopausal women and to include both symptoms resulting from estrogen deficiency (i.e., vaginal dryness, dyspareunia, vulvar and vaginal itching and irritation) and those resulting from both estrogen deficiency and the effects of aging on the bladder and pelvic floor (i.e., dysuria, urgency, bladder and urinary tract infection) [8, 9]. GSM greatly impacts patient quality of life by resulting in sexual dysfunction, avoidance of intimacy, and causing relationship distress [10]. Although sexually active women may be more concerned by GSM, abstinent women can exhibit more severe long-term sequelae of estrogen deficiency such as introital and vaginal stenosis, labial fusion, as well as urogenital infections [10].

A variety of therapeutic options are available for women suffering from GSM including nonhormonal moisturizers and lubricants, low-dose local estrogen therapies,

oral ospemifene (a selective estrogen receptor modulator, SERM), and systemic estrogen products both unopposed and in conjunction with progestogens/progesterone and in combination with BZA (bazedoxifene, a SERM). For women suffering from GSM, but without any additional menopausal symptoms (i.e., vasomotor symptoms), the use of systemic estrogen-based therapy is neither indicated nor advised as unlike vasomotor symptoms that can effectively be controlled with the use of low-dose systemic estrogen, much higher doses of systemic estrogen are typically required to impact focal genitourinary symptoms. In contrast, local estrogen formulations can offer effective relief of genitourinary symptoms without any appreciable systemic absorption of hormone. The global consensus and current recommendations on the choice of menopausal hormone regimen are to initiate treatment at the minimum dose necessary to treat the most bothersome symptom and to use local estrogen therapy for focal vulvovaginal and urinary symptoms of GSM [11]. It is also important to consider the patient's therapeutic preferences and provide close follow-up in an atmosphere of open dialogue.

Differential Diagnoses

For postmenopausal women experiencing vaginal dryness, vulvar and vaginal itching, and irritation, dysuria, or dyspareunia, GSM should be considered the most likely diagnosis. Concomitant etiologies such as infection, dermatological conditions, pelvic floor disorders, or chronic pain syndromes, which can also contribute to symptomatology, should always be considered and excluded through appropriate screening.

Vaginitis In addition to what used to be called atrophic vaginitis, vulvovaginal atrophy, or VVA and is now referred to as GSM where estrogen deficiency is deemed as the underlying cause, additional variants of vaginitis (such as from infection) should always be considered, as these can exacerbate symptoms of VVA. Typical vaginal infections include bacterial vaginosis, trichomoniasis, or candidiasis. These common etiologies for vaginitis can be screened in the clinic by assessing vaginal pH, physical characteristics of any discharge (such as color and odor), and examination of a wet mount/KOH prep under light microscopy; an infectious etiology can be established by culture or utilization of DNA probe technology for common infections such as chlamydia and gonorrhea. Bacterial vaginosis can be treated with oral or vaginal metronidazole or clindamycin [12]. Trichomoniasis can be treated with oral or vaginal metronidazole or oral tinidazole, and candidiasis can be treated with oral or vaginal azoles, such as vaginal terconazole or oral fluconazole [12]. If candidiasis does not resolve with azole treatment, non-*albicans Candida* should be considered and further evaluated by culture. For patients with a history of vulvar pain and sensitivity, oral preparations should be considered the preferred method of treatment over vaginal preparations, particularly in the case of terconazole, which commonly cause vulvar and vaginal irritation [13]. After initiation of estrogen therapy, opportunistic yeast infection must be considered due to the drastic reduction in vaginal pH and increase in vaginal glycogen [14].

Urinary tract infection (UTI) Dysuria, urgency, and frequency are symptoms of GSM and of UTI. Estrogen deficiency can increase the risk for UTI due to urethral atrophy and physiological changes including increased vaginal pH and reduced urogenital lactobacilli, enabling the opportunistic colonization of the urethra and bladder with pathogens including *E. coli* [15]. UTI should be screened for and treated appropriately with an antibiotic indicated by sensitivity on urine culture. Vaginal estrogen is the route of estrogen administration documented to be effective for the reduction of recurrent UTI in women with GSM [16, 17].

Dermatitis Contact dermatitis can result in vulvar itching and irritation from exposure to an irritant or allergen, and the symptoms can mimic GSM. The tissue response can be non-immunologic or immunologic (allergic dermatitis) and can result in an immediate or a delayed reaction, respectively. Common irritants include products with fragrance, color, spermicide, or synthetic material. Identification and elimination of the irritant is imperative. If dermatitis is not improved with removal of the irritant, short-term application of topical corticosteroids of low (hydrocortisone 2.5 %), medium (triamcinolone acetonide 0.1 %), or high (clobetasol propionate 0.05 %, halobetasol 0.05 %) potency based on the severity of the dermatitis can offer relief for symptoms and should be gradually tapered in frequency and potency as the patient's symptoms improve [18].

Lichen sclerosus Lichen sclerosus is a chronic inflammatory condition that can affect women across the life cycle; the affected areas appear as white and wrinkled papules and plaques on the vulva, without vaginal involvement. The lesions are due to thinning of the vulvar squamous epithelium making the involved tissue very fragile. The affected skin areas tear easily from rubbing or scratching, with the involved skin areas often presenting as hypertrophic plaques due to chronic irritation and scratching. Untreated, this condition can result in scarring and anatomical deformity of the vulva, with ensuing introital stenosis, labial adhesions, and an occluded clitoral hood. The primary complaint is severe pruritus with or without burning, soreness, and dyspareunia. The distinctive, parchment-like, hypertrophic lesions frequently distinguish lichen sclerosus from GSM; additionally lesions may involve skin in other areas, such as the abdomen. Lesions of lichen sclerosis are associated with squamous cell carcinomas, and skin biopsy should be routinely undertaken as part of the evaluation; annual vulvoscopy may be required for future risk assessment [19]. Treatment with a potent corticosteroid, such as 0.05 % clobetasol propionate, applied twice daily for 2–4 months should improve the epithelial integrity and color of affected skin, at which point the frequency of corticosteroid dosing can be reduced or a less potent corticosteroid prescribed.

Lichen planus Similarly to lichen sclerosus, lichen planus is an inflammatory dermatological condition. It is rare relative to lichen sclerosus and, unlike the latter, is

seen primarily in postmenopausal women [20]. Lichen planus presents most commonly involving the vulva, the vagina, or even the rectum; the oral mucosa is additionally often affected. These lesions appear as bright red epithelial erosions with or without white reticulates or papules and purulent vaginal discharge can be seen. Untreated, lichen planus can cause scarring and adhesions. Vulvar, vaginal, or rectal burning with pruritus and dyspareunia are the primary complaints. The diagnosis may be confirmed by biopsy from the outer edge of an erosion. The histology of erosive lesions is characteristically nonspecific, and it is notably difficult to distinguish lichen planus from early cases of lichen sclerosus, which have yet to exhibit the characteristic atrophy with edema and sclerosis of the papillary dermis [21–23]. It is necessary to distinguish lichen planus from lichen sclerosus as that will determine the necessity for future cancer screening [21]. There is no cure for lichens planus, but symptom management with topical or vaginal corticosteroids, such as 0.05 % clobetasol propionate or hydrocortisone, is effective. Severe cases may require systemic corticosteroids, such as prednisone, for immediate relief.

Pelvic floor and bladder disorders Symptoms of urinary urgency, frequency, and incontinence can be related to pelvic floor disorders [24, 25]. Stress incontinence resulting in urine leakage with increases in intra-abdominal pressure can be related to poor urethral support, urethral sphincter weakness, or levator ani dysfunction [24]. Female pelvic organ prolapse can exacerbate these symptoms [25]. Urgency incontinence resulting in large involuntary voids of urine results from overactive bladder musculature [24]. An assessment of urinary symptoms by the Valsalva maneuver can help to determine the cause of incontinence [24]. For either stress or urgency incontinence, habitual changes such as fluid restriction, weight loss, timed voiding, and pelvic floor physical therapy can help improve symptoms [25–27]. Stress incontinence may require more aggressive medical intervention such as incontinence pessaries and/or surgery [25]. Urgency incontinence can often be effectively managed with anticholinergic agents although oxybutynin is contraindicated for frail older women [28].

Vulvodynia Vulvodynia is a diagnosis of exclusion in women experiencing vulvar irritation and pain for a duration of at least 3 months with no apparent infectious, dermatological, inflammatory, or neurological etiology [29, 30]. It is unclear the extent to which vulvodynia may be linked to hormonal status as there is no consensus [31], and the etiology is not fully understood, although it is likely multifactorial and patient specific. The discomfort may be localized to the vulva, but can also be generalized, or mixed; pain and irritation may only happen on provocation, occur spontaneously, or be mixed; symptom onset may follow an instigating event or be primary, and the discomfort may vary in its temporal pattern (be intermittent or constant) [29]. Although not fully substantiated, the onset of vulvodynia and long-term estrogen deficiency seem to be linked [31, 32]. Unlike vestibulodynia (localized, provoked) which is primarily managed surgically (vestibulectomy) by excision of the neurologically hypersensitive tissue [33], there is no readily available surgical

treatment for the generalized, unprovoked cases where management relies greatly on off-label treatment with tricyclic antidepressants [34] and anticonvulsants [35] to decrease neural hypersensitivity [36]. Pelvic floor physical therapy [30], surface electromyographic (sEMG) biofeedback training [37], and self-vaginal dilation [38] can help symptoms by strengthening and stretching the vaginal tissue by promoting muscle relaxation and desensitization [30].

Nonhormonal Therapies for GSM

As a first-line option, vaginal lubricants and moisturizers can show adequate reduction in vaginal dryness and dyspareunia. Lubricants and moisturizers (Table 7.1) do not act on any physiologic system, but rather provide temporary relief by reducing friction in the vulva and vagina during everyday and sexual activity. Lubricant options can be water, silicone, or oil based and are commonly used to facilitate sexual activity. Water-based lubricants are the most common, but suffer from

Table 7.1 Formulations of nonhormonal vaginal lubricants and moisturizers

	Composition	Frequency	Pros	Cons
Lubricants	Water	As needed	Most common Compatible with all condoms	Requires frequent reapplication
	Silicone		Long lasting Compatible with all condoms	Expensive Not water soluble Cannot be used with silicone sex toys
	Oil		Long lasting	Not compatible with latex condoms (especially a petroleum product, i.e., mineral oil)
	Hybrid (water/silicone, water/oil, silicone/oil)		Long lasting Compatible with some condoms[a]	Not user friendly, may require mixing before use
Moisturizers	Polycarbophil, glycerin, mineral oil	Every 3 days	Dual purpose, moisturizer and lubricant	Buffering agent, not actively improving tissue
	Lactoperoxidase, lactoferrin	Twice weekly	Dual purpose, moisturizer and lubricant Inhibit yeast and bacteria growth	Buffering agent, not actively improving tissue

[a]Water/silicone is safe with all condoms, but compositions with oil are not safe with latex condoms if the oil is a mineral oil or some exotic oils

requiring reapplication when their water content evaporates. They are short acting. Silicone-based lubricants are long lasting, but typically more expensive and can be difficult to wash off. Further they can "coat" the surfaces of showers and bathtubs creating a fall risk particularly in older individuals with altered proprioception. Oil-based lubricants are long lasting and some prefer them for both vaginal and anal sex. Hybrids of each of these types offer the anticipated benefits of each of the aforementioned types. Hybrids can be more expensive and often require mixing before use, like the oil and vinegar of salad dressing. There are no hard and fast rules on lubricants, and women and couples commonly choose based on availability, cost, and tactile preference. Further, the content is not entirely available from the manufacturers. Postmenopausal women suffering from VVA should avoid lubricants with additives, such as warming agents and spermicides, as they may cause irritation independent of sexual activity. Unlike lubricants, moisturizers can provide longer-term alleviation of mild vaginal atrophy symptoms (especially dryness) by preserving vaginal moisture and buffering effects that lower vaginal pH, thus offering benefit even for women who are not sexually active. Polycarbophilic vaginal moisturizers, which constitute the majority of US-based formulations, however, provide only a transient improvement in vaginal dryness and dyspareunia versus lasting symptom reduction and atrophy improvement with estrogen [39]. Lactoperoxidase/lactoferrin vaginal moisturizers act as to buffer vaginal pH and as a prebiotic to maintain normal vaginal flora by inhibiting candida and bacteria [40].

Vaginal dilation in conjunction with lubricants can be helpful, particularly when progressive introital stenosis and decrease in vaginal caliber and length ensue consequent to avoidance of penetration due to discomfort; this approach can also benefit the nulliparous women in same gender relationships and for those who engage in infrequent sexual activity. In nulliparous women, introital stenosis is to be expected, and extreme cases occurring earlier in menopause are much more common than in multiparous women [4]. Coital activity is known to be negatively correlated with vaginal atrophy and initiating vaginal massage with dilators can help restore vaginal function [41, 42].

Hormonal Therapies for GSM

Local vaginal estrogen treatment should be considered if nonhormonal strategies fail to address symptoms of dyspareunia and vaginal dryness or concomitant with them. Systemic estrogen therapy does not have a place in the management of GSM alone, without concomitant systemic symptoms of estrogen deprivation (i.e., hot flushes, night sweats, and poor sleep) as low-dose vaginal estrogen should be more than adequate for focal symptom relief with minimal adverse effects [43]. Therefore, systemic estrogen will not be a topic of therapeutic discussion. Vaginal estrogens are available in a variety of formulations including tablet, vaginal rings, and creams (Table 7.2). Each of these methods has its own benefits and drawbacks in terms of localization of estrogen, ease of dosing, and modulation of dosing.

Delivery of estrogen directly to the vulvovaginal tissue targets hormone delivery to the affected area while minimizing risk for systemic absorption. This targeting of

Table 7.2 Formulations of low-dose local vaginal estrogen therapies

	Composition	Frequency	Pros	Cons
Creams	Conjugated estrogens (0.625 %)	Initial: 2–4 g/day for 1–2 weeks Maintenance: 1 g/1–3 times weekly	Variable dosing options Focal treatment to vulva and urethra Additional lubrication	Messy Low patient preference and compliancy
	17β-estradiol (0.1 %)	0.5–2 g/day for 21 days then off 7 days or 0.5 g twice weekly		
Tablet	Estradiol hemihydrate (10 mcg)	Initial: 1 tablet/day for 2 weeks Maintenance: 1 tablet/twice weekly	High patient preference and compliancy Option of variable dosing	Dose may be too low. Little or no effect on vulvar tissue
Ring	17β-estradiol (7.5 mcg/day)	2 mg/90 days	High patient preference and compliancy	Constant wear necessary
Oral	Ospemifene	60 mg/day	Oral	Once daily

focal tissue with "local" hormone application however can still contribute to systemic hormone levels as the absorption of estrogen is dependent on dosage of estrogen applied as well as the degree of vaginal atrophy [9]. Thus systemic absorption is not completely eliminated with low-dose local estrogen treatment, particularly in the early stages of treatment when the vaginal epithelium is still atrophic [4, 44]. As the integrity of the vaginal epithelium improves, and the tissue thickens, estrogen absorption decreases, and with regular use, lower estrogen dose regimens can sustain the positive tissue effects of local hormone therapy with minimal systemic absorption [4]. While all local vaginal estrogen therapies available on the market have similar efficacy and labeling, tablets, creams, and rings vary in terms of ease of administration resulting in differing adherence to treatment [45] with users favoring the ring, followed by tablet, above vaginal creams as a method of hormone delivery, thereby resulting in a statistically significant increase in adherence to treatment [45]. Compliance with recommended treatment is critical to effectiveness as GSM is a chronic and progressive condition. Regardless of the convenience, modulation of dosing and ability to provide focal treatment to the vulva is not available for the ring and tablet, formulations, except to the degree that estrogenized vaginal secretions can secondarily act upon the vulva. Creams allow for variable dosing options to meet the patient's individual needs. In addition to vaginal administration with an applicator, treatment directly to the vulvar tissue is also possible from direct application or from vaginal leakage as the available cream warms to physiological temperature and its viscosity changes from cream to liquid. The increased therapeutic coverage helps target the introital and urethral tissue, which can benefit from increased direct exposure. While for some patients this messier dosing method is not preferred, others may benefit from the additional lubrication provided by the cream base that helps to facilitate sexual intercourse and alleviate dyspareunia.

Individualized approaches may require a combination strategy (estrogen cream to the vulva and an insert [ring or tablet] for vaginal symptoms) to best achieve results.

Unfortunately, obstacles for woman seeking local vaginal estrogen therapy exist in the form of estrogen class labeling, insurance coverage, and lack of generic options. Despite the safety of low-dose vaginal estrogen formulations, the boxed warnings ("class labeling") on these products and their package inserts continue to erroneously convey risk profiles that are seen only with systemic administration of estrogen in much higher doses than used in vaginal products [43]. The erroneous estrogen class labeling of adverse events results in a large number of women with GSM not seeking or utilizing treatment due to perceived risk [43]. The perceived risk can also result in primary care physicians advising patients to discontinue local vaginal estrogen therapy without assessing need by consulting with the patient's gynecologist. There is an ongoing and concerted effort by experts in the field of menopause to highlight this misperceived risk escalation of low-dose vaginal estrogen products based on a drug class labeling [43]. Estrogen use-related risks of endometrial cancer [43], breast cancer [46, 47], cardiovascular disorders [48], and of dementia [43] that are displayed in the boxed warnings of vaginal formulations are far removed from the adverse event profile observed during clinical trials of low-dose vaginal estrogen therapy. In fact, the current opinion of The American College of Obstetricians and Gynecologists advocates that low-dose vaginal estrogens (ring or tablet) can be safely used not only for women with a personal history of breast cancer but also for women who are currently experiencing GSM symptoms as a result of current breast cancer treatment [46].

Among factors that impact real-life use of efficacious therapies for GSM, financial considerations loom high. Insurance coverage and out-of-pocket payments can result in a cost barrier restricting access to treatment entirely or necessitating the patient stretch the limits of a single vaginal estrogen prescription by reducing the amount used per dose or the frequency of dosing. Conversely, some patients require more than the recommended dose to alleviate symptoms and are denied additional doses prescribed by their physician based on medical need. The overall absence of generic substitutes for vaginal estrogen formulations in the US market results from the erroneously escalated risk perception as discussed earlier, fueled to some degree by the absence of a former guidance from the Food and Drug Administration (FDA). Only in 2014 were guidance documents revised for conducting generic bioequivalence and pharmacokinetic studies for estradiol creams and tablets [49].

A relatively new and novel addition to the treatment options available to address symptoms of moderate to severe dyspareunia of menopause is a SERM, ospemifene. Relative to other investigational selective estrogen receptor modulators, ospemifene was identified as a viable option to treat dyspareunia related to VVA due to its estrogen agonist effects on both vulvar and vaginal tissues yet weak action on the endometrium [50]. Data on long-term effects of ospemifene are limited, and longitudinal studies are needed in light of the increased risk of uterine cancer that became apparent after 5 years of tamoxifen (another SERM) use [51]. Meanwhile, the quest for the ideal SERM formulation (one which would provide protection against breast and endometrial cancers, mitigate bone loss, and address both vasomotor symptoms and symptoms of GSM) continues; in the interim, the combination of oral

conjugated estrogen and BZA holds promise as the ideal formulation for women with systemic symptoms and without contraindications for use of systemic hormone therapy.

Future pharmacological considerations include vaginal DHEA. DHEA is the precursor to all sex hormones in postmenopausal women [52] and is inactive in serum until it undergoes intracrine processing within target tissues. Vaginally administered DHEA would result in active sex steroids exclusively within the vaginal tissue without systemic involvement [53], which would be highly desirable for the treatment of VVA. Daily vaginal DHEA has shown to improve both physiological and patient-reported outcomes of VVA [54].

Summary and Conclusions

GSM effects at least 50 % of postmenopausal women and has adverse implications for health, sexual, psychological, and social well-being of the affected population [1]. Despite the high prevalence, there remains a general lack of information, among both patients and healthcare providers, about the spectrum of symptoms of GSM, the variety and efficacy of available strategies, and the safety of treatment options [2]. GSM is a chronic condition and, once manifest, will not improve without intervention and adherence to treatment. A number of factors including aesthetics, convenience, dosing regimen, access, and cost may influence patient's choice and therapeutic preference. Once an intervention is initiated, consistent reassessment of symptom burden and management strategies is important to patient satisfaction and treatment success. Moderate to severe GSM is easily, effectively, and safely treated with low-dose local vaginal estrogen products. Hopefully, the advent of generics to the market will lower the cost and expand access to a more diverse variety of vaginal estrogen formulation options for more women whose quality of life is affected not only by the burden of GSM but also by the barriers to pharmaceutical access.

Our Patient Management and Outcomes

Case 1

After a comprehensive exam, the patient's introital stenosis and reduction in vaginal secretions were deemed as primary components contributing to her severe dyspareunia. The patient's nulliparous status likely contributed to the earlier than usual postmenopausal onset of symptoms and sexual pain [4]. Given her reportedly active sex life a few months earlier, the severity of her vaginal atrophy was possibly indicative of an accelerating process with cessation of sexual activity, which itself is protective against involution even in the face of ongoing estrogen deficiency [42]. With the treatment goal being resumption of pain-free sexual activity, the options of low-dose vaginal estrogen therapies or oral ospemifene were discussed with their pros and cons. The patient preferred to initiate focal treatment as a first-line approach with twice weekly bedtime application of 0.5 g of a 0.625 % conjugated estrogen cream. On follow-up 8 weeks later, she reported a significant improvement in her

GSM symptoms. Objectively, the vaginal pH was 4.4 (down from pH of 6.2 at initial presentation); the introital and vaginal tissue elasticity was noted during her pelvic examination to have improved, and she easily tolerated the speculum insertion. Microscopic evaluation of her vaginal secretions revealed no yeast overgrowth, which has been reported after initiation of vaginal estrogen therapy [14]. While the patient verbalized satisfaction with this treatment effect, her only dissatisfaction was with the messiness of the cream and a sensation of excessive wetness that required her to use a panty liner during the day. Her treatment was thus switched to a 10 mcg estradiol vaginal tablet twice weekly. On subsequent follow-up 3 months later, she endorsed continued satisfaction with improved quality of life, and on examination healthy vulvar and vaginal tissues were again demonstrated. She had resumed satisfactory sexual activity and was advised to remain on the low-dose maintenance vaginal estrogen, with follow-up as needed.

Case 2

The severity of symptoms of GSM in this 60-year-old called for hormonal treatment as first-line approach. Vaginal estrogen options (tablet, ring, and cream) as well as oral ospemifene were presented for relief of the moderate to severe GSM symptoms. The patient opted for vaginal estrogen cream and was started on 0.1 % estradiol vaginal cream 2 g nightly for a 2 week period in order to prime the vaginal tissue with sufficient estrogen; the dose was to be reduced to 1 g after the first 2 weeks of treatment. While noting that this dosage reduction (versus dosing frequency reduction) approach was still lower than label instructions, the patient was made aware that the large volume of cream would likely "leak out" during the day and that a panty liner might be required. She was reassured that the volume and/or frequency would be further decreased once the vagina was estrogenized. Additionally, the patient was instructed to apply a pea-sized amount of the cream directly to the urethral meatus for the first 2 weeks with the goal of achieving some relief in her voiding symptoms and her predisposition to recurrent UTIs [4, 55, 56]. Patient was also treated with a course of oral antibiotics to treat the UTI, antibiotic choice being guided by sensitivity testing. Further, she was instructed in general vulvar hygiene measures including reduced use of incontinence products, minimizing vulvar contact with perfumes/soaps/irritants, and the use of only water to cleanse the vulva, as well as in timed voiding practice to reduce urinary stasis, a recognized predisposing factor for UTI recurrence.

A follow-up was planned 12 weeks after initiation of treatment with vaginal estrogen cream. The patient however returned within 3 weeks with worsening vulvar discomfort along with intense itching and insertional pain, yet her urinary symptoms had resolved with the exception of some continued stress incontinence. On examination, a significant improvement in vulvar and vaginal tissues was apparent compared to the initial evaluation. However the vestibular mucosa appeared red and irritated. The vaginal pH was 4.7 (down from pH of 6.0 at initial presentation). The microscopic exam of secretions confirmed the presence of a fungal infection which was treated with oral fluconazole to minimize further local irritation that can occur

with vaginal antifungal creams [13]. Her vaginal estrogen regimen was decreased to 1 g twice weekly.

On follow-up 2 weeks later, she reported persistent vulvar pain despite the elimination of all potential irritants discussed previously. Her exam revealed well-estrogenized vulvar and vaginal tissues with complete resolution of the yeast infection, but persistent and diffuse tenderness to touch with a cotton swab throughout the vulva. A diagnosis of idiopathic vulvodynia was made given the absence of any other findings. Treatment of vulvodynia is not standardized and will require significant time and energy on the part of the patient and practitioner to determine the best course of treatment. In this case, the patient's vulvodynia must be managed in conjunction with her GSM. Based on her history of trauma with child birth, pudendal neuralgia may be contributing to her cause of her vulvodynia pain and urinary incontinence [57, 58]. Pelvic floor physical therapy or sEMG might also be beneficial to her overall treatment plan to improve urinary incontinence and the abnormal pelvic floor tension and instability experienced by many vulvodynia patients. In addition to physical therapy, tricyclic antidepressants in doses effective for neural analgesia such as 50 mg to 100 mg of amitriptyline daily are a "first-line" pharmaceutical option although it has not been thoroughly explored by well-designed clinical trials [26]. Reassessment of treatment efficacy within 3 months of initiation is necessary to assess if the dosage is well tolerated and effective.

Clinical Pearls/Pitfalls

- GSM is common among menopausal women, the symptoms of which most women assume to be a normal part of aging.
- Multiple local treatment options in a variety of preparations are available. Over-the-counter moisturizer and lubricant options abound and are often the first line of therapy.
- Several estrogen options are available by prescription. Cream options offer soothing emollient properties and can effectively deliver estrogen to the vaginal and vulvar tissue via vaginal leakage or direct application, but may be too messy for some patients who might prefer vaginal estradiol tablets or rings. Those wishing to avoid any genital application also have an option, ospemifene.
- GSM is a chronic and progressive disease. Patient treatment preference should always be taken into account as effective therapy requires long-term adherence to the prescribed treatment.
- Physician-patient discussion of known data regarding actual risks of local vaginal estrogen and systemic ospemifene is necessary to dispel misperceived risks associated with "class labeling" in package inserts.
- GSM may need to be managed in conjunction with concomitant disease states (neurological, dermatological, urological, and pain management). If the diagnosing practitioner is uncomfortable with making a holistic assessment, then a team-based approach is warranted.

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Skeletal Fragility, a Common Menopausal Burden: Risk Assessment, Diagnosis, and Management

8

Michael F. Holick

Abbreviations

25(OH)D	25-Hydroxyvitamin D
BMD	Bone mineral density
BMI	Body mass index
DXA	Dual-energy X-ray absorptiometry
FDA	Food and Drug Administration
FRAX	Fracture risk assessment tool
HRT	Hormone replacement therapy
IOM	Institute of Medicine
IU	International unit
NOF	National Osteoporosis Foundation
OJN	Osteonecrosis of the jaw
PTH	Parathyroid hormone
QCT	Quantitative computed tomography
RANKL	Receptor activator of nuclear factor kappa-B ligand
SERM	Selective estrogen receptor modulator
TSH	Thyroid-stimulating hormone
WHO	World Health Organization

M.F. Holick, PhD, MD
Section of Endocrinology, Diabetes and Nutrition, Department of Medicine, Boston University Medical Center, 85 E Newton St, Boston, MA 02118, USA
e-mail: mfholick@bu.edu

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Introduction

The World Health Organization (WHO) defines osteoporosis as "a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhance bone fragility and a consequent increase in fracture risk" [18, 19]. Osteoporosis is more common in older women than heart attack, stroke, and diabetes. It is been estimated that 50 % of women will have a fracture in their lifetime. Annually women over 50 years will experience approximately 1.5 million fractures compared to approximately 500,000 having a heart attack, 250,000 having a stroke, and approximately 200,000 developing breast cancer [1, 2]. Of the 1.5 million fractures, 750,000 are vertebral, 250,000 are forearm, 250,000 are at other skeletal sites, and approximately 300,000 are in the hip [18–20]. The impact of vertebral fractures results in height loss, kyphosis, and chronic musculoskeletal discomfort especially in the lower back [19]. 50 % of women and men who have had a hip fracture require nursing home care and 20 % die within the first year often due to a pulmonary embolus [20]. With these statistics it is equally remarkable that for every patient diagnosed with osteoporosis, 2–3 go undiagnosed [1, 2]. Three out of four women 45–75 years of age will not have had a discussion with their physician about osteoporosis. The goal of this chapter is to give some perspective on how best to prevent and treat this insidious metabolic bone disorder.

Diagnosis

A simple and inexpensive method to assess the patient for osteoporosis is to ask the patient what was their young adult height and to accurately measure their height, preferably with a stadiometer. If they have lost one inch or more in height there is a good possibility that this is due to silent spinal fractures and that the patient by definition has osteoporosis [1, 2, 19]. When the radiologist reports that there is incidental evidence of osteopenia or osteoporosis in a chest or lumbar spine/pelvic X-ray, the patient has lost at least 30 % of the bone mineral density [2]. More sensitive technologies have been developed to determine the bone mineral content; these include dual-energy X-ray absorptiometry (DXA), quantitative computed tomography (QCT), peripheral X-ray absorptiometry, and ultrasonography [19]. The most commonly used is DXA that measures bone mineral density (BMD) at the hip, lumbosacral spine, and forearm. For the purpose of classification of low BMD, WHO uses T score (standard deviation compared to peak BMD matched for sex and ethnicity); i.e., T score −2.0 represents a bone density that is two standard deviations lower compared to the peak BMD matched for sex and ethnicity. Osteoporosis is defined as a T score of <2.5 and osteopenia, now known as low bone mass, as a T score of −1.0 to −2.5 [18, 19]. A low BMD is the single most accurate predictor of increased risk for fracture [18, 19].

There are several groups that have provided guidelines for the use of DXA in screening for osteoporosis. The US Preventive Services Task Force (USPSTF) recommends screening for osteoporosis in women aged 65 years and older and younger

Table 8.1 Major lifestyle factors and conditions that can lead to osteoporosis and fractures

1.	Inadequate sun exposure
2.	Low calcium intake
3.	Inadequate physical activity
4.	Immobilization
5.	Frequent falling
6.	Smoking (active or passive)
7.	Alcohol abuse
8.	Anorexia nervosa

women whose fracture risk is equal to or greater than that of a 65-year-old woman who has no additional risk factors. The National Osteoporosis Foundation (NOF) recommends BMD testing in women aged 65 and older and in postmenopausal women over age 50 who either have had a fragility fracture (sustained as a result of low-impact trauma) or additional risk factors for osteoporotic fractures (Table 8.1). However, the majority of fractures occur in women with BMD above the osteoporosis threshold, typically in the low bone mass range [19].

FRAX, a computer-driven tool easily accessible on the Internet (http://www.shef.ac.uk/FRAX), can help guide physicians with the use of DXA data (when available) along with significant contributors to osteoporotic fracture to assess fracture risk. The FRAX algorithms request a response to 12 questions (BMD at the femoral neck, age, sex, weight, height, previous fracture history, current cigarette smoking, glucocorticoid use, history of rheumatoid arthritis, secondary causes for osteoporosis, alcohol use, and parental history of hip fracture) and calculate a 10-year probability of fracture of the hip and of major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture); this information can then help guide decisions regarding timing of treatment initiation and therapeutic choices [21]. The FRAX has been used as a guide to help clinicians in deciding whether intervention therapy with an osteoporotic medication such as an antiresorptive agent is warranted. The current NOF guidelines recommend treating patients with low bone mass and FRAX 10-year risk scores of $\geq 3\%$ for hip fracture or $\geq 20\%$ for a major osteoporotic fracture, to reduce their fracture risk. Notably, additional risk factors such as frequent falls that are not represented in FRAX warrant individualized clinical judgment.

A patient with a normal BMD does not need to have repeat BMD assessment for at least 5 years, unless there is a change in the clinical picture, when earlier evaluation may be considered. Because of the limitations in the precision of testing, a minimum of 2 years is usually recommended to reliably measure a change in bone density. However, there are some circumstances where a yearly BMD assessment may be of value especially in patients who are on medications that can cause rapid bone loss including glucocorticoids and several antiestrogen medications used in the treatment of breast cancer [19].

Clinicians can be confused when they receive a DXA report that suggests a normal BMD in the lumbar spine and osteoporosis in the hip. There can be several explanations for this dichotomy. The most common reason for a big site

discrepancy in BMD results is due to artifacts in the lumbosacral spine including osteoarthritis, osteophytes, and compression fractures which will falsely increase BMD at the lumbar spine, thus yielding a higher T score. Interpretation of BMD status from a DXA report is based on whatever skeletal site has the lowest T score.

Risk Factors and Prevalence

It is estimated that 43.1 million Americans have low bone mass and another 9.9 million are currently affected by osteoporosis, and further increases in prevalence are expected by 2020 [18, 19]. There are a variety of risk factors for the development of low bone mass and osteoporosis (Tables 8.1 and 8.2). Major risk factors include low BMI (<20), Caucasian extraction, nulliparity, early menopause, positive family history, low physical activity or prolonged immobilization, cigarette smoking, alcohol abuse, anorexia, low calcium intake, chronic vitamin D deficiency, and some medications (Table 8.2) [1, 2, 21–24]. We also found that with premature hair graying, i.e., that if 50 % of the hair turned gray by the age of 40, both men and women had a fourfold increased risk for having low bone mass/osteoporosis [3]. There are a wide variety of additional acquired and inherited causes for low bone mass/osteoporosis as listed in Table 8.2. Some of the major inherited causes of skeletal fragility relate to mutations in genes that are responsible for the production of the collagen-elastin matrix in the skeleton including osteogenesis imperfecta, Ehlers-Danlos

Table 8.2 The more common secondary causes of low bone mass and osteoporosis

Non-medication-related causes	*Medication-related causes*
Vitamin D deficiency	Glucocorticoids (>5 mg/d prednisone or equivalent for ≥3 months)
Hyperparathyroidism	Aromatase inhibitors
Hyperthyroidism	Depo-medroxyprogesterone (premenopausal contraception)
Diabetes mellitus (type I and II)	GnRH (gonadotropin-releasing hormone) agonists
Premature menopause (<40 year)	Anticonvulsants
Cushing's syndrome	Anticoagulants (heparin)
Hyperprolactinemia	Proton pump inhibitors
Androgen insensitivity	Selective serotonin reuptake inhibitors
Athletic amenorrhea	Tamoxifen® (premenopausal use)
Intestinal malabsorption disorders	Cancer chemotherapy
Primary biliary cirrhosis	*Major genetic causes*
Multiple myeloma	Osteoporosis imperfecta
Multiple sclerosis	Ehlers-Danlos syndrome
Spinal cord injury	Marfan syndrome
End-stage renal disease	
Hypercalciuria	

syndrome, and Marfan syndrome [1, 2]. The major acquired secondary causes are associated with endocrine disorders including hyperparathyroidism, hyperthyroidism, hypercortisolism, and hypogonadism and a variety of medications, most notably glucocorticoids [19, 21–26] (Table 8.2).

Clinical and Laboratory Evaluation

Physical examination should include documentation of accurate baseline height, preferably with a stadiometer, for later comparisons to rule out silent spinal fractures where loss of height may be the only overt sign. An increase in skin elasticity or evidence for a "doughy textured" skin and increased flexibility of joints may be evidence for the genetic disorder Ehlers-Danlos/hypermobility syndrome which has been associated with fragility fractures [1, 2]. Other red flag indicators of possible low bone mass include a dowager's hump (raising suspicion for underlying vertebral fracture/s), exophthalmos (suggesting hyperthyroidism as a mechanism for bone loss), blue sclerae (raising concerns for an underlying collagen disorder), centripetal obesity and proximal muscle wasting (hallmarks of cortisol excess), and a history of prolonged immobility. Palpation with thumb or forefinger on the upper portion of the sternum pushing with a reasonable amount of force may help in the diagnosis of vitamin D deficiency osteomalacia especially if the patient is exquisitely sensitive to the maneuver; this is often misdiagnosed as a trigger point for fibromyalgia [4].

Blood tests should include serum total calcium, albumin, phosphorus, alkaline phosphatase, liver function tests, creatinine, and thyroid-stimulating hormone (TSH). Osteocalcin the major non-collagenous protein in the skeleton and procollagen-type 1 N-terminal propeptide are serum markers for osteoblast activity similar to bone-specific alkaline phosphatase. Urine N-telopeptide and serum C-telopeptide are markers of osteoclast activity and bone resorption. These markers are typically used in clinical trials to evaluate the medication effect on bone formation and bone resorption of activity. However, the clinical utility of measuring these bone biomarkers for individual patient care is not well established and as a result is often not covered by health insurance [10].

Neither the Institute of Medicine (IOM) nor the Endocrine Society recommends routine screening for vitamin D deficiency (serum 25-hydroxyvitamin D [25(OH)D]) particularly if women are of normal weight, taking adequate supplements, and not on medications that influence vitamin D metabolism [27]. For women and men with low bone mass or osteoporosis, there is no need to screen for vitamin D deficiency. Instead the recommendation is to evaluate them for their vitamin D intake, and if less than 2000 IUs of vitamin D a day, the recommendation is to supplement following Endocrine Society's Guidelines of 1500–2000 IUs daily. An alternative effective method is to provide the patient with 50,000 IUs of vitamin D once every 2 weeks. This is both safe and effective [5, 6]. However, screening and monitoring vitamin D status with a serum 25(OH)D level is recommended in women with malabsorption syndromes, including Crohn's disease,

ulcerative colitis, and gastric bypass surgery, and in those on glucocorticoids, antiseizure medications, and HIV medications. In addition, the Endocrine Society's Vitamin D Practice Guidelines recommends monitoring vitamin D status in obese women and in those who have a hypersensitivity to vitamin D including Williams syndrome and chronic granulomatous disorders including sarcoidosis and tuberculosis among others [27].

Strategies to Prevent Low Bone Mass and Osteoporosis

Calcium Intake

Adequate calcium and vitamin D throughout life helps to maximize a person's genetically programmed BMD and maintain bone health [27–29]. A low intake of calcium during the formative teenage and young adult years results in a decrease in attainable peak bone mass, which occurs between the ages of 20–30 years. Young adults can lose about 0.25–0.5 % of their bone mass yearly if they are not obtaining an adequate amount of calcium and vitamin D [2]. This unrelenting loss in BMD over several decades can lead to a significant 5–15 % reduction in BMD before the age of 50. After reaching peak bone mass, young adults need to continue taking the recommended daily intake of 1000 mg of calcium from dietary sources and or supplements. Eight ounces of dairy such as skim milk or yogurt provides 300 mg of calcium and is an excellent source of whey proteins and essential amino acids which are important for bone health as well. Given the prevalence of protein deficiency among older women, this author encourages them to consume dairy products not just for calcium but also for the protein content. For those who are lactose intolerant or prefer not to ingest dairy products, soymilk and almond milk are fortified with calcium carbonate. Some commercial orange juices are also fortified with calcium citrate/malate in an amount comparable to milk. Thus ingesting three servings of dairy or calcium-fortified orange juice satisfies the recommended daily allowance (RDA) for calcium for most young adults. For postmenopausal women, they are recommended to ingest at least 1200 mg of calcium daily (through a combination of diet and supplements) [27–31]. However, since dietary sources of calcium are highly desirable even for postmenopausal women 50 years and older, this author recommends three servings of milk or other calcium-containing products without additional calcium supplementation. There is no evidence that increasing calcium intake above the RDA will have any additional benefit on BMD. In fact higher calcium intakes above the recommended RDA increase the risk for kidney stones, cardiovascular calcifications, and stroke [27, 32, 33]. Although there are concerns that women with achlorhydria or iatrogenic achlorhydria due to proton pump inhibitor use may not efficiently absorb calcium carbonate, this limitation may be overcome by ingesting the supplement with food. Also for most kidney stone patients who are likely hyperabsorbers of oxalate, calcium citrate supplements may be a better choice than calcium carbonate [2].

Vitamin D Intake

Vitamin D deficiency can be very subtle and insidious with no obvious clinical manifestations other than nonspecific aches and pains in bones and muscles. Vitamin D-deficient women are often misdiagnosed as having fibromyalgia and chronic fatigue syndrome or are simply dismissed as being depressed [4]. Vitamin D deficiency causes low bone mass and osteoporosis by two mechanisms. Vitamin D deficiency results in a transient decrease in ionized calcium which is recognized by the calcium sensor in the parathyroid glands resulting in an increase in the production of parathyroid hormone (PTH). PTH helps conserve calcium by increasing tubular reabsorption of calcium in the kidneys. It also stimulates the kidneys to produce 1,25-dihydroxyvitamin D [1,25(OH)2D]. Since this hormone circulates at a concentration which is several orders of magnitude below that of 25(OH)D, the blood concentration of this hormone is usually normal or even elevated in a patient who was vitamin D deficient and therefore of no value in determining a person's vitamin D status. A higher PTH level in vitamin D-deficient women also increases the number of osteoclasts in the skeleton which release HCl and collagenases destroying the matrix and releasing calcium into the circulation. In addition, high PTH activity also causes phosphaturia and hypophosphatemia which if sustained can result in an inadequate calcium phosphate product and lead to a mineralization defect known as osteomalacia. Whereas osteoporosis or low bone mass does not cause bone pain, osteomalacia causes aches and pains in the bones and muscles [4]. It is also worth noting that you cannot distinguish low bone mass, osteoporosis, and osteomalacia either by X-ray or bone densitometry [2]

As to how much vitamin D is required to be vitamin D sufficient depends on the circumstances. The IOM assumes that a majority of the population is vitamin D sufficient, i.e., 25(OH)D >20 ng/mL, and therefore recommended a daily intake of 600 international units (IUs) for all children over the age of 1 and for all adults up to the age of 70. The recommendation for adults over the age of 70 is 800 IUs daily [28]. The Endocrine Society concluded that to maximize bone health, a serum 25(OH)D >30 ng/mL should be maintained and a blood level up to 100 ng/mL was considered to be safe [27]. They therefore recommended higher doses (600–1000 IUs daily for children and 1500–2000 IUs daily for adults). For children and adults who are obese, with a body mass index (BMI) >30, a two- to threefold higher dose of vitamin D supplements is required [27]. With that being said, vitamin D deficiency, i.e., 25(OH)D < 20 ng/mL, remains common in all age groups and especially in postmenopausal women [27, 41, 42]. A simple but effective strategy to treat vitamin D deficiencies is to give 50,000 IUs of vitamin D_2 once a week for 8 weeks to fill the "empty vitamin D tank." The reason for vitamin D_2 is that it is the only pharmaceutical form of vitamin D available in United States since it predated the FDA. Vitamin D_3 has never been approved as a pharmaceutical. Supplement manufacturers have provided pharmacies with 50,000 IUs of vitamin D_3 that can be prescribed by providers. We reported that this strategy is effective regardless of whether baseline 25(OH)D is undetectable or just mildly deficient [6]. In those who are severely deficient, blood levels of 25(OH)D rise rapidly to about 20 ng/mL. However, to achieve and maintain optimal vitamin D sufficiency, i.e., a 25(OH)D level of at least 30 ng/mL and preferably in the range of 40–60 ng/mL, as recommended by the

Endocrine Society's Practice Guidelines, continued supplementation is required after the initial 8-week therapy [5, 6, 27]. The rule of thumb is that for every 100 IUs of vitamin D taken daily, the blood level of 25(OH)D is raised by approximately 1 ng/mL. For maintenance of optimal levels after treating the deficiency, patients are recommended 50,000 IUs of vitamin D_2 or vitamin D_3 once every 2 weeks. A study in patients on this regimen for up to 6 years showed that they maintained their blood levels of 25(OH)D in the target range of 40–60 ng/mL without any toxicity [5, 6, 27]. Obese women with a BMI >30 need at least two to three times more vitamin D to both treat and prevent recurrent vitamin D deficiency [7, 27].

Fall Prevention

Fall prevention programs have a dramatic effect on reducing risk for osteoporotic fractures in at-risk populations. Improvement in vitamin D status improves proximal muscle strength, thereby reducing risk for falls [34–36]. Exercise is also important for maintenance of bone health throughout life. Falls are a major cause of skeletal fracture in adults over the age of 50 and improvement in hip girdle muscle tone stabilizes the body and reduces fracture risk [35, 36]. The NOF endorses lifelong activity at all ages [19]. Weight-bearing exercise helps to maintain and increase BMD as well as muscle mass and muscle tone, thereby reducing risk of falling and fracture. Weight-bearing exercise includes walking, jogging, Tai Chi, dancing, tennis, and volleyball playing. It is the pounding on the ground that translates into stimuli to help maintain BMD in the hip and lumbosacral spine as well as improve muscle function in the legs and girdle region. This author recommends walking three to five miles a week, which is a simple yet effective exercise [37, 38].

Smoking and Alcohol Consumption

Cigarette smoking has many detrimental health effects, one of which is increasing risk for bone loss. Thus initiating a smoking cessation program for all with tobacco use disorder is beneficial to bone health [23, 39]. Moderate alcohol consumption has been associated with normal or slightly higher BMD and lower risk of fracture in postmenopausal women. However, alcohol intake of more than two drinks a day for women increases risk for falling and may have a detrimental effect on the skeleton, increasing risk for fracture [22].

Pharmacologic Therapy

Recommendations for Who Should Be Treated

It is generally recommended and endorsed by the NOF that all patients being considered for treatment of osteoporosis should also be counseled on risk factor reduction including improving calcium and vitamin D intake, encouraging exercise

especially walking three to five miles a week and cigarette smoking cessation [19, 27–29, 40]. The NOF guidelines recommend anti-fracture treatment initiation in postmenopausal women and those over 50 in the following situations:

- History of a hip or vertebral fracture (clinically apparent or found on vertebral imaging). The BMD T score is not as important in these patients in predicting future risk of fracture. Patients with spine and hip fractures have a reduced risk for further fracture with pharmacologic therapy.
- BMD T score ≤ -2.5 at the femoral neck, total hip, or lumbar spine.
- Low bone mass (BMD T score between −1.0 and −2.5 at the femoral neck or lumbar spine) and a 10-year fracture probability of $\geq 3\,\%$ for hip fracture or $\geq 20\,\%$ for a major osteoporotic fracture, based on the US-adapted WHO FRAX algorithm. The NOF however notes that there are relatively few studies confirming fracture risk reductions with pharmacotherapy in this group of patients with low bone mass [19].

FDA-Approved Drugs for Osteoporosis

Calcitonin (Brand Name Miacalcin or Fortical and Generic Calcitonin)

The first drug approved by the FDA in the United States was salmon-calcitonin. It was approved for the treatment of osteoporosis in women who were at least 5-year postmenopausal when alternative treatments were not suitable. It reduces vertebral fracture occurrences by about 30 % in those with prior vertebral fracture but has not demonstrated any efficacy for reducing risk of nonvertebral fractures. It is given as 200 IU intranasally or subcutaneously by injection. Because of its limited benefit in only marginally reducing vertebral fractures, this medication is rarely used in the treatment of postmenopausal osteoporosis [43–45].

Intranasal calcitonin can cause rhinitis, epistaxis, and allergic reactions, especially in those with a history of salmon allergy. A meta-analysis of 21 randomized, controlled clinical trials with calcitonin-salmon suggested a possible increase risk of malignancies [44, 45].

Hormone Replacement Therapy (Estrogen Alone or Estrogen Plus Progestin)

Loss of estrogen production that is surgically induced, medically induced, or caused by natural menopause results in a significant increase in bone resorption activity causing on average a 3–4 % decrease BMD in the spine and 2–3 % decrease in BMD in the hip that continues throughout the life of the patient although at a slower rate as the bone mineral content continues to decline. Thus within a decade after menopause, a woman can lose as much as 30–40 % and 20–30 % of their BMD in their spine and hip, respectively. Several estrogen therapies have been approved for the prevention of postmenopausal osteoporosis starting in 1986. Women who have an intact uterus require addition of progestin to their hormonal regimen to reduce the risk for endometrial cancer that can result from unopposed estrogen therapy.

The Women's Health Initiative (WHI) hormonal trials, consisting of two large and long-running randomized, controlled trials, reported that postmenopausal women receiving 0.625 mg of conjugated equine estrogens with and without 2.5 medroxyprogesterone acetate (MPA) for 5 years had a significant 34 % reduction in clinical vertebral fractures and 23 % reduction in hip fractures compared to those on placebo [46]. Due to concerns raised by the WHI about increased cardiovascular [47] and breast cancer risks with hormonal therapies (HT), the use of systemic conventional dose hormonal therapy for postmenopausal osteoporosis prevention has declined starting in 2002, and this issue is discussed in more detail in other chapters of this book. While lower estrogen doses are also FDA approved for osteoporosis prevention, data on fracture risk reduction efficacy of lower estrogen dose hormonal regimens are lacking and the NOF has taken the position that risks of low-dose hormonal regimens should be considered comparable to conventional doses until studies have shown them to be safer. The FDA recommends non-estrogen therapies be considered as first line for prevention of osteoporosis in postmenopausal women who have no other indication for HT. As to women receiving systemic hormone therapy for relief of vasomotor symptoms, skeletal protection can be assumed with traditional dosing and is presumed with low-dose regimens. Rapid bone loss however can resume with cessation of postmenopausal HT and alternative bone sparing agents must be considered when indicated based on fracture risk assessment [19]

Estrogen Agonist/Antagonist (Formally Known as a Selective Estrogen Receptor Modulator (SERM); Brand Name Evista; Generic Raloxifene)

Raloxifene (60 mg daily) mimics estrogen effect on the skeleton while having an antagonist effect on the uterine endometrium and breasts [48]. It was found to reduce risk of vertebral fractures by about 30 % in patients with the prior vertebral fracture and by about 55 % in patients without a prior vertebral fracture over 3 years. It is not been demonstrated however to reduce risk of nonvertebral fractures. Raloxifene is approved by the FDA for both prevention and treatment of osteoporosis in postmenopausal women. It also has the indication for reduction in risk for invasive breast cancer in postmenopausal women with osteoporosis [48–51]. Raloxifene side effects include exacerbation of hot flashes and leg cramping as well as a small increase in the risk of venous thromboembolism and stroke [52–56]

Tissue-Selective Estrogen Complex: Conjugated Estrogens/ Bazedoxifene (Brand Duavee, Conjugated Estrogens Pared with a SERM)

The concept is to combine conjugated estrogen with bazedoxifene, a SERM with tissue-selective estrogen agonist (on skeleton) and estrogen antagonist (on the uterine endometrium) activities; the goal is for having estrogen benefit on the skeleton and treating moderate to severe hot flashes while blocking estrogen's action on the uterus and eliminating the need for a progestin in women with an intact uterus. This combination medication was approved by the FDA for treatment of moderate to severe menopausal hot flashes and prevention of postmenopausal osteoporosis.

Twelve-month trials with this therapy in newly postmenopausal women have shown an increased BMD in the lumbar spine by 1.51 % and by 1.21 % in the hip compared to a placebo [19]. As with estrogens and other SERMs, this therapy is associated with risk for venous thromboembolism. Side effects include, among others, nausea, dyspepsia, and abdominal pain.

Bisphosphonates (Generic and Brand Names Alendronate, Fosamax; Risedronate, Actonel; Zoledronic Acid, Reclast; Ibandronate, Boniva)

The first use of a bisphosphonate was for the treatment of Paget's disease. Etidronate was the first bisphosphonate that was demonstrated, when used in a cyclical fashion, to improve BMD. However, this drug when taken daily for a prolonged period of time also caused osteomalacia [19].

While bisphosphonates have been in use since the 1970s for other indications, Alendronate was the first of the second-generation bisphosphonates to be approved by the FDA in 1995 for increasing bone mass in women and men with osteoporosis and for the treatment and prevention of osteoporosis in women [57, 58]. It was also approved for the treatment of osteoporosis in those on chronic glucocorticoid therapy [59]. The dose of 10 mg daily or 70 mg weekly taken in the morning on an empty stomach with water was found to improve BMD in lumbar spine by 2–3 % and in the hip by 1–2 % annually. This translated into reducing the incidence of fractures in the spine and hip by about 50 % over 3 years in patients with a prior vertebral fracture or in patients who had osteoporosis at the hip [57].

Several other bisphosphonates were subsequently approved by the FDA for the treatment and prevention of postmenopausal osteoporosis. These include the third-generation risedronate, various dose regimen of which are also approved for prevention and treatment of glucocorticoid-induced osteoporosis (5 mg daily, 35 mg weekly, 75 mg on two consecutive days every month, or 150 mg monthly) [60–64] ibandronate (150 mg orally monthly or 3 mg every 3 months by intravenous injection) reduces incident vertebral fractures by about 50 % over 3 years, but reduction in risk of nonvertebral fracture with this bisphosphonate has not been proven [65–68].

Zoledronic acid is the newest and most potent of available bisphosphonate which reduces incidence of vertebral fractures by 70 %, hip fractures by 41 %, and nonvertebral fractures by 25 % over 3 years in patients with vertebral or hip osteoporosis [64, 69–75]. It offers convenient dosing 5 mg by intravenous infusion over at least 15 min annually for treatment and biennially for osteoporosis prevention.

The major side effect of the second-generation nitrogen-containing bisphosphonates when given orally was symptoms of gastritis that could lead to gastric bleeding [57, 75]. All bisphosphonates can affect renal function and are contraindicated in patients with an estimated GFR below 30–35 mL/min. Atrial fibrillation has also been associated with bisphosphonate use and a meta-analysis suggested the relative risk 1.53 with 95 % confidence limits (1.17–2.0) [11, 12]. However, more concerning are reports that both oral and intravenous bisphosphonate therapy increases risk for atypical subtrochanteric femoral fractures and for osteonecrosis of the jaw (ONJ) [12, 72–80]. Although it has been reported that ONJ is a very rare

occurrence 1 in 5000–10,000 cases [71–73], I have seen 14 premenopausal and postmenopausal women who have been on a bisphosphonate for as little as 2 years with these serious side effects. My suspicion is that these side effects are underreported. Often women who have had a subtrochanteric femoral fracture will often experience an additional fracture on this contralateral side requiring hardware placement to stabilize both femurs. For those patients who are being considered for bisphosphonate therapy, it is reasonable for them to have any type of invasive dental procedure performed before prescribing bisphosphonates especially those that are given intravenously. There is no standard recommendation for when to begin bisphosphonate therapy after an invasive dental procedure. It would be reasonable to wait at least 1–2 months after the procedure and healing has been completed. There is also no recommendation for those who are on a bisphosphonate and plan to have a dental procedure as if and when they should stop the bisphosphonate. It probably does not matter since the bisphosphonate is already in the skeleton however to provide a level of comfort to both patients and the dentist. I usually recommend that they stop 1–2 months before the dental procedure and wait 1–2 months after the procedure before restarting their medication. Bisphosphonates have a very long half-life in the skeleton. They affect osteoclast function and ingestion of a bisphosphonate by an osteoclast causes apoptosis, i.e., its death. Bone biopsies performed in patients with subtrochanteric femoral fractures have revealed that there was very little if any bone remodeling activity at the site of the fracture [80]. A study evaluating micromechanical properties in patients treated with long-term alendronate therapy revealed that the therapy altered the size of the calcium hydroxyapatite crystals and compromised the micromechanical properties of the bone matrix, i.e., decrease skeletal strength. This was thought to be in part due to differences in the crystallinity irrespective of the mineral amount and mineral maturity [80]. Concern about increased risk for ONJ and subtrochanteric femoral fractures led to the FDA expert panel to recommend that bisphosphonate should be used short-term, i.e., no more than 5 years. They noted that patients on a bisphosphonate for 5 years who were then switched to a placebo demonstrated a modest decrease in BMD and the femoral neck during the first 1–2 years and then stabilized, whereas BMD in the lumbar spine continued to increase despite discontinuation of bisphosphonate therapy [12, 71–80]. This has introduced the concept of a drug holiday. However, there are no specific recommendations for how long the holiday should last and some physicians will stop for 1 or 2 years and then restart, while most physicians simply have the patient on a permanent holiday never restarting antiresorptive therapy.

Denosumab (Brand Name Prolia)

One of the major downsides for using a bisphosphonate is its prolonged half-life in the skeleton [19]. The recognition that receptor activator of NFKB ligand (RANKL) was a major factor produced by osteoblasts to stimulate the production of bone resorbing osteoclasts led to the development and approval of a monoclonal antibody to RANKL that reduces the formation of osteoclasts and has proven effective for

BMD preservation when given at a dose of 60 mg subcutaneously every 6 months [19, 81, 82]. It has FDA approval for the treatment of osteoporosis in women at high risk of fracture. The drug reduces incidence of vertebral fractures by 68 %, hip fractures by 40 %, and nonvertebral fractures by about 20 % over 3 years. Among other approved indications, denosumab is also indicated for treatment and prevention of accelerated bone loss in women on aromatase inhibitors for hormone receptor-positive breast cancer [19, 81, 82].

Denosumab has been reported to cause hypocalcemia [19]. Thus patients with hypocalcemia should not receive this medication until the serum calcium is normal. This drug has also been associated with increased risk for skin infections (cellulitis), eczema, and skin rash [19, 81]. Similar to bisphosphonates it has also been associated with increased risk for ONJ and subtrochanteric femoral fractures [13]. Unlike bisphosphonates, however, cessation of this therapy after 3 years is often followed by prompt resumption of accelerated decline in BMD to the extent that all of the bone gain is lost within 1 year after stopping the medication [19, 81]. It is unknown whether the loss of bone occurs at the same skeletal sites where BMD increased as a result of the medication or at different skeletal sites that could potentially increase site-specific fracture risk.

Teriparatide (Brand Name Forteo; PTH (1-34)

Teriparatide is the biologically active fragment of parathyroid hormone (PTH) that contains the first 34 of the 84 amino acids of the natural hormone and is known as PTH (1-34) [83]. While all the agents discussed earlier are antiresorptives, teriparatide is the only anabolic bone-active medication approved by the FDA for the treatment of osteoporosis. 20 μg is given by injection subcutaneously on a daily basis for up to 2 years. This drug increased lumbar spine BMD by 10–14 % and femoral neck BMD by 3–5 % after 18 months of therapy and reduced risk of vertebral fractures by about 65 % and nonvertebral fragility fractures by 53 % in patients with osteoporosis [83].

The major side effect of teriparatide therapy is leg cramping [83]. This often occurs within the first 1–2 weeks, is mild in nature, and often resolves. However, on rare occasions, the cramping can be so severe that the medication has to be stopped. Nausea and dizziness have also been reported as side effects. High doses of PTH (1-34) have been associated with increased incidence of osteosarcoma in animal studies, prompting an FDA-mandated black box warning on the label and limiting recommended duration of therapy to 2 years. Patients who are at increased risk for osteosarcoma including Paget's disease of the bone and those having prior radiation therapy of the skeleton, bone metastases, history of skeletal malignancy, or a history of hypercalcemia should not receive teriparatide therapy. Transient hypercalcemia can be observed within 4–6 h after administration that rapidly resolves. As noted by the NOF, once teriparatide therapy is stopped, there is increased bone loss due to the teriparatide-induced increase in bone remodeling activity. To prevent this loss, often patients are placed on an antiresorptive agent, e.g., a bisphosphonates or denosumab, to ensure sustained skeletal benefit.

Strontium Ranelate (Brand Names Osseor and Protelos)

This medication is available in some countries in Europe and in Australia but is not approved for use in the United States. Strontium is a trace element that is chemically similar to calcium. Strontium ranelate stimulates the formation of new bone tissue and decreases bone resorption in animal studies. In a randomized, placebo-controlled trial, postmenopausal women received 2 g of strontium ranelate mixed with water or placebo powder for 3 years reported reduced risk of new vertebral fractures by 49 % at 1-year and by 41 % over a 3-year period. It also reduced risk of multiple vertebral fractures. Strontium gets incorporated into the skeleton, and because it hasn't much higher atomic weight, there is an increase in BMD due to this incorporation independent of its effect on stimulating bone formation and reducing bone resorption. Thus although this drug increased bone mineral density by 14.4 % in the lumbar spine in 3 years when the influence of strontium incorporation into the skeleton was taken into account, it was concluded that there was an 8.1 % increase in BMD in the lumbar spine [14]. In an open-label extension study, BMD increased continuously with strontium ranelate for 10 years at osteoporotic women. This was reflected by a low fracture incidence of vertebral and nonvertebral fractures. During this extension study, the major side effects included headache (1.3 %), nausea (0.8 %), and diarrhea (4.6 %) [15].

Potential New Therapies Under Evaluation

Romosozumab is a monoclonal antibody against sclerostin. Sclerostin has been targeted as a potential treatment for osteoporosis because it is now recognized that osteocytes produce this glycoprotein which is a major downregulator of bone formation. In a phase 2 multicenter, randomized, placebo-controlled parallel group, 8-group study evaluated its efficacy and safety over a 12-month period in 419 postmenopausal women. It was observed that there was a dose-dependent increase in BMD in the lumbar spine with an increase of 11.3 % with the 210-mg monthly dose as compared to a decrease of 0.1 % with placebo and increases of 4.1 % with alendronate and 7.1 % with teriparatide. It was also associated with increased BMD at the total hip and femoral neck as well as transitory increases in bone formation markers and sustained decreases in bone resorption marker. The medication was well tolerated with no significant adverse events compared to the other groups. A phase 3 clinical trial evaluating fracture efficacy is underway [16].

Odanacatib was designed to inhibit cathepsin K which is a collagenase enzyme present in osteoclasts. Its inhibition results in the osteoclast becoming nonfunctional and released from the surface of the bone. This medication is given orally once a week, in a dose of 50 mg. Unlike bisphosphonates it can be given with food. Results from the pivotal trial suggested it had a significant anti-fracture efficacy and this study was stopped early due to its robust efficacy and favorable benefit-risk profile [17]. However, due to recent concerns about safety, it is still under review.

Conclusion

Osteoporosis is a major health concern for aging men and women and particularly for postmenopausal women. As the life expectancy continues to rise and people try maintaining a healthy active lifestyle into old age, there is an increasing need

to prevent and treat osteoporosis with the goal of minimizing fracture risk in the aging population. Adequate calcium and vitamin D throughout life will help to attain and maintain a person's genetically programmed peak BMD. Vitamin D deficiency and calcium deficiency are common in both children and adults. Very few foods naturally contain or are fortified with vitamin D. It is next to impossible to obtain enough vitamin D from dietary sources [84]. Sensible sun exposure in the spring and summer and fall using the app "dminder.info" that this author helped develop [9] will provide users with information, anywhere on the globe any time of the year, as to whether vitamin D can be produced and how much will be produced during sun exposure. It also provides guidance for alerting the user when they have made enough vitamin D and that they should use sun protection to prevent damaging effects from excessive exposure to sunlight.

There is very little calcium in the average American diet. Broccoli which is touted as a dietary source of calcium contains only about 100 mg in a cup, and thus ten cups of broccoli a day would be needed to provide the RDA of 1000 mg of calcium! Dairy and calcium-fortified orange juice are therefore the best sources of dietary calcium. Unlike other sources of calcium, dairy is a good source of dietary protein as well, and it alkalinizes the body, which is not the case with other protein sources such as meat. Meat contains proteins that when digested form sulfuric acid which dissolves the calcium out of the skeleton and increases calcium loss in the urine. Vegetables and dairy do not form this acid when digested and the calcium from these sources can act as a base neutralizing the acid increasing alkalinity. For those who have a lactase deficiency, alternative sources of calcium other than dairy products must be sought.

Estrogen-containing HT is a reasonable strategy to help maintain BMD in symptomatic perimenopausal and newly menopausal women who have no personal or strong family history for breast cancer. For women who have a background history of breast cancer or who are fearful of developing breast cancer on HT, the alternative options of Raloxifene or combination oral conjugated estrogen/bazedoxifene, respectively, can be considered for osteoporosis prevention. It should also be recognized that aging independently increases risk for fracture. What this means is that a 40-year-old woman with a T score of −2.5 in the lumbar spine or hip has about a fourfold less likelihood of a spine or hip fracture compared to a 70-year-old woman with the same T score. With this in mind when I am evaluating premenopausal women with T scores < -2.5, I first evaluate them for secondary causes of low bone mass (Table 8.1). It is outside of the scope of this to review all of them which can be found on the NOF website [19]. The most common secondary causes include vitamin D deficiency, calcium deficiency, hyperparathyroidism, and hyperthyroidism. I recommend to these patients to be on an adequate amount of calcium and vitamin D, i.e., 1000 mg of calcium preferably from dietary sources, 3000 IUs vitamin D_2, or vitamin D_3 daily or its equivalent bimonthly, i.e., 50,000 IUs every 2 weeks, and encouraged them to walk three to five miles a week. This is usually effective in helping to maintain BMD. I use the same strategy for postmenopausal women and will intervene with pharmacologic therapy in women who rule out for secondary

causes and have adequate calcium and vitamin D intake and who have an increase in bone remodeling activity as indicated by having elevated urine N-telopeptide or serum C-telopeptide levels that suggest an osteoclast function dominance [19]. I also intervene with pharmacologic therapy for patients who are at higher risk of falls and fractures or who are infirm and unable to be active. Because of my concern about the potentially devastating side effects of bisphosphonates including gastrointestinal ulcers with bleeding, subtrochanteric femoral fractures, and ONJ, I use bisphosphonates sparingly. I also sparingly use denosumab because of the concern that if the medication is abruptly stopped, then all of the gain in BMD is lost within a year. What is most concerning is that it is unknown where the bone loss is occurring and whether it could potentially result in increased risk for fracture. Teriparatide is very effective in reducing risk of vertebral fractures, and thus women who are losing height or at high risk for vertebral fracture can benefit from this anabolic bone-active medication. Finally for women who may have osteoarthritis or rheumatoid arthritis, making it difficult for them to walk, a vibrating platform which mimics walking can be effective [8]. It not only has a beneficial effect on bone health by increasing bone mineral density but improves stability and can help reduce risk of falling [8]. However, this should not be used if the patient is pregnant, has a pacemaker, or has any current or recent blood clots.

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Sexuality, Sexual Dysfunction, and Menopause

9

Mary Jane Minkin

Case Presentation

A 55-year-old postmenopausal woman complains of complete sexual disinterest. We have taken care of her for many years. She had a fairly uneventful menopause, with some vasomotor symptoms (VMS); her last menstrual period was 4 years ago. The vasomotor symptoms are mostly resolved at this point. She has been married for 30 years; she has two children who have both graduated from college and are out of the house. She is a high school teacher in the neighboring town. Upon investigating her bother, she does note that once she starts participating in sexual activities (or as she states, "once she gets going"), she gets interested, but she could care less about "getting going in the first place." She has recently heard about a new medication, which she has heard referred to as "the female Viagra," and has also recently read an article on the promise of testosterone for sexual health in women. She is coming in to ask whether we thought that might help her situation. Her physical examination is unremarkable except for evidence of vulvovaginal atrophy (VVA), which is a significant change since her last exam a year prior. Her vagina now shows pallor and a loss of rugae. When we checked her vaginal pH, it is now 5.5.

Management Issues

1. Are the patient's concerns reflective of "normal aging process"?
2. What type of sexual dysfunction is the patient actually complaining of?

M.J. Minkin, MD, FACOG, NCMP
Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, 40 Temple Street, Suite 7A, New Haven, CT 06510, USA
e-mail: maryjane.minkin@yale.edu

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3. What are the medical issues involved?
4. Do you need to refer this patient to a sex therapist?

Special considerations for our patient's case as detailed above include a relatively isolated complaint of "lack of sexual interest" in an otherwise asymptomatic 55-year-old. Focal examination however identifies evidence of vulvovaginal atrophy. Potential mechanisms for her presenting symptom including differential diagnoses and management options including hormonal and nonhormonal strategies will be discussed, and thought process for the management approach for the case will be outlined.

Sexuality, Sexual Dysfunction, and Menopause: An Overview

Sexual dysfunctions are classically divided into several different categories. Technically, your patient would be categorized as suffering from hypoactive sexual desire disorder, which is the most common variety [1]. However, in postmenopausal women, symptoms of VVA, now officially referred to as the genitourinary syndrome of menopause (GSM), are a common contributory mechanism underlying varying degrees of sexual dysfunction [2].

The majority of postmenopausal women will develop VVA. In a recent survey of women with VVA, only 7 % reported that they were queried about their symptoms [3]. Your patient tells you that she is quite dry. You ask if she has used any over-the-counter remedies, and she mentions that she has used a lubricant. Most women do not appreciate the difference between long-acting moisturizers, which can offer lasting relief, and lubricants that offer only transient relief and are to be used at the time of intercourse. The use of vaginal moisturizers, particularly the polycarbophil-based formulations should be offered as first-line approach [2].

Management Strategies and Options

For patients who are experiencing bothersome VMS in addition to focal vaginal symptoms, systemic estrogen therapy will effectively address VMS and, based on estrogen dose, can help vaginal symptoms as well. For patients with minimal systemic symptoms whose bother relates to VVA, similar to the discussed case, management should focus on strategies offering vulvovaginal benefit [4].

Menopausal hormone therapy is effective to varying degrees, against the spectrum of symptoms commonly encountered during the menopause transition and in postmenopausal years. From the perspective of vaginal symptoms, a variety of prescription formulations (tablets, rings, and creams) of vaginal estrogens are available (Table 9.1). At the start of treatment, frequent dosing (even daily) of tablets/creams

is recommended for the initial 2–3 weeks followed by maintenance dosing at twice weekly frequency; unlike the tablets and creams, the vaginal ring (Estring) is designed to be retained in place for 3 months at a time. Many women will benefit by both intravaginal therapy (ring, cream, or tablet) and topical application of estrogen cream externally to the vulva and the introitus. While subjective improvements are commonly seen sooner, objective evidence of improvement in VVA is usually seen within 1–2 months of treatment [2].

Also available currently is the first oral non-estrogen therapy for VVA. Ospemifene is an oral selective estrogen receptor modulator (SERM) that recently gained FDA approval for management of symptoms of VVA. It binds to the estrogen receptors in the vagina and effectively improves vaginal lubrication, epithelial integrity, and genitourinary symptoms of menopause [2]. Although there are no head-to-head comparator trials available, the magnitude of symptom benefit from ospemifene use is similar to that seen with the use of vaginal estrogens [5]. Ospemifene may be preferentially considered for women who are esthetically averse to vaginal inserts (creams, tablets, rings). Women who are anxious about the use of estrogens in any form may find ospemifene an acceptable alternative, an agent that is deemed a non-estrogenic formulation; it is however important to appreciate that the action of this class of agents is mediated through the estrogen receptors. Potential side effects related to ospemifene use include a slight chance of transient worsening of hot flashes and leg cramps, which usually resolve quickly. As with all SERMs, there is a slight increase in the risk of thromboembolism [6].

Although from a theoretical perspective, similar to other SERMs including tamoxifen and raloxifene, ospemifene should have a favorable breast profile, clinical data on this aspect are lacking, and ospemifene has not yet been evaluated in breast cancer survivors [7].

All hormonal products available to address symptoms of VVA carry the black box warning attendant with systemic estrogens (even though the systemic absorption of vaginal estrogens is minimal). The North American Menopause Society has been meeting with the FDA to remove these warnings; however, as menopausal hormones including vaginal formulations are still packaged with the warnings, it is appropriate to discuss these with patients before they receive them at the pharmacy [8].

Once treatment is initiated, a reevaluation is indicated after 2–3 months of an intervention or even sooner for those needing more frequent assessment. In addition to a detailed inquiry of symptoms, physical examination to assess for the presence and severity of focal VVA is advised. One can repeat vaginal cytology and pH as indicated. A review of available options should be undertaken as some women may prefer a switch from local to systemic therapy or vice versa.

An important parameter to assess at a follow-up visit is to assess for satisfaction with sexual interest and function. Many women do not recognize that anticipatory vulvovaginal discomfort plays a causative role in dampening sexual desire and

interest [9]. These encounters allow providers with opportunities to discuss any social or emotional underpinnings to relationship issues as, if identified, couples' counseling may offer lasting benefit.

Implications of overall physical and psychological well-being to a woman's approach to sex and sexuality cannot be minimized. Many women in the period of menopause transition or in postmenopausal years while grappling with menopausal symptoms are also dealing with medical issues which may impact on their quality of life and hinder their sexual functioning; alternatively, medications taken to harness medical disorders can actually impact on aspects of sexual functioning. Depression is perhaps the classic, in that both depression can lead to decreased libido and its remedies, such as SSRI and SNRI antidepressants, can all contribute to sexual dysfunction [10]. A number of survey-based tools are available and can be conveniently incorporated in office practice to screen for depressive symptoms. Additionally, directed questioning and verification of medication list are effective strategies to identify potential contributors to symptom burden.

Testosterone levels decline with advancing age and dramatically so after removal of the ovaries [11]. A number of studies have assessed the effect of testosterone on sexual function in women with some that have demonstrated slight but statistically significant improvement in libido in postmenopausal women with testosterone therapy [11]. Currently, there are no FDA-approved formulations of testosterone for use in menopause management in the United States, although options do exist in other countries [12, 13]. For patients in the United States for whom a trial of testosterone is considered, compounded formulations are an option. Discuss with the compounding pharmacy with which you are familiar how they produce their product; you would like to achieve a transdermal dose of 300 micrograms of testosterone. Many pharmacies do compound a testosterone cream or gel that needs to be used daily, and results are cumulative (not to be used as an as-needed drug, such as sildenafil). It may take up to 3 months to see full effects. The major adverse events with testosterone therapy in women are dose related and include features of hyperandrogenism such as facial hair and acne and at higher levels of exposure can include features of virilization including scalp hair loss and deepening of the voice. While acne and to some extent hair excess as well as loss relating to androgen therapy are responsive to the lowering in dose, features of masculinization (voice pitch) may not revert entirely. The North American Menopause Society does not recommend monitoring blood levels, as low levels of testosterone are quite difficult to accurately measure in a standard laboratory. The use of low-dose testosterone regimens in women has not been associated with liver or lipid abnormalities [11]. Originally, transdermal patch studies were done on surgically menopausal women who were also receiving estrogen therapy; subsequent studies have been done on menopausal women who were not treated with estrogen, also showing efficacy [14].

Case reports have appeared on women who despite a diagnosis of breast cancer have been effectively managed with testosterone [15].

Flibanserin has recently been approved by FDA as a pharmaceutical strategy for addressing reduced libido in premenopausal women [16]. While the exact mechanism of action is still unclear, it is deemed to act through dopaminergic and serotonergic pathways [16]. Efficacy of this agent in postmenopausal subjects remains not completely assessed; trial of flibanserin for this patient would be an off-label use of this agent and should take into consideration drug-related side effects including sedation, lowering of blood pressure, and nausea [17].

Mechanical aids may be useful adjuncts in managing certain types of female sexual dysfunction. The use of vaginal dilators, often in conjunction with nonpharmacological aides such as vaginal lubricants or moisturizers (Table 9.2), is simple yet effective approach to managing discomfort of VVA. Vibrators, acting both as stimulators and dilators, may also be helpful and can have direct benefit for vaginal tissue through improved pelvic blood flow [18].

For patients with persistent issues relating to sexual function and satisfaction in the absence of other signs or symptoms of menopause and after attention to focal causes of sexual dysfunction, sex therapy for the individual and for the couple may be helpful, and providers should consider compiling a list of qualified therapists in their areas of practice to help with their patients.

Case

Your patient is in excellent medical health, and she is currently taking no prescription medications. She denies VMS or vaginal discomfort. Her bothersome concerns center on symptom of lacking libido, and she brings up the question of "female Viagra" to address her reduced sex drive. She also wants your opinion of whether she should try testosterone treatment. Of note is that her mother has recently been diagnosed with mild cognitive impairment, so she is visiting mom several times a week to help her with activities of daily living. Upon questioning, the patient acknowledges having started herself on an over-the-counter antidepressant, St. John's Wort, an agent that can act like an SSRI, with potential for dampening sexual function [19].

The use of a depression screen tool, such as Patient Health Questionnaire, can help quantify the presence and severity of depressive symptoms, and this information can help guide further management. If reduced libido is acknowledged in the setting of use of an SSRI (or like agent), consider substitution to an alternative antidepressant such as bupropion (which does not depress libido) [19]. Sildenafil for improvement of orgasmic response in women on SSRIs has a limited role [19]. For patients manifesting moderate to severe depressive symptoms, referral to a mental health provider should be considered.

This patient should clearly be treated for any VVA. If her sexual interest does not improve after therapy, you could discuss with her the role of testosterone. Another option would be to counsel her on the role of sex therapy for her and her husband.

Clinical Pearls/Pitfalls

- VVA tends to get worse over time, compared to VMS, which tends to get better.
- Inquire about focal atrophic symptoms. Get a sense from your patient to see if she would prefer to start with vaginal interventions or an oral medication. Reassure her that if one approach does not work, you have alternative approaches available.
- Always ask about psychosocial pressures as well as medical issues confronting your patient.
- Review list of both prescribed medications and use of over-the-counter remedies. Both the medical condition and its therapy can impact adversely on sexual well-being.
- Once treatment is initiated, periodically reassess efficacy as well as need for further intervention. Discuss other options available, including medications with an off-label indication.
- For symptoms of VVA, once improved with an intervention, lasting benefit will likely require ongoing therapy. Encourage your patient to continue with her interventions, if they are successful.

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The Case for Androgens in Menopausal Women: When and How?

10

Grace Huang and Shehzad Basaria

Case Presentation

A 55-year-old healthy married woman complains of reduced sexual desire and arousal for the past 10 years. She denies any dyspareunia. She underwent a hysterectomy with bilateral salpingo-oophorectomy at the age of 45 for symptomatic uterine fibroids. After the surgery, she started experiencing hot flashes, vaginal dryness, and decreased sexual desire. She was prescribed with a transdermal estradiol patch which relieved her hot flashes and vaginal dryness but did not improve her sexual symptoms. Her total and free testosterone levels are low at 12 ng/dl and 1.5 pg/ml, respectively. She had a normal mammogram within the last year. She asks whether testosterone replacement is an option to treat her sexual symptoms. *How should this patient be assessed and treated?*

Androgen Physiology in Postmenopausal Women

Similar to men, women also experience age-related decline in gonadal steroids [1]. At the time of natural menopause, there is sudden and permanent cessation of ovarian follicle formation and decline in estrogen production. Although serum androgen levels decline with age in women, much of this decline is between the ages of 20–40 years. Furthermore, there is no cessation of androgen production during natural menopause.

The two major sources of androgen production in women are the ovaries and the adrenal glands [2]. In women, testosterone is produced directly by the ovaries and by peripheral conversion of androstenedione and dehydroepiandrosterone (DHEA),

G. Huang, MD (✉) • S. Basaria, MD
Section of Men's Health, Aging and Metabolism, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Ave, BLI-541, Boston, MA 02115, USA
e-mail: ghuang7@partners.org

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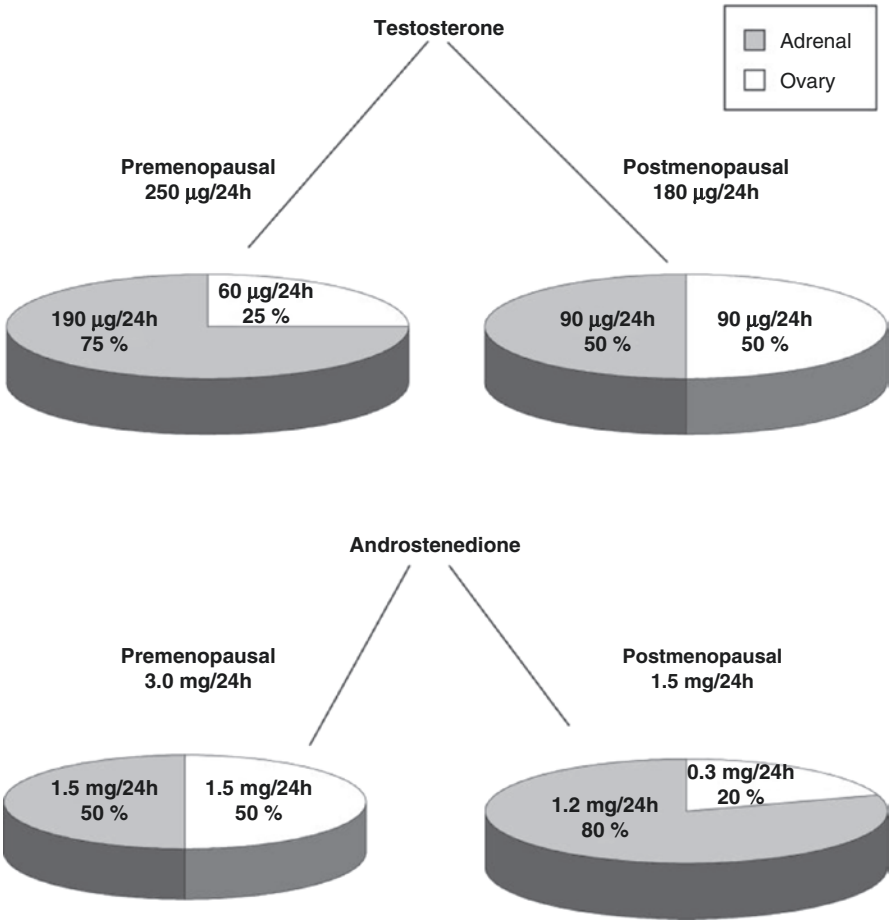

Fig. 10.1 The contribution of the ovaries and the adrenals to serum androgen levels in pre- and postmenopausal women [3]

which are synthesized by the ovaries and the adrenal glands, respectively. In young premenopausal women, the ovary is responsible for approximately 25 % of the testosterone production, while 75 % is derived from the adrenal glands. However, in postmenopausal women, the ovary becomes a major source of androgens and contributes to approximately 50 % of the total testosterone production (Fig. 10.1) [3]. Although the climacteric ovary becomes atrophic and loses capacity to synthesize estradiol, it still continues to secrete substantial amount of androgens under the stimulation of gonadotropins [2]. In fact, the steepest decline in testosterone levels occurs in the early reproductive years between the ages of 20–40 with a plateau through the menopausal transition, followed by a gradual decline with age (Fig. 10.2) [1, 4]. Interestingly, after the age of 80 years, a minor increase in serum total testosterone levels has been reported in one cross-sectional study [4]; whether this

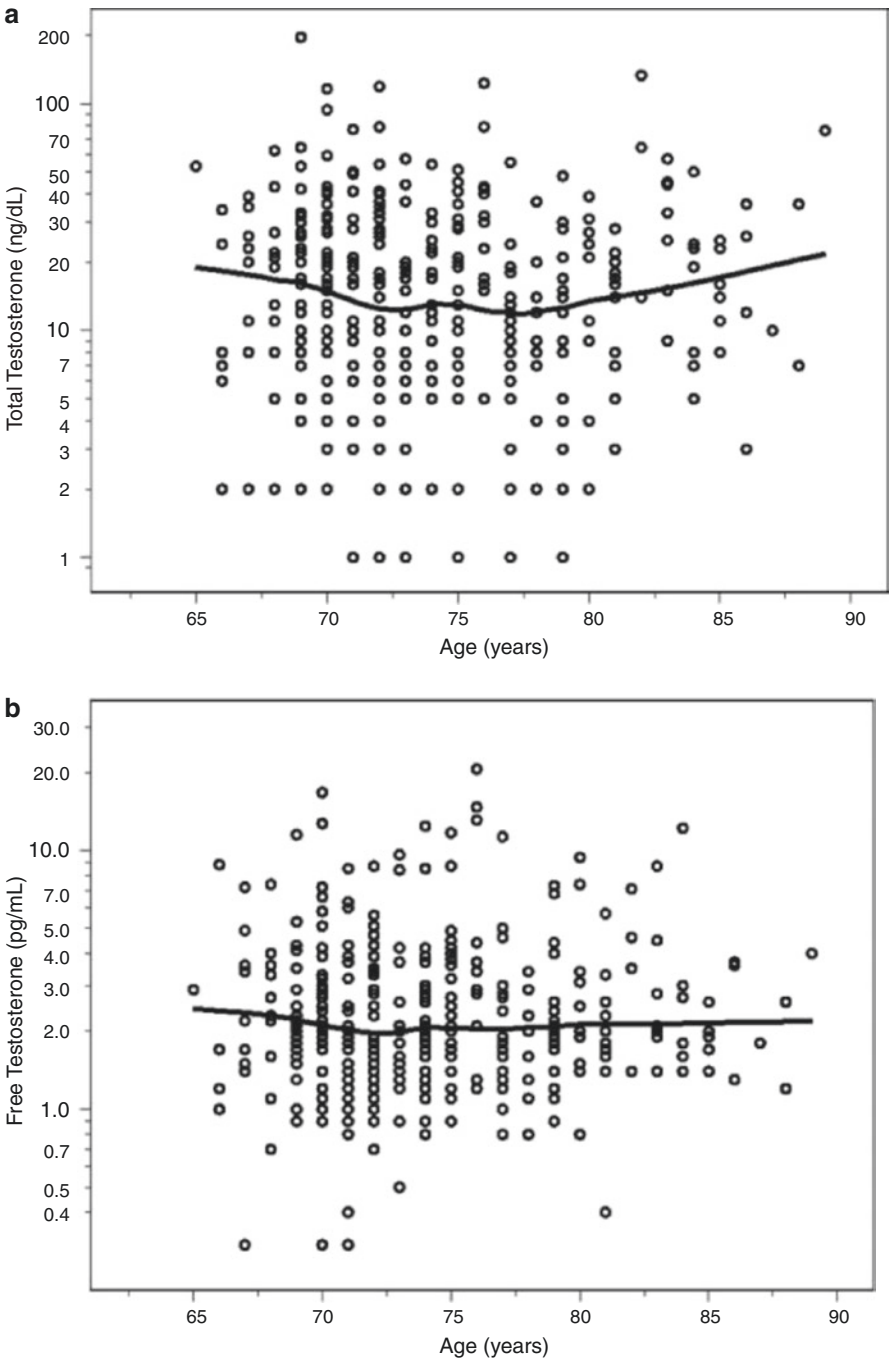

Fig. 10.2 Total and free testosterone levels with age [4]

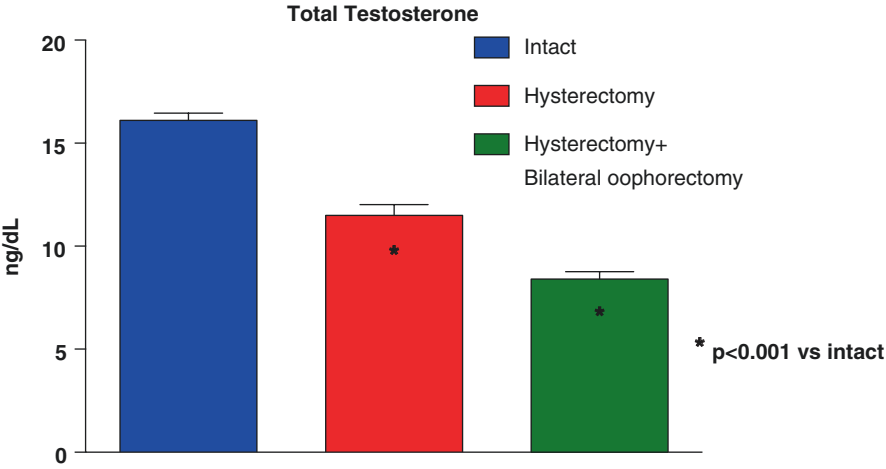

Fig. 10.3 Androgens after hysterectomy and oophorectomy [5]

increase in older women is a true physiological phenomenon is unclear. Thus, the decline in androgens in women appears to be more of a function of aging rather than natural menopause [1, 2]. In contrast to natural menopause, surgical menopause results in a significant decline in androgen levels. Indeed epidemiologic studies show a significant decline in serum testosterone levels by more than 40 % in women undergoing bilateral oophorectomy (Fig. 10.3) [5].

Female Androgen Deficiency Syndrome

The role of androgen therapy in postmenopausal women has been an area of growing scientific and public interest. In June 2001, an international expert panel met at the Princeton Consensus Conference (Princeton, NJ) and established three diagnostic criteria for the Female Androgen Deficiency Syndrome (FADS) [6]. In order to have a diagnosis of FADS, women had to have the following three criteria: (1) clinical symptoms such as diminished well-being, unexplained fatigue, sexual dysfunction, vasomotor instability, and/or decreased vaginal lubrication, (2) be adequately estrogenized (i.e., normal menstruating woman or a postmenopausal woman who is on estrogen replacement), and (3) free serum testosterone levels at or below the lowest quartile of normal range for women of reproductive age (20–40 year). Hence, it has been hypothesized that testosterone replacement might reverse symptoms of FADS in these women [7].

Specific conditions in women that may be associated with a higher risk for androgen deficiency include black race, low body mass index (BMI <18.5 kg/m^2), bilateral oophorectomy, diseases of the hypothalamus, pituitary or ovaries, primary adrenal insufficiency, oral estrogen and corticosteroid use, various malignancies and their treatments, and HIV infection (Table 10.1) [2, 4]. Hence, these subsets of

Table 10.1 Conditions associated with androgen deficiency in women

Condition	*Mechanisms*
Ovarian disease	Unilateral or bilateral oophorectomy Premature ovarian failure Chemotherapy and radiation Infiltrative diseases
Hypothalamic/pituitary disease	Hypopituitarism (any cause) Opioid use High-dose glucocorticoids Systemic hormonal contraception Anorexia nervosa Cachexia
Adrenal disease	Adrenal insufficiency (any cause) Adrenalectomy High-dose glucocorticoids
Chronic liver disease HIV infection Drug-induced (estrogen, antiepileptics)	Increase SHBG (resulting in decrease in free testosterone levels)
Other risk factors	
Age	Natural decline in ovarian and adrenal production with age
Black race	Mechanism unclear (possible differences in testosterone binding)
Low BMI <18.5 kg/m^2	↓ Gonadotropins and/or ovarian dysfunction

women have a greater likelihood of androgen deficiency and, if meeting criteria for FADS, could potentially benefit from testosterone therapy.

Limited data from randomized controlled trials using transdermal testosterone use in physiologic doses in surgically menopausal women who had hypoactive sexual desire and low serum testosterone levels have shown modest improvements in several aspects of sexual function such as sexual desire, satisfaction, and frequency [8–12]. However, although the prevalent dogma is that androgens regulate libido in women, data from epidemiologic studies show that circulating androgen levels in women are only weakly associated with sexual function [13, 14]. Thus, the definition of FADS suffers from (1) lack of consensus on absolute cutoff levels for androgens that define androgen deficiency quantitatively, (2) weak associations between symptoms and androgen levels, and (3) lack of reliable and sensitive testosterone assays to measure total and free testosterone levels in the low range that is seen in women. Thus, the Princeton Consensus Conference panel's inability to establish a precise numerical cutoff for low free testosterone levels was influenced by lack of sensitive assays to precisely detect the lower circulating testosterone concentrations seen in women [6, 15]. Previous studies have measured serum testosterone levels using commercial radioimmunoassays that had wide interassay variability and lacked accuracy and reliability in the low range. Liquid chromatography–tandem mass spectrometry and equilibrium dialysis are now widely considered the gold standard methods for measuring total and free testosterone levels, respectively,

offering the highest sensitivity and specificity [16, 17]. However, these reference methods are not widely available due to challenges in methodology and expense. In addition to the lack of accuracy of testosterone assays, there is lack of normative data on serum testosterone levels in both healthy menstruating and postmenopausal women, making it further difficult to establish thresholds for defining androgen deficiency in women [7].

In spite of the limitations highlighted above, there remains an enormous public interest and media fascination with the issue of androgen replacement in women for the treatment of sexual dysfunction. Although the data from the Heart and Estrogen/Progestin Replacement Study and the Women's Health Initiative hormone trials [18, 19] have generated concerns about the role of estrogen replacement in postmenopausal women, there has been a strong advocacy by some members of the scientific community for androgen replacement in these women [20].

Potential Benefits of Testosterone Supplementation in Postmenopausal Women

Testosterone therapy has been widely promoted in women for the treatment of sexual dysfunction and also for improving body composition, muscle performance, bone mineral density, and cognition [21]. It has been assumed that dose–response relationships for testosterone are different in women than in men and that clinically significant effects on sexual function and other health-related outcomes can be achieved in women with testosterone doses and concentrations that are substantially lower than those required to produce similar effects in men [20]. Here we summarize data from randomized trials that have evaluated the efficacy of testosterone therapy on various efficacy outcomes in women. Some trials have used a dose–response design to evaluate effects of various doses of testosterone using different formulations.

Female Sexual Function, Menopause, and Androgens

The menopausal transition has been associated with decreased sexual responsiveness independent of age [22]. Several studies have shown that women who underwent surgical menopause experience greater deterioration of sexual function compared to naturally menopausal women [23–25]. Indeed, women who have undergone bilateral oophorectomy (resulting in low serum testosterone levels) report impaired sexual function even on estrogen therapy [26, 27], suggesting that androgens play an important role in the regulation of libido in women. In 2000, the first female testosterone transdermal patch was manufactured by Procter & Gamble called *Intrinsa*. This patch is available in 150 ug and 300 ug doses applied to the abdomen twice weekly, providing equivalent to 50 and 100 % daily testosterone production in premenopausal women, respectively [28].

In the last decade, there have been several clinical trials in surgically menopausal women demonstrating improvements in sexual function with physiologic transdermal testosterone replacement that increase serum testosterone levels into the mid- to high-normal range for healthy young women [8, 9, 11, 12]. The first randomized placebo-controlled trial using the patch was published in 2000 [8]. This study was a 12-week trial of 75 surgically menopausal women (ages 31–56) with impaired sexual function (based on the Brief Index of Sexual Functioning for Women Questionnaire) on 0.625 mg of oral estrogen (for at least 2 months) who were randomized to placebo, 150 ug or 300 ug testosterone patch. The mean total testosterone levels increased from 21 ng/dl to 65 ng/dl and 102 ng/dl in the 150 ug and 300 ug groups, respectively. Sexual function (measured by the Brief Index of Sexual Functioning for Women Questionnaire) only improved in the 300 ug-treated group compared to placebo; despite a large placebo response, improvements in sexual thoughts–desire, frequency, pleasure–orgasm, and well-being were seen. Specifically, there was a two- to threefold increase from baseline in percentage of women who had sexual fantasies, masturbated, or engaged in sexual intercourse at least once a week. There was no differences in androgenic (hirsutism, acne) adverse events nor metabolic profile between the groups [29]. Indeed, several follow-up well-designed randomized, controlled studies in both surgically and naturally menopausal women (most trials included women on estrogen replacement) with hypoactive sexual desire disorder (HSDD) have reported that administration of transdermal testosterone resulted in modest improvement in some domains of sexual function such as sexual desire, satisfaction, and frequency [8–12]. Davis and colleagues conducted a trial using the testosterone patch (150 or 300 ug per day vs. placebo) in 814 *non-estrogen*-treated postmenopausal women (natural and surgical) for 24 weeks [11]. A significant increase by an additional 2.1 satisfying sexual encounters per month was seen only in the 300 ug group versus 0.7 satisfying sexual encounters in the placebo group. There were no significant differences in the adverse side effect profile among the groups.

Despite several studies having demonstrated efficacy and short-term safety of physiologic transdermal androgen therapy for sexual dysfunction in postmenopausal women, the improvements seen have been modest and limited by large placebo effects. Furthermore, recently, two large phase III trials using a transdermal testosterone gel (LibiGel, BioSante, Inc.) failed to meet their primary endpoints of improvements in sexual function (sexual desire and total number of satisfying sexual events) in women with HSDD compared with placebo (data not published). In a recent dose–response study of intramuscular testosterone administration (ranging from physiologic to supraphysiologic doses) in 71 estrogen-treated hysterectomized postmenopausal women (ages 41–62 years) who did not have impaired sexual functioning at baseline, testosterone administration was associated with concentration-dependent improvements in sexual thoughts and desires, sexual activity scores, and arousal, but not in other domains of sexual function [30]. However, these improvements were observed only in women who were assigned to the highest testosterone dose (Fig. 10.4).

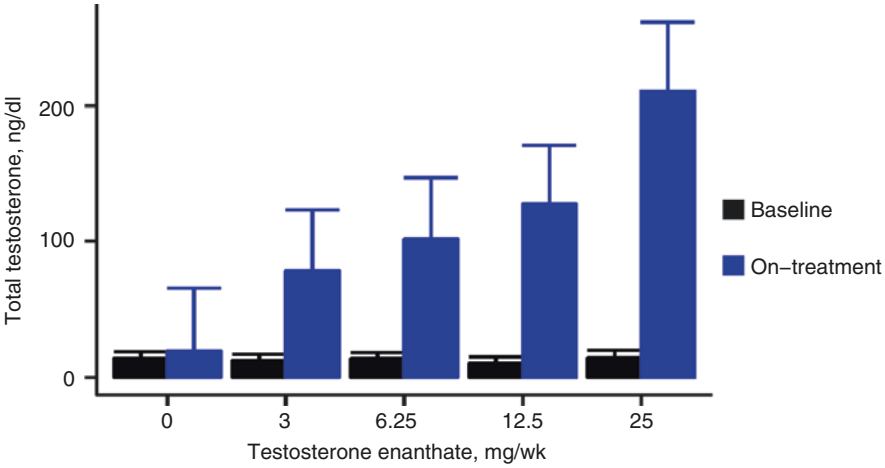

Fig. 10.4 On-treatment total testosterone concentrations. Data represent mean and standard errors at baseline and on-treatment for each testosterone dose group [30]

Although these clinical trials have demonstrated some efficacy of testosterone in the treatment of sexual dysfunction in postmenopausal women, long-term safety of testosterone therapy remains unclear. In 2004, the FDA voted not to approve the transdermal testosterone patch for the treatment of hypoactive sexual desire due to lack of long-term safety data. In 2006, the Endocrine Society recommended against making a diagnosis of androgen deficiency in women due to lack of a well-defined syndrome and normative data for testosterone levels and also recommended against generalized use of testosterone supplementation in women as evidence of safety in long-term studies is lacking [31]. The most updated 2014 Endocrine Society Guidelines on androgen therapy in women continue to recommend against making a diagnosis of FADS and generalized use of testosterone. They also recommended against the use of testosterone therapy in sexual dysfunction, the exception being a postmenopausal women with HSDD, and in the absence of any contraindications, for whom the guidelines suggest a 3- or 6-month trial of testosterone. However, approved testosterone preparations for women are not available in many countries including the United States. Approved testosterone products are available for women in Australia and in some European countries; clinicians in the United States are limited to off-label testosterone preparations, since no testosterone product is FDA approved for use in women.

Body Composition, Muscle Performance, Physical Function, and Androgens

In women, the menopausal transition has been associated with an accelerated loss of muscle mass and strength and decrease in physical function [32, 33]. Although the negative impact of low estrogen on bone health is well established, there is

limited evidence on whether this loss of estrogen significantly influences muscle mass and physical function [34–36].

Menopause is associated with an increase in fat mass and a decrease in lean body mass [37, 38]. Conversely, free serum testosterone levels are associated with increased lean mass in older women [39]. The Study of Women's Health Across the Nation (SWAN) found higher rates of physical limitation in surgically menopausal women compared to women undergoing natural menopause [40]. Indeed, the age-related decline in serum testosterone levels in older women has been associated with frailty [41]. Thus, it is conceivable that women who have undergone surgical menopause and have low testosterone levels may be at a greater lifetime risk for physical disability. Clinical trials using various formulations and doses of testosterone and other androgens have reported some improvements in lean mass and muscle strength, although with few demonstrating improvements in physical function [42–45]. One trial reported modest increase in lean mass in women (aged 19–50 years) with hypopituitarism in response to physiologic testosterone replacement [46]. Another 16-week double-blind randomized controlled trial of 40 postmenopausal women (natural and surgical) who were randomized to either oral 1.25 mg esterified estrogen + 2.5 mg methyltestosterone versus estrogen alone showed that the combined estrogen–androgen group experienced a significant increase in lean mass and muscle strength as well as reduction in total fat mass compared to estrogen alone [42].

Testosterone therapy has also shown beneficial effects on body composition in women who are androgen deficient as a result of another medical condition. Indeed, a study of transdermal testosterone replacement (4 mg/patch) in HIV-infected women with androgen deficiency and 10 % weight loss for 6 months resulted in increases in muscle mass and strength as well as improved muscle function [47]; however, these results have not been confirmed in other studies of women with HIV [48]. In another study of relatively healthy estrogenized postmenopausal women without physical dysfunction at baseline, testosterone administration via intramuscular injections at supraphysiologic doses was associated with significant gains in lean mass, chest press power, and loaded stair climb power; these improvements were observed only at the highest dose (25 mg weekly), with nadir testosterone concentrations of 200 ng/dl [30] (Fig. 10.5). Additional studies are needed to explore the role of androgens in the regulation of body composition, muscle performance, and physical function in various subsets of women (postmenopausal with chronic diseases) with low testosterone levels.

Cognition and Androgens

Epidemiologic studies have suggested that serum testosterone levels in women are associated with specific aspects of cognition, although data regarding the association of circulating testosterone concentrations and cognitive function are inconsistent across studies [49–52]. Testosterone is aromatized to estradiol, both in the periphery and in the brain; in addition to its direct effects via androgen receptor,

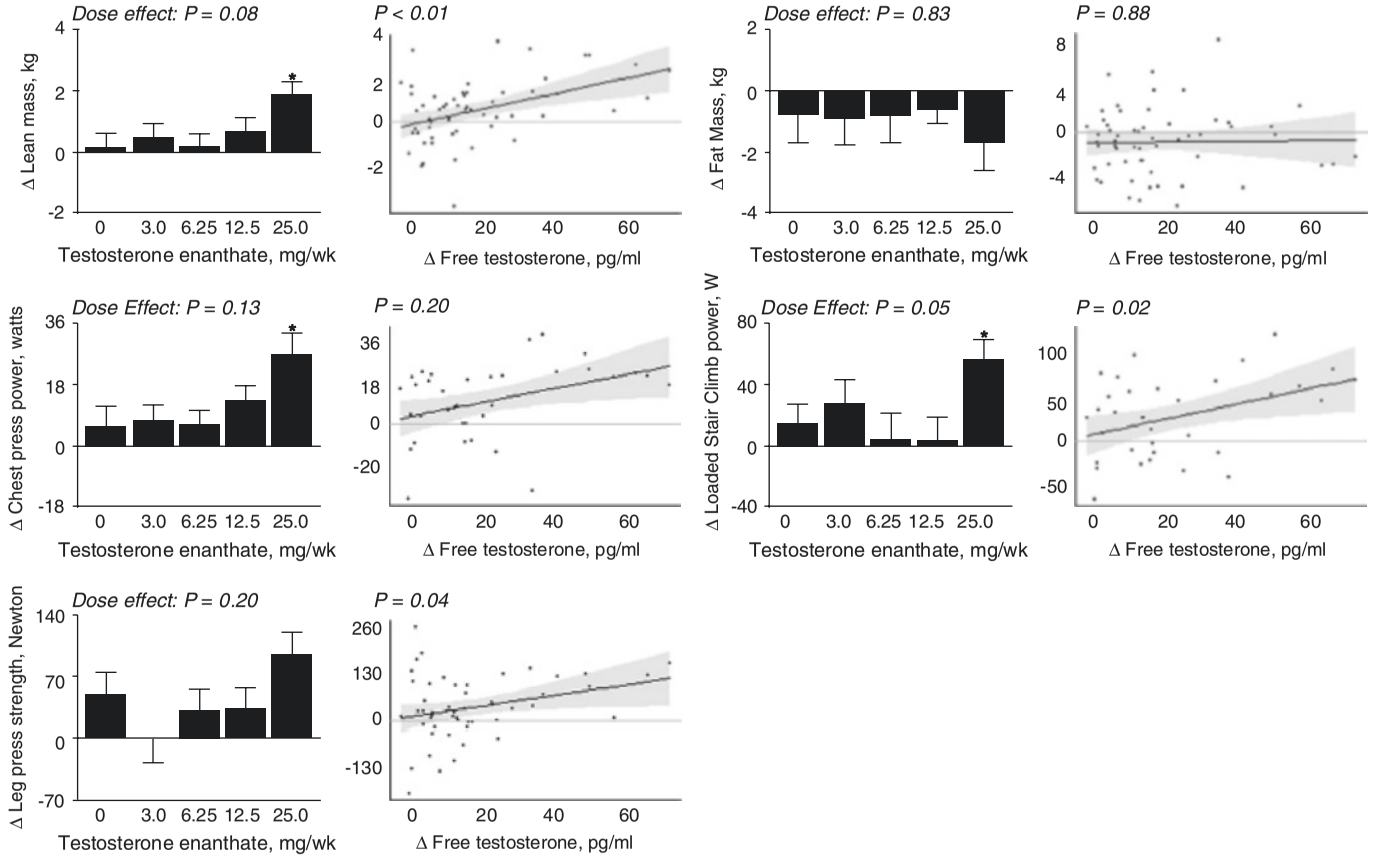

Fig. 10.5 Body composition and muscle performance measures. In the bar graphs on the left, data represent absolute mean (SE) changes from baseline for each treatment group. Scatter plots on the right display estimates and 95% CI for the generalized additive model of change in outcomes as function of free testosterone levels [30]

some effects of testosterone administration might thus be mediated via its aromatization to estradiol [53]. For example, premenopausal women with polycystic ovary syndrome (PCOS) who have higher serum testosterone levels were noted to perform better on spatial tasks and worse on verbal tasks compared to controls [54, 55]. Similarly, endogenous testosterone levels during the menstrual cycle are positively correlated with visuospatial ability and negatively with verbal fluency in healthy women [49, 56]. Similar findings have been noted in some [50], but not in other association studies of endogenous sex hormones and cognition in healthy postmenopausal women [51, 52], and trials of testosterone administration assessing cognitive performance in postmenopausal women have yielded inconsistent results [57, 58]. A 12-week crossover study did not show improvement in cognitive function in surgically menopausal women receiving estrogen alone versus estrogen and intramuscular testosterone [57]. In short-term studies using oral testosterone, improvement in executive function (attention) was noted in one study [59]; however, other studies did not show any cognitive benefits [60, 61]. A recently conducted 24-week dose–response study of testosterone intramuscular injections in estrogen-treated postmenopausal women aged 41–62 years neither showed improvement nor worsening of cognitive performance in a number of domains of cognitive function (spatial reasoning, verbal memory, verbal fluency, and executive function) over a wide range of testosterone doses and concentrations, including doses that achieved supraphysiologic serum testosterone concentrations [62]. In a mechanistic study exploring the role of aromatization on cognition, 71 postmenopausal women who were already receiving transdermal estrogen for 12 weeks were given transdermal 0.5 % testosterone gel and were then randomized either to aromatase inhibitor (letrozole 2.5 mg) or placebo for 16 weeks [63]. Significant improvements in visual and verbal memory were seen with testosterone therapy, and the results were unaffected by aromatase inhibition. These findings suggest that testosterone may have direct cognitive effects independent of its conversion to estradiol. On the contrary, a recently conducted 24-week dose–response study of testosterone replacement in estrogen-treated postmenopausal women neither showed improvement nor worsening of cognitive performance in a number of domains of cognitive function (spatial reasoning, verbal memory, verbal fluency, and executive function) over a wide range of testosterone doses and concentrations, including doses that achieved supraphysiologic serum testosterone concentrations [62].

Contrastingly, some studies have suggested that testosterone therapy may have negative effects on cognitive performance in postmenopausal women. In a study of surgically menopausal women, significant worsening of verbal memory was seen in the group receiving both testosterone and estrogen compared to estrogen alone [58]. Similarly, though in a different context, administration of supraphysiologic doses of testosterone to female-to-male transsexuals has been shown to worsen verbal fluency while improving spatial memory [64]. Long-term, adequately powered trials are needed to evaluate the cognitive effects of testosterone therapy in women. Furthermore, whether testosterone might be beneficial in women with baseline cognitive deficits remains to be investigated.

Androgens and Bone

In women, serum testosterone levels are correlated with trabecular and cortical bone mineral density (BMD), particularly in the older postmenopausal women [39, 65]. Postmenopausal women treated with combined estradiol and testosterone implants for 2 years experienced significantly greater increases in hip and lumbar spine BMD compared to those receiving estradiol implants alone [44]. Two randomized controlled trials in surgically menopausal women compared the effects of a combination of estrogen and methyltestosterone therapy with estrogen therapy alone [66, 67]. One study showed improvement only in the spine BMD in the group receiving testosterone [66], while the other showed improvements at both sites [67]. On the contrary, another study of estrogenized surgically menopausal women who were administered with oral testosterone undecanoate 40 mg daily for 24 weeks did not improve BMD at any of the studied skeletal sites [68]. In yet another small trial of 25 surgically menopausal women on estradiol implants, addition of testosterone for 16 weeks had no significant effects on serum bone markers compared to estrogen alone [69], suggesting that testosterone does not augment the positive effects of estrogen on bone. These results are consistent with studies in young women with primary ovarian insufficiency (who have profound estrogen and testosterone deficiency) where the addition of transdermal testosterone replacement to estrogen did not provide additional benefit [70]. In contrast, another study in postmenopausal women showed that short-term administration of methyltestosterone with estrogen increased markers of bone formation [71].

In summary, data from some, but not all, testosterone intervention studies demonstrate improvement in BMD in postmenopausal women; however, it is unclear whether or not testosterone itself can provide further benefits in the prevention of osteoporosis in adequately estrogenized women. Importantly, the efficacy of testosterone on fracture rates in postmenopausal women remains unknown.

Menopausal Symptoms and Androgens

Currently a combination of oral methyltestosterone and estrogen is FDA approved only for the treatment of moderate to severe menopausal vasomotor symptoms that are not improved by estrogen alone [72]. While the majority of studies have not shown a benefit of methyltestosterone over estrogen [59, 66, 71, 73, 74] in reducing postmenopausal somatic symptoms, two studies have reported greater benefit in menopausal symptoms with methyltestosterone and estrogen combination than estrogen alone [75, 76]. Sherwin et al. reported greater improvements in somatic symptoms in surgically menopausal women treated with combined testosterone and estrogen injections compared with estrogen alone [77]. A large uncontrolled study in 300 pre- and postmenopausal women with symptoms of androgen deficiency showed that continuous testosterone alone, delivered by subcutaneous pellets, was effective in relieving psychological, somatic, and urogenital symptoms, measured

by a validated Menopause Rating Scale (MRS) [78]; however this study is limited by a lacking control group for comparison.

In summary, because of the small number of studies and limitation of study design, more evidence is needed to support the efficacy of the addition of testosterone to estrogen in improving menopausal symptoms in both surgically and naturally menopausal women.

Potential Adverse Effects of Testosterone Supplementation in Women

Undesired Androgenic Effects

Potential adverse androgenic effects of testosterone therapy include hirsutism, acne, alopecia, clitoromegaly, and voice deepening. In the majority of randomized placebo-controlled studies of testosterone administration in postmenopausal women [9, 10, 12, 29, 30, 79], the frequency of androgenic events (mainly hirsutism and acne) was higher in the testosterone-treated groups versus placebo; however, most androgenic events were mild in nature. Furthermore, few women withdrew from these studies because of androgenic adverse events [11, 30]. Four cases of clitoral enlargement were reported in one trial of transdermal testosterone patch (one woman receiving 150 ug/day; three receiving 300 ug/day dose), but all were classified as mild by the investigators [11]. None of these women withdrew from the study and clitoromegaly either resolved or remained stable throughout the trial. However, most of the abovementioned androgenic events were collected by subjective report with only a few studies using validated assessment tools. In one dose–response study of 71 estrogen-treated postmenopausal women, androgenic adverse effects were objectively monitored using validated instruments: hair growth using the Ferriman–Gallwey scale, sebum production using Sebutape, acne using the Palatsi scale, clitoral size using a caliper scale, and voice changes using functional acoustic testing [30, 80]. In this trial, clitoral size, Palatsi score, and sebum production rate did not differ significantly between any of the testosterone dose groups (ranging from physiologic to supraphysiologic) versus placebo. However, there were small increases in Ferriman–Gallwey scores in the two highest dose groups (12.5 and 25 mg testosterone enanthate). In the same trial, testosterone administration in women was also associated with dose- and concentration-dependent reduction in average pitch in the higher dose groups [80]. Interestingly, these changes were measureable even though the participants did not report any subjective changes in voice. Early changes in acoustic parameters prior to clinical manifestation have also been reported in patients with Parkinson's disease, in whom changes in vocal frequency can be detected a decade prior to the clinical diagnosis [81], supporting the notion that detection via functional acoustic testing can be an early marker for subsequent clinical voice changes during testosterone administration. Future clinical trials addressing safety of testosterone therapy should include both subjective and objective evaluations of androgenic side effects.

In summary, the incidence of adverse androgenic side effects of testosterone administration in postmenopausal women at physiologic doses appears to be low and infrequent, and if they do occur, they are generally tolerable.

Cardiometabolic Effects

In women with PCOS, endogenous serum testosterone levels are positively associated with fat mass, proatherogenic dyslipidemia, and insulin resistance [60, 82]. Similarly, in postmenopausal women, higher serum testosterone levels have also been associated with insulin resistance, metabolic syndrome, and coronary heart disease [39, 83]. The data from epidemiologic studies have been extrapolated to suggest that exogenous testosterone administration may also worsen metabolic outcomes in women.

Effects on Body Fat Distribution

Obesity is an important predictor of cardiovascular morbidity and mortality in postmenopausal women [84]. Higher serum-free testosterone levels have been associated with increased total fat mass in older women [39]. There is also evidence suggesting that abdominal obesity is more strongly associated with an androgenic sex hormone profile than generalized obesity in postmenopausal women [85]. Data from SWAN identify a strong positive association between bioavailable testosterone level and increased visceral fat in midlife women [86]. Similarly, women with PCOS have higher subcutaneous and visceral abdominal fat compared to age- and BMI-matched controls [87].

Contrary to epidemiologic studies, data from clinical trials evaluating the effect of exogenous testosterone therapy on central body fat distribution in postmenopausal women are lacking. In female-to-male transsexuals, long-term intramuscular testosterone injections at supraphysiologic doses result in a decrease in subcutaneous fat but increase visceral fat accumulation [88]. In a small study of postmenopausal women who had undergone hysterectomy, the use of low-dose oral methyltestosterone for 1 year showed an increase in visceral fat relative to controls, but was not associated with worsening of insulin resistance [89]. However, this increase in abdominal visceral fat was not seen in a 6-month study of physiologic transdermal testosterone therapy in women with HIV [90]. Another 24-week dose–response study in surgically menopausal women did not show any dose- or concentration-dependent changes in abdominal subcutaneous or visceral fat volumes [91].

Effects on Insulin Resistance

Despite the association between hyperandrogenemia and insulin resistance in PCOS women, most studies in postmenopausal women have not found these associations [92]. Whether insulin resistance precedes or is a consequence of hyperandrogenism still remains unclear. Holmang et al. demonstrated that in an oophorectomized rat model, supraphysiologic doses of testosterone induce

insulin resistance [93], suggesting that these effects are dose and concentration dependent. In one euglycemic–hyperinsulinemic clamp study of postmenopausal women with insulin resistance and high free serum testosterone levels, therapy with metformin for 12 weeks resulted in greater insulin sensitivity than those receiving androgen suppression therapy with leuprolide, suggesting that it is insulin resistance that leads to hyperandrogenism [94]. In contrast, another small trial in postmenopausal women, a combination therapy with oral testosterone undecanoate and estradiol, reported a reduction in insulin sensitivity compared to estradiol alone [95], suggesting that it is hyperandrogenism that might lead to insulin resistance. Conversely, in a trial of hysterectomized postmenopausal women, short-term testosterone administration for 24 weeks did not result in significant changes in fasting glucose, fasting insulin, and insulin resistance, even at doses that achieved supraphysiologic serum testosterone concentrations [91]. Similarly, pivotal trials of transdermal testosterone replacement in postmenopausal women also did not demonstrate any significant effects on fasting insulin and glucose [8–12]. Although there appears to be no evidence of harm of testosterone therapy on metabolic parameters, understanding the mechanisms by which androgens influence insulin action and glucose metabolism needs further study.

Lipid Profile

Some of the concerns regarding long-term testosterone therapy in women is the potential to lower HDL and increase LDL cholesterol [92]. Davis et al. found no significant changes in serum lipid profile in naturally and surgically menopausal women who were receiving physiologic doses of transdermal testosterone patch without concurrent estrogen for 6 months [11]. In another study, combined administration of estrogen and testosterone undecanoate did not significantly change HDL, but a reduction in total and LDL cholesterol was seen [95]. Treatment with DHEA (an adrenal androgen) in postmenopausal women significantly lowers HDL particles [96]. Postmenopausal obese women administered nandrolone decanoate (a non-aromatizable androgen) results in significant reduction in HDL and increases in LDL cholesterol [97]. Thus, it is possible that adverse effects of androgens on plasma lipid profile are limited to supraphysiologic doses of androgens and/or non-aromatizable androgen formulations. In a randomized placebo-controlled 24-week dose–response trial in postmenopausal women, total cholesterol, LDL cholesterol, and triglycerides did not change significantly even in women receiving supraphysiologic doses of testosterone injections [30]. On the contrary, HDL levels decreased in all testosterone dose groups compared to placebo; however, these changes were not statistically significant. In contrast, Basaria and colleagues showed that addition of low-dose oral methyltestosterone to oral estrogen in postmenopausal women (surgical or natural) for 16 weeks significantly lowered plasma viscosity (an established risk factor for cardiovascular disease) [98] as well as lipoproteins (total cholesterol, HDL, and triglycerides) [99]. This lowering of plasma viscosity was achieved despite an increase in fibrinogen levels possibly due to significant lowering of lipoproteins.

Overall, the evidence from the transdermal testosterone patch studies have consistently demonstrated no significant changes in lipid profile [10, 12, 29]; however, these trials were primarily designed to test the efficacy of testosterone on sexual function rather than metabolic side effects. Meta-analyses of studies that have investigated effects of combined oral testosterone with estrogen versus estrogen alone on lipid profiles show that testosterone has favorable effects in reducing triglycerides; however, unfavorable effects of decreased HDL and increased LDL cholesterol have also been reported [21].

Vasculature

Studies investigating relationship between testosterone and indices of atherosclerosis have yielded conflicting results. Some studies have shown that postmenopausal women with low testosterone levels have impaired endothelial function [100], while women with PCOS with high testosterone levels have evidence of carotid atherosclerosis and endothelial dysfunction [101]. These findings suggest that the effect that both low and high levels of serum testosterone levels compromise arterial function and the optimum levels are somewhere in between. This concept is supported in animal studies, where administration of testosterone at physiologic doses to androgen-deficient female rats resulted in an improvement in vasodilation [102]. On the contrary, supraphysiologic testosterone administration in female cynomolgus monkeys fed an atherogenic diet resulted in worsening of coronary atherosclerosis [103]. Long-term clinical trials in women are needed to establish the effects of exogenous use of testosterone on atherosclerosis and cardiovascular outcomes.

Breast Cancer

Androgen receptors (AR) are widely expressed in the majority of breast tumors, for which modulation of AR signaling can be either inhibitory or stimulatory [104]. Thus, in the breast, testosterone may exert its effects directly via AR or indirectly by its aromatization to estradiol. Historically, the oncogenic role of AR has been described in ER−/AR+ subtypes that have been demonstrated to have similar signaling to ER+ breast cancers [105]. On the contrary, preclinical studies in animal models and breast cancer cell lines have demonstrated that androgens may also have apoptotic and antiproliferative effects that protect against the oncogenic effects of estrogen on breast tissue [106]. In fact, androgens have been shown to improve response rates in combination with tamoxifen in the treatment of advanced ER+ breast cancer [107, 108]. However, this has not been studied in large randomized controlled trials and is not standard clinical practice, and similar to the safety concerns with estrogen therapy in postmenopausal women, there have been concerns that exogenous testosterone therapy may potentially increase the risk for breast cancer in postmenopausal women. Interestingly, hyperandrogenic women with PCOS who are exposed to a prolonged unopposed (by progesterone) estrogen state have not been shown to have increased risk for breast cancer [105, 106]. However, combined oral estrogen plus progesterone therapy has been shown to increase risk for

breast cancer in postmenopausal women [18, 109]. In contrast, in estrogen-depleted postmenopausal women, higher endogenous testosterone levels have been shown to be associated with greater breast cancer risk [106]. Thus, there is potential for exogenous testosterone therapy to have either androgenic or indirect estrogenic effects (via aromatization) on breast tissue, potentially increasing breast cancer risk. In one testosterone patch study in postmenopausal women not taking estrogen, breast cancer was diagnosed in three women in the testosterone-treated groups after 4–12 months of randomization; however, the investigators reported that one of these women in retrospect already had symptoms suggestive of breast cancer prior to randomization [11]. In contrast, in one prospective observational study of pre- and postmenopausal women not on estrogen, treatment with subcutaneous testosterone implants alone or combined with aromatase inhibitors was associated with reduced incidence of breast cancer over 5 years compared with that of age-matched historical controls [110], suggesting that the effects of testosterone on the breast may be protective. Furthermore, emerging evidence suggests that selective androgen receptor modulators may even have a beneficial role in specific subtypes of breast cancer. While AR signaling may have an oncogenic role in ER-breast cancers, development of AR-directed therapies may have positive anti-oncogenic roles in ER+ breast cancers.

In summary, the safety data on exogenous testosterone use and risk for breast cancer in healthy women is inconclusive and needs further study in larger adequately powered randomized placebo-controlled trials.

Summary: Back to the Patient

Our patient is a healthy surgically menopausal women with unequivocally low testosterone levels complaining of sexual dysfunction. The Endocrine Society recommends against generalized use of testosterone by women for sexual dysfunction (except for a specific diagnosis of HSDD). Testosterone therapy would be indicated if she was appropriately diagnosed with HSDD as clinical trial evidence supports efficacy and short-term safety of testosterone therapy for this condition. In the United States (US), there is no FDA-approved testosterone product available for the treatment of female sexual dysfunction due to inadequate long-term safety data. In countries where a testosterone formulation is approved for women, a 3–6-month trial of testosterone therapy in women with properly diagnosed HSDD who do not have contraindications could be considered [31]. Long-term use (beyond 6 months) of testosterone therapy in women is not recommended until long-term efficacy and safety data are available. Despite the lack of an approved testosterone product for the treatment of HSDD, testosterone is commonly being prescribed off-label by practitioners, often as a custom-compounded 1 % topical cream or reduced doses of testosterone gels (e.g., Testim, Androgel) approved for men. However, compounded products are not under strict government regulation and are subject to significant variability in terms of quality, purity, and bioavailability. Whereas women using testosterone formulations approved for men are at increased risk for significant

overdosing, the challenges and difficulties in standardizing the dose to achieve physiologic testosterone levels in women can potentially lead to accidental overuse and abuse. Therefore, treatment of women with testosterone products formulated for men or those manufactured by compounding pharmacies is not recommended due to lack of efficacy and safety data.

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Postmenopausal Alopecia (Hair Loss)

11

Lynne J. Goldberg

Case Presentation

A 62-year-old postmenopausal woman presents with a complaint of scalp hair loss. It has been present for several years, but worsened recently several months after a hospital admission for pneumonia, prompting the visit. She noticed an abrupt onset of hair shedding beginning 3 months after her hospitalization, and which lasted for almost 3 months. She reports that her shedding has since slowed and is back to baseline. She is otherwise healthy except for a history of recently diagnosed mild hypertension and osteoarthritis. Her medications include lisinopril, which she has been on for 6 months, and ibuprofen. She reports that her father became bald at a young age, but denies any hair loss complaint among women in her family.

Her physical exam reveals short, dyed scalp hair. The frontal hairline is preserved with mild bitemporal recession and a mildly widened hair part on the crown of her scalp in comparison to the occiput. The hair loss was diffuse without bald patches. There is no erythema, scale, pustules, or atrophy. There is no loss of hair elsewhere on her body.

My Management

A. Counsel the patient on the causes of diffuse hair loss.
B. Explain the treatment options for female pattern hair loss, starting with proper use and side effects of minoxidil, the only Food and Drug Administration (FDA)-approved option.
C. Discuss realistic treatment outcomes and expectations.

L.J. Goldberg, MD
Professor of Dermatology and Pathology & Laboratory Medicine, Boston University School of Medicine, Boston, MA, USA

Director, Hair Clinic, Boston Medical Center, Boston, MA, USA
e-mail: lynngold@bu.edu

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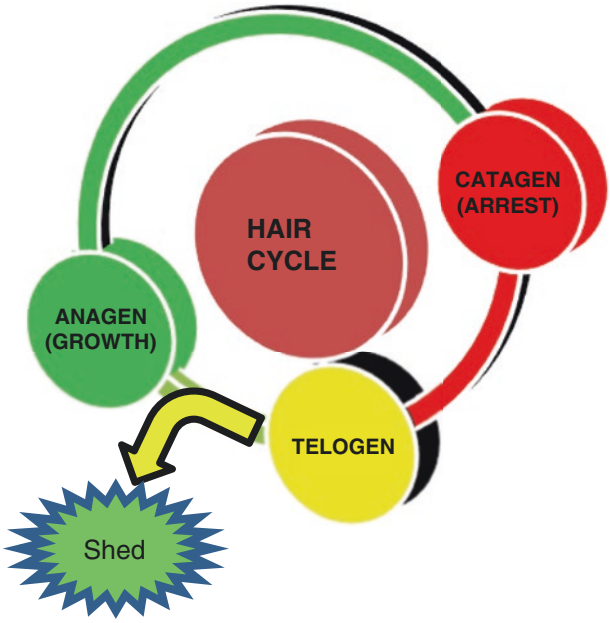

Fig. 11.1 Anagen hair follicle. The dark blue hair matrix gives rise to a light brown hair shaft. Several layers (inner and outer root sheaths) surround the hair shaft (Bhawan J, Sau P, Byers HR. *Dermatopathology Interactive Atlas,* http://dermpathatlas.com/ used with permission)

Hair Growth and Loss: An Overview

Postmenopausal hair loss is a prevalent, burdensome, and yet a poorly understood entity. This chapter aims at discussing the known mechanisms, differential diagnoses, and available management strategies and options to address scalp hair loss in postmenopausal women.

Before one can understand hair loss, a brief review of hair anatomy, the hair cycle, and causes of hair loss, or alopecia, is in order. Hair follicles form during embryogenesis. The hair shaft itself is produced by hair matrix cells in the underlying hair follicle, which is located deep in the skin in the subcutaneous tissue (Fig. 11.1). Each follicle produces a hair shaft in a cyclic fashion in several phases, whose lengths are genetically determined (Table 11.1).

Hair loss is divided into two broad types, scarring (cicatricial) or non-scarring. Scarring alopecias are due to inflammatory processes that result in destruction of the hair shaft. They are diagnosed according to which type of inflammatory cell is present [1]. Non-scarring alopecias are more common and can be either diffuse or patchy. The most common cause of hair loss is genetic (common male and female balding or male and female pattern hair loss), which results in a decrease in the size of the follicle in a reproducible pattern. Another cause of non-scarring diffuse hair loss is a telogen effluvium, caused by alterations in the hair cycle leading to increased hair shedding (Fig. 11.2). Causes of patchy non-scarring hair loss include alopecia areata, an autoimmune disorder, and tinea capitis, which are both more common in children.

Table 11.1 The hair cycle

Cycle	Changes in the hair follicle	Duration
Anagen	Growing phase	6 years
Catagen	Involutional phase	3 weeks
Telogen	Resting phase	3 months

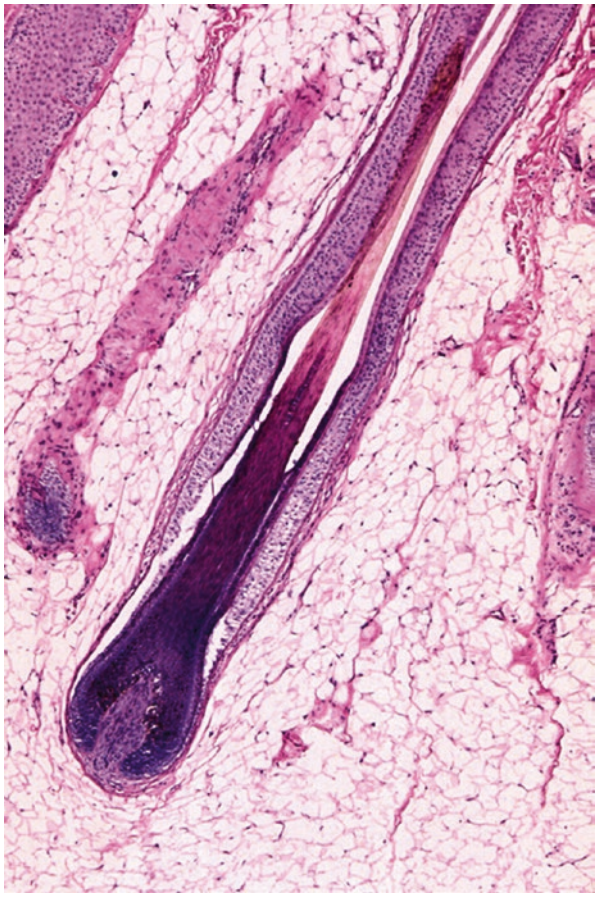

Fig. 11.2 Hair follicles grow in anagen, the growing phase of the hair cycle, for several years during which they produce a hair shaft. They stop growing in the catagen phase, which lasts for 3 weeks, then enter the resting stage of telogen, which lasts for 3 months. During this phase the old hair shaft is shed, and a new one begins to be made as the hair follicle re-enters anagen

Postmenopausal Hair Loss: Diagnosis and Causes

It is estimated that 41 % of postmenopausal women will experience hair loss [2]. Female pattern hair loss (FPHL) is the most common form of hair loss in women of all ages. For the postmenopausal population, diffuse hair loss can be multifactorial [3, 4], with decreased follicular density with advancing age (so-called senescent alopecia), environmental factors, and medications all contributing. Our patient has

a combination of telogen effluvium due to her hospitalization as well as underlying FPHL. When evaluating a woman with diffuse hair loss, it is therefore important to note the duration, precipitating events (if any), whether or not there is active shedding or just thinning, the patient's hair care practices, her medical history including medications, systemic diseases, and the family history of hair loss.

The prevalence of FPHL increases with age, and the condition can begin or become more severe with the onset of menopause as the hair shaft diameter decreases [5]. In hair follicles on the crown of the scalp, testosterone is converted by the enzyme 5-alpha-reductase to dihydrotestosterone, which causes shortening of the hair cycle and a decrease in hair follicle size [6]. After menopause, it is theorized that the cessation of ovarian estrogen production contributes to a hormonal milieu dominated by increased androgen levels relative to estrogen, which contributes to worsening FPHL in genetically susceptible individuals [7]. Because estrogen has complex interactions with other biologically active molecules and different receptors, much is unknown about its effect on the hair shaft [7]. Differences in levels of the androgen receptor and the enzyme aromatase, as well as non-androgen causes, contribute to phenotypic heterogeneity in hair growth [8] (Fig. 11.2).

It is typical of FPHL to be insidious in onset. Some patients notice an increase in hair shedding, while others do not. The diagnosis of FPHL is made clinically, by observing hair density at different locations on the scalp. The density of the posterior or occipital scalp, an area typically spared by loss in this condition, is compared to the top of the head or crown. A visibly widened part on the crown in comparison to the occiput is diagnostic (Fig. 11.3). Some patients with FPHL have normal density on the crown and instead exhibit a decrease in length and thickness of hairs at both temples, sometimes causing recession of the hair line. When the diagnosis is in doubt, a scalp biopsy (read by a dermatopathologist) can be helpful. This will reveal a decrease in the ratio of large to small hairs, called follicular miniaturization [9].

Telogen effluvium is another common cause of hair loss in women. In contrast to the insidious onset of FPHL, telogen effluvium typically occurs acutely, and all patients notice hair shedding. It commonly follows a major stressful physical or emotional event that promotes synchronization of the hair cycle leading to excess hair shedding. Precipitating events include such things as acute illness, hospitalization, death of a family member, divorce, rapid weight loss, etc. The hair loss lasts for several months and is typically self-limited, with return to baseline volume in most patients. Sometimes the shedding can become chronic [10]. Telogen effluvium can coexist with the more common FPHL as it did in our patient, and sometimes a telogen effluvium can lead to the detection of underlying FPHL. Biopsies of telogen effluvium reveal normal follicular size and a variable increase in telogen hairs [9].

Medications play a potentially larger role in hair loss in postmenopausal women in comparison to their younger counterparts, because they are more likely to be on multiple medications. There are many drugs that can cause hair loss, although most do so in only a small percentage of patients [11]. The mechanism of medication-related hair loss is often, but not always, of telogen effluvium. Agents well known to cause hair loss include psychotropic agents such as lithium, fluoxetine and valproic acid, anticoagulants, antihypertensives such as beta blockers and

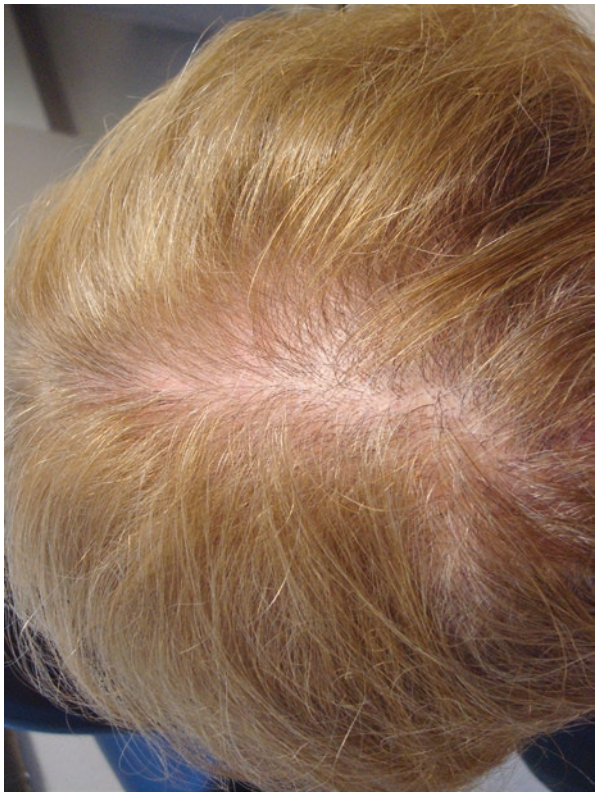

Fig. 11.3 Female pattern hair loss. This patient exhibits a widened part on the crown of the scalp

angiotensin-converting enzyme inhibitors, retinoids, antibiotics such as isoniazid and antiretroviral agents, and exogenous androgens [11]. Stopping an oral contraceptive can also result in telogen hair loss, similar to postpartum loss. Chemotherapeutic agents can cause an anagen or severe telogen effluvium, due to their effects on the rapidly dividing hair matrix. Some of the newer, targeted cancer therapies such as human epidermal receptor, epidermal growth factor inhibitors, and vismodegib can cause alopecia, which can be scarring or non-scarring.

The differential diagnosis of postmenopausal hair loss includes two additional conditions which are encountered less frequently than the ones already discussed. Alopecia areata is a form of focal or rarely diffuse hair loss which is fortunately much less common in postmenopausal women [4]. It is an autoimmune disease that typically causes round areas of complete alopecia and, when severe, can progress to loss of all scalp hair (alopecia totalis) or even all scalp and body hair (alopecia universalis). A rare diffuse form exists that is difficult to distinguish clinically from telogen effluvium. A biopsy of alopecia areata may reveal an increase in catagen hair follicles, inflammation at the base of catagen hair follicles, and a decrease in follicular size [9].

Another type of alopecia that typically occurs in postmenopausal women is frontal fibrosing alopecia. This is a variant of lichen planopilaris (LPP), a scarring

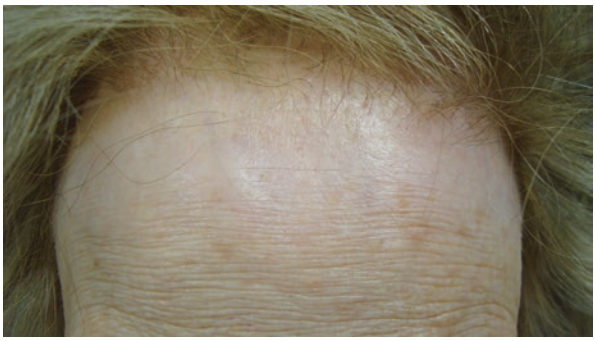

Fig. 11.4 Frontal fibrosing alopecia. Note the recession of the frontal hairline, widely spaced hair follicles, and smooth scalp surface

(cicatricial), permanent alopecia of unknown etiology. LPP presents as small, discrete or confluent, patches of total hair loss with a smooth scalp surface and subtle perifollicular erythema and scale. It typically occurs in middle-aged women on the crown [12]. Frontal fibrosing alopecia causes similar scarring alopecia, but occurs in an older, typically postmenopausal age group and affects the frontal hairline and preauricular areas, as well as can result in loss of eyebrows and sometimes body hair (Fig. 11.4). Since its initial description in 1994 [13], it is increasing in frequency at a rapid pace [14]. The etiology of these disorders is unknown. Biopsy findings include lymphocytic inflammation around the superficial hair follicle, perifollicular fibrosis, and eventual replacement of hair follicles and sebaceous glands by fibrosis [9].

Management

The management of diffuse scalp hair loss obviously depends on the underlying cause. Once recognized, a telogen effluvium requires no treatment beyond reassurance. Simple labs that are helpful to exclude systemic causes of hair loss include thyroid-stimulating hormone and measurement of iron levels and stores. Unlike the premenopausal patient where low iron is often due to heavy menstrual losses, iron deficiency in postmenopausal women may indicate more serious causes which need to be worked up, e.g., gastrointestinal ulcer, malignancy, or malabsorption. Low serum ferritin has been found in women with telogen effluvium and other types of non-scarring alopecia, although the role of iron supplementation in management of hair loss is controversial [15]. Some clinicians will supplement iron for a ferritin level below 70 ng/ml [16], even in the absence of anemia. Vitamin D is being increasingly ordered and supplemented, although there is little written about its association with hair loss [17, 18]. Medication lists should be scrutinized for possible offenders [11]. If the provider is uncertain of the mechanisms underlying loss of hair, a scalp biopsy can be helpful to detect miniaturization, but it requires specialized handling and interpretation by a dermatopathologist.

In cases of acute or severe and progressive hair loss, one should check for signs of androgen excess. In the postmenopausal population, these include, in addition to hair loss, hirsutism and signs of virilization. Women with evidence of this require workup, first, to search for excess androgen and, second, to find the source. Reported sources of androgen excess in women with postmenopausal hair loss include adrenal and ovarian tumors, hilar cell hyperplasia, ovarian hyperthecosis, and inadvertent contact with testosterone gel [19–23]. However, the majority of postmenopausal women with female pattern hair loss will not have elevated androgen levels [24].

The only medication approved by the Food and Drug Administration (FDA) for treatment of FPHL is topical minoxidil. This is available over the counter in two strengths, a 2 % solution that needs to be applied BID and a 5 % foam that can be applied once daily [25]. While it likely has several mechanisms of action, one is to cause vasodilation through its effect on potassium channels [26]. Its use lengthens the growing phase of the hair follicle and reduces miniaturization [26]. Common side effects include temporary shedding after onset of use, excess facial hair (sideburns and above the lateral brows), and irritation. Patients need to be counseled that treatment is best at stopping further loss, although some patients will experience some thickening of existing hair shafts [26]. It is important to note that minoxidil needs to be used continually for the results to be maintained and all hair gained from treatment will be lost upon discontinuation.

Patients who are intolerant of topical minoxidil or those with a limited response can be treated with oral antiandrogenic agents such as spironolactone or finasteride [27]. Note that these are used off-label for this indication and are not approved by the FDA. Spironolactone is a potassium-sparing diuretic approved for hyperaldosteronism and hypertension. It is used in FPHL for its antiandrogen properties, although there are few studies on its use for this indication. The response is dose related, with a high dose (200 mg split twice daily), resulting in maximum efficacy [28]. However, this dose is not appropriate in all patients. Spironolactone needs to be used cautiously in the elderly, especially those on other medications, because it is a diuretic and there is the potential for drug interactions and side effects, specifically hyperkalemia.

Finasteride blocks the activity of 5-alpha-reductase. It is approved in men in a 1 mg dose for male pattern hair loss and in a 5 mg dose for benign prostatic hypertrophy, but is not FDA approved for use in women. A study on the use of finasteride in a 1 mg dose in women with diffuse hair loss failed to reveal improvement in hair loss [29]. However, several case reports have documented variable improvement in both premenopausal and postmenopausal women with FPHL treated with 2.5 or 5 mg of finasteride [30–33]. It is generally well tolerated, with few side effects or drug interactions. It needs to be used very cautiously, if at all, in women of childbearing age due to risks to the developing fetus [34].

Hair transplant surgery is an option for women who have adequate donor hair on the occipital scalp. It is used in addition to, not instead of, medical therapy. Once moved to the crown, occipital hairs retain the properties of the posterior scalp and do not miniaturize [35].

A nonmedical treatment option for female pattern hair loss is low-level laser light with wavelengths in the visible (red) or infrared spectrum, which has been

FDA approved for this indication. Several studies have shown efficacy in regrowing hair in studies up to 24 weeks. It has an excellent safety profile and is available at salons, in doctor offices, as well as in a handheld unit or helmet that is used several times a week [36].

There are no FDA-approved treatments for alopecia areata. In general, treatment options depend on the extent of disease. Local, patchy disease can be treated with a potent (Class I or II) topical steroid applied daily for several months. For persistent areas, monthly injections of triamcinolone at a concentration of 2.5–10 mg/cc can be highly effective [37]). For more severe disease, contact sensitization therapy (the repeated application of an allergen) or systemic agents such as steroids or methotrexate may be required [37].

Frontal fibrosing alopecia is very difficult to treat. Like alopecia areata, there are no FDA-approved medications. Options range from topical and injectable steroids similar to alopecia areata to systemic agents including antibiotics in the tetracycline family and hydroxychloroquine [38]. The fact that most patients are postmenopausal has led to the use of the oral antiandrogens finasteride and dutasteride for this condition, which are reported to be very efficacious [39, 40].

Camouflage techniques can be very helpful to improve the appearance of thin hair. Many commercially available products are available and include keratin fibers that adhere to the hair shaft, causing it to appear thicker, and scalp darkening lotions to minimize the contrast between the hair and scalp [41]. When the hair loss is severe, a partial or full cranial prosthesis (wig) can improve self-confidence. Both human and synthetic hair in various, natural appearing styles are currently available. A good hair stylist is a huge asset for patients suffering from all types of alopecia.

My Management and Case Outcome

The history of acute hair loss following a hospital admission in this patient indicates telogen effluvium. This is a temporary, self-limited hair loss due to synchrony of the normally random hair cycle. Some patients have no discernible hair loss; others may exhibit mild bitemporal loss. The finding on examination of decreased density on the crown of the scalp preceding her admission, however, indicates the coexistence of FPHL. She had no patches of hair loss to suggest alopecia areata or lichen planopilaris, and her frontal hairline and eyebrows were intact, so there was no evidence of frontal fibrosing alopecia. While she was on a medication known to cause hair loss, this was started after the onset of her hair loss and is thus likely not the primary cause of her symptom.

In assessing patients with FPHL, a fair amount of counseling is required. Reassurance that they will not go bald is crucial. I explain that hair shedding occurs normally and that, in the absence of scarring, the hair follicle is already producing a new hair shaft as the old one is shed. Patients need to understand that FPHL is progressive and worsens over time and that treatment needs to be continued indefinitely for it to remain effective. Patients also need to understand that treatment does not reverse the hair loss that has already occurred and is best at preventing further loss.

Women with mild female pattern hair loss are offered 5 % minoxidil foam once daily, which is easier to use than 2 % twice daily. Both regimens are FDA approved. For those who prefer not to use medications, low-level laser light is an alternative. In patients with more moderate or severe loss, I discuss, in addition to minoxidil, the off-label use of spironolactone or finasteride, as well as camouflage options, use of a cranial prosthesis, and hair transplantation surgery.

After much discussion, the patient started topical 5 % minoxidil foam once daily. At a 3-month follow-up visit, she stated that she had no side effects from its use and that her hair shedding had improved a little. She had not seen much change in hair density. She had bought some camouflage powder but had not yet tried it. At her 1-year follow-up appointment, she had mastered the use of the powder, was satisfied with the appearance of her hair, and planned to continue her treatment regimen.

Clinical Pearls/Pitfalls

- The most common cause of diffuse hair loss in postmenopausal women is female pattern hair loss.
- Female pattern hair loss causes thinning of hair on the crown and temples, with a preserved frontal hairline.
- An evaluation for androgen excess is indicated in patients with rapid-onset or severe female pattern hair loss.
- Female pattern hair loss is progressive and incurable, and treatment is aimed at stopping the progression and possibly slightly thickening existing hair.
- Minoxidil is the only FDA-approved treatment for female pattern hair loss, although systemic agents are sometimes used off-label.
- Patients with hair loss often require significant counseling.
- Camouflage agents can be very helpful in managing hair loss.

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Evaluation and Management of Hirsutism in Postmenopausal Women

12

Pinky N. Kurani, Lynne J. Goldberg, and Joshua D. Safer

Case Presentation

A 66-year-old woman, who underwent natural menopause over 10 years ago, presented to her endocrinologist reporting progressive increase in facial and bodily hair growth most notable on the upper lip, chin, mid-chest, and inner thighs. She also acknowledged new-onset acne affecting her face and upper back as well as bothersome and progressive thinning of her scalp hair; these symptoms had become noticeable over the past 1 year. On questioning, she acknowledged noticing an increase in the size of her clitoris over the 1–2 years prior to this presentation; while she denied any change in her breast size, libido, or occurrence of vasomotor symptoms, some family members had commented on a change in her voice.

Notably, the patient had a long-standing history of facial hair excess and was diagnosed with polycystic ovary syndrome in premenopausal years. Her medical history was otherwise significant for well-controlled hypothyroidism and moderately controlled type 2 diabetes (glycosylated hemoglobin 8 %). She denied use of sex hormones, and her active medications included metformin, simvastatin, ergocalciferol, aspirin, furosemide, lisinopril, and levothyroxine.

P.N. Kurani (✉)
Boston University Medical Center, Department of Medicine, Boston, MA, USA
e-mail: pinkykurani@gmail.com

L.J. Goldberg
Boston University Medical Center, Department of Dermatology, Boston, MA, USA

J.D. Safer
Boston University Medical Center, Section of Endocrinology, Diabetes, and Nutrition, Boston, MA, USA

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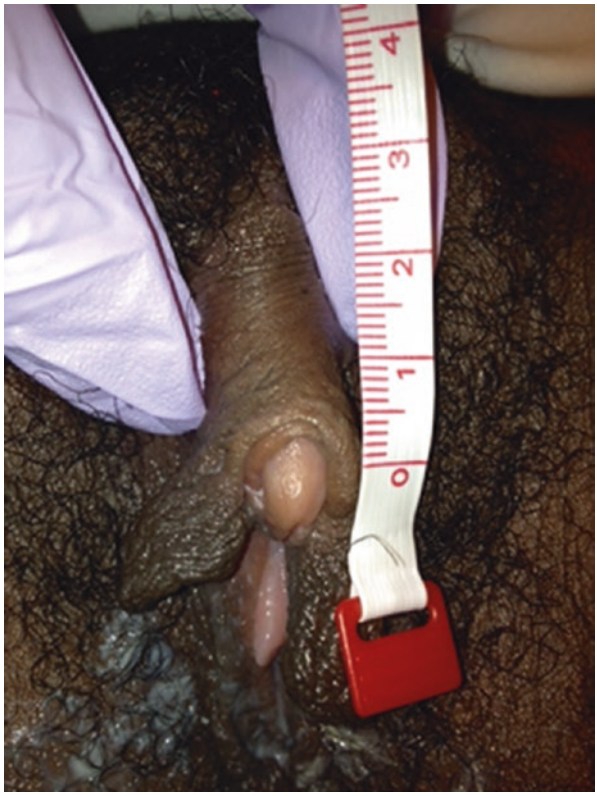

Fig. 12.1 Anagen hair follicle. The dark blue hair matrix gives rise to a light brown hair shaft. Several layers (inner and outer root sheaths) surround the hair shaft (Bhawan J, Sau P, Byers HR. *Dermatopathology Interactive Atlas, http://dermpathatlas.com/* used with permission)

Her social history was unremarkable, and she denied use of alcohol, tobacco, or drugs. While she was sexually inactive, on questioning, she acknowledged an increase in desire and libido. Her family history was notable only for type II diabetes in her father.

On examination, she was a well-appearing normotensive African American woman who was of overweight body habitus (body mass index was 29 kg/m^2). Coarse terminal hairs were noted on the chin and bilateral jaw line, mid-chest, lower abdomen, and medial aspect of thighs corresponding to a Ferriman–Gallwey (FG) score of 2/4 for the upper lip, 3/4 for the chin, 2/4 for mid-chest, lower abdomen, and upper thighs. Cystic acne was appreciated along lower face, and chin and recession of frontal and bitemporal hairline was noted with preservation of hair growth at the crown, consistent with a male pattern type of hair loss. Except for acne as described, her skin was of a normal texture and color without hypopigmentation, or cutaneous striae of the thyroid was of normal size and texture, and there was no lymphadenopathy. Abdominal exam was unremarkable without evidence of tenderness or masses. Examination of the external genitalia revealed a prominent clitoris that met the criteria for clitoromegaly (>10 × 10 mm) (Fig. 12.1). The rest of the pelvic exam was unremarkable, but limited due to patient's body habitus.

Overview of Diagnosis and Management of Postmenopausal Hirsutism

Definition and Prevalence of Hirsutism

Hirsutism in women is defined as the excess of terminal hair growth in a male pattern distribution [1]. Terminal hair is coarse and pigmented as opposed to the vellus hair which is fine, nonpigmented, and soft and covers the entire skin surface except the lips, palms, and soles [1]. The prevalence of hirsutism ranges from 4.3 to 10.8 % in African American and Caucasian women (variable due to some degree of examiner subjectivity), but is lower in Asian women [1]. About 5–15 % of hirsute women have no detectable androgen excess on blood testing [2]. The prevalence of hirsutism in postmenopausal women is not well studied [3], but mild degrees of hair excess are not uncommon in the years following the final menstrual period due to a profound decline in ovarian estrogens relative to the menopausal androgen milieu [4, 5]. The decline in ovarian estrogens and the associated decrease in hepatic sex hormone-binding globulin (SHBG) levels lead to an increase in the free androgen index (FAI), which may explain the common postmenopausal development of terminal hair on the face and chin, as well as the thinning of scalp hair as described in the index case [6].

There exists a regional variation in the degree of sensitivity of terminal hair to circulating androgens [7]. In addition to androgens, terminal hairs are affected by thyroid hormone, growth hormone, and local factors [7]. Areas such as the eyebrows, eyelashes, and lateral and occipital scalp are generally insensitive to androgens, whereas pubic (lower pubic triangle), axillary, and lower arm and leg hair are sensitive to low levels of androgens [7]. Terminal hair, typically in male pattern areas of growth including the sideburns, cheeks, chin, abdomen (male escutcheon/pelvic upper triangle), back, thighs, and upper arms, is sensitive to higher levels of androgens; presence of terminal hair in these locations, unless familial, is generally considered abnormal in women [7, 8].

A widely used classification scheme for hair excess in women is the Ferriman–Gallwey (FG) scoring system [8] that is based on pictorial representation of degrees of hair excess (ranging from 0 to 4 in increasing severity) at nine (originally eleven) androgen-sensitive areas (upper lip, chin, chest, upper and lower back, upper and lower abdomen, upper arms, and thighs). Using the modified FG scale, a score of less than 8 for all nine areas is considered normal [9]. There are considerable limitations to this scoring system, however, including observer subjectivity, omission of some important androgenic areas (sideburn, perianal area, buttocks), and a disregard of racial and ethnic differences in hair growth. Based on a total FG score of 11 at nine areas, the severity of hirsutism for the patient under discussion was deemed as “mild.”

History and Physical Examination

Initial history in any woman with a chief complaint of hair excess should include location and rate of abnormal hair growth and occurrence of additional symptoms of androgen excess including acne, hair loss, and an inquiry about symptoms of

virilization, which can include male pattern hair loss, deepening of voice, increased libido, worsening aggression, increased muscle mass, shrinkage in breast size, clitoral enlargement, and excessive perspiration. A complete history should also note any abdominal symptoms (such as increased girth, bloating, and constipation), nipple discharge, changes in skin coloration, and weight gain or loss. Personal history of medical disorders such as diabetes and hypertension, and family history of hirsutism and of scalp hair loss particularly in female members in the family should be enquired. A thorough review of medications including supplements should be undertaken, and use of topical androgenic agents by partner should be assessed, if appropriate.

Physical examination should include assessment of body mass index and blood pressure, quantitative and qualitative assessment of facial and bodily hair using FG scale, and assessment of scalp hair growth with particular attention to areas of hair loss. Female pattern hair loss primarily affects the crown with preservation of the frontal hair line which contrasts with the male pattern hair loss which involves recession of the frontal hair line and is associated with elevated circulating androgen levels [10]. Evaluation should take into consideration additional cutaneous stigmata such as acne (assess location and severity), facial plethora (Cushingoid feature), cutaneous striae (assessing location, width, and color of striae), fat deposition at the base of the neck (Cushingoid feature), and the presence of acanthosis nigricans or skin tags (markers of insulin resistance). Palpation should focus on detection of thyromegaly and abdominopelvic masses. External genital examination should assess for clitoromegaly.

Laboratory Testing and Imaging

In many cases of mild hirsutism (FG score 8–15), and particularly without other clinical features to suspect an underlying reversible cause, laboratory work-up may not be necessary [11], and empiric therapy may be initiated as discussed below. In cases of moderate to severe hirsutism (FG score over 15) and in cases exhibiting other stigmata of virilization, serum testosterone (total and free) and dehydroepiandrosterone sulfate (DHEAS) levels are the primary laboratory tests to assess for presence and source of androgen excess. Thyroid studies must be undertaken as coarsening of skin and hair loss can be seen in setting of uncontrolled thyroid disorders. Optimally, an early morning plasma-free testosterone level is a more sensitive test which can detect androgen excess states even when total testosterone levels are normal [12, 13]. Assays for free testosterone however are accurate only when measured by equilibrium dialysis, require strict quality controls to minimize operator-dependent variability, and are not therefore widely reliable [14, 15]. Total testosterone assays are more reproducible and widely available and may thus be the preferred test to obtain in general practice [14]. Depending on DHEAS and testosterone levels, imaging may be required to rule out a neoplastic hormone-producing process of the adrenals or ovaries, respectively. Pelvic ultrasound and MRI are most useful for ovarian imaging, and abdominal CT scans are most useful for adrenal imaging [3]. It should be noted that androgen-producing adrenal tumors are often very small in size,

requiring high-resolution CT techniques that can detect lesions which may only be 0.5 cm in diameter [16]. Communication with the radiologist is therefore of paramount importance to optimize radiographic detection yield. Milder elevations of DHEAS levels in certain clinical settings should be further evaluated with a 24-h urinary-free cortisol and overnight dexamethasone suppression test to rule out Cushing's syndrome, a differential diagnosis to consider especially when hypertension, diabetes, and low bone mass coexist with hair growth excess [14]. While late-onset congenital adrenal hyperplasia remains a differential diagnosis to consider in any adult female with hyperandrogenism, this condition will commonly present in early reproductive years; an initial presentation in postmenopausal women is rare.

Differential Diagnosis

Hirsutism in postmenopausal women with no biochemical evidence of androgen excess may be idiopathic or may be related to certain drugs, e.g., glucocorticoids, phenytoin, minoxidil, or cyclosporine [11, 17].

High testosterone levels with normal or mildly elevated DHEAS levels usually suggest an ovarian source of hyperandrogenism, although the possibility of exogenous exposure through topical contact with transdermal androgen products commonly used by men should be considered. The most common cause for androgen excess in women is polycystic ovarian syndrome (PCOS) [17, 18]. While PCOS is a well-recognized entity in the reproductive phase of life, the milieu of androgen excess persists well into menopause in this population [6]. Gynecological history spanning premenopausal period is thus particularly relevant when assessing hyperandrogenism in postmenopausal women, as women with PCOS often acknowledge a long history of irregular menstrual cycles and hyperandrogenic signs and symptoms since menarche, as did the patient under discussion.

Rising pituitary gonadotropin levels (particularly luteinizing hormone (LH)) after menopause can enhance androgen production from ovarian theca stromal cells, particularly for women with PCOS, which along with declining ovarian estrogen can contribute to worsening of hyperandrogenic symptoms. Assessment of gonadotropins can therefore provide useful insight into pathophysiology of postmenopausal hyperandrogenism and should be obtained during evaluation of symptoms of postmenopausal hair excess or scalp hair loss. An extreme form of ovarian androgen excess encountered in postmenopausal women is *ovarian hyperthecosis*, a syndrome where rapid virilization can occur and testosterone levels may even be in the tumor range (>200 ng/dL) [3]. Pelvic imaging often demonstrates enlarged solid-appearing echogenic ovaries without any focal mass [19].

Androgen-producing neoplastic processes of the ovaries and adrenals account for only 0.2 % percent of cases of androgen excess in women [18] and should be suspected when virilization is rapidly progressive and androgen levels exceed certain thresholds. Although some cross over can occur, DHEAS is an exclusively adrenal androgen, while testosterone can originate from both ovarian and adrenal tumors. Therefore, when serum DHEAS levels exceed 700 ng/ml, an adrenal tumor is most likely particularly when clinical and biochemical evidence of glucocorticoid

and mineralocorticoid excess is also present [14]. On the other hand, testosterone levels exceeding 200 ng/dL may originate either from the adrenal or the ovaries, and both organs need to be imaged, particularly when DHEAS is also elevated [14]. Common androgen-producing ovarian tumors in postmenopausal women include Leydig cell tumors, Sertoli cell tumors, and steroid tumors, all of which are often small and unilateral. In the absence of adrenal or ovarian tumors, a tumor range serum androgen level is often due to ovarian hyperthecosis as discussed earlier.

Another hyperandrogenic condition associated with elevated DHEAS levels is nonclassical congenital adrenal hyperplasia (CAH) which accounts for 1.5–2.5 % of causes of hirsutism in women. The commonest variant of nonclassical CAH is due to a 21-hydroxylase deficiency and is commonly associated with elevated serum levels of 17-hydroxyprogesterone (17-OHP), often in excess of 200 ng/dL [14, 17, 18].

Management

The first step in management of a postmenopausal patient with complaints of hair excess and/or scalp hair loss is a thorough evaluation to rule out identifiable and potentially reversible causes of androgen excess, as discussed earlier. In those iatrogenic cases due to certain drugs, significant improvement in hair growth can be expected following discontinuation of the offending agent, which is preferably done in collaboration with the prescribing provider, lest undesirable effects emerge from this alteration in medical regimen. Similarly, hirsutism in women who are hyperandrogenic due to nonclassical CAH will improve after initiation of steroid therapy and consequent decline in adrenal androgen production. Women with evidence of Cushing's necessitate evaluation for the source of cortisol excess (medication, adrenal tumor, pituitary adenoma, and inherited disorders such as multiple endocrine neoplasia). Definitive management would depend on the underlying mechanism for cortisol excess and should mitigate symptoms. For women with thyroid dysfunction, a gradual improvement in hair growth can be expected with attainment of euthyroid status. Due to the prolonged duration of hair growth and differentiation cycle (discussed elsewhere in this textbook), any improvement after intervention for hirsutism may not become clinically evident for several months or even up to a year [11]. Additional cosmetic measures may be required for faster relief, as discussed below.

Pharmacotherapy

The combination oral contraceptive pill (COCP) is the mainstay of pharmacotherapy for hirsutism in reproductive age women, and its use for such can be extended to healthy perimenopausal and early postmenopausal women [14]. The progestin component of COCP suppresses pituitary LH secretion, the main stimulant of ovarian androgen, and, to a lesser extent, adrenal androgen production [20]. Estrogenic component of COCP reduces free androgen levels by increasing hepatic production of SHBG [14]. While effective as first-line strategy in the

younger perimenopausal and early menopausal women, COCP use is not risk-free and formulations containing the lowest estrogen doses should be used to minimize this risk. COCP use is contraindicated for women with a history of breast cancer and other hormone-sensitive tumors, for those deemed at risk for cardiovascular disease (CVD) and venous thromboembolism (VTE), for those with liver disease and uncontrolled hypertension, and for smokers. The choice of formulation should take into account the type of progestin and the dose of estrogenic component of the formulation. Progestins of low androgenic potency, such as norgestimate, norethindrone, and desogestrel, or antiandrogenic effects, such as drospirenone and cyproterone, should be preferentially considered when choosing a formulation to address symptoms of hyperandrogenism [21]. For the older symptomatic menopausal woman experiencing symptoms of hair excess and/or acne, lower dose menopausal hormone therapy (MHT) regimen is preferred to COCP; in addition to providing relief from vasomotor symptoms, estrogen component of MHT, particularly when administered orally, can bring about some decrease in the free androgen index (FAI) through direct effects on hepatic SHBG production and thereby offer cutaneous benefit for some [22, 23]. Decision to initiate MHT for cosmetic benefit alone must take into consideration the overall clinical picture including presence of menopausal symptoms, personalized risk for CVD, thromboembolism, and for fragility fractures. For women similar to our case under discussion, i.e., an older and asymptomatic menopausal woman with comorbidities who is remote from the final menstrual period, potential for harm associated with use of systemic MHT is deemed to outweigh any possible benefit that MHT may offer against hyperandrogenism; MHT should not be a consideration for the case under discussion [24].

Antiandrogens offer an effective and a relatively safe approach to management of hair excess as well as hair loss. Spironolactone, a mineralocorticoid agonist, is a competitive inhibitor of androgens at the level of the androgen receptor and also decreases to some degree the conversion of testosterone to a more potent androgen dihydrotestosterone, through inhibition of the converting enzyme 5α-reductase [25]. Clinically, when used at oral doses of 100–200 mg daily (generally started at 50 mg daily and dose is then gradually titrated up), it can effect a significant 15–40 % decrease in FG score over time [11]. Mild blood pressure lowering effects of spironolactone offer an adjuvant benefit for those with hypertension, as the case under discussion. Finasteride, an inhibitor of skin 5-alpha reductase (types II and III), reduces the peripheral conversion of testosterone to dihydrotestosterone, a potent androgen. While finasteride can theoretically help in hirsutism, its use for this indication in postmenopausal women has not been studied [11]. Flutamide is a pure antiandrogen that acts as an antagonist at the androgen receptor. While small randomized trials have shown efficacy in treatment of hirsutism, the potential for severe hepatic toxicity limits its use [14].

Gonadotropin-releasing hormone analogues (GnRHa), by suppressing pituitary LH drive, are effective at reducing ovarian androgen production and can serve as an alternative to COCP, MHT, and antiandrogen formulations for management of symptoms of androgen excess. Expense and need for parenteral administration limit

the use of this class of agents in the management of postmenopausal hyperandrogenism and are generally reserved for those with hirsutism refractory to other pharmacologic measures [14].

Cosmetic Therapies

Cosmetic measures include temporary and permanent hair removal. Temporary methods that do not destroy the hair follicles include physical shaving, waxing, plucking, and threading, as well as chemical depilatory creams. Permanent hair removal requires destruction of the hair follicles which can be performed using laser energy of different wavelengths or by electrolysis which is considered the gold standard for permanent hair removal. Equipment and procedures are generally standardized, regulated by the FDA, and performed by licensed electrologists [26, 27]. Electrolysis uses electric energy to target each hair follicle individually and is therefore time consuming and expensive as it requires multiple treatment sessions to treat small surface areas of skin. Photoepilation is a more rapid hair removal method that works by causing selective thermal injury to hair follicles. The hair removal machines are approved for use by the FDA and can be performed only by licensed and trained professionals [27]. These strategies, particularly in conjunction with hormonal intervention, can offer varying degrees of benefit for patients seeking permanent reduction of hair growth [28]. Several different types of lasers with specific wavelengths, as well as broad-spectrum light sources with specific filters (intense pulsed light) can be used [29]. These methods are most effective for dark-colored hair, as the pigment is the target of the light. Because of this, and in order to minimize skin side effects, they are best reserved for light-skinned patients, although lasers with longer wavelengths can be used on dark-skinned individuals.

An alternative to facial hair removal is hair growth suppression using a topical cream eflornithine hydrochloride, a chemical that inhibits ornithine decarboxylase, an enzyme required for hair growth [2]. To achieve a lasting effect, this FDA-approved therapy must be used indefinitely, but is often not covered by third-party payors and can therefore be quite expensive. It can be used in conjunction with some of the physical hair removal methods discussed earlier, as this combination can result in a reduction in the number of growing hair as well as contribute to a slowing of hair growth.

Surgery

Management of androgen-secreting tumors requires a definitive surgical approach. Mode and route of surgery and need for adjuvant therapy (chemo or radiation) are dictated by the location, type, and tumor grade and suspicion for malignant potential and stage of disease. Detailed discussion on surgical management of androgen-secreting tumors (adrenal and ovarian) is beyond the scope of this work. Surveillance in the postoperative period should be customized and take into consideration the potential for recurrence, particularly when hormone-secreting ovarian lesions are

managed conservatively (e.g., by ovarian cystectomy). Common modalities of surveillance include periodic imaging, serial measurements of serum androgen levels, and tumor-specific biomarker(s) (if applicable) with the practice individualized to the clinical situation [30–34]. While recommendations for surveillance following surgical management of adrenocortical carcinoma (ACC) are not well established, consensus guidelines suggest imaging (CT or MRI in addition to thoracic CT) and biochemical surveillance every 3 months after ACC following complete resection. This should be continued for 2 years followed by semiannual follow-up, for a minimum of 10 years. In the case of metastatic or locally advanced disease, case-by-case recommendations are reasonable with general guidelines, suggesting CT surveillance at least every 12 weeks to monitor response rate [35, 36].

Case Management and Outcomes

The rapidly progressive signs and symptoms of virilization in our patient were concerning, and an androgen-secreting tumor was high in the list of differential diagnoses; pituitary LH-driven ovarian hyperthecosis was also a plausible consideration. A comprehensive work-up including biochemical and radiological evaluation was pursued, with the diagnostic imperative being to rule out ovarian or adrenal tumor as a mechanism for her clinical picture. Total testosterone level was markedly elevated at 1292 ng/dL (reference 2–45) with minimal elevation in serum DHEAS level at 239 mcg/dL (reference 14–180) pointing to an ovarian source for androgen excess. Serum TSH was normal at 1.14 uIU/ML (reference 0.35–4.9), as were morning serum cortisol levels at 8.7 ug/dl (reference 4–23); interestingly, serum gonadotropin levels were in premenopausal range (FSH 9.1 mIU/ml, LH 6.2 mIU/ml), although estradiol level was in menopausal range at 25 pg/ml.

A transabdominal and transvaginal pelvic ultrasound with Doppler revealed a 3.7 cm solid right ovarian mass with normal blood flow; the contralateral ovary and uterus were unremarkable and endometrial stripe measured 2 mm (in menopausal range). High-resolution CT scan of the abdomen and pelvis with intravenous contrast showed a heterogeneously enhancing complex partially solid, partially cystic mass within the right ovary that measured 4.2 cm in diameter; there was no evidence of lymphadenopathy, ascites, or peritoneal nodules. The adrenals appeared normal as did the left ovary.

The patient underwent an uneventful laparoscopic bilateral salpingo-oophorectomy. Surgical pathology showed a moderately well-differentiated Leydig cell tumor of the right ovary with no involvement of the ovarian surface, tubes, or left ovary. Peritoneal washings and an omental biopsy were negative for microscopic tumor, and no additional therapy was recommended for this stage 1A tumor.

Follow-Up

Three months after surgery, total testosterone level had normalized, measuring 13 ng/dL, and gonadotropins were now in menopausal range (LH at 59 mIU/ml and FSH at 89 mIU/ml). At this writing, nearly 1 year postoperatively, there remains no

evidence of recurrent tumor. Her scalp hair growth and hirsutism have improved markedly, although she continues to shave and pluck albeit at a lesser frequency, but has not required any systemic therapy. She is being monitored for recurrence of tumor clinically with periodic evaluation of symptoms and biochemically with semiannual serum testosterone levels.

Clinical Pearls/Pitfalls

- Mild hirsutism is a common complaint in postmenopausal women and often has a physiologic basis.
- The most common causes of hirsutism in women is PCOS, with symptoms of hyperandrogenism persisting into menopausal years.
- Postmenopausal hirsutism that is new in onset and moderate to severe is less likely to be idiopathic or physiologic and merits systematic evaluation.
- Signs of virilization and sudden-onset symptoms are worrisome for an androgen-secreting tumor.
- Management options include addressing the underlying cause (as in the case discussed), use of steroidal hormones (such as COCP's or MHT formulations), nonsteroidal antiandrogens, and cosmetic hair removal strategies.

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Primary Ovarian Insufficiency/ Premature Ovarian Failure: Management Considerations and Strategies

13

Nanette Santoro

Case Presentation

A 32-year-old Puerto Rican woman with Hashimoto's thyroiditis has been using birth control pills for contraception for the past 10 years. She discontinued the pills 6 months ago in order to begin her family and has not had a spontaneous menstrual period since. Her post-pill amenorrhea is accompanied by bothersome hot flushes and night sweats. Her family history is significant for a father who underwent 4-vessel coronary artery bypass surgery in his early 50's for cardiac ischemia and a maternal grandmother who sustained a hip fracture at age 68. A pregnancy test in the office is negative. An FSH level is obtained and is 50 IU/L.

What Is the Most Effective and Appropriate Management Option for This Patient?

A. Combined hormonal contraceptive (pill/ring/patch) to address vasomotor symptoms and for possible skeletal benefit
B. Bisphosphonate to reduce her lifetime risk for fracture
C. Paroxetine to address vasomotor symptoms and diagnosis-related anxiety
D. Combined estrogen and progestin therapy (EPT) to address vasomotor symptoms and for possible skeletal benefit
E. Soy to help with vasomotor symptoms and for overall health

Special considerations for our patient's case as detailed above include moderate to severe vasomotor symptoms (VMS) associated with decreased quality of life and

N. Santoro, MD
Obstetrics & Gynecology, University of Colorado School of Medicine,
12631 E 17th Avenue, Aurora, CO 80045, USA
e-mail: Nanette.Santoro@ucdenver.edu

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cessation of spontaneous menses occurring at a disproportionately young age and in the setting of fertility considerations; this presentation is suggestive of premature ovarian insufficiency (POI) and needs to be confirmed. Her history of Hashimoto's thyroiditis may be relevant to the pathophysiology of POI. Management considerations should address fertility options as well as long-term health implications, particularly in light of her family history of early-onset cardiovascular disease (Dad) and of skeletal fragility (maternal grandmother). A systematic approach to evaluation, management considerations, and options for the specified scenario will be discussed.

Overview of Clinical Presentation, Evaluation, and Management of Premature Ovarian Insufficiency (POI)

Also called premature ovarian failure, the diagnosis of POI requires presence of hypergonadotropic amenorrhea of at least 4 months' duration in a woman who is less than age 40 [1]. It is found in 1.1 % of the population, but there is significant ethnic/racial variation in its prevalence [2]. In a population-based study of US women, non-Hispanic Caucasians had a prevalence of POI of 1.0 %, whereas 1.4 % of Hispanic women reported this diagnosis. African-American women have a prevalence similar to Hispanic women, whereas Chinese and Japanese-American women had a much lower prevalence [2]. The diagnosis is confirmed with elevated FSH levels obtained on at least two occasions at least 4–6 weeks apart [3].

POI is associated with a number of concurrent medical conditions (Table 13.1), and screening for them is recommended [1]. Autoimmune thyroid disease is a relatively prevalent condition, present in up to 10 % of the overall population [4]. Some but not all studies have found a higher than expected prevalence of thyroid autoimmunity in women with POI [5]. There are a number of additional autoimmune conditions associated with POI, called the polyglandular failure syndromes. Failure of the adrenals, parathyroids, and pancreas has all been reported. Less common associations have been made with autoimmune hepatitis, pernicious anemia, myasthenia gravis, Sjogren's syndrome, rheumatoid arthritis, sarcoidosis, and celiac disease. Autoimmune adrenal failure is a life-threatening condition, and for this reason, it is recommended to screen women with POI with antiadrenal antibody testing (specifically anti-21-hydroxylase antibodies) and to maintain a low threshold of suspicion for impending adrenal failure [6].

There are also a number of genetic associations with POI (Table 13.2). Complete absence of an X chromosome causes Turner syndrome, which usually results in POI at a very young age, along with other somatic signs [7]. However, women with X chromosome microdeletions or Turner mosaicism may lack any phenotypic features of Turner syndrome yet still have POI. Karyotype screening is recommended to detect this condition. Mutations of a variety of genes have also been found to be related to POI, among them the FOXL2 gene (associated with blepharophimosis, ptosis, and epicanthus inversus) and Perrault syndrome (associated with deafness). Women who carry the permutation for the FMR1 (fragile X) gene are at high risk

Table 13.1 Medical conditions associated with POI

Endocrine disorders
Thyroid gland – hypothyroidism
Adrenal gland – Addison's disease
Type 1 diabetes
Autoimmune disorders
Dry eyes
Hashimoto's thyroiditis
Myasthenia gravis
Crohn's disease
Pernicious anemia
Systemic lupus erythematosus
Rheumatoid arthritis
Sjogren's syndrome
Vitiligo
Skeletal fragility
Osteoporosis
Cardiovascular disease
Depression

Table 13.2 Common genetic disorders associated with POI [23]

X chromosome related
Turner syndrome
FMR1 premutation
Autosomal
Galactosemia
Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES)
Bloom syndrome
Autoimmune poly glandular syndrome
Fanconi anemia
Ataxia telangiectasia
Single-gene disorders
ATM gene (ataxia-telangiectasia mental retardation gene) mutation
Inhibin A gene mutation
FSH receptor mutation

for POI and are also at risk of transmitting the full mutation to a male child, and therefore, screening of all women with POI for FMR1 is recommended; about 5 % will test positive [8].

Bone mineral density (BMD) may be compromised in women with POI. Women with POI have reduced bone mineral content compared to normally menstruating

controls [9] and face many years of hypoestrogenemia, which further exacerbates the bone loss. Monitoring for low bone mass, for bone loss, and preventive treatment with hormones, when appropriate, is recommended. Although they provide about five times more estrogen than typical menopausal hormone therapy doses, oral contraceptives are not superior for preservation of bone mineral density, and thus either regimen can be considered bone sparing.

Cardiovascular disease (CVD) is more likely to occur in women who are hypogonadal during their reproductive years. Women with POI who do not take hormone replacement therapy may increase their risk of early-onset heart disease. There is some evidence that a POI diagnosis is associated with a greater risk of death from CVD [10].

Women with POI are at risk for depression. It is not clear whether depression precedes the diagnosis of POI or is partly due to the hormonal irregularities that accompany ovarian failure [11]. The clinician should be aware of the vulnerability of women with POI to depression and recommend treatment appropriately. Because this diagnosis afflicts women in their childbearing years, it often comes as a shock and a barrier to a much hoped-for pregnancy. Providing emotional support for women with POI is an important part of their care.

Fertility is often the overriding clinical concern when the diagnosis of POI is made. This can sometimes cause the clinician and the patient to lose sight of the need to provide holistic management of the patient. While the prognosis for natural fertility is overall poor, treatment-independent pregnancies are reported 5–10 % of women who have been diagnosed with POI [12]. In this respect, POI differs markedly from age-appropriate menopause. Assisted reproductive technology can be used to achieve pregnancy with great success when donor oocytes are utilized [13]. However, there is some evidence that aneuploidy is more common in pregnancies achieved spontaneously [14]. Because POI can be familial, use of sisters as known oocyte donors can be problematic unless careful genetic and phenotypic screening for ovarian reserve is performed [15]. Moreover, women with Turner syndrome and POI who attempt conception using donor oocytes are at high risk for catastrophic pregnancy outcomes due to silent aortic root disease or coarctation of the aorta [16].

Table 13.3 outlines diagnostic tests when suspecting POI. If fertility is not an overriding concern, long-term management of women with POI should include a thorough discussion of the risks and benefits of hormone therapy. Unlike a

Table 13.3 Screening tests recommended for women diagnosed with POI

Karyotype
FMR1 premutation
Antiadrenal antibodies (21-hydroxylase antibodies)
Comprehensive metabolic panel
Complete blood count
Antithyroglobulin and thyroid peroxidase antibodies
Dual X-ray absorptiometry (DXA) for assessment of bone mineral density screening for depressed mood

50-year-old woman who is undergoing natural menopause, a woman who has POI in her 20's or 30's is deprived of estrogen at an abnormally young age, and therefore, "replacement" therapy is recommended to address not just symptoms of hypoestrogenism and improve quality of life but equally importantly to prevent premature cardiovascular and bone aging. Typical doses of estrogen used for women with age-appropriate menopause may be insufficient for full symptom control in women with POI [1]. Because the risks of harm of hormone replacement in women with POI appear to be minimal, clinicians should aim to supply enough hormone to eliminate menopausal symptoms of hot flashes and vaginal dryness.

For women who wish to conceive, there are no proven effective treatments other than oocyte donation. Attempts to predict ovulation and facilitate conception using assisted reproductive technology have not been successful. This is clinically frustrating, as women with POI are likely to have a very small population of remaining oocytes that cannot be mobilized. Research on oocyte activation has provided some potential clinical research opportunities [17] by providing some clues as to the early molecular signals that may allow the remaining small oocyte pool to mature.

Case

The patient was biochemically euthyroid, tested negative for antiadrenal antibodies, had a normal karyotype, and screened negative for FMR1 premutation. A repeat FSH of 65 IU/L confirmed the diagnosis of POI. Her metabolic and hematological parameters were in normal range.

Patient was counseled about her poor prognosis for a successful pregnancy and the possibility of increased aneuploidy with a pregnancy conceived using her own oocytes. The processes of oocyte donation and adoption were described. Counseling was offered, and a follow-up visit was scheduled to allow the patient time to consider her options and react to the unexpected news. The need for ongoing monitoring for maintenance of her long-term health was discussed. A DXA bone mineral density test was ordered to assess her BMD status.

The patient chose to postpone active pursuit of fertility at this time, but wished to retain any background chance of spontaneous conception, and hence exogenous estrogen- and progesterone-based hormone replacement therapy, and not a contraceptive regimen, was deemed an appropriate treatment choice. Transdermal route of estrogen administration was preferentially chosen for this patient with a family history of early-onset CVD (Dad) given observational evidence that supports lesser vascular events with transdermal compared to oral route of estrogen therapy [18].

Premature cessation of ovarian function is associated with increased risks of CVD events [19, 20], of low BMD, and of skeletal fragility [21], and HT appears to reduce these risks [22]. The benefits of hormone replacement were discussed with this patient, which would include preservation of her BMD (particularly relevant given premature loss of ovarian estrogen and history of hip fracture in maternal grandmother) and the likely cardioprotection (particularly relevant given history of early-onset CVD in her father) offered by the early initiation of estrogen

replacement. Since she would like to leave open the 5–10 % possibility of treatment-independent conception, 50 micrograms of transdermal estradiol plus micronized progesterone 100 mg nightly was prescribed. This regimen does not appear to interfere with spontaneous ovulation and implantation.

Patient was advised that barring any significant interval change in her medical status, continuation of hormonal regimen until the average population menopausal age (around age 51) would be reasonable and is recommended. Whenever a decision for cessation of hormonal intervention is made, assessment of her BMD is also recommended as this information will guide future recommendations (such as consideration of antiresorptive interventions such as bisphosphonates would be reasonable if low BMD is identified in the setting of a family history that is concerning for genetic predisposition to fracture).

Psychological burden accompanying a diagnosis of POI can be profound, and this patient was encouraged to seek psychological counseling. In chronologically young women with POI, the decision to initiate antidepressant or anxiolytic agents should be based on presence and severity of symptoms of depression and anxiety, rather than of estrogen deficiency. Efficacy of nonhormonal interventions against vasomotor symptoms is far inferior to that of hormonal regimens; for women with POI, estrogen (plus progesterone for those with a uterus) should be deemed as first-line approach that will not only provide symptomatic relief but will additionally mitigate long-term health risks in this population.

Clinical Pearls and Pitfalls

- Patients who have a clinical history and examination suggestive of POI should undergo the diagnostic workup and have a follow-up visit scheduled to review the findings. Emotional support should be available for a patient who is diagnosed with POI.
- Attention to the patient's long-term health, rather than an immediate focus on pregnancy, is an important supportive stance for the clinician to take when delivering this diagnosis.
- Use of estradiol and progesterone for hormone replacement in women with POI who wish to conceive does not interfere with the low background rate of treatment-independent pregnancy and, at physiologic doses, is not known to be teratogenic.

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Surgical Menopause

14

L. Daniela Michelis and Wendy Kuohung

Case Presentation

A 39-year-old nulliparous female with stage IV endometriosis presented to a reproductive endocrinologist reporting chronic disabling pelvic pain with and outside of her periods, dyspareunia, and intermenstrual bleeding. She was taking naproxen with minimal pain relief. She had a history of a laparoscopic left ovarian cystectomy 2 years prior, at which time she was noted to have a frozen pelvis with no visualization of the uterus or right ovary, dilated tubes bilaterally, dense adhesions, and a 6 cm left hemorrhagic cyst, favoring an endometriotic cyst on pathology. She had a normal Pap smear, and on physical examination, she was in no apparent distress with normal vital signs, a BMI of 20.8 and a genitourinary exam significant for a small tender uterus with decreased mobility and a tender left adnexa with no palpable masses. She had an MRI study of her abdomen and pelvis that showed a complex left adnexal fluid collection approximately 3–4 cm in size, a normal right ovary, bilateral hydrosalpinges, and a 2 cm posterior intramural fundal fibroid. Three management options were discussed with the patient:

1. Medical management with continuous combined oral contraceptive pills, progestin therapy, or a GnRH agonist
2. Conservative surgery with removal of her bilateral hydrosalpinges and drainage of the left adnexal fluid collection with possible removal of her left ovary
3. Definitive therapy with a total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO), and lysis of suspected pelvic adhesions

L.D. Michelis, MD • W. Kuohung, MD (✉)
Department of Obstetrics and Gynecology, Boston University School of Medicine, Boston, MA, USA
e-mail: wkuohung@bu.edu

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This 39-year-old patient opted for a total hysterectomy and BSO as the preferred management approach given her chronic pain and prior failed interventions. The surgical procedure was uncomplicated. She returned to clinic for her 6-week postoperative visit, reporting new onset of hot flashes and continued mild pelvic pain that was greatly improved compared with her preoperative pain.

What Is the Most Appropriate Management Option for This Patient?

A. Combined oral contraceptive pills (OCPs)
B. Progestin therapy only
C. Paroxetine
D. Low-dose oral estrogen-only therapy

Special considerations for this patient include her premenopausal status when deciding to proceed with a definitive surgery that would abruptly subject her to menopause at age 39. Her severe vasomotor symptoms (VMS) and timing of presentation were predictable. Timing of scheduled follow-up raises concerns regarding preparedness of the provider and of the patient who anticipates sudden entry into menopause. Preoperative counseling should include discussion on a preemptive approach to managing symptoms of estrogen loss, as well as on the long-term implications of premenopausal oophorectomy. Management considerations should address patient choice, timing, formulation, route, and duration of pharmacotherapy to address quality of life while mitigating the long-term risks of surgical menopause. A systematic approach to evaluation, management considerations, and options for the specified scenario will be discussed.

Prevalence and Common Indications for Bilateral Oophorectomy in Premenopausal Women

Premenopausal women who undergo bilateral oophorectomy are rendered abruptly menopausal with a precipitous decline in estradiol and progesterone levels associated with loss of ovarian function. This is often accompanied with a sudden onset of vasomotor symptoms that are experienced by 50–82% of naturally menopausal women [1]. In addition, symptoms of vaginal atrophy that prevail in 20–45% of women shortly after natural menopause [2] may also develop prematurely after surgical menopause with significant impact on quality of life. More importantly, given the long life expectancy in the western world, an earlier age of menopause places women at an increased risk of a number of negative outcomes later in life, including ischemic heart disease, cognitive impairment, osteoporotic fractures, and overall mortality [3].

Appropriate benign indications for a bilateral oophorectomy in a premenopausal woman include the presence of tubo-ovarian abscesses unresponsive to conservative management, known genetic predisposition to ovarian cancer, and stage IV endometriosis with intractable pain.

Tubo-ovarian Abscess (TOA)

TOA is a severe and progressive complication of pelvic inflammatory disease (PID) resulting in an inflammatory mass that can involve and damage the fallopian tubes, ovaries, and other surrounding structures [4]. TOA complicates roughly one third of hospitalized PID cases with an estimated annual incidence of 100,000 cases of PID in the USA [5, 6]. TOAs are typically polymicrobial in nature, including aerobic, anaerobic, and facultative organisms [4]. Historically, the treatment was surgical, with the majority of women having a total abdominal hysterectomy and bilateral salpingo-oophorectomy [4]. However, advancements in radiologic techniques have led to increased use of percutaneous drainage procedures prior to proceeding with major surgery. The majority of TOAs (70%) can now be successfully managed conservatively with broad-spectrum antibiotics and percutaneous or laparoscopic drainage of abscesses when necessary [7]. Major surgery, including bilateral oophorectomy, is currently reserved for life-threatening situations where conservative medical and surgical measures have failed or tubo-ovarian abscesses have ruptured [4, 8].

Genetic Predisposition to Ovarian Cancer

In 2012, 20,785 women in the USA were diagnosed with ovarian cancer, and 14,404 died from ovarian cancer [9]. The lifetime risk of ovarian cancer in the general population is 1 in 75 (1.3%) [9]. There is currently no good screening test for early disease. Five to ten percent of ovarian cancer cases are related to inherited genetic risk. These include women with inherited mutations in the BRCA1 and/or BRCA2 genes and those with hereditary nonpolyposis colorectal cancer (HNPCC). The lifetime risk of developing ovarian cancer in women with BRCA1 and BRCA2 mutations is 54% and 23%, respectively [10], and 12% with HNPCC [11]. Current recommendations by ACOG include prophylactic bilateral salpingo-oophorectomy in BRCA1, BRCA2, and HNPCC mutation carriers after completion of childbearing and preferably before age 40 [12]. Also, women with HNPCC will often have a hysterectomy at the time of their BSO because of their 60% lifetime risk of developing endometrial cancer [12].

Endometriosis

Endometriosis is a chronic gynecological disease characterized by the proliferation of endometrial glands and stroma outside of the uterine cavity [13, 14]. It is limited to the reproductive years and is estimated to afflict approximately 10% of reproductive age women [15]. Definitive diagnosis requires histopathological examination of a surgical specimen. However, the diagnosis may be suspected based on clinical signs and symptoms such as severe pelvic pain, dysmenorrhea, deep dyspareunia, and cul-de-sac nodularity and/or tenderness on bimanual pelvic exam. The diagnosis may also be presumed when characteristic features of ovarian endometrioma are seen on imaging. Endometriosis-associated pain may be treated with nonsteroidal anti-inflammatory agents, combined oral contraceptive pills, progestins, danazol,

and gonadotropin-releasing hormone agonists [16]. In women whose pain is recalcitrant or whose disease burden is heavy, i.e., large endometriomas or deeply infiltrating endometriosis implants, surgery may become necessary via laparoscopy or laparotomy depending on pelvic anatomy. For women who desire retention of childbearing capacity, a conservative surgical approach is often adopted with the aim of reducing disease burden and preserving as much ovarian tissue as possible for future natural or assisted reproduction. Women undergoing surgical resection of endometriomas should be counseled about the possibility of diminished ovarian reserve and of recurrent disease postoperatively [17]. For severely symptomatic women who have no desire for further childbearing and whose pain cannot be controlled with medical therapy, definitive surgical management with BSO often becomes indicated and is commonly performed with a hysterectomy. Even after definitive hysterectomy with BSO, about 15 % of women with endometriosis-associated pain may continue to experience some pain, the etiology of which is unclear [18]. It should be pointed out, however, that those in whom ovarian tissue is intentionally or unintentionally retained at hysterectomy have a sixfold higher risk of recurrent or persistent pain, emphasizing the importance of ovarian estrogen in the maintenance and propagation of endometriosis [19].

While premenopausal BSO may be indicated as a risk-reducing strategy in those with heritable cancer-predisposing genes or as part of the treatment plan for a benign (TOA or endometriosis) or malignant condition (endometrial cancer), elective BSO continues to be performed at hysterectomy in premenopausal women with unrelated gynecological disease. Data from 1994 to 1999 from the Centers of Disease Control and Prevention indicates that approximately 40 % of women ages 18–44 and 75 % of women ages 45–54 will have a concurrent oophorectomy at the time of hysterectomy [20]. Thus, conservative estimates suggest that approximately 300,000 women will have a prophylactic bilateral oophorectomy annually [21]. In a recent cross-sectional study spanning 1998–2006, the proportion of hysterectomies accompanied by an elective bilateral salpingo-oophorectomy increased from 38 % in 1998 to 41 % in 2001 and then decreased to 40 % in 2002 and 36 % in 2006. The highest rate of elective bilateral salpingo-oophorectomy was among women age 45–49 (26.5 per 10,000), of which a large proportion was likely premenopausal [22]. One should note here that the practice of elective BSO at hysterectomy in premenopausal women continues despite the recommendation by the American College of Obstetrics and Gynecology (ACOG) to retain normal-appearing ovaries when hysterectomy is being performed in premenopausal women who are considered to be at average risk of ovarian cancer [12].

Overview of the Management of Premature Surgical Menopause

As discussed earlier, the nuisance symptoms of estrogen deficiency after surgical menopause, e.g., hot flashes, night sweats, and vulvovaginal atrophy, are common, occur abruptly, and often have a significant impact on quality of life. A number of hormonal and nonhormonal remedies are available and helpful in this regard and have been discussed in other chapters of this book. Briefly, the most effective therapy for hot flashes is systemic hormone therapy (HT) that may be administered

orally or transdermally [23]. In addition, there are a number of nonhormonal options, albeit less effective including selective serotonin reuptake inhibitors (SSRIs), clonidine, and gabapentin for the treatment of vasomotor symptoms [23]. The only FDA-approved nonhormonal treatment for hot flashes in the USA is the SSRI paroxetine. A number of vaginal estrogen products and lubricants and an oral selective estrogen receptor agonist/antagonist (ospemifene) are also available for treatment of vulvovaginal atrophy to provide relief from dyspareunia [23].

Perhaps more important for this population of young, surgically menopausal women is the potential role that HT may play in moderating the cardiovascular and skeletal sequelae of a state of estrogen deficiency that will be significantly longer and more impactful than that of naturally menopausal women. A case in point is an observational cohort study of women who had BSO prior to age 45: those who did not receive estrogen therapy postoperatively had an 84 % higher risk of mortality from cardiovascular disease within the next 25 years compared to those who received postoperative estrogen replacement therapy until age 45 or later [24]. Further supportive evidence for estrogen's cardioprotective benefits in younger newly menopausal women comes from a stratified reanalysis of data from the Women's Health Initiative (WHI) [25], suggesting that HT prevents cardiovascular disease only if given prior to the establishment of atherosclerosis. This concept has been named the "timing hypothesis." However, in the more recent Kronos Early Estrogen Prevention Study (KEEPS), a randomized trial of HT versus placebo in newly menopausal women aged 45–54 years, there was no difference in surrogate markers of atherosclerosis between those who received placebo versus combination hormone therapy [26]. Of note, the KEEPS trial was a relatively short trial and not powered to evaluate hard clinical endpoints, but only surrogate markers of coronary risk.

Given that the majority of surgically menopausal women have also undergone a hysterectomy, HT in most cases is simplified to estrogen alone given that the only rationale for adding progestin to a postmenopausal hormone regimen is to prevent endometrial pathology as a consequence of unopposed estrogen use. In the absence of a uterus, there is no need for progestin except when endometriosis was the reason for surgical menopause (discussed below). The advantages of estrogen-only therapy, as used in women without uteri, include a more favorable long-term risk/benefit equation for breast cancer risk, as well as a better cardiovascular profile than with use of combination estrogen/progestin therapy (required in women who retain their uteri). Supporting evidence for this comes from the WHI trial that showed that those on long-term unopposed conjugated estrogen did not exhibit an increase in breast cancer risk, while those on combination estrogen/progestin therapy had a 26 % increased risk [27]. It should also be noted here that a lower than average age of menopause, be it natural or surgically induced, is associated with a significantly lower than average risk of breast cancer [28], and it is not entirely clear whether estrogen-only therapy negates the protective benefit of early menopause on breast cancer risk. Limited evidence does suggest some loss of this protective benefit in women over 40, but not in those under 40 when initiated on estrogen replacement [29].

Up to 15 % of women who have undergone definitive treatment (total hysterectomy and BSO) for endometriosis may have recurrence of pelvic pain [18]. There is also concern that unopposed estrogen may lead to malignant transformation of

residual endometriotic lesions, with 20 reported cases of this in the literature [30]. Patients in whom endometriosis is the indication for surgical menopause are a unique population likely to benefit from inclusion of a progestin formulation in their menopausal hormonal regimen despite lacking uteri, to minimize risk of recrudescence of microscopic residual foci of endometriosis [31].

Based on the preponderance of evidence and consensus among professionals in the field, the benefits of long-term HT in women with premature surgical menopause outweigh the risks, particularly in those women under 40. Conventional dose unopposed estrogen therapy is often required in many of these women for symptomatic relief and may be continued until the average age of menopause, at which time it can be stopped or replaced by low-dose HT or nonhormonal therapies depending on the clinical situation. In some cases, estrogen and progestin combination therapy might be indicated as discussed in the case below. Contraindications to hormone therapy include severe uncontrolled hypertension, cardiac valvular or ischemic heart disease, history of thromboembolic event, known thrombophilic mutation (such as factor V Leiden), migraines with aura, systemic lupus, personal history of breast or endometrial cancer, liver cirrhosis, or hepatocellular adenoma [32]. In women with relative contraindications, i.e., mild hypertension or other components of metabolic syndrome, transdermal estrogens may be safer as far as thromboembolic risks are concerned [33].

Case

Given her young age and premenopausal state at time of BSO, the patient's severe and bothersome symptoms of sudden onset estrogen deficiency are predictable. Preoperative counseling included discussion on available strategies (hormonal and nonhormonal) for addressing vasomotor symptoms resulting from estrogen loss, potential implications of loss of ovarian androgens for sexual function, and risk of recurrence of endometriosis foci from estrogen-only therapy. Discussion of the long-term implications of premenopausal BSO including the impact on chronic health conditions including cardiovascular disease, skeletal fragility, and cognitive well-being [34] was also undertaken.

As the patient was young, hormonal intervention was identified as the most effective of available options for addressing menopause-related symptoms and to optimize her quality of life. The use of estrogen-only hormone replacement therapy in this scenario is controversial due to the concern that it may reactivate microscopic or residual endometriotic implants and cause worsening symptoms, as discussed earlier. Therefore, a combination hormone regimen containing estrogen and progestin is recommended to address menopausal symptoms in this patient. Continuous use of combination oral contraceptive pill offers benefit against vasomotor symptoms while suppressing any residual endometriotic foci and was the strategy preferred by this patient.

Consideration of timing of initiation of HT following surgical menopause is highlighted in this case. For surgical procedures that are relatively uncomplicated

and achieved through the minimally invasive approach, preemptive initiation of HT following BSO can be considered in the immediate postoperative period; symptom control can then be maximized through dose titration over subsequent weeks. For complicated surgical procedures and in situations where the patient is deemed at high risk for thromboembolism, clinicians may prefer to defer initiation of HT for a few weeks. When to start HT postoperatively following BSO remains an open question as currently there is minimal research in this area. A small retrospective cohort study suggested that the risk of recurrent pain was the same among women who received estrogen therapy immediately after surgery versus those who were started 6 weeks postoperatively [35]. The mechanism underlying this finding is unclear. Age of the patient, anticipated severity of vasomotor symptoms subsequent to BSO (the younger the age, the higher the burden), intraoperative complexity, and postoperative course should all guide the decision regarding timing of initiation of HT following BSO undertaken in a premenopausal woman.

Our patient was started on continuous oral contraceptive pills at her 6-week postoperative visit after she first reported her new onset vasomotor symptoms. Her hot flashes improved on this treatment, and her pelvic pain, though not completely resolved, remained tolerable. Choice of regimen was dictated by her young age and symptomatic severe endometriosis as the indication for BSO.

Clinical Pearls/Pitfalls

- Surgical menopause is caused by the abrupt drop in estrogen and progesterone levels after surgical removal of ovarian tissue and is often accompanied by vasomotor symptoms and vaginal atrophy.
- Early menopause is associated with increased risk of cardiovascular events, bone loss, cognitive impairment, and overall mortality.
- Hormone management of early surgical menopause with estrogen only in patients who have also undergone hysterectomy is recommended as it has been shown to decrease mortality from cardiovascular events with minimal increase in breast cancer risk.
- Combined estrogen/progesterone therapy should be considered in patients who have retained their uterus or who have endometriosis.
  - Patients should be informed of the increased risk of developing breast cancer if therapy is utilized for more than 5 years.
- Contraindications to hormone therapy include severe uncontrolled hypertension, valvular or ischemic heart disease, history of thromboembolic event, known thrombophilic mutation, migraines with aura, systemic lupus, history of breast or endometrial cancer, liver cirrhosis, or hepatocellular adenoma.
  - In women with relative contraindications (i.e., mild hypertension), consider transdermal estrogen that has not been associated with an increased risk of thromboembolic events.

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Bothersome Vasomotor Symptoms: Management in Women with Type 2 Diabetes Mellitus (Case 1) and Differential Diagnostic Considerations (Case 2)

15

Cynthia A. Stuenkel

Case 1: Older Woman, Obese, Recently Diabetic, and Well into Menopause with Bothersome Hot Flashes

A 58-year-old patient presents to our menopause clinic for treatment of bothersome hot flashes. Her last menstrual period occurred at age 52. The patient learned at age 56 that she had type 2 diabetes mellitus. A random blood glucose on a chemistry panel ordered for evaluation of fatigue was elevated, and the diagnosis was confirmed by an HgA1C ≥6.5 %. Glucose control has been normalized on metformin therapy. The patient is also hypertensive and well controlled with a combination of a calcium channel blocker (amlodipine) and an angiotensin-converting enzyme inhibitor (benazepril). She knows her medical concerns would be improved by weight loss but she seems stuck at 200 pounds (BMI 32 kg/m^2). She isn't refreshed after a night's rest and wants relief from her hot flashes. She also notes that her husband has started to complain about her snoring. What are the options for treating her hot flashes? How best should you prioritize her medical concerns and balance her management choices?

My Management

A. With the composite cardiovascular disease (CVD) risks factors of diabetes, obesity, hypertension, likely dyslipidemia, and possibly obstructive sleep apnea in this patient approaching age 60, non-hormonal prescription strategies should be considered as first-line approach for managing common vasomotor symptoms (VMS) including hot flashes and night sweats (symptoms of menopause are extensively covered in other chapters in this book).

C.A. Stuenkel, MD
University of California, San Diego, School of Medicine, Department of Medicine, Division of Endocrinology and Metabolism, La Jolla, CA, USA
e-mail: castuenkel@ucsd.edu

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Table 15.1 Criteria for the diagnosis of diabetes mellitus [2]

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h[a]
2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water[a]
Hemoglobin A1C ≥6.5 % (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay[a]
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L)

FPG fasting plasma glucose, *h* hour, *PG* plasma glucose, *OGTT* oral glucose tolerance test, *WHO* World Health Organization, *NGSP* National Glycohemoglobin Standardization Program, *DCCT* Diabetes Control and Complications Trial

[a]In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing

B. Establish plan for diet and exercise with the goal of 5–7 % weight loss to improve insulin sensitivity and metabolic parameters.
C. If the patient successfully loses weight with subsequent improvement or remission of diabetes and associated risk factors, one may then cautiously consider (if the patient is in agreement) a trial of low-dose transdermal estrogen therapy if bothersome VMS persist despite trial of non-hormonal strategies.
D. Proceed with recommendations for comprehensive care and cardiovascular risk management of a patient with diabetes.

Assessment and Diagnosis

Diabetes mellitus is increasingly common in clinical practice. In 2012, 29.1 million Americans, or 9.3 % of the population, had diabetes [1]. In the same year, 86 million Americans age 20 and older had prediabetes [1]. The American Diabetes Association has established criteria for diagnosing diabetes (Table 15.1) and prediabetes (Table 15.2) and recommendations for testing asymptomatic adults (Table 15.2) [2]. The US Preventive Services Task Force recommends screening for abnormal blood glucose in adults aged 40–70 years who are overweight or obese [3].

The constellation of menopause and diabetes poses unique challenges. Some diabetic women anecdotally report sensations similar to hot flashes with highs or lows of blood glucose [4]. Our patient checks her blood glucose regularly and has not observed a relationship between the feelings she interprets as hot flashes and excursions of blood glucose. Her symptoms sound like typical menopausal hot flashes. Upon further questioning, the patient reveals that VMS are annoying during the day, but are also associated with nighttime awakenings. She feels that sleep disruption contributes to her fatigue during the day and interferes with her effectiveness at work. She is definitely interested in exploring options to reduce VMS as well as improve her sleep.

As patients diagnosed with type 2 diabetes may have diabetes for years prior to their diagnosis, a comprehensive diabetes medical evaluation should be initiated that includes assessment of current lifestyle patterns and for existence of microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary

Table 15.2 Criteria for testing for diabetes mellitus or prediabetes in asymptomatic adults [2]

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and have additional risk factors:
Physical inactivity
First-degree relative with diabetes
High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
Women who delivered a baby weighing >9 lb or were diagnosed with gestational diabetes mellitus
Hypertension (≥140/90 mmHg or on therapy for hypertension)
HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.83 mmol/L)
Women with polycystic ovary syndrome
Categories of increased risk for diabetes (prediabetes) on previous testing
Impaired fasting glucose, 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) *or*
Impaired glucose tolerance, 2-h plasma glucose 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) *or*
A1C 5.7–6.5 % (39–46 mmol/mol)
Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
History of cardiovascular disease
2. For all patients, testing should begin at age 45 years
3. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status

heart disease, cerebrovascular disease, and peripheral arterial disease) complications of diabetes [5]. This provides a baseline for future clinical management and, in this case, facilitates decisions about treatment of VMS. Although the diagnosis of diabetes has been confirmed in this patient, it would be reasonable to repeat the A1C level to confirm the level of diabetic control on metformin therapy over the past 3 months [5]. Additional laboratory testing should include annual fasting lipid profile, liver function tests, spot urinary albumin-to-creatinine ratio, serum creatinine, and estimated glomerular filtration rate [5]. For diabetic women > age 50, thyroid-stimulating hormone determination is also recommended [5]. Depression affects 20–25 % of people with diabetes [5]. Our patient does not complain of depression or appear depressed, but an office-based screening (such as with the patient health questionnaire 2 PHQ-2) is recommended [5].

Our patient's husband notes that she snores more than in the past. The prevalence of obstructive sleep apnea (OSA) in patients with type 2 diabetes may be as high as 23 %; in a study of obese patients with type 2 diabetes, it exceeded 80 % [5]. Referral to a sleep specialist for evaluation including full overnight polysomnography with cardiac rhythm monitoring is recommended by the American College of Physicians as the preferred diagnostic tool for sleep breathing disturbances [6]. Management of sleep apnea with continuous positive airway pressure significantly improves quality of life and blood pressure control [5, 7, 8].

Although this patient has no symptoms of coronary heart disease or past history of CVD events, cardiovascular disease is a major contributor to morbidity and mortality associated with diabetes in women [9]. Formal assessment of CVD risk with the American College of Cardiology/American Heart Association 10-year CVD risk calculator [10] could facilitate decision-making regarding level of CVD risk and appropriate choice of therapy for VMS relief [11] (further discussed under management) as well as regarding CVD preventive strategies [12, 13].

Diabetes increases the risk for osteoporotic fractures regardless of bone mineral density. The added risk is attributed to low bone turnover, low bone quality, and increased risk of falls [14] (osteoporosis risk assessment and treatment options are covered elsewhere in this volume). Providers should assess fracture history and risk factors in older patients with diabetes and recommend measurement of BMD if appropriate for the patient's age and sex [5]. Fracture prevention strategies for people with diabetes are currently the same as for the general population [5]. For patients with type 2 diabetes with fracture risk factors, thiazolidinediones and sodium–glucose cotransporter 2 inhibitors should be avoided as their use has been associated with a higher risk of fractures [5, 14].

Diabetes is associated with increased cancer risk. In recent meta-analyses, elevated risk of breast (20 %), colorectal (27 %), and endometrial (97 %) cancers were found in women with diabetes [15]. Patients with diabetes mellitus should be encouraged to undergo recommended age-appropriate and country-specific cancer screenings [16] and to reduce modifiable cancer risk factors (smoking, obesity, and physical inactivity) [5]. (Case XXX includes a detailed discussion of recommended cancer screening for all postmenopausal women.)

Management

Our patient, complaining of bothersome vasomotor symptoms (VMS), also presented with obesity, recent diagnosis of type 2 diabetes, and hypertension. As with many patients with type 2 diabetes, our patient also had dyslipidemia with HDL < 50 mg/dL, LDL > 100 mg/dL, and triglycerides > 200 mg/dL. The choice of therapy for relief of VMS in patients with CVD risk factors such as diabetes, obesity, hypertension, and dyslipidemia must be dictated by the adage, "First, do no harm." Because randomized clinical trials show increased rates of heart attacks and strokes with oral menopausal hormone therapy (MHT) in women of advanced age, increasing time since menopause, and with established CVD, MHT use is generally not recommended for women in the high CVD risk category [11]. For a woman with diabetes mellitus and additional CVD risk factors (as the patient under discussion), a conservative approach seems merited, as adequately powered clinical trial evidence of CVD outcomes of MHT use in women with diabetes is lacking. Of note, women meeting criteria for the metabolic syndrome at trial initiation in the Women's Health Initiative randomized clinical trial of combined (estrogen plus progestin) hormone therapy in women with a uterus were found to be at increased risk of CHD outcomes when assigned to oral hormone therapy with daily conjugated equine estrogens 0.625 mg combined with medroxyprogesterone acetate 2.5 mg [17].

As experienced clinicians are aware, the diagnosis of diabetes mellitus represents a clinical continuum, and not all women with diabetes mellitus present with multiple CVD risk factors. The Endocrine Society Clinical Practice Guideline on Treatment of Symptoms of Menopause [11] allows that some women with diabetes mellitus, after formal evaluation of CVD risk, who fall into the "low"- or "intermediate"-risk category [10], might be candidates for low-dose transdermal estradiol therapy with micronized progesterone (for endometrial protection in women with a uterus), as these hormonal preparations are less metabolically active and possibly less likely than oral menopausal hormone therapies to contribute to risk of venous thrombosis and stroke [18]. From the standpoint of effect of MHT on glucose control in women with diabetes mellitus, a number of small, short-duration randomized controlled trials showed either improvement or neutral effects [19].

Aggressive cardiovascular risk factor management is paramount [12]. In addition to treating hypertension to blood pressure goal of <140/90 mmHg, for patients with diabetes mellitus aged 40–75 years with additional atherosclerotic CVD risk factors (such as our obese, hypertensive, dyslipidemic patient), consider using high-intensity statin and lifestyle therapy [13]. Although elevated LDL-C level is not usually the major lipid abnormality in patients with type 2 diabetes mellitus (they are more likely to have low HDL-C and elevated levels of triglycerides), as demonstrated in clinical trials, statin therapy reduces the risk for major coronary events independent of baseline LDL-C and other lipid values [12]. According to the American Heart Association and the American Diabetes Association Scientific Statement on prevention of CVD in adults with type 2 diabetes mellitus, patients between 40 and 75 years of age with LDL-C between 70 and 189 mg/dL should be treated with a moderate-intensity statin [12]. Statin therapy of high intensity should be given to individuals with diabetes mellitus between 40 and 75 years of age with a ≥7.5 % estimated risk of arteriosclerotic CVD [12]. Lipid levels should be measured at least annually to assess compliance with therapy [12].

It is essential to remember to emphasize a healthy lifestyle—including diet and exercise—to achieve weight loss. In the Diabetes Prevention Program, weight reduction of just 5–7 % was associated with a 58 % reduction in evolution to diabetes for those with prediabetes [5]. Depending upon degree of weight loss (>7 %), the duration of diabetes (<5 years), the baseline A1C (<8 %), and medical therapy (<2 oral medications for diabetes mellitus), the metabolic disturbances characteristic of type 2 diabetes mellitus can improve and, in some patients, result in remission of diabetes [20, 21].

For women with diabetes, current recommendations for prevention and treatment of osteoporosis should be followed, as there are no specific guidelines for women with diabetes [14]. Good glycemic control to reduce complications of diabetes and efforts to prevent falls are important ongoing measures. In the midst of all the other surveillance required by a patient with diabetes mellitus, do not forget to maintain country-specific recommendations for cancer screening and detection.

Outcome

This patient's VMS reflected her postmenopausal status, and because of her history of diabetes mellitus and CVD risks, a non-hormonal strategy was agreed upon as a

conservative first-line approach. Given that poor nocturnal sleep was a dominant symptom, gabapentin was chosen from among the various available non-hormonal options available for relief of VMS [22]; non-hormonal options for treatment of menopausal VMS are covered in detail elsewhere in this volume. As a side effect of gabapentin therapy includes drowsiness, bedtime administration is preferred [22]. For our patient, therapy was initiated at a dose of 300 mg orally taken at bedtime. Although the patient reported some improvement by the end of the first month of gabapentin therapy, because of persistent nocturnal VMS, the bedtime dose was increased to 600 mg orally. After another month of therapy, the patient reported improvement in both VMS as well as sleep disruption.

Motivated by her daughter's upcoming wedding, after enrolling in an intensive lifestyle program at the local YMCA, the patient lost 20 pounds (approximately 10 % of her baseline weight). Concordant with the weight loss, her blood glucose progressively normalized, and the metformin was eventually discontinued. Her blood pressure is now adequately controlled on a lower dose of a calcium channel blocker and angiotensin-converting enzyme inhibitor. Metabolic improvements were attained within 3 months of weight loss with triglyceride levels now below 150 mg/dl and an increase HDL cholesterol level. Although diabetes appears to be in remission, the patient has elected to continue statin therapy given her age, hypertension, and predisposition to diabetes.

Continuation of the gabapentin therapy (rather than a switch to transdermal estrogen therapy) was preferred by the patient. The patient reported subjective improvement in sleep with control of nighttime VMS, although a formal sleep study did demonstrate characteristics of obstructive sleep apnea. Continuous positive airway pressure (CPAP) was advised, with additional improvement in nocturnal sleep and symptoms of daytime fatigue.

Clinical Pearls/Pitfalls

- VMS symptoms can be more bothersome in an obese postmenopausal woman compared to those of normal weight. In some trials, weight loss is associated with improvement in VMS.
- In the setting of diabetes and presence of additional CVD risk factors, a non-hormonal approach to treatment of VMS is most prudent.
- Diabetes mellitus in women portends an increased risk of CVD; aggressive measures to control risk factors are indicated.
- Weight loss via diet and lifestyle can be associated with remarkable improvement in metabolic risks including in some patients, remission of type 2 diabetes.
- Sleep apnea should be a consideration in the setting of symptoms of daytime fatigue and poor nighttime sleep, particularly in an obese, diabetic, postmenopausal woman.
- Given that type 2 diabetes mellitus augments risks for osteoporotic fractures and some cancers, follow general recommendations for screening and preventive strategies.

Case 2: A 55-Year-Old Suffering from Severe Diaphoresis, Hypertensive (Focus on Differential Diagnosis of Menopause-Like Picture)

A 55-year-old postmenopausal woman presents with complaint of episodes of intense sweating. She describes the episodes as coming on suddenly associated with a perceptible increase in heart rate. They last usually a few to no more than 10–15 min. She started noticing them shortly after she stopped menstruating at age 52. To her, they seem similar to the episodes described by her friends with hot flashes. Shortly after menopause, she was also diagnosed with hypertension. Her doctor told her that hypertension was incredibly common with half of all his menopausal patients over age 50 years having elevated blood pressure. Given that she was otherwise healthy and bothered by these episodic symptoms, her doctor started her on a course of transdermal estrogen therapy. After several months of a trial of menopausal hormone therapy (continuous transdermal estrogen with cyclic progesterone), she returned to his office noting no improvement in sweating episodes. He refers her to you for additional evaluation and treatment.

My Management

A. Agree with the primary doctor's decision to a trial of transdermal (rather than oral) menopausal hormone therapy, particularly in light of concurrent hypertension
B. As the patient's symptoms persisted without any relief from the transdermal estrogen, this is one of the few instances when measurement of the serum estradiol level would be indicated.
C. If the patient's serum estradiol level reflects the dose of estradiol administered and confirms adequate absorption, in the absence of symptom relief, it would then be appropriate to evaluate the patient for other causes of episodic sweating.

Assessment and Diagnosis

For the vast majority of women, the diagnosis of menopause is clinical, based upon the cessation of menstrual cycles in an age-appropriate woman [11, 23]. Concordant with absent menses, vasomotor symptoms (VMS), the quintessential symptom of the menopause transition, appear in as many as 75 % of women (symptoms of menopause are extensively covered in other chapters in this book). Women, however, have no point of reference to recognize VMS when they occur, and in rare instances, patients may interpret other episodic symptoms as VMS when in fact, they may represent medical conditions that merit prompt diagnosis and treatment.

When should the clinician suspect that episodic symptoms are not caused by estrogen withdrawal? Clinically, one of the first clues may be failure to respond to estrogen therapy, which in rare instances may reflect inadequate absorption. If

patients still do not experience symptom relief after an oral estrogen formulation has been switched to a transdermal preparation and adequate serum estrogen levels have been documented, it is time to reconsider the nature of the symptoms. The presence of additional characteristic symptoms or findings on examination might provide clues to other syndromes that can be associated with episodic sensations of flushing and sweating. If these findings are compelling, evaluation would be recommended prior to additional attempts at symptom control.

For the most part, a careful history, physical examination, and straightforward laboratory evaluation will reveal the most common conditions that may mimic VMS (Table 15.3) [11, 23]. From the standpoint of endocrine disorders, thyroid hormone excess is the most common, but carcinoid syndrome and pheochromocytoma, although rare, should also be considered along with a few other "zebras" highlighted below. Consultation with an endocrinologist is recommended to facilitate diagnosis and management of these conditions.

Thyroid Hormone Excess

Symptoms of thyroid hormone excess include nervousness, sleep difficulty, weight loss, palpitations, heat intolerance, amenorrhea, and frequent bowel movements [24, 25]. Family history of thyroid disease is often present. Evaluation includes measurement of thyroid-stimulating hormone (TSH), free thyroxine (FT4), and total triiodothyronine (TT3) [24, 25]. If the patient has thyrotoxicosis due to hyperthyroidism (either Graves disease or toxic multinodular goiter), TSH will be suppressed, and the FT4 and possibly TT3 will be elevated [24, 25].

A radioactive iodine-123 uptake scan of the thyroid gland distinguishes hyperthyroidism (diffuse increased uptake in Graves disease versus focal increased uptake in a toxic nodule) from thyrotoxicosis due to thyroiditis with thyroid gland destruction and subsequent release of thyroid hormones (decreased uptake on thyroid scan) [24, 25]. Ingestion of exogenous thyroid hormone (either surreptitiously or in error) is another possible etiology of decreased uptake on thyroid scan in a thyrotoxic patient.

Treatment options for hyperthyroidism include antithyroid drugs such as methimazole, radioactive iodine-131 thyroid ablation, and thyroid surgery [24, 25]. Thyrotoxicosis due to thyroiditis is usually self-limited; symptomatic therapy with beta-blockers can treat tachycardia resulting from elevated serum thyroid hormone levels. Manifestations of thyroiditis can evolve over time from transient thyrotoxicosis to transient or permanent hypothyroidism [24, 25].

Carcinoid Syndrome

Carcinoid syndrome is characterized by cutaneous "dry" flushing, secretory diarrhea, and right-sided valvular heart disease; additional symptoms may include abdominal pain and bronchospasm [26, 27]. Carcinoid syndrome usually reflects excess serotonin or other vasoactive amine (prostaglandins, histamine, and

Table 15.3 Conditions that may cause or mimic vasomotor events and that can be distinguished from menopausal symptoms by history, examination, and investigations, as indicated [11]

Hormone excess
Thyroid hormone
Carcinoid syndrome (flushing without sweating)
Pheochromocytoma or paraganglioma (hypertension, flushing, and profuse sweating)
Dietary factors
Alcohol
Spicy food
Food additives (e.g., monosodium glutamate, sulfites)
Pharmaceuticals
Chronic opioid use
Opiate withdrawal
SSRIs (may cause sweats)
Nicotinic acid (intense warmth, itching lasting up to 30 min)
Calcium channel blockers
Medications that block estrogen action or biosynthesis (tamoxifen, raloxifene, aromatase inhibitors)
Other medical conditions
Chronic infection (increased body temperature)
Postgastric surgery dumping syndrome
Mastocytosis and mast cell disorders (usually with gastrointestinal symptoms)
Some cancers: medullary carcinoma of the thyroid, pancreatic islet cell tumors, renal cell carcinoma, lymphoma
Anxiety disorders

tachykinins) production by small bowel (midgut) carcinoid tumors but also by bronchial, ovarian, and other foregut carcinoids [26, 27]. As these substances are inactivated by the liver, carcinoid syndrome presents primarily in the presence of liver metastases unless the tumor is of foregut origin. Flushing may be brief or prolonged—up to 30 min—and results in a red to violaceous to purple hue of the face, neck, and chest. Vasodilation can result in hypotension and tachycardia.

Carcinoid syndrome occurs in less than 10 % of patients with carcinoid tumors [26, 27]. Although a number of vasoactive substances have been implicated in symptoms associated with carcinoid tumors, measurement of 24-h urine 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, is recommended as the initial laboratory evaluation. Plasma chromogranin A is another marker of neuroendocrine tumors [26, 27]. Diagnostic imaging studies to locate carcinoid tumors include computed tomography, magnetic resonance imaging, somatostatin receptor scintigraphy (Octreoscan), and still under investigation, positron emission tomography scanning [26, 27]. Tissue confirmation is required to complete the diagnosis [26, 27].

Surgical resection of the primary tumor can be challenging because of extensive mesenteric lymphatic involvement; the approach to managing hepatic metastases should be considered separately depending upon the extent of liver involvement and

need to manage carcinoid symptoms. Somatostatin analogues (octreotide and lanreotide) are the primary treatment for symptoms of carcinoid syndrome, as most tumors are metastatic at presentation [26, 27]. These agents may also control the growth of well-differentiated tumors.

Pheochromocytoma

Pheochromocytomas (adrenal medullary tumors) and paragangliomas (catecholamine-producing tumors located outside the adrenal gland) can present with the triad of headaches, palpitations, and diaphoresis [28, 29]. Hypertension and hyperglycemia are associated signs [28–30]. Plasma-free or urinary fractionated metanephrines are recommended as initial laboratory screening tests [28, 29]. 2f biochemical screening is positive; abdominal computed tomography or magnetic resonance imaging should follow for tumor localization. Most tumors are found within the adrenal gland, with 25 % occurring at other sites [28, 29].

Surgical excision is the preferred therapy. Preoperative blockade of effects of catecholamines with phenoxybenzamine, a nonselective, noncompetitive α-adrenergic receptor blocker, is recommended to reduce blood pressure and surgical morbidity and mortality [28, 29]. After adequate α-blockade is achieved (which can result in tachycardia and orthostasis), *B*-blockade (for tachycardia) and hydration along with high-salt intake (for catecholamine-associated volume depletion) should follow and reduce postoperative hypotension [28, 29].

Four to eight weeks after surgical tumor excision, plasma metanephrines should be measured to ensure complete resection. Annual determination of plasma metanephrines is recommended lifelong to detect additional primary tumors, tumor recurrence, or metastatic disease [28, 29]. Given that up to 40 % of patients with pheochromocytoma have a germline mutation in a known susceptibility gene (currently 13 known genes), all patients should be referred for genetic counseling and potential testing [31, 32].

Other Medical Conditions

Other medical conditions that may cause or mimic VMS (Table 15.3) include postgastrectomy dumping syndrome, mastocytosis and mast cell disorders (usually associated with gastrointestinal symptoms), and other cancers: medullary carcinoma of the thyroid gland, pancreatic islet-cell tumors, renal cell carcinomas, and lymphoma [11, 23]. Anxiety disorders, particularly when presenting with panic attacks, can be mistaken for VMS [11, 23]. Dietary factors such as alcohol, spicy foods, and food additives may cause flushing [11, 23]. Medications including chronic opioid use, opiate withdrawal, SSRIs (may cause sweats), nicotinic acid, calcium channel blockers, or drugs that block estrogen action (selective estrogen receptor modulators such as tamoxifen, raloxifene, or ospemifene) or estrogen biosynthesis (aromatase inhibitors) can contribute to VMS [11, 23].

Case Management

As the patient's symptoms did not respond to a 50 mcg transdermal estrogen patch, serum estradiol (E2) levels were measured at least 12 h after applying the patch. An E2 level of 50 pg/ml was considered adequate to provide some measure of symptom relief in most naturally menopausal women. Given the persistence of her symptoms despite an adequate serum E2 level, estrogen therapy was discontinued without noticeable difference in the patient's complaints, and alternative diagnoses were considered. Upon further questioning, the patient described severe headaches during sweating episodes, associated with "racing of her heart." Although her blood pressure in the office was 140/90 mmHg, during a later episode, her blood pressure was recorded at 175/100 mmHg (as determined by a home blood pressure monitor), with a pulse rate of 110 beats per minute. Pheochromocytoma was considered in the differential diagnosis. A plasma-free metanephrine level was drawn in the office (with the patient supine for 30 min prior); a 24-h urine collection for fractionated metanephrines was also initiated. The results of these tests were consistent with a catecholamine-producing tumor (levels threefold above upper cutoff) [28, 29]. An abdominal CT scan with contrast identified a 1 cm tumor of the left adrenal medulla.

In preparation for surgery with preoperative anesthesia consultation, the patient received 10 days of alpha-blockade to control her hypertension and to minimize the risk of intraoperative adrenergic crisis. She was also treated with a high-salt diet and fluid intake to compensate for pheochromocytoma-associated volume depletion. Blood glucose monitoring demonstrated intermittent elevation of blood glucose, but not frank diabetes [30].

Outcome

Surgical excision was accomplished via minimally invasive laparoscopic left adrenalectomy. Although the patient's intraoperative blood pressure initially spiked during tumor manipulation, it normalized postoperatively. The patient experienced complete resolution of her symptoms in the immediate postoperative period. Biochemical indices including blood glucose and urine metanephrines also normalized postoperatively, providing reassurance regarding complete excision of the tumor. On gross pathology, there was no invasion of the tumor into surrounding tissues which suggested a benign lesion. Microscopic examination was consistent with the preoperative diagnosis of pheochromocytoma. Postoperative recovery was unremarkable.

Consistent with current guidelines, genetic testing was discussed, and the patient requested referral for clinical genetic testing [28, 31]. Pheochromocytoma/paraganglioma susceptibility genes are mostly inherited in an autosomal dominant pattern and include *NF1 (neurofibromatosis type 1)*, *RET (multiple endocrine neoplasia type 2)*, *VH (von Hippel–Lindau)*, *SDHx genes (familial paraganglioma syndrome), and others: TMEM127*, *MAX*, *EPAS1, FH, and MDH2* [32]. According to the Endocrine Society Clinical Practice Guideline, at least one third of all patients with

pheochromocytoma or paraganglioma have disease-causing germline mutations [7]. Mutations of *SDHB* lead to metastatic disease in 40 % or more of affected patients [28, 32]. Establishing a hereditary syndrome in the presenting patient would be intended to result in earlier diagnosis and treatment of pheochromocytomas and paragangliomas and other manifestations of associated genetic syndromes in her family members [28]. The Endocrine Society recommends a clinical feature-driven diagnostic algorithm to establish the priorities for specific genetic testing in patients with suspected germline mutations [28]. After reviewing our patient's presentation (> age 45 years, a single tumor, intra-adrenal location, lack of symptoms suggesting other relevant syndromes, and lack of family history), she was relieved, as anticipated, to not be a carrier of the relevant genes.

All patients should have biochemical testing (plasma or urine metanephrines) measured within 4–8 weeks after surgery to confirm complete excision of the tumor and then annually lifelong to detect disease recurrence or metastatic disease [28, 32].

Clinical Pearls/Pitfalls

- Menopause associated VMS can be confused with other episodic clinical disorders.
- Although VMS are experienced by the majority of postmenopausal women, a lack of response to adequate doses of estrogen therapy should suggest another possible etiology of episodic events such as flushing and sweating.
- Suspicion for non-menopausal origins of symptoms should also arise when uncharacteristic symptoms such as diarrhea, wheezing, headache, or palpitations are associated with flushing or diaphoresis.
- Careful history and physical examination usually suggest a constellation of symptoms and signs to direct the clinical investigation.
- Diagnosis of other etiologies of episodic events is straightforward with readily available laboratory tests.
- As these are often rare disorders, referral to an endocrinologist or other relevant specialists for diagnostic confirmation and management is recommended.

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Part III

Managing Menopause in Cancer Survivors

Pharmacological Therapy for Vasomotor Symptoms in Breast Cancer Survivors

16

Lindsay P. Bonnett, Xuezhi Jiang, and Peter F. Schnatz

Case Presentation

A 48-year-old female presents to the office complaining of bothersome hot flashes and difficulty sleeping. Her past medical history is significant for an estrogen receptor-positive breast cancer treated surgically 6 months ago. She is currently on tamoxifen for endocrine therapy. Her last menstrual period was 4 months ago, and over the past 4 months, she has experienced moderate hot flashes and trouble sleeping due to night sweats. In addition, she has difficulty concentrating at work due to sudden and frequent hot flashes, which has impaired her work performance. She notes that her symptoms have not been relieved with lifestyle changes and nonprescription approaches.

L.P. Bonnett, MD
Reading Hospital, Department of ObGyn, Reading, PA, USA

X. Jiang, MD, PhD, FACOG, NCMP
Reading Hospital, Department of ObGyn, Reading, PA, USA
e-mail: Daniel.Jiang@readinghealth.org

Sidney Kimmel Medical College of Thomas Jefferson University, Departments of ObGyn, Philadelphia, PA, USA

P.F. Schnatz, DO, FACOG, FACP, NCMP (✉)
Internal Medicine, Reading, PA, USA

Internal Medicine, Philadelphia, PA, USA

Sidney Kimmel Medical College of Thomas Jefferson University, Reading Hospital, Department of OB/GYN – R1, P.O. Box 16052, Reading, PA 19612-6052, USA

Reading Hospital, Department of ObGyn, Reading, PA, USA

Sidney Kimmel Medical College of Thomas Jefferson University, Departments of ObGyn, Philadelphia, PA, USA
e-mail: Peter.Schnatz@readinghealth.org

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What Is the Most Effective and Appropriate Management Option for This Patient?

A. Combined estrogen and progestin/progestogen therapy (EPT)
B. Estrogen therapy (ET) only
C. Progestin/progestogen therapy (PT) only
D. Paroxetine
E. Gabapentin
F. Clonidine
G. Black cohosh

Special considerations for our patient's case as detailed above include moderate to severe vasomotor symptoms (VMS) associated with decreased quality of life, history of breast cancer, current tamoxifen therapy, and a desire to be treated pharmacologically after a failed trial of nonprescription approaches. Potential options for therapy, special considerations, side effects, and treatment regimens for VMS will be discussed below as well as the thought process for the management approach for the case above.

Overview, Assessment, and Diagnosis of Vasomotor Symptoms in Menopause

Vasomotor symptoms (VMS) include a common constellation of symptoms experienced by women undergoing the menopausal transition. Women also refer to these symptoms as hot flashes, hot flushes, and/or night sweats. This is the second most common complaint among perimenopausal and early menopausal women after irregular menses. Recent studies show up to 75 % of reproductively aging women will experience VMS [1].

Hot flashes are described as recurrent, short-duration episodes of flushing and intense heat felt over the upper body and face, typically lasting from one to five minutes. Hot flashes may range from mild to severe. Mild hot flashes come less frequently and are tolerable, whereas severe VMS are more frequent, occurring up to every hour, and bothersome. Women with severe VMS may experience diminished quality of sleep, irritability, difficulty concentrating, and thus diminished quality of life. Most women experience VMS for 6 months to 2 years during the menopausal transition, but some women may experience hot flashes for many years or even indefinitely [1]. The median duration of VMS has been reported as 4.0–10.2 years. VMS may start in the early phase of the menopausal transition and extend beyond the years surrounding the last menstrual period [2]. Risk factors for VMS include a high BMI, smoking, and decreased physical activity [3]. Moreover, report of VMS varies according to race; African American women report VMS most frequently, while Asian women report VMS least frequently [2]. Alterations in diet or physiology may account for this difference, or it could be

due to ethnic dissimilarities and cross-cultural perceptions which may alter willingness to report VMS [2].

The pathophysiology of VMS is poorly understood, and multiple factors are believed to contribute. One key factor is that VMS are precipitated by hormone fluctuations, and they have been shown to be improved with administration of estrogen. Observational studies show that VMS are specifically associated with decreased levels of estrogen and increased levels of follicle-stimulating hormone (FSH) [2]. It is believed estrogen withdrawal precipitates a central event in the body stimulating an increased core body temperature which results in peripheral vasodilation, flushing, sweating, and consequently the experience of a hot flash [4]. In addition, the thermoregulatory zone becomes narrowed and is more sensitive to small changes in the core body temperature during the menopausal transition. The hypothalamus is the thermoregulatory center of the body, and norepinephrine and serotonin are the most recognized neurotransmitters in the hypothalamic thermoregulation process. Estrogenic metabolites, catechol estrogens, stimulate the production of the β-endorphins in the hypothalamus. The estrogenic metabolites and endorphins act as a negative feedback mechanism to halt the production of norepinephrine in the hypothalamus. It is supposed that the loss of estrogen takes away this negative feedback mechanism and precipitates uncensored stimulation in the thermoregulation center by norepinephrine in the hypothalamus, thus precipitating a transient increase in body temperature and the sensation of a hot flash [4]. In tandem, increased variation in FSH levels during the menopausal transition have been shown to be a strong predictor of VMS risk, and this variation may also contribute to the pathophysiology of a hot flash [5]. Furthermore, VMS may likewise be surgically induced via a bilateral oophorectomy prior to menopause, precipitated by estrogen-blocking therapies such as tamoxifen or raloxifene, or drugs that inhibit estrogen biosynthesis such as aromatase inhibitors [1]. Of note, medications such as selective serotonin reuptake inhibitors (SSRIs) nitrates, and niacin may induce sweating and can be mistaken for menopausal hot flashes [1, 6].

Premenopausal or perimenopausal women who undergo treatment for breast cancer are at an increased risk of experiencing VMS due to hypoestrogenemia resulting from ovarian failure secondary to gonadotoxic therapy. Alternatively, worsening VMS may be experienced by menopausal women with the use of aromatase inhibitors, which can bring about profound reductions in circulating estrogens. An estimated two-thirds of women undergoing treatment for breast cancer will experience hot flashes.

Non-gynecological conditions which may masquerade as VMS should be considered in appropriate clinical settings. For example, VMS may be a presenting symptom of thyroid disease, epilepsy, infection, insulinoma, pheochromocytoma, carcinoid syndromes, leukemia, pancreatic tumors, autoimmune disorders, new-onset hypertension, alcohol use, diabetic autonomic dysfunction, mast-cell disorders, lymphoma, and tuberculosis. These differential diagnoses should be considered in patients who have treatment-resistant VMS [1].

Non-pharmacologic Management of Menopausal Vasomotor Symptoms

Conservative measures can offer relief and should always be considered, such as wearing loose clothing, dressing in layers, consuming cold drinks, and smoking cessation. Weight loss and mindfulness-based stress reduction are also good strategies that may help to decrease mild VMS, but more studies are needed to further determine their efficacy. Cooling techniques, avoidance of triggers, exercise, yoga, paced respiration, and acupuncture have been shown to offer benefit for some. Trials of over-the-counter supplements, herbal therapies, and chiropractic interventions are not recommended due to negative, insufficient, or inconclusive data demonstrating their efficacy [7].

Cognitive behavioral therapy (CBT) and clinical hypnosis are non-pharmacologic therapies which have been shown to be effective in reducing VMS. CBT was effective in two randomized controlled trials [7] in which 65–78 % of women enrolled in CBT reported a statistically significant decrease in VMS [8, 9]. Clinical hypnosis demonstrated efficacy in decreasing VMS in three randomized controlled trials. In one such trial, participants attending five hypnosis sessions per week for 12 weeks demonstrated a 74 % reduction in VMS frequency compared to the control group with a 17 % decrease [10]. Studies specifically addressing these modalities in women with breast cancer have also shown promising benefit [11–13]. Behavioral therapies are attractive treatment options in women with a history of breast cancer because they are low risk and cost-effective and may be beneficial. Time commitment and difficulties finding credentialed providers may be potential barriers to CBT or clinical hypnotic therapy.

In our patient's case, symptoms were not relieved with lifestyle changes and/or conservative measures; hence an explanation of pharmacologic therapies will be discussed below. In addition, special considerations for women with VMS and breast cancer will be discussed.

Considerations in Breast Cancer Survivors

In the United States, breast cancer accounted for approximately 29 % of cancers diagnosed in women in 2015 [14]. The lifetime risk of breast cancer in women is one in eight [15]. The estimated number for new breast cancer cases in 2016 in the United States is 249,260 [16]. The median age of diagnosis of breast cancer in 2013 was approximately 57 years old for African American women and 62 for white women [17]. It is a disease that will affect many women in the menopausal transition and will be relevant to our practices.

Breast cancer arises when breast epithelial cells undergo a series of molecular alterations and transition into a state of uncontrolled growth. Risk factors include increasing age, positive family history or personal history, early menarche, nulliparity, obesity, alcohol consumption, and radiographically dense breast tissue [18]. Hereditary syndromes account for only 3–5 % of breast cancer cases. Patients

diagnosed with breast cancer at a younger age and with a positive family history of breast or ovarian cancer may be at greater risk for having a hereditary breast cancer syndrome [19]. The most well-known hereditary breast cancer syndrome consists of the BRCA1 and BRCA2 gene mutations, accounting for 90 % of hereditary breast cancers. Other risk-increasing genetic mutations include p53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome), and STK11 (Peutz-Jeghers syndrome) [20]. The BRCA1 gene mutation is found to have a lower prevalence of hormone-receptor (estrogen receptor (ER) and progesterone receptor (PR))-positive breast cancer with only 10–24 % of cancers being hormone receptor positive. In contrast, BRCA2 is associated with a higher prevalence of hormone-receptor-positive breast cancer, at 65–79 % of cases. Receptor-positive breast cancer was found to be a positive prognostic factor in the first 5 years after diagnosis [21]. A prospective cohort study by Dunnwald et al found a 2.6–3.1-fold increased risk of mortality in receptor-negative breast cancer compared to receptor-positive breast cancer [22]. Our patient was diagnosed with breast cancer at the age of 48. There is no mention of her having a positive family history of breast cancer. Given the information provided, there are not enough criteria to apply genetic testing to her case. If she had a family history of two first- or second-degree relatives with breast cancer, then it would be reasonable to offer genetic screening for her and her children as applicable.

Hormonal therapy has a specific role in estrogen and/or progesterone receptor positive (ER-/PR-positive). Women with hormone-receptor-positive tumors have substantial benefit from treatment with estrogen agonists and estrogen antagonists, also known as selective estrogen receptor modulators (SERMs), aromatase inhibitors, and ovarian ablation modalities. These strategies aim to downregulate estrogen, which decreases its ability to serve as a growth factor in receptor-positive breast cancer. Receptor-positive breast cancer accounts for almost two-thirds of all breast cancer cases [15]. Risk factors for ER-/PR-positive breast cancers include nulliparity, delayed childbearing, early menarche, and postmenopausal obesity. Conversely, risk factors such as alcohol consumption, family history, or premenopausal obesity increase breast cancer risk in general, irrespective of receptor status [23]. Hormone-receptor-negative disease is much less responsive to these therapies [15, 24].

Tamoxifen is approved in healthy women with hormone-receptor-positive breast cancer in both the premenopausal and postmenopausal states for treatment and to prevent recurrence. It is typically given for a course of 5–10 years [18]. Tamoxifen has little or no effect on hormone-receptor-negative breast cancer [23]. Recent guideline recommendations from the American Society of Clinical Oncology (ASCO) recommends tamoxifen use for up to 10 years for women with nonmetastatic hormone-receptor-positive breast cancer for secondary prevention [25]. In addition to secondary prevention, SERMs are being investigated for use in primary prevention of breast cancer in high-risk women [26]. Several prospective randomized controlled trials have shown tamoxifen to reduce risk of a new primary breast cancer in high-risk women by 40–50 % [27]. Raloxifene is another SERM approved by the FDA for the prevention of invasive breast cancer in high-risk postmenopausal

women and has been shown to have similar efficacy to tamoxifen [28]. Lastly, toremifene has an approved indication for treatment of metastatic breast cancer [15], although a detailed discussion is beyond the scope of this paper.

While, as discussed, SERMs are effective in breast cancer chemoprophylaxis, they can also exhibit tissue-specific adverse effects depending on the estrogenic action of the drug and the site of tissue action. Tamoxifen, for example, has antiestrogenic effects at the breast (hence its use in breast cancer) but has proestrogenic effects on the uterine endometrium, cardiovascular system, and bone. Risk for endometrial pathology is well described in tamoxifen users; premenopausal women on tamoxifen may experience irregular bleeding, increased rates of ovarian cysts, endometrial polyps, and leiomyoma growth [15]. Postmenopausal tamoxifen users can experience postmenopausal bleeding due to endometrial proliferation, polyps, hyperplasia, or even carcinoma during the course of tamoxifen treatment for breast cancer management [15]. In a review of seven randomized controlled trials, and one head-to-head study, tamoxifen was found to be associated with a relative risk of endometrial cancer of 2.13 (95% CI, 1.36–3.32) compared to placebo [15, 29]. Endometrial evaluation is therefore advised for tamoxifen users experiencing abnormal uterine bleeding; routine endometrial evaluation however is not advised for asymptomatic tamoxifen users [15]. Also, there is a small increased risk of thromboembolic events with SERM use due to its proestrogenic effects. This risk increases with age and varies according to the type of SERM used [15].

Common side effects of tamoxifen include fatigue, mood swings, as well as VMS and vaginal dryness or discharge [18]. In clinical trials, approximately 30–40% of patients on tamoxifen experienced hot flashes [30], usually increasing in frequency within the first 2–3 months of treatment before plateauing [4]. It has been found in clinical trials that approximately 25% of women do not adhere to tamoxifen therapy due to side effects, and for women not in clinical trials that number may increase up to 50%. It is paramount symptoms of antiestrogen therapy, specifically VMS, should be addressed and controlled via potential modalities discussed below to improve adherence to therapy [31].

Aromatase inhibitors (AIs) are a second class of hormone modulators and are used to treat hormone-receptor-positive breast cancer in postmenopausal women or those rendered surgically menopausal via oophorectomy. AIs have been found to be more effective than tamoxifen in treatment of early-stage hormone-receptor-positive breast cancer in this population [15, 32]. AIs work by decreasing the peripheral conversion of androstenedione and testosterone into estrogen, which decreases the amount of circulating estrogen, thereby preventing hormone-receptor-positive tumor growth. Aromatase inhibitors are not indicated in the management of premenopausal women with breast cancer as they decrease the level of circulating estradiol and thereby decrease negative inhibition of estrogen production by the ovary at the level of the pituitary gland. This leads to increased gonadotropin release by the pituitary gland, which stimulates the ovaries, and results in an increase in estrogen production [15]. In addition, the AI, exemestane, is recommended as a

potential option for primary breast cancer prevention in high-risk postmenopausal women [26].

Symptoms of estrogen deficiency are frequently associated with AI use such as arthralgias, VMS, and vaginal dryness. Furthermore, AIs may exacerbate preexisting symptoms of estrogen deficiency in this postmenopausal population. In contrast to tamoxifen, aromatase inhibitors do not increase the risk of thromboembolic events and do not have a harmful side effect profile on the endometrium, thus leading to decreased rates of uterine bleeding [15].

Ovarian ablation (surgical or radiation) and ovarian suppression strategies are uncommonly utilized in the management of premenopausal breast cancer but are associated with vasomotor symptoms [18]. Ovarian ablation can be accomplished by permanent strategies, including oophorectomy or with pelvic radiation therapy (RT) targeted to the ovaries. The end result is a permanent hypoestrogenic state which may be associated with severe bothersome menopausal symptoms as well as long-term health effects, including cardiovascular disease and osteoporosis. By contrast, ovarian function can be temporarily suppressed with the gonadotropin-releasing hormone (GnRH) agonists. Emerging data from the combined results of the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) support the use of ovarian suppression plus the AI, exemestane. This is superior in regard to disease-free survival (DFS) in premenopausal women with ER-positive breast cancer, while compared with ovarian suppression plus tamoxifen, however, the toxicities seem to be higher in ovarian suppression plus the AI group [33]. Whether or not the combination of ovarian suppression with an AI is more effective than extended treatment with tamoxifen (10 years) is yet to be determined [15]. Cyclophosphamide, an alkylating chemotherapeutic agent, accounts for the majority of the observed ovarian toxicity associated with breast cancer treatment [15]. Although ovarian suppression with GnRH agonists has been theorized to protect the ovary in the setting of a toxic insult such as chemotherapy, these treatments are of unproven benefit for fertility preservation [15].

In summary, bothersome menopausal symptomatology is common in women undergoing therapy for breast cancer and merits attention so as to improve the overall quality of life for the survivors and adherence to therapy. Various treatment strategies for VMS, and their risks and benefits, will be discussed below along with special considerations relevant to our patient.

Pharmacologic Management of Bothersome Vasomotor Symptoms (VMS)

A major consideration in the pharmacologic management of menopausal VMS is targeting and individualizing therapy according to the patient's personal history, risk factors, and goals of care. We have attempted to outline the spectrum of available options and place in perspective the relevance of each class of agents for our patient.

Menopausal Hormone Therapy (MHT)

Estrogen (E), either alone or in combination with a progestogen (P) regimen, is an effective option for decreasing VMS. Progestogen component of the MHT mitigates risk of endometrial pathology well described with the use of E alone [29]. MHT efficacy is primarily dependent on the E dose of the formulation. A 2009 Cochrane meta-analysis found EPT, or E alone (in women without a uterus), reduced the frequency of VMS by 75 % [6].

Randomized controlled trials started in the 1990s were halted when early findings suggested an increased risk of breast cancer recurrence in MHT users [15]. The Women's Health Initiative Estrogen plus Progestin (WHI-EP) trial conducted in an elderly postmenopausal population found a 26 % increased risk of breast cancer after 5 years of continuous use of conjugated equine estrogen and medroxyprogesterone acetate (MPA), a synthetic progestin [34]. In contrast to the WHI-EP, no increase in breast cancer risk was seen with estrogen therapy alone in the WHI-E trial [35]. Conversely, however, The Million Women Study indicated estrogen-only therapy may also increase the risk of breast cancer [36, 37].

The HABITS (Hormonal Replacement Therapy After Breast Cancer Diagnosis—Is It Safe?) study, a randomized controlled trial, found women with a history of breast cancer on MHT carried a threefold increased risk for new primary or recurrent breast cancer [38]. In contrast, a large quantitative review of published data specifically studied women with a history of breast cancer on MHT and did not find an association with risk of breast cancer recurrence, or cancer-related mortality, in comparison to nonusers of MHT [39]. Similar findings were reported by the Stockholm randomized trial. After 10.8 years of follow-up, there was no significant difference in new breast cancer events between HRT and control groups [40]. The increased recurrence in HABITS has been attributed to higher progestogen exposure [40]. In summary, there are studies supporting the increased risk of breast cancer with MHT use and studies that do not.

The increased risk of breast cancer seen with MHT is most applicable to hormone receptor positive breast cancers. The hormone withdrawal response, when estrogen is blocked in cases of hormone-receptor-positive breast cancers, results in decreased tumor growth. Therefore, it can be theorized that MHT may stimulate the growth of preexisting receptor-positive breast tumors. Alternatively, hormone-receptor-negative breast cancer is biologically different, and its growth is thought to not be stimulated by estrogen or progesterone. Studies to date have not demonstrated harm with MHT in women with a history of hormone-receptor-negative breast cancers [15].

Testosterone in combination with MHT has been investigated for treatment of menopausal symptoms. Except for improved sexual satisfaction, testosterone poses no benefit and comes with multiple risks including detrimental effects on lipid parameters, clitoromegaly, hirsutism, and acne [2, 41–43]. Testosterone alone is currently not FDA approved for use in women [2].

Bazedoxifene (BZA), a SERM combined with conjugated estrogens (CE), belongs to an emerging class of drugs called tissue selective estrogen complexes

(TSECs) and is available in the United States for the treatment of postmenopausal VMS [2]. BZA/CE has apparently neutral effects on the breast according to the 1-year Selective Estrogens, Menopause, and Response to Therapy-5 (SMART-5) trial [44]. Bazedoxifene 20 mg and conjugated estrogens 0.45 and 0.625 mg did not increase mammographic breast density or breast tenderness over the course of 1 year and had a favorable breast-related safety profile [44]. Since the long-term effect of BZA/CE on the breast is unknown, it is contraindicated for women with known, suspected, or past history of breast cancer or estrogen-dependent neoplasia [45].

Overall, existing data remain controversial regarding the risk of breast cancer as it relates to MHT, and use of hormones for menopause management is currently not recommended as a first-line approach for women with a history of breast cancer. However, those failing to achieve respite from non-hormonal interventions can be reassured regarding potential safety of short-term use of MHT in breast cancer survivors to improve quality of life.

Progesterone and Progestin Therapy (PT)

Progesterone-only formulations have also been used off-label for management of VMS. A randomized controlled trial of 109 women showed those treated with a single dose of depot MPA 400 mg had a greater reduction in VMS (79 % versus 55 %) compared to those on venlafaxine 37.5 mg/day for 1 week and then continued on 75 mg/day [46].

As discussed above, progestogens have a special role in protecting the endometrium against endometrial cancer in estrogen users and therefore are most commonly used as an adjunct to estrogen therapy. Systemic use of progestogens has been linked to an increased risk of breast cancer, as previously discussed, and associative studies have implied this risk may be higher for synthetic progestins, such as MPA, compared to natural progesterone [47]. For these reasons, progesterone only is not recommended as a first-line therapy for VMS control in patients with personal history of breast cancer.

The levonorgestrel-releasing intrauterine system (LNG-IUS) has shown promise against tamoxifen-induced endometrial pathology in breast cancer patients and as a mode of PT with minimal systemic exposure. In a review of three randomized controlled trials, LNG-IUS was effective in preventing tamoxifen-induced polyps, without any increase in breast cancer recurrence or association with cancer-induced death [48]. Other studies have shown controversial data on the effects of LNG-IUS use on breast cancer recurrence in patients receiving adjuvant tamoxifen treatment [49]. At present, long-term concerns relating to LNG-IUS use cannot be fully quantified in the breast cancer survivor population; larger and longer follow-up studies are necessary to determine its efficacy and the risk of breast cancer recurrance.

In conclusion, progesterone-only therapy should not be recommended as a first-line therapy for the patient due to her history of breast cancer.

SSRI/SNRI

Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) have been shown to be more effective than placebo in treating VMS. They have been shown to reduce the frequency of VMS by approximately 25–69 % and the composite score of frequency and severity from 27 to 61 % [7]. Paroxetine salt, an SSRI, is the only FDA-approved non-hormonal treatment for VMS at a low dose of 7.5 mg/day [6]. Guthrie et al conducted an analysis of three randomized controlled trials (RCTs) and found that escitalopram, low-dose E2, and venlafaxine showed comparable, albeit modest, reductions in VMS when compared to placebo [50].

Commonly used SSRI regimens for VMS include fluoxetine 20 mg/day, paroxetine salt 7.5 mg/day, paroxetine 12.5–25 mg/day, citalopram 10–20 mg/day, and escitalopram 10–20 mg/day. Commonly used SNRI regimens include venlafaxine 37.5–75 mg/day and desvenlafaxine 100–150 mg/day [1, 6].

Side effects of SSRIs include cardiovascular effects (sinus tachycardia and prolonged QT intervals), sexual dysfunction, suicidal thoughts, weight loss or gain, headache, and agitation. Side effects of SNRIs include nausea, dry mouth, dizziness, and anxiety [6]. Using the lowest effective dose, and tapering therapy over 1–2 weeks on discontinuation, is recommended to reduce risk of withdrawal and relapse of vasomotor symptoms [1, 6]. The risks and benefits of treatment should be reevaluated every 6–12 months due to limited data on long-term use [1].

Importantly, from the perspective of topic under discussion, prescribers must pay due attention to the choice of SSRI/SNRI in patients on tamoxifen therapy. Tamoxifen is metabolized via the cytochrome P-450 2D6 pathway into multiple active metabolites; one main active metabolite being endoxifen [1]. SSRI/SNRIs are also metabolized via this same pathway and may interact with the breakdown of tamoxifen into the metabolites confering chemoprophylaxis against breast cancer. Studies have shown serum tamoxifen levels may be reduced as much as 24–64 % with concomitant SSRI/SNRI use due to metabolism interactions via cytochrome P-450 2D6 [1]. Other studies have shown lower plasma levels of endoxifen when paroxetine is used with tamoxifen [51]. Notably, paroxetine use during tamoxifen therapy for breast cancer has shown increased risk of death from breast cancer [52], reinforcing concern that use of SSRI/SNRIs with tamoxifen may decrease the efficacy of tamoxifen. Certain SSRI/SNRIs have been shown to have variable effects on the inhibition of the CYP2D6 pathway. Strong inhibitors of the pathway include fluoxetine and paroxetine; these drugs may have the greatest potential for interacting with tamoxifen and decreasing its efficacy. Conversely, citalopram, escitalopram, fluvoxamine, sertraline, and venlafaxine are less likely to inhibit the CYP2D6 pathway. Of these weak inhibitors, citalopram and venlafaxine are as effective as some of the strong inhibitors in decreasing VMS and therefore should be used preferentially in concomitant tamoxifen users [53]. It is important to consider the extent of inhibition on the CYP2D6 pathway when considering using an SSRI/SNRI with tamoxifen (Table 16.1).

Table 16.1 Degree of inhibition of CYP2D6 and efficacy versus placebo for hot flashes

Inhibition of CYP2D6 pathway	SSRI/SNRI	Efficacy vs placebo for hot flashes
Strong	Fluoxetine	50 % vs 36 %, $p=0.02$
Strong	Paroxetine	62 % vs 37 %, $p=0.007$
Weak or not at all	Citalopram	49 % vs 23 %, $p=0.0021$
Weak or not at all	Sertraline	36 % vs 27 %, $p=0.03$
Weak or not at all	Venlafaxine	60 % vs 27 %, $p<0.0001$

Adapted from Table 2 [53]

In conclusion, due to the interaction between tamoxifen and certain SSRI/SNRIs, paroxetine use should be avoided for the patient above as it is a strong inhibitor of the CYP2D6 pathway and may decrease the efficacy of tamoxifen on breast tissue. Other SSRI/SNRIs, such as venlafaxine or citalopram, are weak inhibitors of the CYP2D6 pathway and have shown benefit against VMS. These may be safely considered as first-line pharmaceutical approach for managing this patient's VMS.

Gabapentin

Gabapentin is an anticonvulsant and is commonly used to treat neuropathic pain [15]. While not FDA approved for the management of VMS, it has been shown to be more effective than placebo in reducing the frequency of menopausal VMS. Gabapentin 900 mg per day was found to have a 45 % reduction in hot flash frequency and a 54 % reduction in composite score (frequency and severity) of VMS in a small RCT [54]. Both treatment effects were statistically significant when compared to placebo with 29 % and 31 % reductions, respectively [54]. In another small RCT, gabapentin 600 mg was shown to reduce severe-intensity and severe-frequency VMS by 60.6 % and 58.9 %, respectively [55].

Potential side effects include dizziness and drowsiness, which may resolve after 2 weeks of therapy. In addition, weight gain may be seen, and any anticonvulsant may increase suicidal thoughts or behavior [6]. It is recommended to avoid antacid use within two hours of dosing, due to decreased absorption, and to taper the dose on discontinuation [1]. Risks and benefits of treatment and therapy options should be reevaluated every 6–12 months due to limited data on long-term use [7].

Pregabalin is a newer compound that works similarly to gabapentin and may be effective in the treatment of VMS. A randomized controlled trial using pregabalin 75 mg twice a day showed a 65 % decrease in VMS score compared to 50 % with placebo, which may be similar to the efficacies of gabapentin and other SSRI/SNRIs in the treatment of VMS [56].

There are no concerns regarding use of gabapentin in the setting of breast cancer or tamoxifen use, and gabapentin may therefore be considered as an effective option when hormone therapy is not desirable. A trial of gabapentin can safely be considered for the patient above and holds promise of reducing the magnitude of symptom burden to an appreciable degree.

Clonidine

Clonidine is an antihypertensive agent that may have a mild effect on VMS. It is thought that clonidine may decrease VMS by reducing peripheral vascular reactivity, though evidence is contradictory regarding its efficacy [6]. A small RCT showed clonidine and venlafaxine have similar efficacy in the reduction of VMS, although a more immediate reduction of hot flash scores was seen in the venlafaxine group [57]. A meta-analysis of ten RCTs demonstrated no improvement in the severity of VMS in 6 of the 10 RCTs, though improvement was seen in the remaining four RCTs [58].

Potential side effects may include hypotension, difficulty sleeping, dry mouth, constipation, itchiness (with use of patch), and drowsiness [6]. Nonetheless, it is generally well tolerated at low doses. Dosing formulations include 0.05 mg twice daily to 0.1 mg twice daily or the clonidine patch, which delivers 0.1 mg daily. Weaning the dose on discontinuation is recommended to avoid rebound hypertension and other side effects [1].

Clonidine is a potential option for the patient above because it is a non-hormonal therapy and there are no concerns for use with a history of breast cancer or being on tamoxifen therapy. However, the efficacy of clonidine is less than that of other non-hormonal options, including SSRIs/SNRIs and gabapentin. Therefore, it would likely not be the most effective selection for the patient above. It should be considered a second-line approach, in the event that trial of gabapentin or a non-paroxetine SSRI is contraindicated or fails to offer significant benefit.

Complementary and Alternative Medicine (CAM) Therapies

Many alternative and complementary therapies have been investigated for the treatment of VMS of menopause with inconsistent results [6]. On review of evidence in the English literature, there has been no difference between placebo and any of the herbal remedies such as black cohosh, dong quai root, evening primrose oil, kava kava, ginseng root, vitamin E, or omega-3 fatty acids [1]. There is a high placebo effect observed when studying the efficacy of therapies for VMS, which may obscure the interpretation of results.

In some studies, phytoestrogens, which are plant-derived substances with estrogenic biologic activity, such as soybean isoflavones, have shown a statistically significant decrease in VMS compared to placebo. A systematic literature review from Eden et al. in 2012 concluded isoflavones are slightly superior than placebo, but the degree of effect was small and not clinically significant [59]. Dang gui bu xue tang, a Chinese herb, was found to be more effective than placebo in one study in the treatment of mild VMS [60]. Notably, caution is advised when considering use of CAM agents in the setting of hormone-sensitive cancers, as implications for tumor recurrence and risk for metastases are entirely unclear [1].

In summary, CAM strategies would not be recommended for our patient due to lack of evidence displaying efficacy, possibility for estrogenic effects with some agents such as phytoestrogens, and unquantifiable implications for her personal risk for breast cancer recurrence.

Other Strategies

Eszopiclone is a hypnotic medicine that has been shown to decrease nocturnal VMS [1] as well as improve symptoms of depression and anxiety, therefore improving overall quality of life in peri- and postmenopausal women [61]. Eszopiclone 1–3 mg/day is commonly used in breast cancer survivors and is especially ideal for patients with sleep initiation difficulties due to short half-life of ~1 h [62].

Stellate ganglion block (SGB), a minimally invasive intervention, was shown to decrease VMS by 45–90% in four uncontrolled, open-label studies [63–66]. It involves an injection of a local anesthetic into the stellate ganglion at the level of the sixth cervical vertebra. SGB shows great potential as a means of reducing the number of hot flushes and night awakenings in breast cancer survivors [67, 68]. In addition, SGB may be an effective treatment for breast cancer-related lymphedema [69]. Overall, efficacy data are variable, and more clinical trials need to be performed to further determine the efficacy and safety profile of this novel technique in the treatment of VMS [70].

Case

An ideal treatment strategy for a woman with moderate or severe VMS should decrease VMS without detriment to breast tissue and the endometrium and additionally have favorable effects on the vaginal mucosa, increase bone mass density, and decrease the risks of coronary heart disease (CHD), venous thromboembolism (VTE), and stroke. There are many special considerations and risks involved in the management approach for treating VMS in breast cancer survivors. Treatment strategies should be targeted to best treat the patient based on their unique risk profile.

After detailed discussion of the available options and review of individualized risks versus benefits for each strategy, the patient opted for a trial of gabapentin while initiating lifestyle modifications. If gabapentin therapy had failed, a trial on a specific SSRI/SNRI (a weak inhibitor of the CYP2D6 pathway such as venlafaxine or citalopram) was planned as an appropriate next step with trial of MHT as a last resort in the event that all non-hormonal options failed to provide relief. The patient verbalized being comfortable with the outlined systematic approach and was initiated on gabapentin 300 mg daily with significant relief of VMS and improvement in nocturnal sleep. She likewise found it easier to focus during the day, and her work

performance was restored. She continued with tamoxifen treatment for breast cancer without complications or undue adverse effects. She continued gabapentin therapy for one and a half years, at which time she was weaned off without difficulty or side effects.

Clinical Pearls

- Vasomotor symptoms are the second most common complaint during menopause, and up to 75 % of women will experience VMS.
- Women undergoing therapy for breast cancer are at an increased risk of developing moderate or severe VMS, and this may affect their ability to continue breast cancer treatment.
- Bothersome VMS can result from adjuvant therapies utilized in the management of breast cancer (SERMs, aromatase inhibitors, and ovarian ablation modalities). Menopausal hormonal therapy is the most efficacious of available treatments for management of VMS, but may hold risk for breast cancer recurrence, and is to be avoided as first-line approach to VMS management in breast cancer survivors.
- SSRIs/SNRIs and gabapentin are effective non-hormonal options for VMS in breast cancer survivors, but certain agents such as paroxetine and fluoxetine are to be avoided in tamoxifen users.
- CAM strategies have not been shown to be superior to placebo in the treatment of VMS. Certain agents such as phytoestrogens have been shown to have a mild estrogenic effect in some studies and are to be avoided in breast cancer survivors.
- Current recommendations prioritize non-hormonal strategies as first-line approaches for menopausal symptom management in breast cancer survivors.
- Continued research is necessary to further innovate and design safer and more effective treatment options for hormone-sensitive cancer survivors suffering from menopausal symptoms.

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Hormonal Therapy for Menopausal Symptoms in Gynecologic Cancer Survivors

17

John Durfee

Case Presentations

Case #1 A 47-year-old underwent robotic hysterectomy, bilateral salpingo-oophorectomy, and staging for grade 1 endometrioid endometrial cancer. Final pathology showed a 4 cm tumor, 1/23 mm depth of myometrial invasion, no lymphatic or vascular space invasion, negative washings, and 42 negative lymph nodes. She started experiencing bothersome vasomotor symptoms (hot flashes and night sweats) within days after surgery. At her 1-month post-operative visit, she acknowledged severe bother from her symptoms and inability to sleep and was prescribed zolpidem 5 mg nightly for insomnia. At 4 months, she continued to experience severe, frequent hot flashes, with ongoing sleep disruption without much benefit from the prescribed zolpidem regimen.

Case #2 A 42-year-old underwent abdominal hysterectomy, bilateral salpingo-oophorectomy, and debulking of large omental and peritoneal tumor masses; final pathology showed a serous borderline tumor with noninvasive implants. At the end of the surgery, she had innumerable remaining 2–3 mm tumor lesions scattered on the bowel and mesenteric surfaces, but no residual large lesions. Due to the histology, adjuvant chemotherapy was not indicated. She developed hot flashes within a month after the surgery which were bothersome, though not extremely so.

The cases detailed above highlight symptom burden faced by patients rendered surgically menopausal in the setting of gynecological cancer and management considerations that treating healthcare providers must consider when helping to optimize

J. Durfee, MD, FACOG
Department of Obstetrics and Gynecology, Boston University School of Medicine, Boston, MA, USA
e-mail: John.Durfee@bmc.org

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the quality of life for this population. Potential options for therapy, special considerations, side effects, and treatment regimens for vasomotor symptom management in gynecological cancer survivors will be discussed.

Overview of Hormone Replacement Therapy (HRT) in Patients with a History of Gynecologic Cancer

Approximately 25 % of gynecologic cancers occur in reproductive age women [1], many of whom will undergo an abrupt transition into menopause as a result of surgery, radiation therapy, or chemotherapy. While the ovaries in premenopausal women undergoing surgery for cervical cancer can often be spared [2], the surgical management of ovarian and endometrial cancers most often includes a bilateral salpingo-oophorectomy (BSO). Women undergoing pelvic radiation as primary treatment for cervical cancer will also lose ovarian function unless the ovaries are surgically transposed out of the radiation field prior to treatment [3]. An abrupt loss of ovarian function in young women is often associated with severe vasomotor symptoms (VMS), adversely impacting the quality of sleep and compounding their distress. Partially effective nonhormonal therapies can help and will be discussed elsewhere in this book. This chapter will concern itself with the role of estrogen therapy in the treatment of VMS in gynecological cancer survivors.

There are no definitive clinical data proving that estrogen therapy (ET) in patients with a history of uterine or ovarian cancer increases the risk or rapidity of tumor recurrence. There are, however, theoretical reasons for concern, including the presence of estrogen receptors in many gynecologic tumors, particularly in endometrial, ovarian, and uterine mesenchymal malignancies, as detailed below. In counseling those who might seek HRT to ameliorate VMS, providers may find useful guidance in concepts that emerged from the use of adjuvant antiestrogen therapy after surgery for breast cancer. It is clear that such therapy in women with estrogen receptor-positive breast cancer does improve disease-free survival when measured at an arbitrarily chosen point in time [4]. What remains uncertain is whether this clinical benefit of antiestrogen therapy is a function of enhanced death of residual microscopic disease or just a delay in growth and ultimate clinical recurrence. By extension of this argument to survivors of hormone receptor positive gynecological cancers, it also remains unsettled whether withholding hormone therapy will prevent a recurrence, or just delay its onset if one is destined to occur. At this point in time, there is no firm clinical evidence that hormone replacement therapy can cause a recurrence of a gynecologic cancer that would not have otherwise occurred, given adequate survival. There remains a clinical concern, however, that HRT could stimulate an earlier recurrence in survivors of hormone receptor-positive gynecological cancers, and this chapter will examine the evidence pertaining to specific gynecologic cancers.

Another important consideration for gynecologic cancer survivors contemplating hormone replacement therapy is the increased risk of venous thromboembolism (VTE) associated with such therapy and more specifically with standard estrogen

dose formulations. This is particularly relevant to those whose baseline VTE risk is already elevated due to residual or active cancer, recent surgery, or ongoing adjuvant chemotherapy [5]. The potential additional risk of VTE should be assessed carefully with particular attention to dose and route of therapy in gynecologic cancer patients for whom estrogen replacement is felt to be necessary.

Endometrial Cancer

Endometrial cancer is well known to be a hormone-related malignancy, the risk of which is increased with long-term exposure to high levels of unopposed estrogen, be it from exogenous sources or endogenous ones that commonly prevail in obese women and those with chronic anovulation [6].

According to the Surveillance, Epidemiology, and End Results program of the National Cancer Institute (SEER), nearly 15 % of endometrial cancers occur in women under 50 years of age [7], and this percentage is likely to rise as obesity rates in young women continue to climb. Given the role of estrogen in the genesis of most endometrial cancers, there is a natural and justifiable concern about hormone replacement in endometrial cancer patients. This concern is supported by the fact that endometrial cancers express estrogen receptors, with a frequency that is related to histologic grade and type. In one immunohistochemical study, estrogen receptor (ER) positivity was localized within the malignant epithelium in 92 % of grade 1 endometrial cancers, 62 % of grade 2 tumors, and 12 % of grade 3 tumors [8]. In another study, well-differentiated endometrial adenocarcinomas expressed ER and progesterone receptors (PR) with higher frequency, and in much higher density, than poorly differentiated tumors [9]. Even in endometrial cancers not considered hormonally related, such as papillary serous tumors, ER was expressed in 30 % of cases [10]. In a randomized, placebo-controlled trial examining ET after surgery for endometrial cancer, 1,236 patients with stage 1 and 2 tumors were randomized to ET versus placebo [11]. The trial was closed prematurely after results from the Women's Health Initiative (WHI) hormone trials were released making it difficult to accrue new patients and to maintain those in the treatment arm on estrogen [12]. Upon data analysis, the median age of subjects was 57 years, and the median follow-up duration was 3 years. Ninety-one percent of study subjects had grade 1 or 2 tumors, 15 % of those on ET had discontinued it within 6 months of enrollment, and only 41 % of patients randomized to the ET arm remained compliant with their assigned therapy for the entire treatment period. The cancer recurrence rates were 2.3 % in the ET arm and 1.9 % in the placebo arm, which was not a statistically significant difference. In addition, a number of smaller retrospective studies [13–16] have also found no worse outcomes from endometrial cancer in those treated with ET compared to those who were not, although conclusions are limited by selection bias inherent in retrospective study designs. In aggregate therefore, the existing clinical evidence provides no conclusive evidence regarding the absolute safety of ET use in endometrial cancer patients after surgery. However, the evidence does lend support to the position that symptomatic endometrial cancer patients whose

baseline recurrence risk after surgery is low may be reasonably offered ERT for symptom relief after careful consideration and discussion of the pros and cons.

Progestin therapy has been used, with some success, as a treatment for patients with recurrent endometrial cancer [17]. Progestins are also effective for treatment of menopausal VMS [18]. Whether progestin added to estrogen could enhance efficacy against VMS and reduce recurrence risk in symptomatic endometrial cancer patients is an intriguing though speculative idea at this time. Ayhan et al. [19] prescribed daily 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate to 50 endometrial cancer patients who initiated therapy 4–8 weeks after surgery. Forty-eight patients took the medication for at least 24 months with no documented recurrences in any of them. These theoretical advantages of progestins in hysterectomized endometrial cancer patients should be balanced, however, by concerns about increased breast cancer and cardiovascular risks associated with combination estrogen-progestin use, as were evident in the WHI estrogen plus progestin trial [12]. In the absence of firm clinical data about superior recurrence outcomes with combination estrogen-progestin therapies, this author prefers ET alone in carefully selected and counseled patients whose probability of disease recurrence is low.

There is also a lack of data regarding vaginal estrogen use in patients with a history of endometrial cancer. A study in breast cancer patients compared 75 users of vaginal estrogen, without oral estrogen, to matched nonusers and found no increased risk of recurrence, and clinicians treating gynecologic cancer patients may take some reassurance from this study [20]. Rahn and colleagues in 2014 reported a systematic literature review on vaginal estrogen and noted that with the exception of high dose vaginal estrogen cream (2 g daily of conjugated equine estrogen), other formulations of vaginal estrogen therapy that were tested did not increase serum estrogen levels beyond the normal postmenopausal range [21]. Based on these data, and the lack of demonstrated elevated recurrence risk even with systemic estrogen in endometrial cancer patients, low-dose vaginal estrogen appears to be a reasonable treatment for endometrial cancer survivors with symptoms of vulvovaginal atrophy resulting from estrogen deficiency.

Epithelial Ovarian Cancer

Symptomatic menopause in ovarian cancer patients is not uncommon, because ovarian cancer surgery often includes BSO, and close to 30 % of new ovarian cancer patients are less than 50 years old [22]. Although most patients undergoing chemotherapy for ovarian cancer will have already undergone BSO, an occasional patient may have preservation of one normal ovary, but needs postoperative chemotherapy due to final pathologic findings, and chemotherapy has toxic effects on the ovaries and can induce menopause, either temporary or permanent. While ovarian cancer is not thought of as a hormone-dependent cancer to the same degree that is endometrial cancer, there are several theoretical concerns about HRT use in ovarian cancer patients, which have originated from epidemiologic studies and laboratory investigations.

From an epidemiologic point of view, an association between postmenopausal HRT and ovarian cancer risk has been known for some time. In a recent meta-analysis of 52 epidemiologic studies, the relative risk (RR) of ovarian cancer among current and recent HRT users was significantly higher than past and never-users [23]. The RR was 1.37 (95 % CI 1.29–1.46; $p < 0.0001$) and the increased risk was similar for estrogen-only and estrogen-progestin users, with the highest risk in current users. When data were stratified by histologic types, an increased RR was noted among HRT users for serous (RR 1.53, 95 % CI 1.40–1.66; $p < 0.0001$) and endometrioid (1.42, CI 1.20–1.67; $p < 0.0001$) cancers, but not for mucinous and clear-cell tumors. This discrepancy is interesting and relevant given that serous and endometrioid tumors are the ovarian cancers most likely to express estrogen receptors as discussed below. While these epidemiologic findings do support a possible cause–effect relationship between HRT and ovarian cancer, caution is advised due to inherent study limitations, including selection bias in two of the large studies that dominated the meta-analysis [24, 25]. Nevertheless, the epidemiologic evidence does raise concerns about HRT potentially provoking an earlier clinical recurrence in patients with occult ovarian cancer. It should be noted, though, that hormonal mechanisms possibly involved in new ovarian tumor initiation are likely different from those that could promote recurrence of treated ovarian cancer.

The expression of hormone receptors in ovarian cancers has been another source of concern when HRT is being considered. The rate of ER positivity varies markedly depending on the histology of the tumor, with 64 % of serous, 56 % of endometrioid, and 17 % of mucinous ovarian tumors expressing ER according to one series [26]. In a particularly large multisite immunohistochemical and microarray study which included 2,933 patients with invasive epithelial ovarian cancer, strong expression of ER alpha and progesterone receptors was found in over 60 % of serous and endometrioid tumors, but only in about 15 % of mucinous and clear-cell tumors [27]. Other studies have corroborated these findings and found that ER expression in serous tumors is also related to degree of tumor differentiation (and thus inversely with tumor aggressiveness), with expression rates exceeding 90 % in borderline tumors, greater than 50 % in grade 1 tumors, and under 30 % in grade 2–3 tumors [28, 29]. Furthermore, tissue culture studies on ER-positive ovarian cancer cell lines demonstrated increased growth with an addition of 17-beta-estradiol, which was not observed in ER-negative cell lines and which was blocked with addition of tamoxifen, a selective estrogen receptor modulator [30]. Another tissue culture study demonstrated that the growth rate with estradiol was enhanced in ovarian cancer cell lines expressing ER alpha but not ER beta [31].

In the clinical setting, the use of antiestrogen therapies in women with recurrent ovarian cancer has been attempted, with variable results. One study reported a 17 % partial CA125 response rate (>50 % decrease in the serum level) and a 9 % partial radiologic response rate to an aromatase inhibitor (letrozole), with subgroup analysis showing higher response rate correlating with higher tumor expression levels of ER [32]. Another study however showed only a 2 % partial response rate to another aromatase inhibitor anastrozole, with a mixture of ER-positive and ER-negative tumors [33]. As to borderline serous ovarian tumors, there is paucity of data, but in

one study, two women with relapsed chemotherapy-resistant disease were reported to achieve complete long-term remission with anastrozole therapy [34]. At present, it is appropriate to conclude that aromatase inhibitors have real potential value in the treatment of grade one ovarian cancers (specifically endometrioid and serous tumors) and serous borderline ovarian tumors, but further study is warranted.

While tumor response to antiestrogens does not prove that ET will of necessity accelerate growth of tumor in patients, it does lend some support to that concern. On the other hand, studies that have directly analyzed HRT use in ovarian cancer patients do provide some reassurance. In one retrospective analysis [35], 78 ovarian cancer patients treated postoperatively with HRT were compared with 295 patients who were not treated with hormones; ET alone was used in 32 patients, estrogen and progestin in 38 patients, and progestin or testosterone alone in 8. Cox regression analysis was done to address differences in prognostic factors. There was no statistically significant difference between the groups in terms of survival or disease-free survival. In a randomized trial of 130 patients with advanced stage, high-grade epithelial ovarian cancer [36], patients were randomized to oral conjugated estrogen (0.625 mg daily), or not, after surgery. Nineteen patients were lost to follow-up or stopped taking the estrogen or started estrogen in the group randomized to no estrogen. After more than 4 years of minimum follow-up, there was no adverse effect found in the estrogen group in terms of recurrence rate, disease-free survival, or overall survival. In 2015, the results of a randomized trial with a median follow-up of 19 years in surviving patients were reported [37]; 150 patients with any stage ovarian cancer were randomized to HRT or no HRT after surgery. The median age was 59 years. The hormone replacement was planned for a minimum of 5 years, if tolerated; 53 patients received estrogen alone, 19 patients received estrogen plus norgestrel. Forty-six out of 72 patients discontinued the HRT at some point during the follow-up period, and the median estimated time taking the HRT for patients assigned to this arm was 1.14 years. Sixty-seven percent of the patients in the HRT group died of ovarian cancer versus 75 % in the control group with the overall survival being significantly higher in the HRT group (hazard ratio, 0.63; 95 % CI, 0.44–0.90; $p = .011$). The authors concluded that women with severe menopausal symptoms after treatment for ovarian cancer can safely take HRT without compromising their survival.

Ovarian Granulosa Cell Tumors

Adult granulosa cell tumors (GCTs) are uncommon ovarian cancers, presenting in both premenopausal and postmenopausal women. They are indolent tumors which usually present at an early stage, and while most are cured with surgery, very late recurrences have been reported [38]. Between 32 and 66 % of GCTs are ER-positive [39], leading to concerns about stimulating tumor recurrence with ET in patients who have undergone BSO as part of treatment. The typically long latency period makes the issue of provoking an earlier recurrence more problematic, and reports of tumor response to antiestrogenic therapy [39] also support a degree of concern regarding potential pathophysiological relevance of estrogen for these tumors.

The published literature, consisting of case series and case reports including a total of 31 patients, regarding hormonal therapy in advanced-stage and recurrent ovarian GCTs was the subject of a recent review [39]. Treatments included a wide variety of hormonal agents, including aromatase inhibitors, tamoxifen, progestins, and GnRH agonists (goserelin and leuprolide). Overall tumor response rate to these agents was 71 %. Of the cases reviewed, there were seven patients with ER and PR status reported; three were ER-positive and four ER-negative, and six were PR-positive and one PR-negative. The aromatase inhibitors showed the best response rate, though limited by small numbers (nine patients). Correlation with hormone receptor positivity and response was not demonstrated, although again this interpretation is limited by small numbers. The authors concluded that overall study quality on this subject was poor and that prospective studies are needed to draw firm conclusions.

This author has treated one 45-year-old, premenopausal patient with ovarian GCT with ET for severe menopausal symptoms following hysterectomy and BSO, after extensive discussion of risks, benefits, and limitations of existing data on the subject. It should be acknowledged, though, that other authors [1] have advocated avoidance of ET in these patients.

Cervical Cancer

Removal of ovaries is generally not necessary in the surgical management of squamous cell carcinomas of the cervix, but adenocarcinomas of the cervix have a higher rate of metastasis to the ovaries, so some premenopausal patients, particularly with larger tumors, will undergo bilateral oophorectomy [2]. Since this may lead to symptomatic surgical menopause, the question of HRT safety can arise. Cervical cancers are not considered hormone responsive [1], so HRT can be offered in otherwise appropriate cases. Radiation therapy is also a common treatment in cervical cancer, either as a primary modality or an adjuvant after hysterectomy in those with node-positive disease. Such radiation will destroy the endocrine function of the ovaries unless they are surgically transposed out of the radiation field. Primary radiation therapy is also likely to obliterate the endocervical canal making endometrial biopsies technically challenging and theoretically causing delays in the diagnosis of an early endometrial cancer. For this reason, unopposed ERT without progestins cannot be recommended in irradiated non-hysterectomized cervical cancer patients.

Uterine Mesenchymal Tumors

Uterine sarcomas are rare tumors and most patients are over the age of 50 [40], but occasionally the question of hormone replacement can arise in a symptomatic patient after hysterectomy and bilateral oophorectomy. Uterine sarcoma nomenclature has evolved, such that leiomyosarcoma (LMS) is considered a high-grade malignancy, whereas tumors with concerning histological features but not meeting

diagnostic criteria for LMS can be diagnosed as smooth muscle tumors of uncertain malignant potential (STUMP tumors) [41]. Nearly half of uterine mesenchymal tumors do express estrogen and progesterone receptors, and in keeping with the general tendency observed in other gynecologic cancers, the more aggressive LMS tumors express those receptors either less frequently or with lower intensity than STUMP tumors and benign fibroids [42, 43]. In studies that have looked at clinical outcomes as a function of hormone receptor status, one study showed better survival in receptor-positive LMS tumors compared to receptor negative tumors [42], but another smaller study found no such correlation [43]. Thanopoulou et al. [44] found tumor response in 12 % and stabilization of disease in 50 % of 16 patients treated with aromatase inhibitors for advanced uterine LMS with positive ER/PR and measurable disease. Prolonged progression-free survival was more likely with lower grade sarcomas and higher expression of estrogen receptors.

It is not clear at present whether hormonal stimulus is an important factor in the growth and recurrence of LMS. It is logical to think that some tumors with E2 receptors, or at least those with stronger receptor expression, could have their growth modulated to some degree by hormones, in which case HRT after oophorectomy and symptomatic menopause could conceivably worsen the patient's outcome. In a review of soft tissue sarcomas, Grimer et al. [40] write of uterine sarcomas that "some low grade tumors may be sensitive to estrogen deprivation, although there are very few published data on this situation."

Estrogen replacement in STUMP tumors may risk stimulating recurrence, since subclinical disease may be quite indolent, though most patients with STUMP tumors do not recur [45]. Estrogen replacement seems unlikely to substantially affect the outcome in patients with true LMS, who in most cases are either cured by surgery or face rapid progression of metastatic tumor. Conceivably one could consider the presence or absence of estrogen receptors to help decide about offering ERT in patients with apparently early stage LMS after surgery which results in severe menopausal symptoms.

However, given the high rate of recurrence of LMS, probably 50 % or higher even in disease which is initially apparently confined to the uterus [46], there should be some concern with promoting venous thromboembolism in patients with subclinical tumor by prescribing estrogen, since uterine sarcomas are particularly thrombogenic relative to uterine cancers generally [47]. As well, the recurrence rate of these tumors is very high, usually leading to death after recurrence [46], so both doctor and patient may want to consider the impact of wondering if estrogen might have accelerated her recurrence.

Endometrial stromal sarcoma (ESS) is a rare tumor, but worth mentioning since these tumors are generally considered hormone sensitive. Ten to twenty-five percent of ESS patients are premenopausal [48]. ESS tumors generally express ER and PR [49], whereas undifferentiated endometrial sarcomas do not [40]. Chu et al. [50] reported that four of five patients with ESS recurred after ERT, whereas four of eight patients with retained ovaries recurred. Four of eight patients with recurrence experienced a complete tumor response with progestin treatment, demonstrating that hormonal manipulation can affect outcome in these patients. Thanopoulou et al.

reported a 46 % objective tumor response in ESS to aromatase inhibitor, progestin, or GnRH analogue [49]. Based on these studies and others, estrogen replacement after bilateral salpingo-oophorectomy for ESS is considered contraindicated [1, 40, 49].

Case Management and Outcomes

Case #1 After the discussion of pros and cons, this 47-year-old with endometrial cancer was prescribed oral estrogen with marked improvement in her symptoms. It was discussed that theoretically she could experience an earlier recurrence of tumor if she still had tumor cells, but that this is not a proven phenomenon, and that stroke and VTE risk are at least temporarily elevated with the ERT though with a low absolute risk. This author's comfort in prescribing ERT for her was based in large part on the randomized trial [11], showing no statistical difference in recurrence rates with ERT, and also on the very low likelihood of recurrence in her particular case.

Case #2 For this 42-year-old with serous borderline tumor of the ovary with residual tumors after surgery, it was recommended to her that she not take systemic estrogen due to the ongoing presence of tumor cells that could be stimulated by estrogen and lead to earlier symptomatic recurrence. This was based largely on known high levels of estrogen receptors in serous borderline tumors of the ovary and case reports showing tumor response to antiestrogenic therapy. The option of testing her tumor for ER to inform a decision about ERT was discussed but declined. It is hoped that the decrease in estrogen after loss of both ovaries could potentially shrink the tumors, and it was decided to reserve aromatase inhibitors as a possible future therapy if and when tumors cause symptoms again. She declined nonhormonal pharmacologic treatment. At 11 months postoperatively she was without clinical evidence of tumor and feeling well overall, though still having hot flashes.

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Management of Osteoporosis in Postmenopausal Breast Cancer Survivors

18

Xuezhi Jiang, Peter F. Schnatz, and Risa Kagan

Case Presentation

A 55-year-old Caucasian postmenopausal woman with BMI of 22.5 kg/m^2 presents to the clinic for follow-up to discuss the results of her recent dual-energy X-ray absorptiometry (DXA) bone mineral density (BMD) scan. She has a personal history of premenopausal early-stage hormone receptor-positive breast cancer at age 47 and a family history of parental hip fracture. Following her initial breast cancer treatment, she received tamoxifen for 5 years (Age 47–52) followed by anastrozole (an aromatase inhibitor) until the current time. The DXA scan reports *T*-scores of −1.8 at the total hip and −1.6 at the lumbar spine. What would be your preferred management?

X. Jiang, MD, PhD, FACOG, NCMP
The Reading Hospital, Department of ObGyn, Reading, PA, USA
e-mail: Daniel.Jiang@readinghealth.org

Sidney Kimmel Medical College of Thomas Jefferson University, Departments of ObGyn, Philadelphia, PA, USA

P.F. Schnatz, DO, FACOG, FACP, NCMP
Internal Medicine, Reading, PA, USA

Internal Medicine, Philadelphia, PA, USA

The Reading Hospital, Department of ObGyn, Reading, PA, USA

Sidney Kimmel Medical College of Thomas Jefferson University, Departments of ObGyn, Philadelphia, PA, USA

R. Kagan, MD, FACOG, CCD, NCMP (✉)
East Bay Physicians Medical Group, 2500 Milvia Street, Berkeley, CA 94704, USA

University of California, Department of Obstetrics, Gynecology, and Reproductive Sciences, San Francisco, CA, USA
e-mail: kaganr@sutterhealth.org

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A. Use Fracture Risk Assessment Tool (FRAX) to assess her 10-year fracture risk prior to pharmacological intervention
B. Repeat DXA in 1–2 years with a plan to initiate antiresorptive treatment if there is a significant decrease in BMD (e.g., annual BMD decrease ≥5 %).
C. Start antiresorptive therapy immediately.

Management deliberations for the patient detailed above include considerations for fragility fracture in the setting of plausible genetic predisposition with additive iatrogenic risk. The relevance of bone mass and metabolism for fracture risk is being covered elsewhere in this textbook. This chapter will focus on evaluation, risk quantification, and treatment options and provide an overview of management approach to the case.

Assessment and Diagnosis

The risk of bone loss and fractures increases in women with breast cancer regardless of skeletal metastasis, age, and menopausal status [1, 2]. In addition to the systematic secretion of parathyroid hormone-related protein (PTHrP), which is expressed in breast cancer tissue [3, 4], breast cancer treatment and treatment-induced menopause likely increase the risk of bone loss and fractures [5–7]. Multiple studies including a meta-analysis have established that high bone mineral density (BMD) was considered one of the risk factors for developing breast cancer [8, 9]. Although the risk of accelerated bone loss and fracture increases after breast cancer diagnosis, these patients may also start with a higher baseline BMD. It is an important research question to ask whether a diagnosis of breast cancer is an independent risk factor for osteoporosis and osteoporotic fractures, regardless of baseline BMD. Due to the accelerated rate of bone loss associated with breast cancer treatments (aromatase inhibitors [AI] therapy, premature ovarian suppression, surgical ablation, or chemotherapy if indicated), osteoporotic fracture prevention, including pharmacotherapy in this patient population, might be different from what is generally recommended for non-cancer postmenopausal women with osteoporosis. In addition, tamoxifen, the most widely used endocrine treatment for breast cancer worldwide, has a different bone effect in pre- and postmenopausal women [10]. In premenopausal women, tamoxifen predominantly has an antiestrogenic effect due to high levels of circulating estrogen from the ovaries in this population, which causes an increased bone loss at a rate of 1–2 % for 1–2 years; however, this effect is not persistent through 5 years of tamoxifen therapy [11]. In contrast to premenopausal women, however, use of tamoxifen protects against bone loss in postmenopausal women [12]. This patient was treated with tamoxifen during her pre- and perimenopausal transition and early postmenopausal years, the final effect of tamoxifen on her bone health, therefore, is unclear. After 5 years use of tamoxifen and 3 years use of an AI, she

has evidence of low bone mass at both the hip and lumbar spine regions. Unfortunately, she did not have a baseline DXA prior to the initiation of her breast cancer treatment. Therefore, her DXA testing is unlikely to appreciate the net effect of breast cancer diagnosis and subsequent treatment on her BMD. While recognizing that because of ongoing AI therapy, she is at an increased lifetime risk of progression to osteoporosis and for skeletal fractures compared with a generally healthy postmenopausal woman with low bone mass (Table 18.1) [13, 14]; this case raises questions of how best to manage this patient to optimize and protect her bone health and reduce her risk for fragility fractures.

Table 18.1 Summary of risk factors for fragility fracture [13, 14]

Risk factors	
Advanced age	
Female gender	
Personal history of fragility fracture as an adult	
Parental history of hip fracture	
Lifestyle factors	Vitamin D insufficiency
	Low calcium intake
	Smoking (active or passive)
	Alcohol (3 or more drinks/day)
	Falling
	Inadequate physical activity/immobilization
	Thinness/low body mass index
Medical Disease	Osteoporosis
	Rheumatoid arthritis
	Malabsorption (celiac disease, inflammatory bowel disease, gastrointestinal surgery, etc.)
	Cystic fibrosis
	Hyperparathyroidism
	Diabetes mellitus
	End-stage renal disease
	Sickle cell disease
Medications	Oral glucocorticoids ≥5 mg/day of prednisone for ≥3 months (ever)
	Aromatase inhibitors
	Tamoxifen® (premenopausal use)
	Anticoagulants (heparin)
	Androgen deprivation agents
	Anticonvulsants
	Cancer chemotherapeutic drugs
	Proton pump inhibitors
	Selective serotonin reuptake inhibitors (SSRIs)
	Thiazolidinediones

Management

Lifestyle and Dietary Interventions

Weight-bearing exercise and calcium/vitamin D supplementation might not be sufficient to prevent AI-induced bone loss and fracture [15, 16]; however, such supplementation in breast cancer survivors may help improve overall bone health [17]. Vitamin D deficiency is quite prevalent in the general population and also among postmenopausal breast cancer patients [18–20]. If patients are on a bisphosphonate for skeletal protection, clinicians must recognize that the antiresorptive action of bisphosphonates will be attenuated by low-serum concentration of vitamin D [21]. Given that many patients have unrecognized vitamin D deficiency at the time of their breast cancer diagnosis [22], assessment of baseline serum vitamin D concentration and evaluation of compliance with calcium/vitamin D dietary and supplements are imperative, although there is no guideline on routine baseline assessment of 25(OH)D levels in breast cancer population. A serum 25(OH) D concentration greater than 30 ng/mL is generally considered to be an adequate target value; however, the accuracy of measurements varies between individual laboratories and between different assays. The efficacy of vitamin D on fracture prevention among breast cancer patients is also not well studied.

Fracture Risk Assessment Tool (FRAX)

FRAX was developed by the World Health Organization (WHO) to help identify and counsel those over 40 without osteoporosis, who nevertheless may be at high risk for skeletal fracture. Pharmacotherapy intervention is recommended when the 10-year risk of a hip fracture is 3 % or higher or when the risk of a major osteoporotic fracture at all sites (hip, spine, forearm/wrist, and shoulder) is 20 % or higher. While this tool is helpful, it is far from perfect. A meta-analysis of seven large population-based prospective studies including over 50,000 subjects have assessed the predictive value of FRAX and found it to be poor. Using current intervention thresholds, the pooled sensitivity of FRAX for predicting major osteoporotic fractures within 10 years was 10.25 % [CI 3.76–25.06 %] and 45.70 % [CI 24.88–68.13 %] for predicting hip fractures [23]. In other words, FRAX may underestimate the risk of fractures and leave a substantial number of treatment candidates untreated using the above-recommended intervention thresholds. Notably, FRAX is not designed for fracture risk assessment in women with breast cancer receiving AI therapy and may substantially underestimate the risk of fractures in this population. Indeed, AI-associated bone loss (AIBL) occurs at more than twice the rate of BMD loss associated with natural menopause [24]. Besides a decreased BMD, bone microarchitecture measured by the trabecular bone score (TBS) was also significantly decreased at the lumbar spine and the hip after 2 years of AI (anastrozole) treatment [5]. As a result, women receiving AI therapy for breast cancer, like the patient being discussed, are at increased risk for fractures and particularly for acute

fracture risk during active AI treatment [25, 26]. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, the annual fracture rate in patients receiving anastrozole for breast cancer was about twofold higher than the fracture rate in healthy, age-matched postmenopausal women with osteopenia (2.2% vs. 1.3%) [27]. Our patient has been on an AI for 3 years, and although she is not osteoporotic and does not meet FRAX treatment threshold (FRAX 10 years probability of major osteoporotic fracture = 14%, hip fracture = 0.8%), according to most treatment guidelines (Table 18.2), this patient belongs to a high-risk group and should receive pharmacologic fracture reduction therapy; a bisphosphonate would be an appropriate choice [11, 15, 28–31].

Fracture Prevention Treatments in Breast Cancer Survivors

Bisphosphonates

Bisphosphonates work effectively to inhibit osteoclast-mediated bone resorption. Bisphosphonates are a first line pharmacotherapy for fracture prevention. The commonly used bisphosphonates in clinical practice include alendronate, ibandronate, risedronate, and zoledronic acid (Table 18.3) [32], of which zoledronic acid is the most potent osteoclast inhibitor and has been by far mostly studied for fracture prevention in breast cancer survivors [33].

Although oral bisphosphonates have been shown to prevent AIBL in several small-scale prospective studies [34–36], high-quality evidence derived from four randomized controlled trials (Z-FAST, ZO-FAST, E-ZO-FAST, ABCSG-12) with more than 2,500 women with breast cancer receiving an AI supports the efficacy of intravenous zoledronic acid (4 mg every 6 months) for prevention of AIBL [37–40]. This benefit was maintained during the long-term follow-up of the ABCSG-12 (94.4 months) [41] and the E-ZO-FAST (36 months) studies [42]. Whether this advantage in BMD preservation translates into a fracture reduction efficacy for zoledronic acid remains unknown, as fracture rates were not a primary outcome and study power was insufficient. Nevertheless, given the strong inverse association between BMD and fracture risk [43], it is reasonable to assume that prevention of AIBL with a bisphosphonate does prevent fractures [44–46].

The optimal time for initiation of bisphosphonate therapy in postmenopausal breast cancer survivors on AI is a subject of debate. Two approaches have been studied on zoledronic acid; an immediate or prophylactic therapy (initiation of zoledronic acid regardless of the baseline BMD status) versus delayed therapy (initiation when a post-baseline BMD *T*-score reaches a level of <−2.0, or the patient has a fracture). Both the Z-FAST [37] and the N03CC (Alliance) trials [47] have shown that immediate therapy with zoledronic acid was more effective in preventing AIBL after 5 years of follow-up without a significantly higher incidence of adverse events compared with delayed treatment in postmenopausal women receiving letrozole for breast cancer. While the studies were not adequately powered to detect differences in fracture rates, there appears to be a trend toward fewer fractures in women receiving immediate zoledronic acid therapy, with the rib and foot as the most common

Table 18.2 Treatment guidelines for bisphosphonate uses in women with breast cancer

Source	Criterion for treatment	Bisphosphonates	Regimen	Duration and follow-up
International Expert Panel (Hadji et al.) [28]	AI therapy and *T*-score < −2.0 Any two of the following risk factors: *T*-score < −1.5, age >65, low BMI (<20 kg/m^2), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use >6 months, smoking	Zoledronic acid	4 mg i.v. q 6 months	2 years or above, possibly as long as AI therapy
International Expert Panel (Aapro et al.) [29]	*T*-score < −2.0 *T*-score < −1.5 and one of the following risk factors: AI use, age >65, corticosteroid use >6 months, family history of hip fracture, personal history of fragility fracture after age 50 Two or more aforementioned risk factors when *T*-score is unavailable	Zoledronic acid	4 mg i.v. q 6 months	-
ASCO [30]	*T*-score ≤ −2.5 Individualized therapy when −2.5 < *T*-score < −1.0	Alendronate Risedronate Zoledronic acid	–	–
UK Expert Group [11]	Premenopausal women with ovarian suppression/failure and at least one of the following: AI therapy and *T*-score < −1.0, *T*-score < −2.0, vertebral fracture, annual bone loss > 4 % at lumbar spine or total hip Postmenopausal women receiving AI therapy with at least one of the following: *T*-score < −2.0, vertebral fracture, annual bone loss > 4 % at lumbar spine or total hip	Alendronate Risedronate Ibandronate Zoledronic acid	70 mg/week 35 mg/week 150 mg po/month or 3 mg i.v. q 3 months 4 mg i.v. q 6 months	Reassess in 2 years

(continued)

Table 18.2 (continued)

Source	Criterion for treatment	Bisphosphonates	Regimen	Duration and follow-up
Swiss Guidelines [31]	Two or more of the following: AI therapy; *T*-score ≤ −1.5, age > 65, corticosteroid use >6 months, family history of hip fracture, personal history of fragility fracture after age 50 *T*-score ≤ −2.0 *T*-score ≤ −1.5 and one other risk factor FRAX to determine risk	Any nitrogen-containing bisphosphonates	–	–
Belgian Bone Club [15]	*T*-score < −2.5 −2.5 < *T*-score < −1.0 and other risk factors Personal history of fragility fracture	Zoledronic acid Other bisphosphonates may be considered	4 mg i.v. q 6 months	–

fracture sites [37]. Current American Society of Clinical Oncology (ASCO) treatment guidelines for maintaining bone health in women with breast cancer are less specific, recommending antiresorptive therapy when *T*-score ≤−2.5 and individualized therapy if *T*-score is between −2.5 and −1.0 (Table 18.2) [30]. According to the European Society for Medical Oncology (ESMO) guidelines issued in 2014, patients with cancer receiving chronic endocrine therapy known to accelerate bone loss (e.g., AI, ovarian suppression, or oophorectomy for breast cancer and androgen deprivation therapy for prostate cancer) should receive bisphosphonates along with weight-bearing exercise and vitamin D/calcium supplements, if their *T*-score is <−2.0 or any two of the following risk factors were identified: age > 65, *T*-score < −1.5, smoking (current and history of), BMI <24 kg/m^2, a family history of hip fracture or personal history of fragility fracture above age 50, oral glucocorticoid use for >6 months. No treatment is recommended, except exercise and vitamin D/calcium supplement, if the *T*-score is >−2.0 with no additional risk factors (Fig. 18.1) [48, 49]. This patient's *T*-score was >−2.0, but she had a history of a parental hip fracture and a *T*-score of <−1.5 which would have qualified her, per the ESMO guideline, for immediate bisphosphonate therapy. Her options include semiannual intravenous injections of 4 mg zoledronic acid, weekly oral 70 mg alendronate, weekly oral 35 mg risedronate, or monthly oral 150 mg ibandronate. BMD needs to be monitored every 1–2 years while a patient is on oral bisphosphonates and individualized for those on IV bisphosphonates (although the 1–2 year time frame is also reasonable) [49]. If patients do not meet the criteria for initiating an antiresorptive treatment, BMD and risk status need to be reassessed at yearly intervals; in the event of annual BMD decrease of ≥5 % using the same DXA machine, secondary causes of bone loss including vitamin D deficiency should be evaluated, and an antiresorptive therapy should be initiated. For patients demonstrating ongoing loss in BMD while

Table 18.3 Summary of commonly used and FDA-approved bisphosphonates [32, 33]

Agents	Dosing regimen	Indication	Contraindication	Adverse effects	Special handling	Duration of therapy
Alendronate	5 mg qd or 35 mg qw, PO	Prevention of osteoporosis	Renal insufficiency w/CrCI <35 mL/min(Canadian labeling only), abnormalities of the esophagus, hypocalcemia, hypersensitivity, inability to stand or sit upright for at least 30 min	Bone/joint/muscle pain, atypical femur fracture, gastrointestinal mucosa irritation, hypocalcemia, osteonecrosis of the jaw, ocular infection,	Taken on an empty stomach in the morning with 6–8 oz of plain water and ≥30 min before breakfast or other medications/supplements; stay upright for ≥30 min and until after first food of the day to reduce esophageal irritation. Tablet should be swallowed whole; do not crush or chew	Not yet defined. Consider D/C after 3–5 years in patients at low risk for fractures Reevaluate fracture risk periodically after D/C
	10 mg qd or 70 mg qw, PO	Treatment of osteoporosis				
Risedronate	5 mg qd or 35 qw or 150 mg qmo, PO	Prevention and treatment of osteoporosis	Abnormalities of the esophagus, hypocalcemia, hypersensitivity, inability to stand or sit upright for at least 30 min			
Ibandronate	150 mg qmo, PO	Prevention and treatment of osteoporosis	Abnormalities of the esophagus, hypocalcemia, hypersensitivity, unable to stand or sit upright for at least 60 min, Not recommended if CrCl <30 mL/min	Bone/joint/muscle pain, atypical femur fracture, gastrointestinal mucosa irritation, hypocalcemia, osteonecrosis of the jaw	Same as above except taken 60 min before the first food or beverage of the day and remain upright position for 60 min following administration	
	3 mg qmo, IV	Prevention and treatment of osteoporosis. Unable to tolerate oral therapy			Serum creatinine prior to each IV dose; administer as a 15–30 s IV bolus; do not mix with calcium-containing solutions or other drugs. For osteoporosis, do not administer more frequently than every 3 months	
Zoledronic acid	5 mg q24mo, IV	Prevention of osteoporosis	CrCI <35 mL/min or acute renal impairment, hypersensitivity, uncorrected hypocalcemia, avoid invasive dental procedures	Acute phase reaction (arthralgia, headache, myalgia, fever), osteonecrosis of the jaw, atypical femur fracture, ocular infection, hypersensitivity reactions	Infusion over 15 min, acetaminophen prior to infusion	
	5 mg q12mo, IV	Treatment of osteoporosis				
	4 mg q6mo, IV	Prevention of aromatase inhibitor-induced bone loss in breast cancer (off-label use)				

Abbreviation: *qd* once a day, *qw* once a week, *qmo* once a month, *CrCl* creatinine clearance, *PO* orally, *IV* intravenously, *D/C* discontinuation

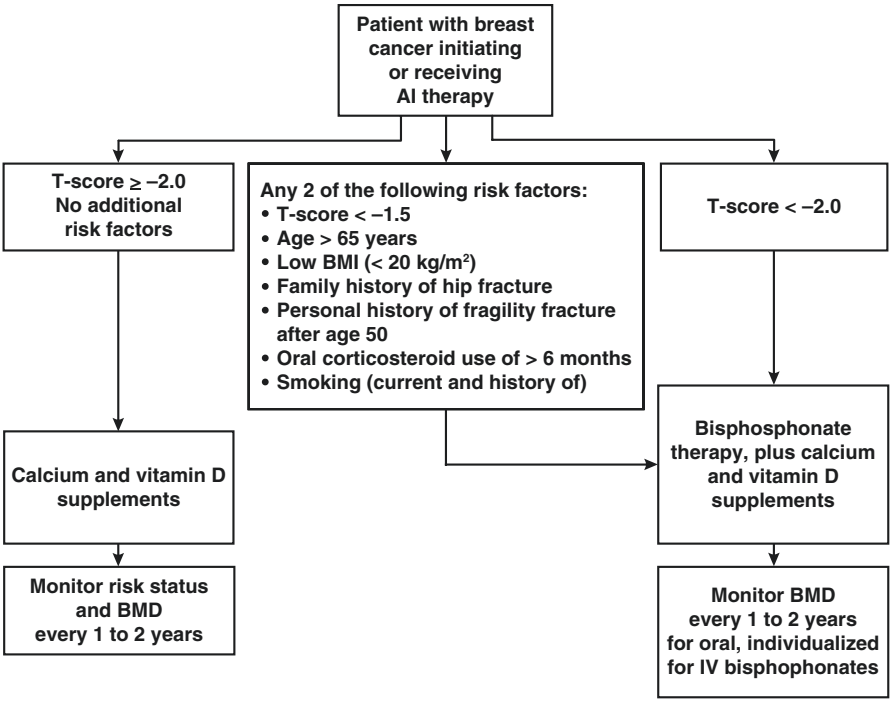

Fig. 18.1 Recommended management strategy for patients with breast cancer receiving aromatase inhibitor (AI) therapy [48, 49]

on antiresorptive therapy, provided that patient compliance with therapy especially for oral bisphosphonates is first confirmed, a switch to an alternative regimen (from oral to IV) or agent should be considered [28]. Denosumab may be an alternative to bisphosphonates for patients who are either unable to tolerate or fail to respond to trial of bisphosphonate [48–50].

Besides preserving BMD and preventing fractures, emerging evidence indicates that early zoledronic acid therapy may have additional antitumor and antimetastatic effects on the bone of breast cancer women regardless of menopausal status [41, 51]. In the AZURE randomized open-label phase 3 trial, zoledronic acid improved invasive disease-free survival (IDFS) in those who were over 5 years since menopause at trial entry ($N = 1041$, HR 0.77, 95 % CI 0.63–0.96) but not in all other menopausal groups (premenopause, perimenopause, and unknown status) [51]. A recent large meta-analysis was conducted by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) to clarify the risks and benefits of adjuvant bisphosphonate treatment in breast cancer. It was concluded that adjuvant bisphosphonates (e.g., zolendronic acid, ibandronate, pamidronate, clodronate) reduced the metastatic bone recurrence rate and improved disease-free and overall survival in women with breast cancer; however, these benefits were only observed in women who were postmenopausal when treatment began [52].

Bisphosphonates are contraindicated in patients with a low glomerular filtration rate (GFR < 30 ml/min/1.73 m^2), hypocalcemia, or sensitivity to bisphosphonates. In accordance with the US Food and Drug Administration (FDA)-approved labeling, the American Society of Clinical Oncology expert panel recommends that serum creatinine should be tested prior to each dose of zoledronic acid [30]. If unexplained renal dysfunction is identified, defined as an increase in serum creatinine of ≥0.5 mg/dL over baseline or an absolute level of ≥1.4 mg/dL among patients with previously normal baseline serum creatinine levels, discontinuation of zoledronic acid is warranted. These patients should be reassessed monthly, and zoledronic acid should be reinstituted cautiously if the renal function returns to baseline [30]. In the absence of other contraindications, intravenous bisphosphonates can be used in patients with esophageal disease [11]. Further studies are needed to guide decisions about duration of bisphosphonates therapy and drug holidays. Limited data from randomized controlled trials generally suggest that the risk of vertebral fractures is reduced, with the continuation of bisphosphonate therapy beyond 3–5 years [53]. However, consistent evidence of a significant reduction in non-vertebral fracture with bisphosphonate therapy beyond 5 years is lacking [53]. While recommendations for discontinuation of bisphosphonates need to be drug-specific (Table 18.3), in general, drug holidays can be considered for patients who have been persistently on bisphosphonate therapy for 3–5 years and for those who have a stable BMD, no previous vertebral fractures, and who are at low risk for fracture in the near future [28, 33, 48, 53]. In addition, a healthy lifestyle with weight-bearing exercise and calcium/vitamin D repletion is encouraged if dietary intake is not adequate. Continued bone loss despite adherence to these guidelines suggests an overlooked secondary cause of osteoporosis, poor compliance with recommended therapies, or a true nonresponse to bisphosphonates. A referral to a local metabolic bone expert and consideration of alternative bone protective agents discussed below should be considered in these situations.

Denosumab

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-kappaB ligand (RANKL), an osteoclast differentiating factor. It inhibits the formation, function, and survival of osteoclasts, resulting in decreased bone resorption, increased BMD, and reduced fracture risk (vertebral, non-vertebral, and hip) [54, 55]. The FDA-approved denosumab for the treatment of men and postmenopausal women with osteoporosis who are at high risk for fracture (history of osteoporotic fracture, multiple risk factors for fracture) or patients who have failed or are intolerant of other available osteoporosis therapies [56]. The recently published and presented results from the FREEDOM study, a large international multicenter randomized trial evaluating the fracture prevention effect of denosumab in postmenopausal osteoporotic women over 60, showed persistent reductions of bone turnover markers, with progressive BMD gains, a low annual fracture incidence, and a consistent safety and side-effect profile for up to 10 years of treatment [57, 58].

While the age and baseline BMD profiles of many breast cancer survivors receiving AI therapy may be significantly different from those evaluated in the FREEDOM trial, there is evidence that the fracture reduction benefits of denosumab does extend to these patients [50]. This therapy has been approved by FDA to increase bone mass in patients at high risk for fracture including breast cancer patients on adjuvant AI therapy [59], it can thus be considered as an effective alternative for those older patients who have difficulty with the dosing requirements of oral bisphosphonates or who have contraindications including markedly impaired renal function. It is commonly administered at a dose of 60 mg subcutaneously every 6 months which offers advantages as far as compliance is concerned. Serious risks associated with denosumab partly overlap with bisphosphonates, including hypocalcemia, osteonecrosis of the jaw (ONJ), atypical femur fractures, and serious infections. However, in the osteoporosis clinical trials, denosumab was generally well tolerated. Overall, the most common adverse effects were arthralgia, hypercholesterolemia, cystitis, and cellulitis at injection site [56, 57]. Like the bisphosphonates, denosumab should not be given to women with hypocalcemia unless the hypocalcemia has been corrected. In view of the high prevalence of vitamin D deficiency among breast cancer patients, screening for and replacement of vitamin D deficiency is advisable before initiation of fracture-reducing therapies, including denosumab [54]. Patients with conditions predisposing to hypocalcemia (e.g, chronic kidney disease and creatinine clearance <30 mL/min) should be monitored for hypocalcemia. Regular dental care and attention to oral health also is advisable in patients with breast cancer receiving both AI and denosumab [49].

Raloxifene

Raloxifene at an oral dose of 60 mg/day is the only selective estrogen receptor modulator (SERM) in the USA approved by the FDA to prevent and treat osteoporosis in postmenopausal women. It is an SERM with beneficial effects on bone mass and bone turnover and proven efficacy for both primary and secondary prevention of vertebral fractures [60–63] but continued uncertainty regarding fracture reduction efficacy at other sites. The fracture reduction efficacy of raloxifene has been shown comparable to that of alendronate in a recent meta-analysis of seven randomized controlled trials [64], but raloxifene has the added advantage of reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis [65, 66]. Raloxifene, however, is not without serious risk as it has been associated with an increased risk of venous thromboembolism and fatal stroke, although the absolute risk remains small [66]. Raloxifene is safer than tamoxifen at the level of the endometrium in non-hysterectomized women [67]. However, there is concern that both tamoxifen and raloxifene may interfere with the antitumor efficacy of anastrozole in breast cancer patients treated with this AI [68]. Therefore, unless new evidence indicates otherwise, concurrent administration of a SERM with an AI should be avoided [68]. Bazedoxifene (BZA) is a SERM approved in Europe and Japan for treatment in women at increased risk of fracture, which has also been shown to function as pure estrogen receptor antagonists in animal cellular model of tamoxifen-resistant breast cancer [69]. In USA, BZA is only approved by the FDA for the prevention of

osteoporosis while paired with conjugated equine estrogens (CEE) [70]. As mentioned earlier, such patients may be better off with a bisphosphonate or denosumab. As with all fracture risk-reducing therapies, diet, weight-bearing exercise, and calcium/vitamin D repletion when indicated are paramount as is the need to monitor therapeutic efficacy with serial DXA BMD measurements every 1–2 years.

Case

Our 55-year-old patient with evidence of low BMD and a family history of parental hip fracture, who has been on AI treatment for the past 3 years, is deemed at an enhanced lifetime fracture risk. Ideally, she should have been initiated on an antiresorptive agent (preferably a bisphosphonate) at time of initiation of AI therapy. Nonetheless, she should receive an antiresorptive medication, preferably zoledronic acid in conjunction with lifestyle modification that should address optimization of calcium (through combination of diet and supplementation) and vitamin D intake and regular weight bearing exercise. She was counseled in the office with her increased risk of fractures and proposed management plan. She was not vitamin D deficient or hypocalcemic prior to receiving a bisphosphonate. She was put on zoledronic acid 4 mg i.v. q 6 months in conjunction with lifestyle modification. A year later, a repeat DXA scan shows her BMD is stabilized. The plan is to continue zoledronic acid for maintenance of bone health until 5 years of AI therapy is completed. BMD assessment will be reassessed every 1–2 years, and an antiresorptive therapy will be restarted as clinically indicated.

Clinical Pearls/Pitfalls

- Postmenopausal women with breast cancer who are receiving or have been treated with aromatase inhibitors (AI) are at higher risk of osteoporosis and fractures than their age-matched generally healthy postmenopausal women. Baseline BMD should be measured prior to initiation of AI therapy and reassessed along with their risk status every 1–2 years thereafter.
- Vitamin D deficiency and hypocalcemia should be screened, and adequate supplementation of deficiencies should be achieved prior to initiation of an antiresorptive medication.
- Antiresorptive therapy should be initiated if: (1) *T*-score <-2.0 or prior fracture and (2) any two of the following risk factors were identified: age >65, *T*-score <-1.5, smoking (current and history of), BMI <24 kg/m^2, family history of a hip fracture or a personal history of a fragility fracture above the age of 50, or oral glucocorticoid use for >6 months.
- For patients with BMD T-scores >-2.0, if there is evidence of annual decline in BMD of $\geq 5\,\%$ using the same DXA machine, secondary causes of bone loss including vitamin D deficiency should be evaluated, and antiresorptive therapy should be initiated regardless of *T*-score.

- Current evidence supports the use of intravenous zoledronic acid 4 mg every 6 months for at least 2 years or possibly as long as AI therapy is maintained, which is usually 5 years.
- Bisphosphonates should be considered as first line antiresorptive agents in breast cancer survivors. Accumulating evidence suggests that adjuvant bisphosphonates may have additional antitumor and antimetastatic effects on the bone and hence reduce the metastatic bone recurrence rate and improve disease-free and overall survival in postmenopausal women with breast cancer.
- For those patients who are not candidates for bisphosphonates or not responsive to the treatment, denosumab 60 mg SC every 6 month is the most favorable alternative antiresorptive agent and regimen.
- Raloxifene is of limited use for osteoporosis prevention and treatment in breast cancer patients.

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Management Strategies for Sexual Health After Breast Cancer Diagnosis

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Eve Overton, Erin Hofstatter, Devin Miller, and Elena Ratner

Case Presentation

A 48-year-old female presents to the office complaining of vaginal dryness and painful intercourse. Her past medical history is significant for an estrogen receptor-positive breast cancer treated surgically 6 months ago. She is currently on tamoxifen for endocrine therapy. Her last menstrual period was 4 months ago, and over the past 4 months, she has experienced moderate hot flashes and trouble sleeping due to night sweats for which she initiated gabapentin with significant benefit. She notes that her personal life and relationship is being affected by the vaginal symptoms.

What Is the Most Effective and Appropriate Management Option for This Patient?

A. Combined estrogen and progestin/progestogen therapy (EPT)
B. Estrogen therapy (ET) only
C. Vaginal estrogen
D. Paroxetine
E. An oral selective estrogen receptor modulator (SERM) recently approved by FDA for treatment of menopausal dyspareunia

E. Overton (✉)
Yale University School of Medicine/Yale New Haven Hospital, New Haven, CT, USA
e-mail: eve.overton@yale.edu

E. Hofstatter
Department of Medical Oncology, Yale New Haven Hospital,
333 Cedar Street, PO Box 208063, New Haven, CT 06520-8063, USA

D. Miller • E. Ratner
Department of Obstetrics and Gynecology, Yale New Haven Hospital,
333 Cedar Street, PO Box 208063, New Haven, CT 06520-8063, USA

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Special considerations for our patient's case as detailed above include focal vaginal symptoms related to iatrogenic estrogen deficiency impacting her quality of life (QOL), a personal history of hormone-sensitive breast cancer on current tamoxifen therapy, and a desire to be treated pharmacologically after a failed trial of nonprescription approaches. Potential therapeutic options in such a setting will be discussed along with their side effects. The thought process behind the management approach for this case will also be outlined.

Sexuality, Cancer, and Hormones: An Introduction

Breast cancer impacts sexuality and intimacy both during therapy and in survivorship. Sexual functioning can be affected by illness, surgical intervention, pain, anxiety, anger, stressful circumstances, and medication. A large quantity of literature exists showing that the diagnosis and life with cancer substantially alters a woman's intimate relationships, sexuality, sexual functioning, and sense of self. There is growing evidence that health-care providers are not addressing the concerns of cancer survivors [1].

Management of breast malignancy is dependent on the pathology, histological subtype, and disease stage, with some patients receiving small excisional procedures, while others are subject to extensive surgeries, chemotherapy, endocrine therapy, and radiation treatment [2, 3]. It is difficult to predict how each individual's sexual health and intimacy will fare during and after cancer treatment. However, studies suggest risk factors for worsened sexual function after breast cancer diagnosis, and treatment includes age, interval since treatment, lower levels of self-esteem or body image, worsened physical symptoms, anxiety, and depression [4, 5]. Further, the treatment modalities which enable patient survival contribute to patient symptomatology, for example, ovarian suppression and hormonal modulators such as tamoxifen, can induce hypoestrogenic symptoms, and chemotherapy regimens may induce a permanent early menopause for some patients [6–8]. Breast cancer survivors, particularly when premenopausal at time of diagnosis, may experience climacteric symptoms, including hot flashes, sleeping and mood changes, as well as vaginal atrophy and dryness which in turn can result in dyspareunia and decreased sexual drive.

Sexuality, intimacy, and relationships are integral to QOL at any time, and their value is particularly meaningful for women during breast cancer treatment and long after its completion [9]. Physical, biological, and psychological complexity of sexual health in breast cancer survivors presents an opportunity for the provider to impact quality of life and patient satisfaction. Such impact can be achieved through careful and thoughtful consideration of hormonal and nonhormonal pharmacotherapies and also through non-pharmacological approaches.

Effects of Breast Cancer on Sexual Function

Several studies have examined patient-reported QOL in short- and long-term cancer survivors and report overall significant alteration in quality of life over many aspects of health and psychological well-being [9]. At baseline, it is well established that health-related quality of life (HRQOL) and sexual functioning are closely associated [10]. Female sexual function disorder (FSD) is defined as a disturbance in or pain during the sexual response which can be further delineated into hypoactive sexual disorder, orgasmic disorder, sexual pain disorder, and sexual arousal disorder [11]. FSD is a common women's health issue that is magnified in breast cancer survivors. Rates of FSD range from 25 to 63 % of the general population based on several variables, and it is accepted that over 50 million US women are currently living with some form of FSD [12]. The rate of FSD is thought to be substantially higher in breast cancer patients [11].

Given the emotional, psychological, and sensuous connotations of breasts, sexuality is impacted from the time of breast cancer diagnosis, with additive insults resulting from treatments undertaken. Many cancer survivors report symptoms of sexual arousal disorder which can result in the recurrent inability to attain or maintain an adequate sexual response which causes significant distress or interpersonal issues [13]. Sudden surgical or chemical withdrawal of sex hormones, new medications, and postoperative sequelae can all contribute to sexual arousal disorder in this population [14, 15]. Furthermore, emotional and psychological components of a cancer diagnosis in and of itself can hinder the sexual response. Depression and anxiety, of which rates increase with cancer diagnosis, can also significantly affect sexual function [16].

Sexual pain disorders are common in breast cancer survivors and a frequent cause of sexual dysfunction for these patients [4]. Vaginal dryness resulting from estrogen deficiency (a sequel to medical castration that constitutes one first-line approach following surgery) can be identified as the earliest pathophysiological underpinning to the cascade of events that follow, i.e., dyspareunia, persistent pain with penile vaginal intercourse, and resulting vaginismus, which is a persistent difficulty in allowing vaginal entry, despite the expressed wish to do so. Patients may begin to avoid intimacy altogether as intercourse and sexuality may be associated with fear of physical discomfort.

Studies have shown 50–70 % of women with a breast cancer diagnosis report some major symptom of sexual dysfunction [4, 5, 17]. Although body image disturbance related to mastectomy may be associated with impaired sexual function in patients, symptoms are most frequent and most severe in women whose treatment includes chemotherapy regardless of their surgical history [14, 15]. Patients undergoing chemotherapy often report significant deterioration in QOL due to physical side effects, such as fatigue, nausea, and diarrhea, and psychological sequelae related to changes in body image due to loss of scalp hair, for example [18]. Chemotherapy-related neuropathies are additional recognized detriments to sexual

function in women with breast cancer [19]. Further, sexual symptoms are most severe in patients who experience premature ovarian failure with hypoestrogenism as a result of gonadotoxic chemotherapy [20]. Complaints of sexual symptoms are reported at higher rates among those breast cancer patients diagnosed at a younger age and with premenopausal status at diagnosis [21, 22]. Further, increased concerns related to sexuality are associated with an increased level of overall patient distress after primary treatment in younger patients [21].

Effects of Breast Cancer Diagnosis on Relationships and Partners

Women, whose sexual capacity is compromised by a breast cancer diagnosis, are not only coping with concerns about their own health and survival but are also worried about their partner's QOL and overall well-being. Indeed, partners of women with cancer are dramatically affected by loss of sexuality and intimacy. Hawkins et al. demonstrated that cessation or decreased frequency of sex and intimacy was reported in 79 % of male partners of women affected by breast cancer. Renegotiation of sexuality and intimacy after cancer was reported by only 14 % of these partners. These alterations to sexuality were associated with feelings of self-blame, reflection, sadness, anger, and lack of sexual fulfillment [23]. Further, male partners of women diagnosed with breast cancer often express several conflicting emotional states including feeling worried about their significant other's health, having the desire to engage in sexual activity, and feeling guilty about wanting to increase sexual intimacy. These feelings, in turn, can lead to resentment and withdrawal from their partner and overall relationship discord [24]. Evidence suggests partners of breast cancer patients greatly benefit from increased social support even years after an apparent cure [25]. Specifically male partners who take on a new role as caregiver in the relationship experience difficulties with emotional changes, challenges to their masculinity, and new stressors [26]. These new roles and feelings also contribute to changes in sexuality and intimacy in relationships, making support for partners all the more necessary.

Iatrogenic Factors That Contribute to FSD in Breast Cancer Survivors

Whether or not hormonal adjuvant therapy will be a primary treatment in breast cancer in a given case depends on histological subtype, stage of disease, and patient characteristics. Approximately 60–75 % of all breast cancers are estrogen/progesterone hormone receptor positive (ER+, PR+) [27]. For the ER+/PR+ histological variants of breast cancer, endocrine therapies are well established for both early-stage and advanced disease with regimens varying by menopausal status at diagnosis, with reduced risk of recurrence and improvement in survival achieved with long-term therapy [28].

Tamoxifen is a selective estrogen receptor modulator (SERM) which acts as an estrogen antagonist in breast tissue (a benefit), but as an estrogen agonist in the endometrium and other tissues (conferring potential for harm). Tamoxifen is used as an adjuvant treatment in managing premenopausal breast cancer in the setting of ER+/PR+ tumors [29]. Its estrogen receptor agonist activity in some tissues yields several associated risks. These risks include an increased rate of ovarian cysts observed, as high as 20 % in premenopausal patients, an increased rate of abnormal

uterine bleeding and endometrial cancer (a 2.7 fold risk while on therapy), as well as a small but significant increase in rates of uterine sarcoma [30–32]. In addition to these concerns, several studies have observed sexual complaints associated with tamoxifen use. A cross-sectional study observed dyspareunia in 54 % of patients regardless of patient age, surgical treatment of the primary cancer, or chemotherapy [33, 34]. This finding is supported by several other studies noting a high rate of gynecological and sexual complaints in patients on tamoxifen [35]. A longitudinal study of breast cancer patients placed on tamoxifen after chemotherapy observed frequent dyspareunia (47 %) and low sexual interest (44 %) in these patients regardless of chemotherapy regimen, with a high correlation between gynecological complaints and decreased sexual interest ($p < 0.0005$) [34]. However, several studies have assessed hormonal treatment in the context of other therapies and have found the strongest correlation of sexual side effects to chemotherapy with weak or absent correlation between tamoxifen and sexual symptoms [36–38]. A prospective study in postmenopausal breast cancer patients on tamoxifen assessed sexual function after 6 months of therapy in comparison to pretreatment baseline measures. This study revealed a significant increase in gynecological symptoms ($p < 0.0001$); however there was no increase in the percentage of women who reported sexual dysfunction (30 % at both baseline and after 6 months of treatment) [39].

Raloxifene is another SERM which has demonstrated a decreased risk of breast cancer recurrence in receptor-positive disease and is also approved for the treatment of postmenopausal osteoporosis [40, 41]. Raloxifene and tamoxifen were directly compared in a two-arm, randomized, double-blinded clinical trial of 19,747 women for over 5 years of treatment. This study found increased efficacy of tamoxifen in prevention of recurrence of invasive breast cancer, with risk ratio of 1.24 for raloxifene/tamoxifen (CI, 1.05–1.41.2), with significantly lower rates of endometrial cancer, uterine hyperplasia, and thromboembolism observed in the raloxifene arm and no significant differences in mortality between the two arms [42]. Patient symptom analyses from the same trial indicated that sexual function was slightly better for participants assigned to tamoxifen (age-adjusted repeated measure odds ratio, 1.22 %; CI, 1.01–1.46) however greater mean symptom severity for gynecological problems ($p < .001$) and vasomotor symptoms ($p < .001$) as compared to the raloxifene group [43]. There is otherwise limited data on raloxifene's impact on sexual function in breast cancer patients, and studies of raloxifene in osteoporosis therapy have not demonstrated significant changes in sexual function with this agent [44–46].

Aromatase inhibitors (AIs) are almost exclusively used as an adjuvant strategy in postmenopausal patients with hormone-responsive (ER+/PR+) tumors. By inhibiting the enzyme aromatase, AIs prevent tissue-level conversion of endogenous androgens to estrogens and have been shown to improve patient survival in this population [47]. Side effects of these therapies often include significant vasomotor symptoms, as well as vulvovaginal atrophy (VVA), vaginal dryness, and dyspareunia. A population-based study comparing sexual symptoms in patients taking AIs for breast cancer therapy with age- and menopausal status-matched controls demonstrated decreased sexual interest in 50 % of AI patients, sexual dissatisfaction in 42.4 % of patients, and

inadequate vaginal lubrication in 72% of patients. All of these rates were significantly more common ($p < 0.05$) than in matched controls [48]. A prospective study of tamoxifen versus AI use found significantly greater genitourinary symptoms of menopause in AI users compared with tamoxifen. These symptoms were consistent with the strong estrogen suppression achieved with AI [22].

For premenopausal breast cancer patients with hormone-responsive cancer (ER+/PR+), ovarian suppression, either through use of GnRH agonists or with bilateral oophorectomy, may be used to optimize results and minimize recurrence risk [29]. In general, premenopausal women who experience abrupt surgical or chemical menopause often experience immediate and severe vasomotor symptoms that contribute to QOL deterioration in this vulnerable population. An increasing number of premenopausal women with breast cancer may face treatment with ovarian suppression, given recently published data from the Suppression of Ovarian Function (SOFT) trial suggesting a survival benefit in a subset of premenopausal women when ovarian suppression was used in combination with aromatase inhibition [49]. Additionally, many pre- and postmenopausal women are now being advised to extend adjuvant hormonal therapy beyond the previously established 5-year course based on a small but statistically significant long-term survival benefit with 10 years of tamoxifen use compared to 5 years [50]. An increased duration of tamoxifen exposure has been associated with a higher prevalence of vaginal atrophy [51], with higher rates of sexual dysfunction to be expected in those patients.

Hormone Replacement Therapy and Hormonal Interventions

Given the many emotional and physical issues going on at the time of treatment for malignancy, it can be difficult to delineate what proportion of sexual problems are caused by or enhanced by vasomotor symptoms, sleep disorders, and vaginal atrophy. While direct hormonal replacement can benefit symptoms of sexual function, patients as well as their providers are often reluctant to pursue these modalities in the setting of active or recent breast cancer diagnosis [52, 53].

Systemic Hormone Replacement Therapy

Hormonal therapy (HT) has long been recognized as the most effective therapy for management of hypoestrogenic symptoms of menopause, including vasomotor symptoms and symptoms of vaginal atrophy. Efficacy relates to dose of estrogen component of HT formulations, as well as route of therapy (vaginal route of estrogen being most effective against focal vaginal symptoms) [54]. While the past decade has witnessed an evolution in our perspective on the place of HT in the menopause management for the healthy aging female population, little has changed as regards our understanding of safety or additive risk of HT use in breast cancer survivors.

The role of HT in breast cancer patients remains contentious, and data in this regard are sparse and predominantly observational. In a systematic review of eleven observational trials, Col et al. determined that there was no quantitative increase in

recurrence risk among breast cancer patients using HT. This review compared 214 breast cancer survivors on heterogeneous systemic HT regimens for a mean of 22 months compared to 623 patients without HT therapy. The women on HT were on average 52 months post initial breast cancer diagnosis at the time of HT initiation. Controlling for disease stage, heterogeneity of initial trial design, and distance from date of diagnosis, a relative recurrence risk of 0.64 (CI 0.36–1.15) was observed in patients who had received HT [55]. An absence of increased risk of breast cancer recurrence has been replicated by a number of other case control and observational trials over the last two decades [56–59]. While these studies have all been methodologically limited by their retrospective design, there have been two major prospective clinical trials examining HT in breast cancer survivors, one of which did demonstrate a significant increase in breast cancer recurrence. The Stockholm study ($n=378$) and Hormone Replacement After Breast Cancer Therapy – Is It Safe? (HABITS) ($n=438$) trials were both conducted in Sweden in the late 1990s. The HABITS trial was an open trial of breast cancer patients randomized to either 2 years of hormone replacement (estrogen only or continuous combined estrogen-progesterone) or to best-alternative options for menopausal symptoms (although specific non-HT therapies were not detailed). The study was designed to demonstrate non-inferiority between arms, and the primary end point was any new breast cancer event with a planned follow-up of 5 years. The trial was halted early in 2003, at mean follow-up of 2.1 years, due to a significant increase of recurrent breast cancer in the HT arm with a hazard ratio of 3.5 (95 % CI = 1.5–7.4) [60]. At 4 years reevaluation after closure of the HABITS trials, the increased risk of cancer recurrence remained significant with a cumulative recurrence rate of 22.2 % in the HT arm and 8.0 % in the control arm (HR = 2.4, 95 % CI = 1.3–4.2). However, no differences in cancer mortality were observed between study arms [61]. The Stockholm study ran concurrently with, and was structurally similar to, the HABITS trial except for its use of lower progesterone exposure through cycled sequential progesterone dosing. The Stockholm study was halted after a median follow-up of 4.1 years because of the findings of the HABITS trial. Upon cessation of the trial, there were no significant differences in breast cancer recurrence between HT and non-HT arms, with a hazard ratio of 0.82 (95 % CI = 0.35–1.9) [62]. Analysis of Stockholm Study participants at 10 years follow-up showed no increased risk of breast cancer recurrence in the HT arm as compared to the non-HT arm, with cumulative recurrence rates of 32 % in the HT group and 25 % in the non-HT group (HR = 1.3; 95 % CI = 0.9–1.9). There was also no difference in mortality between the Stockholm study arms at 10 years follow-up [63]. Notably, there were some limitations to these studies. HT regimens were not standardized in either trial, and some patients were taking both tamoxifen and HT simultaneously, which is not a standard practice in the United States [64]. Nonetheless, based on existing data, the official position of the American College of Obstetricians and Gynecologists is that patients with a history of hormone-sensitive breast cancers should not use HT as a first-line therapy for hypoestrogenic symptoms. Current ACOG guidelines further state that breast cancer survivors choosing to initiate HT to improve QOL should be counseled about the potential for breast cancer recurrence with hormonal therapy [65].

Synthetic Hormone-Like Formulations for Symptom Management

Concerns over the risks associated with HT have recently led to the development of newer third-generation SERMs for symptom management with the goal of limiting risk. Ospemifene (trade name Osphena) is reported both preclinically and clinically to have antagonistic or neutral effects on breast, with agonist activity on bone and vaginal tissue [66, 67]. It is currently available as an oral preparation, FDA approved for the treatment of moderate dyspareunia caused by VVA, and with ongoing research into its effects on bone density. There is currently no data on its use in breast cancer survivors, and it is not currently indicated for these patients as long-term data is not available, nor is data on this population available. Clinical trials in the postmenopausal population have demonstrated improvement in genitourinary menopausal symptoms and improvements in histologic signs of vaginal atrophy [68]. There is a low rate of reported systemic side effects, with the most common complaint of facial flushing with use [68, 69]. Although its estrogen antagonistic effect on the breast tissue makes it an appealing symptomatic therapy for study in breast cancer patient, safety and efficacy of this agent in cancer survivors are yet to be established [70].

Tibolone, while not a SERM, is a synthetic steroid with activity on estrogen and progesterone receptors and mainly acts as an agonist at estrogen receptors [71]. It is prescribed outside the United States for osteoporosis and is being investigated as treatment for female sexual dysfunction [72]. Efficacy on vasomotor symptoms has been positive thus far. However, one group recently examined tibolone in the setting of breast cancer patients in a prospective randomized controlled trial and reported an increased risk of breast cancer recurrences in women receiving tibolone for HT [73]. A separate case-control study confirmed tibolone's safety for endometrial cancer survivors, another hormone-sensitive cancer, with no adverse effects on disease-free or overall survival [74]. However, tibolone has not received approval for use in breast cancer survivors for any indication in the United States or Europe.

Topical Hormonal Therapies

For postmenopausal women with symptoms of atrophic vaginitis, topical estrogen therapy can be very helpful [75]. Many formulations are available including creams, tablets, and rings, and a recent Cochrane review has indicated that all formulations have proven more beneficial than placebo or nonhormonal lubricants for control of symptomatic VVA [76]. While many symptomatic breast cancer survivors may be interested in low-dose topical estrogen therapies, there remains however a theoretical concern with their use, particularly by those with hormone receptor-positive cancers given the potential for systemic absorption and the slight increases in circulating estrogen concentrations reported among some vaginal estrogen users [77, 78]. This issue of systemic absorption was evaluated in few trials; in one such trial, systemic absorption was limited to a short interval after initiation of vaginal estrogen therapy, yet the magnitude of systemic absorption was significantly reduced as the trophic effects of estrogen on vaginal epithelium developed few weeks later [77]. In another trial, non-hysterectomized postmenopausal women receiving commonly used doses of vaginal estrogens demonstrated no increased risk of

endometrial proliferation or hyperplasia suggesting minimal absorption [78]. As to the risk of recurrent breast cancer among vaginal estrogen users, data remains quite limited and the quality of evidence is low. Le Ray and colleagues performed a case-control study with 13,479 adult women with a previous diagnosis of breast cancer demonstrating no increase in the risk of recurrence in tamoxifen-treated patients using local hormonal therapy over the course of 3.5 years of follow-up [79]. Vaginal estrogen type, duration of therapy, and dosage were not assessed. Rates of recurrence in those patients using vaginal estrogen therapy while undergoing aromatase inhibitor therapy versus patients on aromatase inhibitors alone have not been directly compared [80]. Notably, although available evidence has been reassuring, safety concerns often limit patient use of topical hormonal therapies. Some trials show rates as low as 3 % of hormone receptor-positive breast cancer patients using this treatment modality [79, 81].

Nonhormonal Therapies for FSD in Breast Cancer Survivors

For those breast cancer survivors who wish to completely avoid hormonal interventions, or for whom their oncologists prefer they avoid these methods, nonhormonal topical therapies are available. These methods focus mainly on symptom management and have been found to be helpful in some studies. Although generally found to be less effective than hormonal options, over-the-counter vaginal moisturizers and lubricants can be particularly helpful in managing vaginal dryness in those patients who wish to avoid hormonal therapy altogether [76, 82]. They should be recommended to women to help with intercourse and atrophic symptoms with or without estrogen therapy. Additionally, recent studies have also demonstrated benefits of topical lidocaine gel for postmenopausal breast cancer survivors suffering from dyspareunia. In a randomized placebo-controlled trial, Goetsch and colleagues demonstrated that 4 % aqueous topical lidocaine was effective in reducing severe dyspareunia in postmenopausal breast cancer patients when the source of their dyspareunia was limited to the vulvar vestibule. Patients applied the lidocaine vs. placebo to the vulvar vestibule three minutes before vaginal penetration for 1 month. Users of the lidocaine reported significantly less pain during intercourse or tampon use [83]. The authors recommended liquid lidocaine compresses to the vulva before penetration as a suggested method for more comfortable intercourse.

Pelvic Floor Physical Therapy

Pelvic floor physical therapy is well studied and utilized frequently for urinary incontinence and pelvic organ prolapse; however it is understudied in areas of sexual dysfunction [84–86]. Evidence continues to emerge as to the efficacy of physical therapy programs not only for urinary and defecatory disorders but also for sexual dysfunction. The physical therapist may employ educational sessions, cognitive behavioral therapy, vaginal dilator therapy, pelvic floor muscle strengthening, and relaxation techniques with biofeedback, stretching, and massage. A recent review article by Rosenbaum highlighted the idea that there are promising studies in this

area [87]. While there is limited data, biofeedback in particular has undergone controlled studies for treatment of sexual dysfunction specifically in the setting of vulvar pain syndromes [87]. A recent small phase I/II trial assessed the efficacy and tolerability of pelvic floor physical therapy combined with protocolled vaginal lubrication in 25 breast cancer patients with complaints of dyspareunia over 4 weeks with follow-up extending through 26 weeks. Patients reported significant improvements in dyspareunia, sexual function, and quality of life over the course of the study, with maximum benefit achieved by 12 weeks and no reported adverse events [88]. Although research in pelvic floor physical therapy and dilator use continues to develop, the absence of serious side effects and the benefits observed to date indicate that they may be a helpful addition in a multidisciplinary approach to treatment of pelvic floor dysfunction in breast cancer patients.

Dilator Therapy

Vaginal dilators are useful in postmenopausal patients experiencing sexual dysfunction in a graduated fashion. They are particularly useful in patients for which intercourse has been or is currently painful as they can provide feedback to women and to aid in controlling tension and pelvic floor muscles [89]. Painful intercourse can cause reflexive tensing of muscles which can worsen attempts at intercourse. Dilators can enhance confidence in the ability to accommodate penetration without pain. There is minimal evidence regarding dilator usage in this population; however particularly in women for whom intercourse is painful and/or who report decrease in vaginal caliber, they may be helpful. Several companies sell dilators online without need for prescription, and many cancer centers supply them in their stores.

Herbal Remedies

Given the controversy surrounding use of hormonal replacement therapy in addressing symptoms in breast cancer patients, nonhormonal therapies have been the focus of symptomatic management. Recent studies have shown that complementary and alternative therapies, primarily herbal remedies, are popular among breast cancer patients, with usage rates as high as 75% [90, 91]. Several supplements are available over the counter and marketed for the improvement of menopausal symptoms, including symptoms of vulvovaginal atrophy and other symptoms which contribute to sexual dysfunction. Caution is advised however due to lack of quality controls and the fact that some of these products have estrogenic agonist activities.

Phytoestrogens

Phytoestrogens, sometimes referred to as dietary estrogens or isoflavin extracts, are herbal remedies that are claimed to alleviate climacteric symptoms in addition to a variety of other health benefits. These supplements are typically red clover or soy derived, with structural and functional similarities to mammalian estrogens. They are thought to exert receptor-dependent effects variably in hormone-responsive tissue, in a manner similar to SERMs [92]. The literature is mixed on the agonist/antagonist effects of various phytoestrogens. Health claims of phytoestrogens have ranged from menopausal symptoms to breast cancer risk reduction, cardiovascular

benefits, and osteoporosis prevention. However, data to support these claims are sparse and inconsistent [93]. A 2006 meta-analysis of nonhormonal therapies for menopausal symptoms by Nelson and colleagues included subset analysis of 17 studies of phytoestrogens which showed no benefit over placebo [94]. A recent Cochrane review on effect of phytoestrogens on vasomotor symptoms could find no benefit of phytoestrogens in reducing the frequency of hot flashes and reported inconclusive findings regarding phytoestrogen effects on vaginal symptoms and vaginal pH [95]. Both of these analyses were limited by the poor quality of available trials, with the Cochrane review finding only 5 of 43 potential trials adequate for analysis. Additionally, given phytoestrogen's high affinity for endogenous estrogen receptors, theoretical concerns regarding stimulatory effects on hormone receptor-positive cancer cells and cancer recurrence risks persist. In vitro studies assessing cancer risk associated with phytoestrogens have been inconclusive, with some results indicating proliferative and antiproliferative effects varying with the particular phytoestrogen use [96, 97]. Clearly, further well-designed trials are needed to make definitive commentary on the potential use and safety of phytoestrogens in breast cancer survivors.

Black Cohosh

Black cohosh (*Cimicifuga racemosa*) is an herbal preparation derived from a North American buttercup which is also marketed for menopausal symptom relief. The mechanism of action for black cohosh is controversial. Some studies posit that it functions as a SERM, though the majority of trials suggest that it lacks any estrogen-like effect, rather impacting climacteric and psychiatric symptoms through serotonergic and dopaminergic neural effects. A lack of impact on hormone receptors has made black cohosh an appealing option for managing menopausal symptoms in breast cancer patients. However, studies have demonstrated mixed results with regard to its efficacy. A systematic review of trials evaluated nine studies comparing black cohosh to placebo for the alleviation of climacteric complaints in menopausal women and showed mixed results, though comparison of studies were limited by varying study designs [98].

Most studies investigating black cohosh for menopausal and sexual health symptoms are small and short term. Most also provide conflicting data. Black cohosh is used more widely in Germany and other European countries for climacteric complaints. A German study evaluated the effect of black cohosh on menopausal symptoms with a randomized double-blind clinical trial for 12 weeks and found it to be most effective for subjective assessment of hot flashes and that better effect was seen when initiated closer to the time of symptom onset [99]. Another German study examined subjective report of menopausal symptoms using the Menopause Rating Scale (MRS) before and after treatment with placebo, black cohosh, and conjugated estrogens and found statistically significant improvement in atrophic symptoms and sexual function with black cohosh and not estrogen and also demonstrated increased vaginal epithelium after treatment [100]. While with limited data, these studies are somewhat promising for improvements with regulated medication.

There has been limited study of black cohosh's efficacy specifically in the breast cancer patient population. A 2011 prospective observational study found that among 50 tamoxifen-treated breast cancer patients, climacteric symptom scores declined significantly over a 6-month treatment period, with 90 % reporting good tolerability of the supplement [101]. However, a randomized trial comparing black cohosh to placebo therapy for 2 months in tamoxifen-treated patients showed no significant differences in patient menopausal symptom scores, nor differences in FSH or LH [102]. These limited studies did not include specific analyses of the agent's effect on sexual health.

While data on black cohosh's toxicities is limited and most studies report good tolerability to the supplement, most common reported side effects in clinical trials include nausea, vomiting, headaches, dizziness, mastalgia, and weight gain [103]. There have been limited case reports of fulminant hepatotoxicity during black cohosh therapy, but causality has not been established [104].

Combination Herbal Remedies

Various combinations of herbal remedies are utilized by patients, and some combinations have been formally assessed in the literature. St. John's wort (*Hypericum perforatum*) is an herbal supplement most frequently taken for depressive symptoms and mood support. There is little to no information regarding improvement in sexual function with combination herbal remedies. There are two clinical trials assessing its use in combination with black cohosh for menopausal symptoms in breast cancer patients which have found significant improvement in vasomotor symptoms as compared to placebo; however no comment regarding sexual function was made [105, 106]. The Herbal Alternatives for Menopause (HALT) study was a multiarmed prospective randomized trial comparing black cohosh alone, black cohosh combined with phytoestrogens, and black cohosh combined with multibotanical supplements, compared to placebo and systemic HT in 351 women suffering vasomotor menopausal symptoms over the course of 1 year. Combination methods did not improve sexual function. HT was the only intervention which demonstrated a significant difference in patient vasomotor symptoms, vaginal dryness, and increased serum estradiol at any time point. Conversely, HT was also the only therapy with a significant increase in abnormal uterine bleeding [107].

In sum, herbal remedies such as phytoestrogens and black cohosh have shown good tolerability but weak evidence for efficacy in a variety of trials, although conclusions are limited by a dearth of high quality evidence. Specifically, very little has been found regarding their use for sexual function or dyspareunia. Further, as with all herbal supplements, there is limited quality control over individual preparations in the United States as the FDA does not regulate these agents. Thus the safety of ingredients and effective dosing in supplements cannot be guaranteed. In both Canada and Europe, herbal supplements are more tightly regulated by their governing bodies; in Europe each herbal supplement requires authorization by an individual country's regulatory body [108]. Despite these limitations and concerns, herbal remedies remain a highly popular complementary therapy in breast cancer patients and survivors. Patients who choose to take these products should be encouraged to

share this information with their health provider. Recent studies have indicated that 25–50 % of patients using herbal or other alternative therapies do not disclose this information to their treating physician [109]. Thus, targeted discussions regarding usage of these products with the understanding that the studied efficacy is for vaginal and sexual symptoms are needed, as these medications are known to have significant clinical implications for patients.

Antidepressants

Breast cancer patients suffering prominent vasomotor symptoms have limited alternatives to HT, as clinicians must balance potential medication benefit with potential exacerbation of other medical and psychological issues, including sexual dysfunction.

The use of SSRIs and SNRIs for vasomotor symptoms was pioneered by medical oncologists for men with hot flashes secondary to GnRH agonist therapy for prostate cancer as well as women with breast cancer [110, 111]. However, while these medications are known to have partial efficacy in improving vasomotor symptoms, they may worsen sexual symptoms, a well-known side effect of antidepressants [112]. There is variation of the reported rates of sexual dysfunction associated with various antidepressants, and clinicians may take the likelihood of sexual side effects into account when prescribing SSRIs or SNRIS [113]. More recently developed SSRIs, such as citalopram and its enantiomer escitalopram, have shown significant improvements in vasomotor symptoms and were better tolerated than venlafaxine and fluoxetine [114, 115]. Additionally, limited uncontrolled studies of mirtazapine, a structurally unique SSRI, and bupropion, which acts on dopamine and norepinephrine, have shown significant decreases in hot flash symptoms and are less associated with sexual side effects than SSRIS/SNRIS [116, 117]. Of note, there is theoretical interaction with tamoxifen and many of the SSRIs, as both are metabolized through the CYP2D6 liver enzyme pathway, which could potentially limit tamoxifen's efficacy [118]. Though an impact on breast cancer outcomes has not been proven to date, many oncologists will limit antidepressant use to the SSRIs citalopram and escitalopram and SNRI venlafaxine for their patients on tamoxifen, as these are felt to be among the lowest risk for interference with tamoxifen metabolism.

Other pharmaceutical options for menopausal vasomotor symptoms include gabapentin and adrenergic agonists; however, these medications have little relevance for sexual function or satisfaction in postmenopausal women. There is no evidence for improvement in sexual or vaginal symptoms in these populations or for cancer survivors.

Case

The 46-year-old patient discussed at the onset of this chapter has multiple ongoing issues. She is currently receiving tamoxifen treatment and will likely be using this agent for several years. She has multiple options for her symptoms of vaginal dryness and painful intercourse. In the office, she would undergo evaluation with

thorough history of her symptoms including clearly defining what is painful for her and when her symptoms are bothering her most, i.e., does she have pain only with initial penetration or does she have dyspareunia throughout intercourse including with deep penetration? It would be important to see if she had tried anything for her symptoms thus far. Discussion regarding treatment options could commence after a pelvic exam to confirm the presence of atrophy versus another vulvar or vaginal disorder. Nonhormonal strategies such as lubricants, moisturizers, and lidocaine jelly along with vaginal dilators should be deemed as safe first-line interventions. If a discussion about hormonal therapeutic options is to be had, this can involve her oncologist and a careful review of available data. She and her partner may also benefit from both being present for the discussion, and they may also benefit from counseling if it is felt that some of her symptoms may be a result of distress from her symptoms or perhaps about her diagnosis.

Conclusion

Though remarkable improvements in breast cancer detection and treatment have emerged over the past two to three decades, a growing number of women are now living with long-term consequences and side effects from breast cancer treatment, including vasomotor symptoms and worsened sexual function. Providers should be proactive in discussing these issues with their patients, as many women may not be willing to raise these concerns for fear of not seeming "appreciative enough" of their cancer treatment and survival. Several options exist to assist breast cancer survivors with symptom relief, and selection of therapy should be tailored to meet the needs and values for each individual patient. Despite these options, future research is needed to find more effective interventions for women undergoing breast cancer treatment and survivorship.

Clinical Pearls/Pitfalls

- Sexual dysfunction is a common complaint in survivors of breast cancer, particularly in those patients who receive chemotherapy as a component of treatment and those who were premenopausal at the time of diagnosis.
- Patients with complaints of dyspareunia and vaginal atrophy should be offered vaginal moisturizers and lubricants as first-line therapy with the possible edition of dilators.
- Many oncologists will limit SSRI use to citalopram, escitalopram, and venlafaxine for their patients on tamoxifen, as these are felt to be among the lowest risk for interaction with tamoxifen metabolism.
- Herbal remedies such as black cohosh and phytoestrogens have no evidence of efficacy in treating sexual symptoms in breast cancer survivors but are frequently self-administered by patients. Providers should ask patients whether they are taking OTC herbal remedies.

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