Each Woman's Menopause: An Evidence Based Resource

For Nurse Practitioners, Advanced Practice Nurses and Allied Health Professionals

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This book is dedicated to Helen Doughty, MSLS, and to all medical librarians. Excellent clinicians never stop learning. The contributors to this volume have academic associations of varying formality, but each of the authors also has a vocation for delivering care. The highest quality care cannot be provided without the support of an integral part of the healthcare team, the medical librarian. These professionals assist in the dissemination of the information necessary for evidence-based healthcare to all clinicians regardless of academic affiliation, geographical location, or clinical preparation.

I particularly wish to dedicate this book to the person who has supported me, and thus informed my direct care of women as well as the indirect care stemming from a teaching and writing career, Helen Doughty, MSLS, Medical Librarian at John Muir Health System. Ms. Doughty works with skill, enthusiasm, and humility. She has seen the advent of all the tools we take for granted in information sharing today: the electronic transmission of large quantities of

knowledge, the algorithmic search engine, and the vast amount of online information. As she acquired new skills, the goal of her mission never changed. She is dedicated to supporting the clinician in the provision of care. Yet as we worked together over many decades, she deferred gratitude, viewing her critical contribution always as a part of the team. It is now my privilege to put in print a wholehearted thank you to Helen and to all her medical librarian colleagues.

Patricia Geraghty

Preface

Menopause is a shared developmental transition for every woman in the world fortunate enough to enjoy a typical lifespan. However the experience and the options for symptom management vary widely among groups and between individuals. The title of this book, *Each Woman's Menopause*, is chosen to spotlight this diversity, as well as the importance of adapting the body of knowledge to each person. A goal of every author has been inclusivity. It is challenging in medical literature to overcome identifying one population as the "norm," which then classifies all remaining individuals as "other." Clinicians providing care in regions outside of Europe or North America, and in diverse groups within those areas, often find the people they see are invisible in the data. The authors have faced the same challenge. The history of menopause includes women's stories from every continent. Likewise, the exploration of menopause symptoms illustrates the variability of both the experience and the impact on individuals within regions and with different social opportunities for health. The effect of chronic disease and the ability to optimize age-related health trajectories are tied to both the region's and the individual's resources. Finally, the management of symptoms and of related challenges includes therapies widely available as well as options pertinent to specific regions.

We are all at different levels in meeting women's health requirements. Many high resource countries extensively support pregnancy planning and outcome. For other nations, even menstrual care is absent. The implementation of menopause transition care faces formidable cultural barriers. All individuals deserve education and anticipatory guidance. Failure to treat those with moderate to severe symptoms increases healthcare costs and leads to further negative individual financial and health impact. If we apply the same standards to menopause transition care that we apply to pregnancy, the contrasts are staggering. The goal is that no one has intolerable menopause-related symptoms unless by choice. The tools to meet this goal require a vast and deep body of science with multiple and affordable management options and the availability of knowledgeable providers.

This book was also written to respond to the needs of health providers. The women's lived experience chapter reveals individuals in the stages of late reproduction, perimenopause, and postmenopause increasingly advocating for themselves and seeking solutions, only to be met by a lack of clinicians ready to respond. Menopause transition training in medical, nursing, dietetic, and other advanced practice programs is either absent or extremely limited [1, 2]. Content on women's

health is missing at most general medical and health conferences. This chasm leaves women open to interventions lacking evidence, increased costs, and the diversion of resources to those ready to exploit individuals in need. The science and the answers do exist. This volume consolidates the expertise of a multidisciplinary team so that providers in various settings can meet the needs of their clients.

Yet no analysis of a work is adequate without discussing its limitations. This book describes care for and cites research on women as a sex in a binary classification system using biological attributes such as chromosomes and anatomy. The menopause transition story of trans individuals, including transwomen, transmen, and nonbinary, has not been captured. A survey of transwomen indicated a desire to continue gender affirming hormones through and beyond midlife, but these individuals are not represented in any of the existing research [3]. The necessary precision of vocabulary and gender inclusive research guidelines are in their infancy [4, 5]. We look forward to a time when these individuals may also receive evidence-based care.

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Contents

Part I

Women's Perspective and Physiology of the Menopause Transition

History and Overview of the Menopause Experience

1

Patricia Geraghty

1.1 Evolutionary Theories of Menopause

Although the mean human lifespan through most of history was measured as a few decades, this was influenced by childhood and childbearing mortality. For women who survived these milestones, survival beyond menopause was typical [1].

The criteria for menopause, 12 month cessation of menses, is not adaptable across species as fertility cycles and symptoms vary. Using physiological markers other than cyclical bleeding, menopause can be defined in all mammals. However, excepting humans and four species of toothed whales—orcas, short finned pilot whales, narwhals, and beluga whales [2], the post-reproductive lifespan is relatively short [3, 4]. The rarity of a prolonged post-reproductive lifespan among all animals (see Fig. 1.1) is consistent with evolutionary theory that states there should be no selection for survival beyond reproduction. The evolutionary benefit for the more rare cessation of reproduction midlife was proposed by Medawar in 1952 as the promotion of increased offspring survival when a non-reproducing grandmother is available to assist in childrearing [5].

This has become known as the "Grandmother Hypothesis" [6]. In species with extended time from weaning to reproductive maturity, a non-reproducing and relatively young and vibrant grandmother provides generationally extended survival benefit to her kin by caring for children while the reproductive daughter or daughter-in-law continues to give birth and obtain food. Conversely, a grandmother contemporaneously reproducing with her daughter or daughter-in-law may hinder survival of both her own children given reduced years for childrearing, and of the next generation given competition for parental resources [7]. These hypotheses are supported by similarities in family structure and roles between the mammalian species

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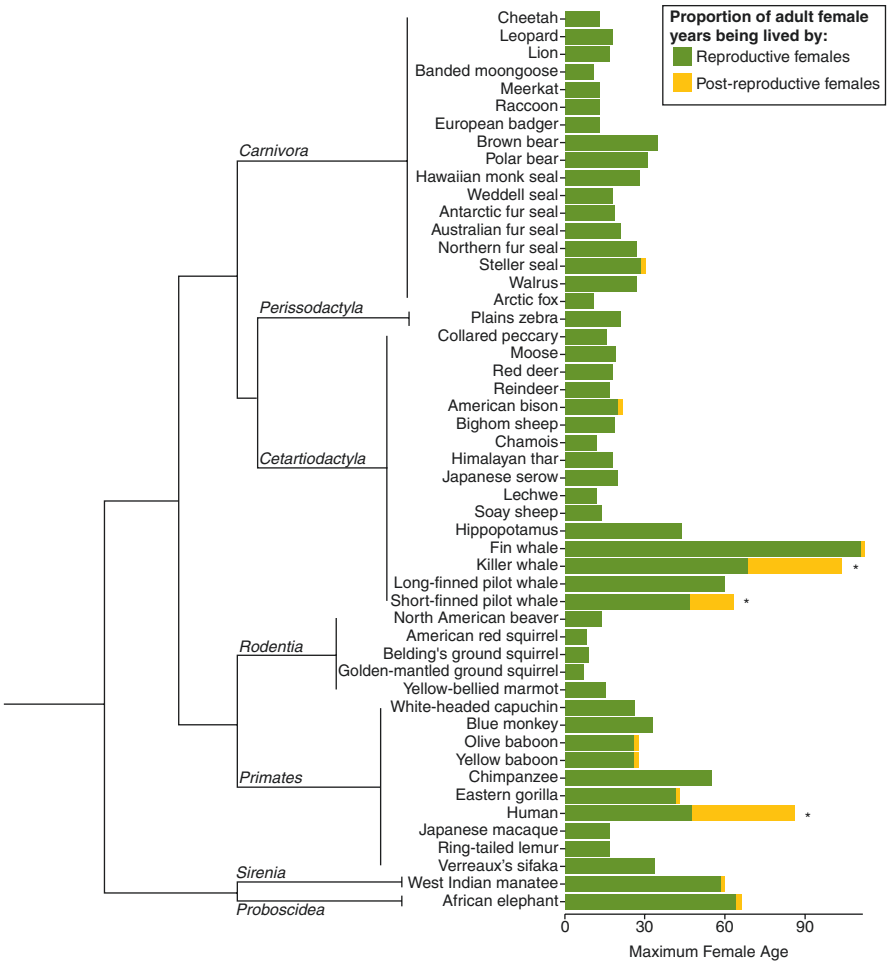

Fig. 1.1 Proportion of female years in the population being lived by post-reproductive individuals, scaled by maximum female age in 52 species of mammal. Each bar (right) shows the proportion of female years in the population being lived by reproductive (green) and post-reproductive (orange) females. The length of the bar is equivalent to the maximum female lifespan of the species. A significant proportion of adult females years being lived by post-reproductives is indicated by an asterisk (*). Species are ordered by family according to Meredith et al. [123] and within family alphabetically. Phylogeny (left) represents the relationships between mammalian orders [123], branches are unscaled. (From Ellis S, Franks DW, Nattrass S, et al. Postreproductive lifespans are rare in mammals. *Ecol Evol*. 2018;8(5):2482–2494. Published 2018 Jan 31. https://doi.org/10.1002/ece3.3856. Used with permission)

with midlife reproductive cessation [7], "natural fertility" hunter-gatherer contemporary populations [6], and historical birth records [8].

Orca whales are the only mammal with prolonged postmenopause lifespan other than humans for whom there is long-term data. In orca family structure, both male

and female offspring remain in the natal pod and mate non-locally with other pods. This structure allows for joint parental and post-reproductive grandparental support of offspring who share the pod's genetic make-up. Older, post-reproductive females enhance pod survival as food gatherers and leaders [9].

In hunter-gatherer societies with natural fertility and reduced access to modern healthcare, lifespan after menopause is still measured in decades. Blurton-Jones [10] looking at the Hadza community of hunter-gatherers in Tanzania, showed that the 40% of newborn girls who survived beyond childhood infectious disease and childbearing to age 50, then went on to survive into their 70s [10] . Hawkes and colleagues have described these women as "hardworking grandmothers" [6].

Finally, in order for the Grandmother Hypothesis to drive the evolution of a post-menopause extended lifespan, enhanced survival of all offspring must be shown when reproduction ends midlife. Engelhardt and colleagues looked at the Catholic Church baptismal and death records from 1621 to 1799 of French settlers in The St. Lawrence Valley of what is now Quebec, Canada. Daughters who began to reproduce while their mothers were still living had significantly more offspring and raised significantly more offspring to age 15 years than did their sisters who began reproducing when their mothers were already dead. Furthermore sisters who stayed within a 25 km range of their mothers had more "successful" offspring than sisters who moved further away from their mothers [8].

The Grandmother Hypothesis can be tested in animal models, in current natural fertility populations, and in historical records. The hypothesis supports a very positive effect for menopause and post-reproduction lifespan in women. The role of the post-reproductive woman providing productive leadership and guidance is beneficial to the social group.

1.2 History of Menopause

1.2.1 Antiquity

Most early historical documentations of menopause discuss either the state of menopause as an absence of fertility or mention only the age of menstrual cessation. Ancient Egyptians knew of menopause, but written reference in the time of Ramses II, about 1250 B.C.E., exists only in relation to sterility. Aristotle (384–322 B.C.E.) is credited with the earliest documentation of the cessation of menses in western medicine. As in most recordings of the classical antiquity, the focus is on age of menopause which he stated as 40 years up to age 50 years [11]. Subsequent records continue to discuss menstruation and childbirth but not menopause [12, 14]. It is almost another 900 years before Paulus Aegineta (600 C.E.) authors the first extant record of menopausal symptoms in a section on osteoporosis from his seven volume work *Epitomes iatrikes bibio hepta*. Given the real threat of maternal and neonatal mortality in childbirth and the small percentage of women who survived to midlife, we can infer many generations had both other priorities than menopause and small samples for observation.

An over-riding theme to the view of women from antiquity was that women's menses were inherently impure and dangerous to men, and sometimes to women. The retention of the menstrual blood, as presumed in menopause, made women vulnerable to multiple maladies [15].

One such malady was identified as hysteria, a mental disorder associated with the uterus and first identified in ancient Egypt, confirmed by Plato, later Hippocrates, and with continued support into the nineteenth century. Hysteria is purportedly caused by the uterus variously malpositioned, suffocated by intestines, or even wandering about the body. Illness arises when the uterus is "unhappy" with a lack of sexual activity or failure to conceive. Hysteria is not exclusive to the menopause transition but, with the cessation of menses and fertility, is seen as almost inevitable in menopause. Ancient symptom descriptors are vague, usually involving depression, anger, tremors, sense of suffocation, paralysis, or poor judgement. Soranus (first/second century) conversely, attributed hysteria to the toils of procreation and prescribed virginity, along with massage and exercise [12, 13].

1.2.2 Rituals as a Window to Menopause History

As in classical Greece and Rome, most surviving records from antiquity worldwide focus on menstruation rather than menopause. Many rituals around menstruation were incorporated into religious thought. Ritual practices, although dynamic, may provide early documentation of social views, particularly in the absence of other written records [16]. Most of these view menstruation as "impure" or "unclean." Tribal cultures and indigenous religions are each distinct, but grouped together represent a large portion of the world's population. Many tribal cultures restrict women's interaction with her community while menstruating. She may be confined to or simply reside in special living quarters during menses (7). In Kenyan creation myth, women founded the tribes and ruled ruthlessly. In response, men made all the women pregnant at the same time to preoccupy them, allowing the men to seize control. This mythology of pregnancy weaponized extends to women becoming more dangerous when they are no longer fertile [18]. Ancient Hindu mythology explains menstruation as a sign of guilt. Ancient Indian texts severely restrict women in social and religious activities during the reproductive stage of life, a ban that is lifted upon menopause. Singh et al. propose a positive attitude toward menopause in India today as women are allowed to more fully participate in society [19]. Both early Judaism and Islam restrict women's interactions with either her family or her entire community during menstruation, which is followed by ritual cleansing. There are no such rituals associated with menopause [20]. Christianity has no rituals specific to menstruation or menopause, but women may be considered weaker and inherently more sinful with the inherited guilt of Eve [15, 16]. Buddhism, in contrast, teaches that women stop menstruating when they enter the level of enlightenment of *arhatship* and are seen to have achieved control over their bodies [16].

What is striking from early concepts of menopause, menstruation, and of women as a gender, is the absence of the voices of women themselves [17]. The ancient

record is based on observation shared from the male perspective exclusively. This, in feminist philosophy, explains the focus on progeny and on women's only natural value in the bearing heirs to males [18]. All cultures lack the record of what may be presumed to be a rich oral tradition from mother to daughter and sister to sister. We can still wonder at the knowledge women shared in the privacy of female-only company despite cultural taboo on menstruation, sexuality, and menopause.

1.2.3 Early Concepts of Menopause

In the middle ages, Galen's (200 C.E.) model of the four elements (air, fire, earth, and water), with the corresponding four humors (blood, black bile, yellow bile, and phlegm) and the four temperaments continued to dominate physiological and medical theory [15]. Menstruation was viewed as a detoxification. Retained menses, or menstrual cessation as in menopause, placed the woman at risk for many diseases, many of which were non-reproductively related [21]. Hildegard of Bingen, a twelfth century Benedictine abbess, physician, and philosopher, only briefly described menopause within her extensive writing. Consistent with elemental and humoral theory, Hildegard used menstrual flow as an indicator of both personality and disease risk. She followed Aristotle's view. All theory of fertility and menopause continued to center on the womb as recipient of men's seed rather than on any contribution from the ovaries [22]. The prevailing view of both women's menstruation and women's menopause as dangerous did not change.

In the years encompassing the late Middle Ages and continuing through the Renaissance eras throughout Europe and later expanding into Colonial North America, women were tried and executed as witches [11, 23]. The numbers of those lost can only be estimated, and range from 35,000 to 100,000 women. The impact of fear and domination on survivors cannot be measured. The causes of this femicide are a complex mix of social change, church authority, and gender status [24]. Overwhelmingly these women were of menopause age, beyond the reproductive control of men. Often these women also provided reproductive healthcare including contraceptives and abortifacients to other women [11, 23, 25].

With the eighteenth and nineteenth centuries, as the plagues and the wars of Europe came to a hiatus, not only women of wealth and nobility but also more of the common women had longer lifespans [11]. Women began to demand management of menopausal symptoms either from motivation to "retain youth" or to ameliorate truly bothersome effects of hot flushes, sexual problems, and mental illness ascribed to this life stage. Western medicine took an interest in menopause for the first time.

In 1816 French physician De Gardanne coined the word menopause, establishing the life stage as a medical concern [21]. The age-related cessation of menses was discussed as a treatable disease or malady. Treatments were idiosyncratic, based on individual physician's opinions and standard humoral treatments of the time including bleeding, purging, emennogogues to stimulate menstrual flow, setons (a strip of linen or horse hair threaded into the dermal layer to promote drainage of inflammation) and leeches applied to the genitals or cervix [21]. Edward Tilt, a founder of the

London Obstetrical Society in 1858, held that the madness caused by menopause could only be cured by the removal of the uterus (hysterectomy) or by sedatives, opium, vaginal injections of lead or pulverized cow's ovaries [26].

Conversely, at the same time period and through the Victorian Era in England, the menopause transition was viewed as a normal life passage that must be endured. Fothergill [27] said that, as menopause was natural, nature would be the cure. Physicians who treated menopausal symptoms were derided [11]. This contrast established a dichotomy of menopause philosophy in Western Medicine, a natural event or a medical disease, rather than a continuum of classification encompassing both natural life stage with possible medical concerns.

East Asian medicine in the forms of traditional Chinese medicine, Japanese kampo, and Korean medicine began to address menopause in the late nineteenth century for the first time. Physiological theory then and now centers around kidney control of all aspects of growth, metabolism, and aging. A decrease of the kidney forces of both *shen yin* and *shen yang* occurs with aging. Menopausal symptoms develop when there is a relative excess loss of *shen yin*, allowing *shen yang* symptoms such as hot flashes to predominate. Diagnosis is achieved through tongue characteristics. Treatments were, and continue to be today, individualized, involving mixtures of herbs and acupuncture [28, 29].

The development of endocrinology The science of endocrinology was developing at the same time as the medical culture of menopause. Secretions of "emanations" critical to body function were mentioned as early as 1775 [21]. Organotherapy used transplanted or injected ground testes and ovaries [21, 30]. With the twentieth century, the term "hormone" was proposed by Starling and adopted into use by 1905. Extracts of sow's ovaries, follicular fluid, again from sows, and derivatives of cattle amniotic fluid were administered to women to relieve amenorrhea, dysmenorrhea, and menopausal symptoms [21, 30].

Doisy and Allen identified the follicle, rather than the corpus luteum or ovary, as the source of estrogenic activity in 1923. By 1929 active hormone was detected in urine of pregnant women and named estrone. The more potent estradiol was subsequently isolated by several laboratories from pregnant women's and pregnant sows' urine [21]. Nomenclature for estrogen and the various forms estrone, estradiol, and estriol was introduced in 1932 [30]. Parallel research on the function of the corpus luteum led to the isolation and identification of progesterone by independent laboratories in 1934 [21, 30, 31].

1.2.4 Menopause in the Twentieth and Twenty-First Centuries

The commercial production of estrogens for clinical use in Western medicine was rapid. In mere years from identification of estrone, orally bioavailable conjugated estradiol was isolated in the urine of pregnant women and marketed as Progynon[1]

[1] Progynon (Schering 1928) is a distinct formulation from the Progynon Depot/estradiol valerate (Cadila) available in Japan, Sweden, and India.

from Schering (Germany) in 1928 and from placental tissue marketed as Emminem from Ayerst (Canada) in 1930 [21, 32] . There remain only scattered reports that the conjugated estrogen products alleviated symptoms of the menopause transition without identification of the numbers of women treated or the characteristics of these women.

Major challenges in production of these products limited use and resulted in extreme costs despite high market demand [21]. Estradiol products extracted from urine of pregnant women had unsatisfactory taste and odor [30]. Then estradiol was identified and isolated in the urine of pregnant mares. Within two years this resulted in the launch of Premarin [conjugated equine estrogen (CEE)] in 1941 in Canada and 1942 in the United States. Modern hormone therapy was born [21, 33, 34].

Menopause in general health Concurrent with the development of the field of endocrinology, general medicine focused on the epidemiology of age-related disease as early as the late eighteenth century. "Hardening of the arteries" was noted to occur after menopause but attributed to be the result of ovarian vascular changes. In 1882 Bruns noted increased fractures in postmenopausal women. Postmenopausal osteoporotic fractures were documented in both natural and induced menopause by Bruns et al. in 1940. Similar associations of cardiovascular disease with premenopause, postmenopause, and induced menopause were documented in the initial data of the Framingham Study (Massachusetts, USA) in 1948 and in two later studies in Edinburgh, Scotland published in the early 1960s [11]. Associating mental health issues with women and women's roles continued [19]. With the development of Milltown® (meprobamate) and Equinil® (reserpine) in the mid-1950s, tranquilizers quickly became established as a treatment for women unhappy in their roles if not specifically for the menopause transition. Although gender bias is difficult to discern in the early years after release, when 1 in 20 Americans had a prescription for Miltown® or Equinil®, it quickly became the most marketed drug in the United States and the large majority of the marketing targeted women [35].

With menopause thus defined as a disease and the etiological target focused on deficiency of estrogen, marketing of conjugated equine estrogen also exploded after World War II. The use of hormones to prevent diseases perceived as due to menopause became obligatory in Western Medicine. Hormones, mostly CEE in the United States, and more often combined estrogen with progestin to control bleeding during therapy in Europe, were used as "replacement" for the "failure" of the ovaries [36]. In an article published in 1963 in the *Journal of the American Geriatrics Society*, Robert Wilson wrote "From a practical point of view, a man remains a man until the end. The situation with a woman is very different." He used the word "castrates" to identify postmenopausal women [37]. The same author published *Feminine Forever* in 1966, a book subsidized by Ayerst Laboratories and directed at the consumer, establishing the term and concept of hormone replacement. It became an immediate best seller, further driving Premarin sales [21, 38]. By 1975, estrogen had overtaken sales of tranquilizers to become the most commonly prescribed drug in the United States [19, 21, 38].

Many countries of the world did not participate in this hormone replacement consumerism. The governments of the Soviet block and other communist countries had trade barriers. Traditional medicine was more easily accessed and accepted in most other regions. Within the United States and the United Kingdom, non-white women and women with reduced economic resources did not adopt universal hormone replacement [36].

Within the healthcare professions, debate continued on the appropriate role of the menopause transition and exogenous hormones in women's health. A critical turning point in the conversation was an editorial and two independent studies published in the *New England Journal of Medicine* in 1975 showing increased risk of endometrial cancer in postmenopausal women using estrogen [39–41]. Utian cited this development as a decisive moment in the science of menopause, attracting more researchers and initiating the explosion of data that has occurred in the past 50 years [38]. Other health issues, including breast cancer, myocardial infarction, and thromboembolic events, subsequently began to surface [42]. The International Menopause Society, with a peer-reviewed dedicated journal *Maturitas,* was founded in 1978 to promote further scientific investigation. Australia and Micronesia, many countries in Latin America, and nearly all countries in Europe, North America, and Asia have established individual scientific menopause societies [19, 38, 43]. The science of menopause developed from retrospective to prospective and longitudinal observation and then to randomized controlled trials for the first time in 1970 [44].

The Women's Health Initiative This was the investigational milieu in which the Women's Health Initiative (WHI) study was designed and data collection began in 1991. Hormone replacement therapy was held to be universally recommended for prevention of osteoporosis, cardiovascular disease, and other aspects of aging. This contrasted with a growing push back from some women's and clinicians' beliefs that medicalization of menopause was an opportunity to reframe a normal life stage as a medical disorder and to garner increased profits for pharmaceutical companies [45].

The premise of the WHI was that hormones were of such benefit to women in the prevention of coronary heart disease (CHD) and osteoporotic fractures, the results would justify keeping women on hormones lifelong. Only postmenopausal women with age-related increased risk for CHD were included in this study of 16,608 women, mean age 63.5 years, using CEE and medroxyprogesterone acetate (MPA) or placebo, and 10,739 women who had previously had hysterectomies taking CEE alone, the largest randomized controlled trial of menopause management to that date [46, 47]. The CEE-MPA arm of the study was stopped at 5.6 years (planned 9 years) when slight increased risk for breast cancer was detected in the hormone group (revised later to RR 1.24; 1.01–1.53) [47]. Data were reported on the group of women taking CEE alone in 2004. There was no increased risk of breast cancer in this group; however, increased risk of stroke and VTE in both groups prompted early discontinuation of the CEE only arm of the study [48] (See Chap. 6). Though the public and many clinicians may have sought a "yes or no" answer to the question of menopause hormone use, possibly the largest contribution of the WHI to the management of the menopause transition was the dawning recognition of the

complexity of patient selection and the timing and duration of hormone use in relation to both risks and benefits.

The effect of the WHI discontinuance was almost immediate. Newspapers ran stories on the front pages. Health plans sent letters to their enrollees telling them to stop hormones. No distinction was made for late postmenopause use from menopause transition use or for women using estrogen only. In 2000, roughly 40% of women in their 50s and 30% of women in their 60s in the United States used menopause hormone therapy. By 2010 only 7% of women in both age groups did so [46].

The total history of the beliefs and science surrounding the menopause transition continue to influence all aspects of care of the woman in midlife today. Positive or negative attitudes to the life stage influence symptom profile, women's help seeking behavior, and both clinical training of health professionals and health professional's interaction with the midlife woman.

1.3 The Stages of Menopause

Within the modern explosion of menopause-related research in Western medicine, something crucial was missing. Experts noted the lack of diversity in the population of women from which data was drawn. Clinical studies were dominated by North America and Europe. The women were overwhelmingly of European descent [49]. Attempts at diversifying information were hampered by inconsistent nomenclature within the menopause transition worldwide [49]. Although vernacular use often refers to "menopause" as the time period when menstrual cycles and fertility are changing to the lifespan after cycles stop, or to the time period when symptoms presumptively related to ovarian aging are present, scientific terminology must be more precise if cross-cultural data is to be analyzed. The World Health Organization definition of menopause is the final menstrual period, defined by 12 months without menses due to the loss of follicular activity [50, 51]. Perimenopause is the time period from the onset of menstrual irregularities to the end of the first year after the final menses [52]. The Stages of Reproductive Aging Workshop (STRAW) sought to establish nomenclature and a more precise system for the menopause transition based on menstrual and qualitative hormonal criteria in 2001, and subsequently updated the staging system in 2012 (STRAW + 10) [50, 53–56]. The STRAW + 10 has become the gold standard for defining the menopausal transition. See Fig. 1.2.

There are nine stages of reproductive aging in life from menarche to postmenopause with seven of these stages pertaining to the menopause transition. The principle defining criteria is the change in menstrual flow, supported by hormone levels and ovarian antral follicle count on ultrasound. The supportive criteria may be difficult to obtain in low resource settings and are subject to a lack of uniform assay standardization. Symptoms were studied as outcomes of the progression through the stages and are thus excluded as criteria in staging [50]. The staging criteria have been validated in the ReSTAGE review of multiple cohort studies [57]. Strengths of the STRAW + 10 system are the non-subjective, noninvasive, and inexpensive staging criteria, and the generalizability of the system to women regardless of social

	Menarche					Menopause				
Stage	**−5**	**−4**	**−3b**	**−3a**	**−2**	**−1**	**+1a**	**+1b**	**+1c**	**+2**
Terminology	**Reproductive**				**Menopause Transition**		**Postmenopause**			
	Early	Peak	Late		Early	Late	Early	Late		
	Begins w/ menarche				*Perimenopause*					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)	3-6 years		*Remaining lifespan*
STRAW+10	Variable to regular menses	Regular	Regular	Subtle changes flow/length with shorter cycles (NAMS)	Variable cycle length Persistent ≥ 7-day difference (w/in 10 cycles)	Interval of amenorrhea of >= 60 days	No cycles			
FSH			Low	Variable	↑Variable	↑25IU/L	↑ Variable	↑ Stabilizes		
AMH			Low	Low	Low	Low	Low	Very Low		
Inhibin B				Low	Low	Low	Low	Very Low		
AFC			Low	Low	Low	Low	Very Low	Very Low		

Fig. 1.2 The Stages of Reproductive Aging Workshop (STRAW + 10) stages of reproductive life. (Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ; STRAW + 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab. 2012 Apr;97(4):1159-68. Used with permission Oxford University Press). *FSH* follicle stimulating hormone, *AMH* anti-mullerian hormone, *AFC* antral follicle count

demographics, age, body mass, or lifestyle characteristics such as smoking. The exclusion of symptoms as a staging criteria facilitates direct comparison of variations in the menopause experience across cultural backgrounds, economic and educational levels, and social settings [50, 58]. A limitation of STRAW + 10 is that while data was drawn from more ethnically diverse groups, clinical sites were limited to North America and Australia. Further, STRAW + 10 has limited application to women who do not have regular menstrual cycles such as women with polycystic ovarian syndrome, hysterectomy, endometrial ablation, or the use of a progestin IUD [50]. Some national menopause organizations do include symptoms as a criteria for initiation of the menopause transition before there is irregularity in menses, the STRAW + 10 late reproductive stage, even while acknowledging that menopause transition symptoms may be difficult to distinguish from other endocrine aging and normal aging [59].

The final menstrual period is a single point in time, stage 0. There is no endocrinological marker for the final menstrual period. The transition from the late reproductive stage to early menopause, stage −2, begins when there is a persistent ≥7-day variability in the menstrual cycle repeated within 10 cycles and is characterized by fluctuating levels of FSH on cycle day 2–5. When a woman has a cycle of ≥60 days, she is in stage −1, late menopause transition. At this point the FSH is more consistently elevated >25 IU/L and vasomotor symptoms are likely (see Chap. 8). While the duration of stage −2 is variable, typically stage −1 has a duration of 1–3 years. The first 12 months following the final menstrual period, though the woman and her clinician are as yet uncertain of her final menses status, is stage +1a. Stage +1b is the second 12 months after the final menstrual period, and +1c is the following 3- to

6-year time frame. In both stages +1b and +1c vaginal bleeding is absent, FSH stabilizes at an elevated level, and estradiol remains at a low level. Vasomotor symptoms are most likely in these stages. The remainder of the woman's lifespan is the late postmenopause, stage +2. At this point most women no longer have vasomotor symptoms and health issues of postmenopause predominate (see Chaps. 5 and 13), including symptoms of genitourinary syndrome of menopause (see Chap. 11) [50, 59].

1.4 Age at Natural Menopause

With all continents of the world contributing to the body of knowledge on the menopause transition, we have a more complete understanding of the variability of perimenopause symptoms and the age of final menstrual period among different genotypes, social settings, educational and economic levels, and ethnic and cultural backgrounds. Understanding the variability of the age of natural menopause, the factors that influence this marker, and the variability of menopause transition symptoms is helpful to the clinician counseling women with anticipatory guidance and with opportunities for modification of health risk. Early menopause, before age 45 years, has been associated with earlier onset cardiovascular disease and increased incidence of osteoporosis [60] (See Chaps. 4 and 13). Later menopause, after age 55 years, is associated with increased risk of breast cancer [60] (See Chap. 14).

1.4.1 Genetic Control of Age of Menopause

Estimates of the genetic control of the age of menopause from twin studies and familial studies vary widely, with heritability from 30% to 85% [49]. As menopause is dictated by follicular atresia, investigation into the genetics of follicular aging in premature ovarian insufficiency (POI), final menstrual period before age 40 years, and of delayed age of menopause, after age 55 years, have identified several genetic loci involved in control of the age of menopause [61] Most recently, antral follicle count as a measure of ovarian reserve, natural conception and childbearing after age 40 years, and healthy longevity have been correlated with identified genetic markers for menopause. This further illuminates the genetic control of the final menstrual period [62, 63].

A large number of DNA variants, each with relatively small effect size, typically underlie heritability of any trait. Overall large genome wide association studies (GWAS) with approximately 14,000 women have implicated 17 loci related to the age of menopause. These genes are involved in meiosis in the ovary, repressor of transcriptional RNA in the pituitary-adrenal axis, and in DNA repair. Genes regulating immune function and mitochondrial function also appear to have impact on the age of menopause. The identification of genetic markers has potential in determining ovarian reserve as a measure of fertility and in predicting age of menopause [61–64].

1.4.2 Lifestyle, Socioeconomic, and Health Influences on Age of Menopause

Research into age at natural menopause among diverse groups demonstrates the influence of social status and lifestyle factors as well as biology. Prospective longitudinal studies are rare and retrospective cross-sectional data is subject to many threats to validity including recall bias, the influence of contemporaneous social events, and inclusion of menopause due to other than natural follicular atresia. Comparison of data is further hampered by differences in measures reported, mean or median age [49].

Median and mean ages of menopause vary only slightly worldwide (See Table 1.1). In high resource countries and in women of Northern European or Caucasian ethnicity, the median age of the final menstrual period is 50–52.5 years [30]. This is generally the latest median age reported and similar age is seen in women in Japan [65]. In India, the mean age of the final menstrual period is between 45 and 46.2 years with a significant association of economic vulnerability and earlier menopause [66, 67]. There are consistent findings for the impact of decreased education and economic security, rural living, and lifestyle factors such as smoking with lower age of menopause across cultures and ethnic/racial groups [66–68, 70–72]. Inconsistent associations with age of menarche, parity, and maternal age at menopause have been found in studies of Turkish populations and other demographic groups [49, 60, 74, 75].

Tobacco smoking, with a clear dose response relationship, is consistently linked to an estimated impact of one year earlier natural age of menopause [60, 76]. Current smoking is of more impact than ever smoking. Passive tobacco smoke exposure has demonstrated inconsistent impact on age of menopause [60, 77]. Increased body mass index is also consistently associated with later age of menopause [78, 79]. Alcohol and physical activity have less defined effect on age of menopause with some studies demonstrating earlier menopause with high levels of physical activity or later menopause with low activity [78, 80, 81].

Studies vary in the parameters measured and these parameters may be subject to many social and economic variables. Markers that indicate economic vulnerability such as trouble paying for basics or experiencing food shortages may be obvious, while other markers such as a diet high in seafood but low in meat may more subtly reflect the effect of local food cost [60, 68]. A study of women in Latin America and the Caribbean demonstrated that sociocultural effects were cumulative [72]. A woman experiencing six or more indicators of socioeconomic adversity had a lower mean age of menopause than women with no indicators.

Controlling for socioeconomic variables within a region equalizes the age of menopause between racial/ethnic groups. The Study of Women Across the Nation (SWAN) is an ongoing prospective longitudinal study of 16,065 women drawn from 7 sites in the United States with 5 ethnic/racial groups including African American, white (Caucasian), Japanese, Chinese, and Hispanic. A factor identified with reaching menopause earlier was not being Japanese or white (Caucasian) identity, along with health/lifestyle factors such as smoking, diabetes, and poorer self-rated health

Table 1.1 Comparison of median or mean age of natural menopause with significant factors influencing timing of the event from studies selected for regional representation.

Author	Population as described in study and study design	Age menopause in years mean/ median	Factors influencing early menopause	Factors influencing later menopause
Taylor et al. [30]	Northern Europe/Caucasian *Meta-analysis*	51–52 median		
Tamada et al. [65]	Japan *Cross-sectional, retrospective*	50 mean		Uterine fibroma
Bharadwaj et al. [66], Ahuja et al. [67]	India *Cross-sectional, retrospective*	45–46.2 mean	Lower socioeconomic level Widowhood or broken marriage	Decreased parity
Wang et al. [68]	China *Cross-sectional, retrospective*	48.94 mean	Current smoking Underweight Higher physical activity Diet (increased seafood, less fruit, increased eggs, taking vitamins) Experience of severe food shortage Earlier age menarche Older age first birth	Diet (eating meat) Higher educational level
Okonofua et al. [69], Anolue et al. [70]	Nigeria *Cross-sectional, retrospective*	47–48.4 mean	Urban	Rural
Castelo-Branco et al. [71], Velez et al [72]	Latin America *Cross-sectional, retrospective*	49.4–50 mean	High altitude Lower educational level Low gross national product Smoking Nulliparity Multiparity (>5)	
Sahin [73]	Turkey *Cross-sectional, retrospective*	47 mean		

(continued)

Table 1.1 (continued)

Author	Population as described in study and study design	Age menopause in years mean/ median	Factors influencing early menopause	Factors influencing later menopause
Gold et al. [60]	United States *Multiethnic Longitudinal, prospective*	52.5 median	Difficulty paying for basics Smoking during follow-up Maternal natural menopause age under 49 years Not being Japanese or Caucasian identity Ever having diabetes Never having been married Having poorer self-rated baseline health Reporting more physical activity	Maternal medically induced menopause at ≥55 years or at 45–49 years Having some college or finishing college Prior use of hormonal contraceptives Employment Not smoking during follow-up Higher baseline weight Greater alcohol consumption Better self-rated health Lower physical activity

Table 1.2 Median incidence and range of menopause symptoms across geographical regions based on Makara-Studzinska [84]

Symptom	Median (%)	Lowest incidence/ region	Highest incidence/ region
Muscle, joint, and back pain	75	18% Europe	95% Europe
Vasomotor symptoms	56	18% South America	97% Europe
Urogenital symptoms and sexual disorders	58	15% North America	92% Africa
Mood changes	50	20% Australia	85% Europe
Sleep disruption	47	23% Australia	84% Africa

and with economic factors such as difficulty paying for basics, never having been married, and lower education. However, there were no racial/ethnic differences in median age of menopause when socioeconomic, lifestyle, and health variables were controlled [60, 82].

1.5 Menopause Transition Symptom Profile

Symptom experience at midlife is a complexity of menopause transition symptoms, symptoms of aging, and the societal context in which the symptoms occur. None of these factors have concise definitions and may overlap. Differences in study methodologies including age or menopause stage of inclusion and measurement instruments make comparison difficult [83]. The majority of women worldwide, 70–85%, have some menopause transition symptoms, but the type, severity, and clustering of symptoms must be viewed within the lens of culture as well as biological factors [76, 83, 84].

Menopause transition symptoms vary widely among regions. Epidemiological studies from Europe, North America, South America, and China represent much larger numbers of women than studies from Africa. A review of studies of menopause transition symptoms published between 2000 and 2014 of women living in Africa, both Americas, Australia, and Eurasia found the median and range of incidence of specific symptoms (See Table 1.2) [84].

Reports of myalgia/arthralgia, vasomotor symptoms, and sleep disruption are consistently the three most reported symptoms across regions [84–87]. Women also report qualitative cognitive changes in short-term memory and processing associated with the menopause transition. There are few longitudinal studies on menopause cognitive changes and these changes are difficult to discern quantitatively [88].

1.5.1 Cultural Influence on the Menopause Transition Experience

The experience of symptoms is not independent of the significance within the cultural setting. Some studies classify symptoms as psychological, somatic, and

vasomotor and others as psychological, somatic, and urogenital [89, 90]. Most of the regions of the world, with the exception of North America and Europe, experience somatic complaints such as muscle pain and joint and back pain as the primary menopause symptoms [84, 91, 92]. Muscle and joint pain, gastrointestinal complaints, and fatigue have physiological sources and are also appropriate ways of expressing psychological distress in some cultures. Sievert and Obermeyer looked at symptom cluster across regions. Women in the USA and Spain did not associate somatic symptoms with psychological symptoms, while women in Morocco and Lebanon reported emotional distress associated with dizziness, fatigue, heart palpitations, shortness of breath, headaches, and gastrointestinal complaints [92].

Culture also affects what symptoms are reported and how these symptoms are viewed. The frequency of reports of vaginal, urogenital, and sexual disorders may reflect opportunity and acceptability of discussing these topics with health clinicians [93]. Japanese women report "chilliness" associated with menopause transition sexual-vasomotor symptoms, but there is no Japanese language word for "hot flashes" [94]. Women of Japanese heritage (JA) were compared to women of European heritage (EA) in Hilo, Hawaii. Although the subjective experience of hot flashes showed significantly lower incidence in the JA group in baseline retrospective interviews, these differences were not seen in either 24-h subjective interviews or in objective nuchal skin temperature monitoring [95]. Finally, when symptoms are discussed in health texts using words such as "suffering" without data to substantiate the severity of the experience, the lens of the medical culture also comes into play [96].

Within regions, subcultures and racial/ethnic groups experience the menopause transition differently. The predominant perimenopause symptoms in North America and Europe are vasomotor symptoms [85]. When vasomotor symptoms are studied within race/ethnicity in the United States, increased incidence of clusters of vasomotor symptoms, sleep disruption, and psychological distress and the severity of these symptoms were correlated with lower educational level and African American race [31].

Neither are reports of symptoms static. Although there are still very few studies from Africa, the reported incidence of all symptoms exceeds other regions, and the incidence of women reporting vasomotor symptoms increased from 39% of women surveyed in 2009 to 77% of women in 2012. Reports of arthralgia increased from 59% in 2009 to 84% in 2012 [84].

1.5.2 Symptom Cluster Patterns

Women who experience one perimenopause symptom are most likely to experience multiple symptoms, each causing varying distress. The dominant symptom differs between groups of women. Symptom clusters may reflect shared etiology, shared variance, or different outcomes of individual symptoms [97]. Several studies have developed models of menopause symptom clusters [31, 92, 96, 98, 99]. Woods et al. determined five classes of symptom clusters in a multiracial/ethnic group of North

Table 1.3 Clustering and frequency of moderate to severe menopause symptoms from MsFLASH trials. Adapted from [100]. USA based multiracial/ethnic population (n = 899). Women w/o symptoms excluded. Sample included moderate to severe symptom 50% and mild symptoms 50%. College education 55% and secondary school or less 11%

Class (% of cohort) and descriptors with incidence				
Class 1: 10.5%	Class 2: 14.1%	Class 3: 39.6%	Class 4: 7%	Class 5: 28.7%
Hot flashes severe 39% **Sleep disruption** moderate to severe 69% **Pain** moderate to severe 20%	**Hot flashes** severe 21% **Sleep disruption** severe 96% **Mood** moderate depression 38%/ anxiety 28% **Pain** moderate 32%	**Sleep disruption** moderate to severe 60% **Hot flashes** severe 3% All other symptoms mild or none	**Sleep disruption** moderate 36% **Mood** moderate to severe depression 27%/anxiety 27% All other symptoms mild or none	**Low severity** hot flashes moderate 27% All other symptoms none or mild

American women in late perimenopause and early postmenopause. Women without symptoms were excluded from this study. Urogenital symptoms were not specifically assessed. The profiles yield a picture of how symptoms and severity clusters display across a population (See Table 1.3).

Similarly, the SWAN investigators identified a symptom cluster of vasomotor and sleep disruption associated with FSH levels. They did not include assessment of mood or urogenital symptoms. Women again grouped into five classes with incidence ranging from a low of 12% moderate VMS and moderate sleep disruption with low FSH rise, 13.2% high VMS and high sleep disruption with intermediate FSH rise, 14.4% dominant sleep disruption with lower VMS and high FSH rise, 21.2% dominant VMS with lower sleep problems and high FSH rise, to 39.2% low VMS and low sleep disruption with high FSH rise [101]. These studies demonstrate that symptoms appear in clusters as well as independently and verify the variety of experiences among women. The importance of thorough assessment and individualized management is confirmed.

1.6 Trajectory and Duration of Menopause Symptoms

Yet again, variability among and between women in the trajectory and the duration of menopause transition symptoms is the dominant characteristic. Inconsistency in adoption of the STRAW + 10 staging system creates challenges in analyzing trajectory and duration of symptoms across different studies [50]. Age-defined inclusion criteria is more likely to include the experience of women in late reproductive stage. When symptoms develop, worsen, or improve appears linked to duration.

Cross-sectional studies show variance of symptom clusters with time over the menopause transition. A trend of increased symptom type and symptom severity is observed in the progression from early to late perimenopause and then to early postmenopause [86, 89, 91, 98]. Women who experience surgical menopause with

ovaries removed report more severe symptoms than women who experience natural menopause [102, 103].

Among women who experience vasomotor symptoms, the duration of moderate to severe symptoms is much longer than previously thought, a median of 7.4 years in the SWAN cohort [104] and 10.4 years in the Penn Ovarian Aging Study (POAS) [105]. Women in both cohorts who experienced hot flushes early in the menopause transition, had more than 11 years duration of vasomotor symptoms.

There are few longitudinal studies on sleep problems. The SWAN cohort analyzed annual or biennial sleep reports. Sleep maintenance issues were present in 20–25% of the group at 10 years prior to menopause, then increased in frequency starting 3–4 years prior to the FMP, and continued to increase until stabilizing at 35% of women by 3 years after FMP. Sleep disruption did not demonstrate improvement in the 10 years after the FMP [106].

Weight gain occurs linearly starting during or just prior to the perimenopause stage, but is inconsistently defined as a perimenopause symptom or a symptom of aging or lifestyle [107, 108]. However, the linear weight gain masks a change in body composition. With the start of the menopause transition, the rate of increase of fat mass doubles while lean mass declines. After the menopause transition, the rates again equalize and flatten [107].

Genitourinary syndrome of menopause is an inclusive term for the urinary, genital, and sexual function issues associated with low estrogen. The symptoms are progressive across and beyond the menopause transition. Only 15% of women report symptoms prior to the FMP. This number increases to 40–54% postmenopause [109].

1.7 Concept of Symptom Management

If menopause is viewed as a life stage with possible distressing symptoms, then menopause management is about symptom management and risk avoidance, rather than disease management [110]. Symptoms can cause risk in themselves. Sleep deprivation is linked to chronic disease including diabetes and obesity [111–113] (See Chap. 9). Changes in behavior to avoid symptoms based on inadequate information may lead to illness independent of the symptom etiology. The woman who goes on a restrictive diet with the goal of alleviating somatic symptoms of menopause may induce complications [114, 115] (See Chap. 12).

While menopause symptoms are not an expression of disease, failure to treat symptoms can also cause harm. Duff et al. evaluated women living with HIV where a minority (17%) received menopause symptom management. Untreated severe symptoms were positively correlated with less use of retroviral medication and increased injection drug use and sexual/physical violence [116]. Tang et al. prospectively followed women with vasomotor symptoms who were or were not treated

with conjugated estrogen. When adjusted for age and co-morbidity, the treatment group had significantly lower 1-year total healthcare costs (−$1601 vs. −$503; $p = 0.044$) and inpatient costs (−1431 vs. −$28; $p < 0.0001$) than the untreated group [117].

The gold standard of symptom assessment is the woman's report of her experience [110]. All symptoms must be assessed. The parameters of assessment include intensity, location, temporal nature, frequency, affective impact, and threat posed by the symptom. The meaning of the symptom to the individual woman may affect her perception of the symptom and is critical to establishing management priorities and shared decisions [110]. The woman's report of her symptom is evaluated within the domains of her demographics and her culture. Culture is more than ethnicity or region (See Chap. 3). The individual's belief system around health and healthcare must be part of the assessment and the management plan. Each individual brings to the clinical encounter her beliefs influenced by the history of women's healthcare, her individual background and social needs, and her understanding which may be based on sources that lack depth or nuance [73, 118].

Good communication is critical to good outcome. Utilization of standardized menopause staging and assessment tools facilitate both communication and longitudinal assessment of the individual woman. The STRAW + 10 staging system has been previously described. There are many choices of symptom assessment tools [44, 89, 90, 119, 120]. The practice setting, time constraints, and clinical population cultural and language skills will dictate choice. The Menopause Rating Scale II is an 11-item subjective questionnaire that has been validated across cultures and languages internationally. It includes the presence and severity of somatic, psychological, and urogenital symptom clusters and is available for clinical and research use online (See Fig. 1.3).

1.8 The Clinician and the Woman in the Menopause Transition

Evaluation of menopause symptoms is also influenced by the clinician's own culture [121]. When the woman in the menopause transition and the clinician disagree on the importance of a symptom, shared decision making is more difficult to achieve [110]. The opportunity for education is bi-directional between patient and clinician and education begins with the first encounter. The goal is shared decision making that is well informed and effective.

Clinicians with differing academic preparation and licensure approach the interaction with the woman in the menopause transition with unique expertise and goals. The goal shared by all, however, is a shared decision approach of individualized symptom management and risk reduction.

Menopause Rating Scale (MRS)

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply. please mark 'none'.

Symptoms:	none	mild	moderate	severe	very severe
Score =	0	1	2	3	4
1. Hot flushes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3. Sleep problems (difficully in falling asleep, diffcully in sleeping through, waking up early)	☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5. Irrtabilty (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6. Anxiety (inner restessness, feelling panicky)	☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burrning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

Fig. 1.3 Menopause Rating Scale. (Heinemann L, Potthoff P, Schneider H. International versions of the menopause rating scale (MRS). Health Qual Life Outcomes. 2003; 1:28. Copyright © 2003 Heinemann et al; licensee BioMed Central Ltd, used with permission)

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Women's Voices: The Lived Experience of the Path to Menopause

2

Nina Coslov

2.1 Author Perspective and Chapter Context

The first half of this chapter will follow my path through surprise and confusion at changes I noticed before my cycles became irregular, the various types of sources I came across as I attempted to figure out what was going on and my experience seeking healthcare, to eventually becoming an advocate for menopause-related education. I will weave in other voices with my own. I've learned from listening to women over the past 5 years that my experiences are all too common. My personal investigation led to the creation of an online resource, Women Living Better (womenlivingbetter.org) to share my learning with others. I want to acknowledge that my story represents some people, but not all. Some are not symptomatic as they approach menopause. Some who seek healthcare find a provider that is knowledgeable, supportive and able to validate their experience. As a result, their path to menopause is very different. Every facet of this transition is a reminder of the uniqueness of each person's journey.

The second part of the chapter goes beyond my personal experience to cover women's experience with the Genitourinary Syndrome of Menopause (GSM), the broader impact that a symptomatic transition can have on relationships, caregiving and career, and what might create more successful healthcare interactions from a patient's perspective. Lastly, I focus on the importance of better understanding and recognition of the symptoms some women may experience during the STRAW late reproductive stage (LRS). My hope is that all of this will help healthcare professionals better understand those in the menopause transition who come through their door seeking information and support.

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2.2 Lack of Education Leads to Misattribution, Confusion, and Fear

Most women assume that menopause-related changes will happen at age 50 or later. When asked to think back to when they were 30 about at what age they assumed changes associated with the menopause transition would begin, 59% of women anticipated changes at 50 or later and another 28% said 45–49 years old. Only 13% assumed changes would begin before age 44 [1]. Because they haven't been given anticipatory guidance to expect changes in their late 30s or early 40s as ovarian follicles significantly decline and reproductive hormone patterns change, when the first changes occur, most don't know what is happening to them or within their bodies. It can be frightening. Women commonly describe, "feeling like they are going crazy" or "I'm just not like myself." Women are prepared through curricula for puberty and childbirth, but where is the education about this transition to menopause?

In 1996, a paper by LeBoeuf and Carter [2] stated that "the worst thing about perimenopause for most women is not knowing what to expect." In 2003, a study reported in JOGNN designed to understand how well women ages 30–50 could attribute symptoms to perimenopause and how often they discussed symptoms with a healthcare provider, concluded with, "the results of this study suggest that education and anticipatory guidance for women in the menopause transition should begin with women in their 30s. With many symptoms occurring as early as age 35, recognition of symptoms can greatly reduce the discomfort and fears that women experience during the perimenopausal transition" [3].

A 2014 survey of Korean women concluded, "that comprehensive education which is delivered as soon as possible on knowledge, attitude, symptom and management of menopause should be regarded as crucial for Korean midlife women. Education and intervention programs on menopause symptoms are thought to be essential in middle-aged women" [4].

Despite these repeated calls, the lack of preparation for and education about this normal life transition persists and as a result, women don't know when to attribute symptoms to hormonal changes. For many this creates fear about other than hormonal causes. In a 2016 Women Living Better (WLB) online survey, half of all women who possibly had hormone-related symptoms said they didn't seek help from a healthcare provider. When asked why, their responses reflected a lack of awareness about what experiences are related to changing hormones and the age at which this process can start:

> I believe my night-waking and trouble falling asleep after waking, have to do more with stress than menopause. —Beth[1]

> I honestly have never thought about these 'symptoms' or 'annoyances' as symptoms of menopause that could or should be discussed with my doctor.
> —Elaine

[1] All names have been disguised to preserve privacy. Quotes were sourced from submissions to the Women Living Better website and posts from The Menopause Chicks and the Perimenopause Hub Facebook Groups with permission from moderators.

> I didn't really perceive the increase in anxiety and mood swings etc. being linked to hormones, and being only 39, I felt they can't be linked to menopausal symptoms as I'm too young! I feel that I don't really have the forum to talk about these changes with a health care provider but having discussed with friends I realize we all are experiencing greater extremes of moods etc. in our cycles. —Amari

Although some women take these changes in stride, others describe feeling scared and alone.

> I searched the internet, talked to my doctor, talked with my husband and felt completely alone and desperate for answers. I was 43 when I first experienced many of these side effects and perimenopause never crossed my mind. —Susannah

> Doctors do not have the time or interest in this crippling phase of life leaving women feeling scared and alone until finding your site. —Kim

> Because I have to admit I feel a little overwhelmed and scared by it. —Mia

And others share feelings of loss of control, not like themselves and feeling unwell.

> About to turn 43 in a couple of weeks. I'd say I've been feeling 'different' now for about a year & I do seem to be experiencing symptoms common to perimenopause, mainly mood swings, anger, anxiety, forgetfulness (brain fog) & night sweats. Everything kicks off about 5 days before period is due. Sometimes there's a feeling of out of body experience- almost like I feel drunk & out of control. —Lisa

> Over the last 6+ years I haven't been feeling well but the GP hasn't been sure what the problem is. Over the last 12 months I have had lots of new symptoms such as joint pains, headaches, occasional night sweats, receding gums, anxiety, feeling tearful, hair loss, dry skin, cycle changed from 32 days to 25 days and feeling generally bleugh! —Toni

> I'm 47 (next month) and I've been "unwell" for a long time (approx. 2 years) with fatigue, joint pain, anxiety but not every day, brain fog, brutal periods – pain and heavy bleeding. I've suspected it may be perimenopause causing the symptoms but the delightful doctors I've seen wave their hand and dismiss my concerns. I think they think I'm a paranoid, hypochondriac middle-aged pain in the arse.... —Colette

Some women, in hindsight, express anger about the lack of guidance.

> The menopause symptoms that I experienced were ridiculous, and I was incensed that there had been no pre-warning about these... the fact that I was learning about them first after suffering for a year (and having them impact my relationship and my self-esteem) so greatly, was inexcusable. —Carlotta

Not only do women believe menopause-related changes will begin at 50 or later [1], but they assume they will skip a period before symptoms occur. In fact, early changes in experience often come before a skipped period or cycles that are dramatically different in length, but most people don't know this. The hot flash is the hallmark menopausal symptom and when something else arises first, such as

waking in the middle of the night or mood changes, most women assume something else is going on. This is the case especially when periods are still regular.

My Story
I didn't recognize my early menopausal symptoms. When I was 42, I began waking up at 2 am with lots of energy. I was often unable to get back to sleep for several hours. It seemingly came out of nowhere. I had no idea what could have caused it. My periods were still coming every month. Nothing in my life had changed.

Others echo similar confusion about new symptoms with regular periods and have no idea about the cause.

> My period just started to be unpredictable in the last 6 months. This is my main symptom. Before that started though I've had anxiety, weight gain and heart palpitations over the past 2 years that felt like they came out of the blue - not related to changes in my life or my behavior. —Rochelle

2.3 A Broader Range of Symptoms Than Commonly Recognized

In addition to sleep disruption, another early symptom for many is mood changes (see Chap. 10). Commonly women describe increased irritability resulting in sudden anger, mood swings, flying off the handle easily, or feeling rage towards others (often loved ones).

> I think I am on the cusp of perimenopause or just beginning, I haven't missed a period yet, but I have had some irregularity (period 2x a month). I get very bloated, more bloated than when younger, very irritable, I feel almost unhinged. —Leela

Other common mood changes are anxiety-related, feeling less able to cope with things, feeling more worried, and having panic attacks. On the Women Living Better website, women have described their feelings; "I feel like I'm in fight or flight all the time," and "I'm jumpy and have a sensitive startle reflex."

In a 2005 NIH State-of-the-Science Conference Statement on management of menopause-related symptoms, only vasomotor symptoms and vaginal dryness were linked to the hormonal changes of the menopausal transition. Sleep disturbance was noted as, "having some positive evidence of a menopausal link" [5]. In a 2020 WLB survey aimed at creating a better understanding of women's experience during the menopausal transition, participants were queried about 61 symptoms gathered from a variety of sources, that are sometimes associated with the menopause transition. Only two symptoms, vaginal pain in the absence of sex (3%) and more interest in sex (9%) were reported by fewer than 10% of women, all others were reported by more than 10% of people surveyed [1]. Most people associate the menopausal

transition with hot flashes, but lesser-known symptoms are also common. These include middle-of-the-night waking, mood changes, palpitations, dizziness, cognitive challenges, changes to the gastrointestinal system (such as nausea, heartburn, bloating, or constipation), changes to hair and/or skin and joint and/or muscle pain and have been investigated with respect to hormonal fluctuations in a few research studies to date [6, 7].

This is the research that hasn't made its way to provider training or mainstream media. As a result, women don't know to attribute symptoms to something possibly related to changes in hormonal patterns. Mood symptoms, in particular, can be frightening when they arise. Women start to question themselves and wonder what about their circumstances may be causing these sudden increases in irritability, anxiety, fearfulness, tearfulness, and sudden rage. Those who have relatives with mental health challenges, worry they are following a family pattern. In addition, these changes often come when women are intensively caring for young children or teenagers going through their own hormonal changes, when career challenges are peaking, and aging parents may require increasing attention. Uncertainty about the cause of mood changes, the fear about what they may signify, and the lack of time for self-care are all contributors to women's distress at this time.

So, what does a woman living in the twenty-first century do to figure out what is happening to her?

At first, she will tell herself it's probably caused by her busy life and try to ignore it, hoping it will pass. If she's lucky enough to have an older sister, coworker, or close friend, perhaps she'll ask her. However, there is a surprising lack of knowledge sharing by mothers or between friends. Do mothers not want to break the bad news to their daughters about what is coming? Or like childbirth, do they forget once they are through it? Is it because the path to menopause and menopause itself are stigmatized, and for many, undiscussable topics? Among friends, it seems that menopause is a topic that is either uncomfortable for the one who has questions, or the information seeker is concerned that they might make a friend feel awkward by broaching the topic.

> I didn't know what to expect with perimenopause and menopause. I wish it were a thing for mothers to talk to their daughters of what to expect so we're not convinced we're dying from something when it happens. I know so much of it is a social construct, but why do we not talk about this with women in their 40s, so they are prepared for it?? —Alanna

> I just want to say thank you. I am 45 years old, experiencing all the symptoms and NONE of my friends talk about it. We talk about everything else, but the word menopause/perimenopause is never brought up. No one expects it, and no one feels old enough for it. Thank you for a place where I can get real info. —Monique

And there may be cultural norms at play. As part of a large 2007 online study of menopausal experiences, a secondary analysis was done with women in four ethnic groups. Women in these groups opted-in to join online forums that met for 6 months to discuss menopause-related topics. In the Hispanic online forum one participant shared, "I feel that historically the women in our culture have been less open about

menopause as a whole which makes it difficult to get information from my mother or her peers. She will never share those types of issues because in her eyes, they are private matters." And another, "I feel that our culture makes us a little less likely to ask questions or share our concerns with others. I was always told to not make a fuss if wasn't feeling well...suffer in silence... A lot of patience is needed during this time. And don't forget that silence is the golden rule in menopause" [8].

2.4 Seeking to Determine the Source of New Experiences Is Hit or Miss

For the woman who doesn't have a friend or family member with whom to compare notes, or for whom her midlife experiences are not culturally discussable, she has no choice but to "tough it out" as long as she can. At some point though she realizes her new symptoms are interfering with her life and that she just doesn't feel like herself. At this point, if she has access to the internet, she will likely go online to research possible causes. Figure 2.1 below outlines the path that many women with internet access take to investigating and managing unexpected symptoms at midlife.

Online content increasingly has more to offer, both good and bad, related to the menopausal transition. A search today yields many more evidenced-based sites in the first 10 offerings than just 3 years ago. Menopause-related content, diagnostics, products, and programs are rapidly increasing in numbers. The word is out that there are many perimenopausal women who are suffering and looking for help. The menopause products and services marketplace is projected to be valued at $600BN by 2025 [9].

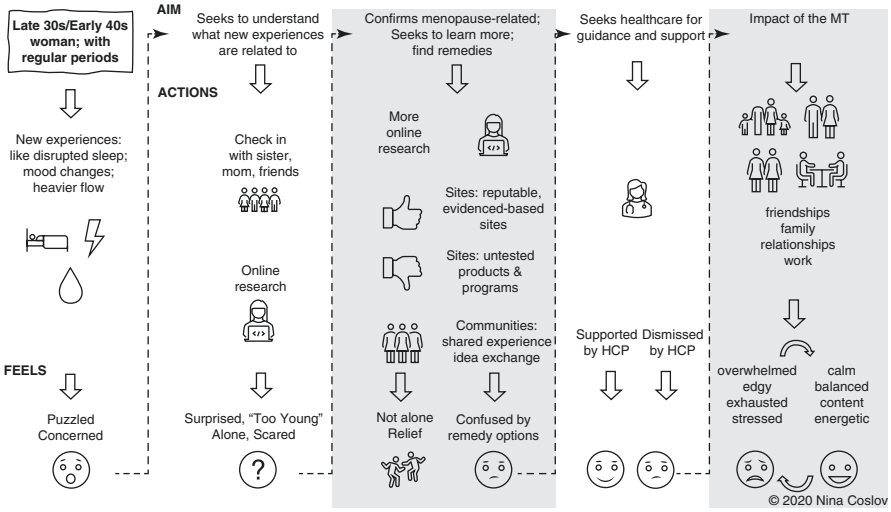

Fig. 2.1 A woman's aims, actions, and feelings as she tries to understand and manage changes at midlife

Online content available to those in perimenopause has many permutations. There are non-commercial entities: evidenced-based information-only sites created by medical institutions with affiliated research centers, professional organizations, or public-funded research institutions. There are also multiple versions of commercial entities: ad-supported medically oriented consumer information sites and sites selling products or programs and educating alongside their offerings. There are also sites offering information alongside community interaction and support.

Content may be created by individual providers (e.g., gynecologists, pharmacists, nutritionists, naturopathic doctors, etc.) who have their own sites, podcasts, or social media platforms. Some of these are aimed at providing information only. Others are hoping to build their professional practice. And still others have their own formulation of a supplement, a hormone therapy product or a program for balancing hormones or weight management on offer. What type of site one lands on depends on what words are used to search online.

The following story highlights the potential hazards of searching online for remedies and using them without the guidance of a knowledgeable healthcare provider,

> I went to the internet, looking for answers, and I finally found Dr. John Lee and more recently, Smoky Mountain Natural topical estrogen and progesterone "bio-identical" creams. I thought these were safe to use, but recently, a friend using a topical cream came down with aggressive uterine cancer. I don't want to stop using the cream, but now I'm concerned. Why is this such a completely unknown and unexplored territory when talking to doctors? Even an endocrinologist I talked with didn't know anything about bioidenticals. —Lorraine

A provider can help patients be better consumers of online information by recommending high-quality, reliable sources and suggesting a critical lens when reading any information presented alongside something that is for sale.

2.5 Confusing Messages About Research

Mainstream media, health information sites, and research intermediaries make the latest research available online to a mass audience. Too often, this comes with eye-catching headlines, terminology, and explanations that are difficult for a layperson to decipher. Even the articles that are accurate come with terms that without explanation leave a reader to draw their own conclusions about the differences between different types of progestogens. When interpreting research about HT and breast cancer, that might be an important distinction.

The 2020 JAMA article titled: *Association of Menopausal Hormone Therapy with Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials* talks about the breast cancer risk associated with CEE alone and CEE and MPA. The lay reader is unlikely to know that CEE is an estrogenic product, but not 17-beta-estradiol. She is also unlikely to know that MPA is a progestin but not progesterone. These things of

course matter in interpreting the results vis a vis therapies available to manage symptoms.

A BMJ study from October of 2020 titled *Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD* databases was summarized by Science Daily, an advertising-supported site whose tag line is, "Your source for the latest research news." The Science Daily title for this same study was: *New estimates of breast cancer risks associated with HRT. Results add to existing knowledge and should help doctors and women make the best treatment choices.*

Here the laywoman reads about "HRT" with no indication of which type of estrogen or progestogen was used. The article also uses the term "progestogens" as the causative agent for increased risk of breast cancer without explaining whether it was a progestin or progesterone or naming the agent used. How is a woman without in-depth knowledge supposed to interpret this in a way that will help her make a good decision for her? She can't. Only the trained reader will understand that there are different estrogen and progestogens studied, the subtlety about the "timing hypothesis," and the importance of absolute risk versus relative risk, but for a woman this is all very confusing. If she asks her provider, she may not get the clarity she's seeking either.

2.6 Online Support

A reassuring resource for many people are private interactive social media groups. These are sites that offer community support and information. I connected with two activists who started private Facebook groups to help others after their own experiences of not being able to find good information or support when perimenopause started for them. Their stories echo many of the sentiments expressed previously.

2.6.1 Shirley's Story

Even before she experienced changes related to the menopausal transition, Shirley Weir saw her older sister go through menopause early due to childhood cancer. At 36 years old, her sister was told, you better take hormones or everything will "sag and dry up."

Shirley was dismayed at the negative attitude her sister experienced but saw how hormone therapy was associated with her sister's restored health and quality of life. She had a primary care doctor whom she loved to support her through it. She knew it would be a time of change, but she was ok with that. So, at 41 when Shirley started experiencing PMS for the first time, brain fog and began raging with her children, "the little people I loved the most," she went to her doctor and hypothesized that this was the start of her menopausal journey. "I thought there would be a conversation about hormone therapy either now or down the road."

She was taken by surprise when her doctor said, "Oh you are 41, you are too young, if you want to go back on the birth control pill, I can do that. Or I can give you sleeping pills or low dose anti-depressant. You are too young for menopause." Neither perimenopause nor the late reproductive stage (LRS) was mentioned.

Shirley felt disappointed. This wasn't how she thought it would go, but then as she related, "I quickly went [from disappointed] to curious. I thought, there is no way I am the only one who is feeling like this." That curiosity and certainty that she couldn't be the only one, led to the creation of Menopause Chicks, a private Facebook group that has 30,000 members as of March 2021. The active rate is 80% which means that 24,000 people are active every month. Menopause Chicks is a social learning platform that offers both community and educational guides by topic.

2.6.2 Emily's Story

Emily Barclay was 39 when symptoms began. She was gaining weight, experiencing new fatigue and her moods felt extreme. She was worried something was really wrong. As she explains, over the next three and a half years she saw five different GPs—all at the same surgery in the UK. Each had different ideas about what might be wrong and sent her for different tests. None had answers.

A painful memory for her was the appointment where she had a sticky note with her list of symptoms to discuss and the GP took it and handed her a requisition for a "managing stress" group. Emily felt dismissed and assumed her doctor was chalking it all up to mental health symptoms when she was sure there were physical changes too. But she did go to the group and her biggest takeaway was, "you should sleep more." Looking back, she recalls that the very first GP she saw said, "this could be related to the menopause." But Emily thought, "I'm only 39 and I'm still getting regular periods." She reflected, "How I wish I knew then what I know now!"

At the end of the three and a half years of tests and medical appointments, she ended up back with that first GP. "I love her." Emily relates, "She and I together concluded it was the path to menopause and just having an idea of what it was provided so much relief."

Other women share this relief at finally understanding the source of their symptoms:

> I'm 43 and haven't had a period in a number of months. My doctor kept telling me I was too young but here I am. I am a bit relieved because perimenopause helps explain a lot about what I have been feeling for the last year or so. —Tanita

This overwhelming sense of relief was something Emily wanted others to feel. She felt sure that her journey with all the worry and fear must be happening to other women.

In May of 2019, Emily launched Perimenopause Hub—a private Facebook group for those on the path to menopause. Her vision was to create a resource with hubs of experts. The hubs include Fitness, Nutrition, Acceptance, Medical and Holistic.

In September 2019, after recruiting her first few experts, she launched the companion website perimenopausehub.com where the hubs live. As Emily puts it, "Each woman has her own set of challenges during this time, and each is going to want to tackle those challenges in different ways. I wanted to provide [options] for all women." Within 18 months, in March of 2020, her FB group had 8000 users and as of March 2021 it has 15,500 members, 14,925 of them active in the past month. She now has 40 experts contributing. Clearly these groups fill an unmet need.

2.6.3 The Challenges of Monitoring Online Support

In both Menopause Chicks and the Perimenopause Hub Facebook groups, people are admitted to the community once they've agreed to a set of ground rules. They can post freely and the impact of a post/comment format in the absence of clinical monitoring has been a challenge. Both Shirley and Emily use "post approval" so they can review each post before it's live. Shirley reads every post submitted and is the first one to comment sharing relevant content from either one of her educational units or an interview she's done with an expert. In this way, she aims to guide the conversation. After that, she lets it evolve.

Emily has two ground rules: (1) No multi-level marketing and (2) No diet speak. She leans towards letting most posts through, as she doesn't want to silence any women's experiences or feelings but will remind women of the rules when necessary. She has other moderators helping now that the group has grown, and they manage members who are treading close to violating community rules. Even still, people push the boundaries. They join the group, make a few innocuous posts, and then begin to subtly market their product or program. Emily and her co-moderators locate these people and promptly remove them. People find these groups highly affirming. One doesn't have to scroll far before uncovering someone struggling with something very similar. Being a member drives home the critical message: "You are not alone!"

2.6.4 Benefits of Online Support; Shared Experience Is Key

The network of shared experiences may be the single most valuable outcome of these communities. Women express incredible relief at realizing they aren't alone or going crazy.

> To realize I'm not going mad, I'm not alone in my situation and to be given such fab advice has made a world of difference to me. —Corinna

> I don't need answers, because I know there aren't any and whilst my [husband] is fab, he will try to fix what he can't. But I know you ladies understand and can help to cheer me on, because I've seen lots of that here and that's what we all need, encouragement, cheerleaders, chocolate and wine. Thank you for reading this and for being there, even though you don't know me. —Marta

> Brand new member here popping in to say that I've been dealing with my body and brain changes pretty much alone for the past year or two and am exhausted and depressed. I'm so happy to have found this group and its sisterhood for commiseration, advice and learning. —Sandy

> Hi Ladies and thank you for letting me join this group. I would like to say hallelujah I'm not alone! Have felt like a complete basket case thinking this can't all be just menopausal. —Priya

> … because I was experiencing the symptoms earlier than friends and colleagues, I felt very alone. —Dominique

The Perimenopause Hub has 67 posts a day and several comments in response to each of those posts. These private groups are providing connection and support for so many people.

However, there are many like Emily or Dominique whose symptoms begin earlier than they were expecting so they don't know the cause. They don't connect with a close friend or family member. And they don't seek an online group to help since they aren't thinking perimenopausal changes might be at play. Their next step is often seeking healthcare. It was Emily's next step and mine as well.

My story continued

I made an appointment with my excellent, experienced primary care physician to tell her about my new pattern of sleep disruption. I also attempted to describe a new feeling of not being able to cope as well as I used to, a feeling of increased fragility that was most definitely not like me. I followed with, could it be hormonal? Her question back to me was, "are you still getting a regular period?" When I responded, "yes," she observed that I was busy with three kids under 6 and offered me a sleeping pill and an anti-anxiety medication. With regular periods, she concluded the changes I was experiencing were not hormonally based. I left feeling misunderstood, disappointed, concerned, and certain that something else was going on

2.7 Dissatisfaction with Healthcare Interactions

Many women report similar experiences of disappointing healthcare interactions and being told they are too young.

> I'm now 41 and have been going to the doctor with peri symptoms for 2.5 years yet she (yes, female doctor) won't acknowledge perimenopause and says I'm too young to be menopausal. I don't know where to go now. —Yudy

> I spoke to my GP about perimenopause, but she thinks it's unlikely as I'm too young (at 43 I don't think so) I don't really know what to do at the moment. I'm unsure where to go for advice on what to take (supps or meds) and what to do next! —Amira

> I'm 44 and have been experiencing symptoms of what I've assumed to be Perimenopause since about age 40. I've experienced similar rejection [as] others by GPs on the basis of being too young, so I've been trying to manage the symptoms on my own. —Katrina

> At one point, I was told by a male physician that I just needed to deal with it with a very dismissive manner. —Stella

From the aforementioned 2007 online study of women's menopause experiences across ethnic groups, "women wished for better treatment by their physicians regarding their menopausal symptoms." Findings from the white, non-Hispanic group cited that women were largely dissatisfied with their healthcare interactions. "Many of the women had a surprisingly similar desire: they wanted healthcare providers to start 'listening to what the women report'. The women tried to justify their perception of not being heard. They identified their belief that physicians rushed into a decision for treatment without listening to what the women were reporting partially because of busy clinic schedules" (reprinted with permission of John Wiley and Sons from Im, 2008). This phenomenon has been corroborated by submissions to WLB website, the WLB 2020 survey, and confirmed in other online communities.

Currently, many providers aren't aware that symptoms can begin before cycle irregularity. As a result, women's concerns are often met with a dismissive response. The most common of these is that they are too young for perimenopause. This causes mistrust or lack of confidence in the provider, and sometimes with healthcare as a whole. This may leave a woman searching for alternative help and open to other possibly less evidenced-based remedies to mitigate symptoms or to practitioners offering unapproved and potentially unsafe products.

2.7.1 Confusion over the Value of Testing Hormone Levels

Many people seek certainty about whether they are perimenopausal and they push for hormone level testing. They are further frustrated by the healthcare provider who doesn't offer it or tells them their results are in the normal range.

> My doctor is invalidating. Can't be bothered with testing. He told me a couple of years ago I was too young. —Sumiko

> Dr. isn't interested, he says I'm too young and still having periods so that's it. He's agreed to do a blood test next month but said 'when it comes back normal, will you accept you need counselling for anxiety?' — Alicia

Women don't understand that testing in perimenopause tells you little to nothing due to wide fluctuations in hormone levels during this part of the female lifespan (see Chap. 4).

2.7.2 The Challenge for Healthcare Providers Who Care for Midlife Women

Healthcare providers are in a tough spot. The woman in the menopausal transition often has a range of symptoms—too many to cover in an 8 to 15-minute appointment. Women come to that appointment confused and looking for certainty on what is going on. A short amount of time and lack of a method to definitively diagnose perimenopause set this interaction up for failure. Furthermore, some symptoms such as heart palpitations, headaches, or dizziness elicit concerns about causes more serious than the MT and lead to the need for medical testing.

Those clinicians who work in a menopause-focused clinic, those who see lots of 40ish women in their practices, or those who have entered this phase themselves are perhaps best equipped to support women through this transitional phase.

Multiple factors contribute to why many clinicians aren't equipped to validate women's experiences, particularly when symptoms begin before consecutive cycles differ by 7 days. There is an historic lack of research about midlife women's health. Until the Stages of Reproductive Aging Workshop (STRAW) in 2001 [10] with revision in 2011 [11], the absence of a defined way to demarcate the stepwise or erratic progression though the MT hindered a more complete understanding. Even since STRAW, many studies haven't incorporated the staging framework, making it hard to harmonize findings [12]. Further, knowledge translation is slow [13] so recent research about the MT hasn't made its way into training curriculum [14]. And healthcare providers admit this. A respondent to the 2016 WLB survey commented:

> As a women's healthcare provider, I am embarrassed to admit that I know very little about this topic. I am surprised by the limited number resources relating to menopause. —Natalie

A comment on the Women Living Better website by an emergency room nurse was similar:

> I am 53 and so many changes are happening. The funny part is that I am an ER nurse of 20 years and you would think I would know a thing or two about women's issues at this stage, but that is proof of the lack of education out there for this life changing human transition, it has put things into prospective...this [information] and shared thoughts from other women is a comfort and has changed my perspective of this stage of my life, I have devoted my life to caring for others, it is comforting to know that there are others who give me tools to better care for myself...Thank you. —Celine

Another physician, a family medical doctor, made the following comment to Shirley Weir of Menopause Chicks, "I have 6 or 7 minutes with a woman. My waiting room has a backlog of patients. I know how to write a prescription, but I don't have the education around this [menopause]. The women in my community need someone to talk to."

A member of a community site shared:

> I love my doctor too, but she has admitted knowing very little about menopause. That's why I have two people I work with. — Faith

2.8 Cycle Tracking Yields Information About the Beginning of Hormonal Changes and Is a Source of Empowerment

Women can gain important knowledge and a sense of empowerment by tracking their cycles and symptoms. The recent explosion of menstrual cycle apps for smart phones is making this easier to do and increasingly common. This information can also be helpful to the provider who is trying to understand and offer support.

My Story Continued

When I saw my healthcare provider, I hadn't known that while regular, my cycles were shortening. I had had a 33–35-day cycles for many years but I had stopped tracking my cycles as I wasn't trying to get pregnant and pregnancy prevention was no longer a concern as my partner had had a vasectomy. I was still getting a period every month, but when I started tracking again, my cycle had shortened and was now 29–30 days. Had I known then what I've come to learn, I would have been able to link my sleep and mood changes to fluctuating hormones. Some healthcare providers don't know that a shortening cycle is an early sign of changing hormonal patterns so I'm not sure my physician would have attributed my experience to the MT even if I had told her my cycles were regular but shortening.

For those who do learn they have cycle irregularity through tracking, it's comforting to connect their experiences of disrupted sleep and/or mood or cognitive changes to fluctuating hormones but it still comes with some shock and surprise that this is happening much sooner than expected.

> Finding it so hard coming to terms with the reality of my situation, changing body, feelings. It's so hard, its end of era, yet in my head I'm young. All the symptoms, taking my body for granted. Sex, moisture, no flush, no moods, just me. Hit me like a train today. Feeling useless, what's the point! It's like, "that's it, you had your time" done. Sad. Sorry to be negative Nancy, but it's kind of overwhelming. —Jade

2.9 Optimizing the Healthcare Visit

After listening to many women, what becomes evident is the wide range of what they want in terms of support. Some women want confirmation that what they are experiencing is normal, some want to know that it's linked to hormonal changes.

Others want to learn about remedies to relieve symptoms. Here again, there are varied desires; some want non-hormonal remedies, and some want hormonal remedies. What we hear from many women is, "I want to know the root cause of my symptoms." And when they don't know the root cause, they are hesitant to follow through with their provider's recommendations.

At WLB, we created a tool called The Perimenopause Snapshot for women to use before their healthcare visit. This guide allows women to gather their cycle data, list a history of symptoms, and note their most bothersome ones. It further encourages them to think about what will constitute a successful outcome of their visit. Do they only want to understand the cause of their symptoms? Or do they also want to mitigate them? Which remedies would they consider: lifestyle changes, hormonal, non-hormonal options? The tool is available on the WLB website for anyone to use. Perhaps if healthcare providers sent a similar tool for completion and return in advance of the appointment, it could facilitate enhanced shared decision making, better patient–provider discussions, increased adherence to a treatment developed jointly by patient and provider. This would ultimately lead to better care and patient satisfaction.

2.10 A Later Symptom: Largely Undiscussed and Yet Treatable

All of the symptoms mentioned previously happen earlier in the menopausal transition, sometimes before significant cycle changes or more frequently as cycles become irregular before the final menstrual period. The genitourinary syndrome of menopause (GSM) is a cluster of symptoms related to the decline in estrogen, which happens closer to the final menstrual period or in the years just after. GSM can include vaginal dryness, itchiness, and pain with sex due to less lubrication and/or anatomical changes. GSM is estimated to affect 30–90% of women in studies in the USA, China, and Europe [15, 16] (see Chap. 11). GSM is a topic that most healthcare providers don't ask women about during healthcare visits [17] and most women don't raise it either [18]. GSM symptoms are the only symptoms that can be progressive rather than transitional and there are remedies that can help.

The lack of patient-provider discussion is a huge, missed opportunity. As stated in the 2020 North American Menopause Society's GSM Position Statement, "Clinicians can resolve many distressing genitourinary symptoms and improve sexual health and the quality of life of postmenopausal women by educating women about, diagnosing, and appropriately managing GSM" [19]. Women with untreated GSM symptoms can experience anatomic changes that are irreversible. Some women express anger that they weren't made aware of potential vulvovaginal changes and/or of treatment options [20].

2.11 Impact of Symptoms on Relationships and Work

After the surprise of symptoms earlier than expected and a possibly unsatisfactory interaction with the healthcare system, a woman has to contend with the broader impact her symptoms may have on her ability to be a good partner, parent, caregiver, employer or employee, collaborator and leader. This is an additional source of stress during a time when less stress is called for.

In the workplace:

> I had been running global projects for years and I suddenly found myself struggling to make decisions, I was filled with self-doubt. Lost so much confidence in myself. Also had this underlying fear of so many things.— Sabrina

> I'm starting a new career (at 46) and seem to be unable to take criticism without starting to cry! This has never been a problem before. I seem to be taking everything so personally and getting upset in front of managers etc. It really annoys me because I don't do that! —Tania

> How does everyone cope at work dealing with the symptoms? I've been off work with stress overload the last 3 months. Now recognizing a lot was to do with being perimenopausal leading up to a complete burnout!! —Ruth

> So, I had my appraisal in work yesterday and mentioned about my perimenopause clouding me for the last few months, I know I haven't been on my A game. Was offered counselling-aww that's so nice but I don't need counselling I just need a little more time than normal - I think??"—Malie

With children:

> I explained I can't concentrate, VERY intense mood swings that scare me and my children. —Selma

> I need help with my temper never really had a problem before, but I've noticed I have a really short fuse with my daughter and then last night my hubby really wound me up I shouted he shouted back he threw the milk across the side and I smacked him on the back and swore at him. I know I'm out of order for hitting him and I am angry with myself for doing it he is fuming with me and we had a huge argument. —Anita

With partners:

> 4 weeks ago, I went to my GP as I realized something had to change. My symptoms were getting worse, and I was regularly on the verge of punching my husband in the face. —Sharon

> Husband has accused me today of being distant and weird and not caring about his feelings. He cannot accept how I'm feeling these days and tells me to pull myself together...like it's that easy. —Orli

> How do I get my husband to stop blaming me and my hormones for everything? …Husband not been very understanding and saying I need therapy! Any suggestions how I can him to

understand and support me through this awful time that could go on for years gratefully received not sure I can cope anymore with the constant blaming me and my hormones.... it's making me even more tearful... thank you in advance. —Tamiko

I'm only peri menopause and it's like someone turned the power off. Sometimes not interested and he can't get me to climax, and other time not interested at all. —Heidi

It's been almost a year since my husband and I (who have been married for 17 years) had sex and I don't miss it an ounce. I have absolutely no desire.
—Angela

While mood-related symptoms affect many kinds of relationships, GSM symptoms sometimes coupled with lower libido directly impact intimate relationships.

2.12 What Would Be Game Changing in Menopausal Care: Recognition of the LRS

According to the STRAW framework, entry to the MT begins when cycles differ by 7 days. The stage immediately preceding this is the Late Reproductive Stage (LRS). There is much room for improvement in the care of midlife women by better understanding, educating and supporting women in this earlier stage.

The LRS is a single stage within the STRAW framework; however, there are at least three groups of women represented in this phase. There is the LRS woman who is hoping to extend her fertility. There is the LRS women who aims to prevent pregnancy. And there is the LRS women who is starting to experience symptoms related to the MT and seeks support managing those. And these three aims are not mutually exclusive as Fig. 2.2 shows:

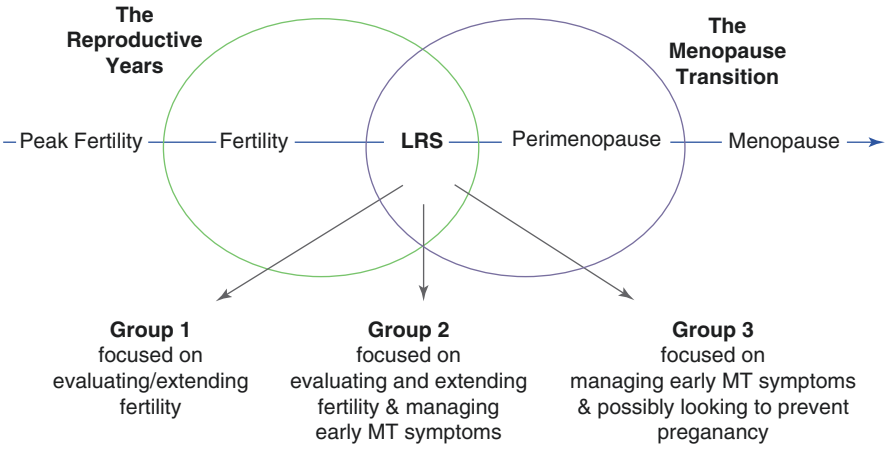

Fig. 2.2 The late reproductive stage—at the intersection of the reproductive and non-reproductive years—represents 3 groups, each with different aims. (© 2020 Nina Coslov)

2.13 Conclusion

Three things are needed to best navigate this transition. First, access reliable information that is not conflated with commercial motivations around selling a product or a program. Second, healthcare providers who understand the very broad range of symptoms that can arise, that these can begin while cycles are regular, and who stand ready to listen, support, and provide access to available remedies. And third, people need to know they are not alone. When these needs are met, it will be beneficial not only during the path to menopause but for the years that follow.

The final part of my story

As mentioned earlier, after all I had learned investigating my own experience with symptoms before cycle irregularity, I knew I had to share it with others. I co-founded womenlivingbetter.org, an evidenced-based website to provide education about how our bodies change.

I'll close with this message exchange from the Women Living Better Facebook page as it represents so many women's voices.

FB communication, Feb 2021.

RL: Hi I just wanted to say thank you so much for the website. It has helped me to feel sane again. I've read some articles from other women that explain perfectly what I am experiencing, and I don't feel so alone! and like I'm losing control of myself! I'm very grateful that I managed to stumble across this site while searching the Internet aimlessly like a blind woman with no idea of what I was searching for but needing someone to reassure me that what I'm going through can be perfectly normal for 40-year-old women. Thank you. Thank you. Thank you.

WLB: Thank you so much for reaching out. Your message perfectly explains why we created WLB. Please share with anyone you think might be helped.

RL: I will definitely be telling everyone about it!! I've even told my husband to have a look because it can help him understand some of what I'm going through.

WLB: Absolutely! Partners (and kids if you have them) definitely need to understand what we are going through. Isn't it hard to believe that we don't know about this until we get here and do our own research? I'm hopeful that we can change that. We all need to talk about it! Thanks so much for helping to spread the word.

RL: There definitely needs to be more awareness about it. I started noticing changes 12/18 months ago and I honestly thought I was going crazy. Thank god there is a website like yours to help us along this journey. And I've been talking and tell anyone that will listen to me about what's been going on because I'd hate for other women to feel that way... taking about it is definitely the way to go.

Health care providers could use more training in this area. When I went to the doctor, I went through all of my changes I've been experiencing over the last 12 months, but he would only say I was in the perimenopausal stage if my periods became irregular! Disregarding everything else I'd mention! That can be very hurtful and damaging to a woman who's not feeling herself.

Acknowledgement With gratitude to all those who share their personal stories. Together we can collectively fill the research gap and let each other know we are "not alone" and most definitely "not crazy," just perimenopausal.

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Communication with Women in the Menopause Transition

3

Juliette G. Blount

3.1 Introduction

Communicating with women about the menopause transition can create a unique challenge for healthcare providers. Talking about menopause symptom management requires the healthcare provider, who discusses vaginal health, sex and sexuality, risks, benefits, and side effects of treatment options, to have a level of knowledge and comfort. The patient must feel safe enough to ask and answer questions about these topics honestly for the best possible healthcare experience and outcomes. Culture contextualizes the lived experience of women transitioning to menopause, thus needs to be understood by the clinician. Effective communication with women at this pivotal moment in their lives can be facilitated by a patient-centered approach and by practicing cultural humility.

3.2 Cultural Competence vs. Cultural Humility

Ethnicity
The term ethnicity usually refers to social, cultural, religious, linguistic, and other affiliations of people grouped according to common ancestral origin or background. Like race, it is sometimes linked to perceived biological markers [1] such as skin color and facial features.

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Culture
Culture is often used as a proxy for non-white racial identity and, as a result, should be interpreted with caution [2]. This limited perspective of culture does not include other aspects, including age, sexual orientation, gender identity, geographic location, and many other factors

3.2.1 Cultural Competence

Cultural competence involves learning about the ethnic and cultural experiences, language, and traditional practices of multiple groups and identities. Many healthcare providers have attended cultural competence training and have been encouraged to practice cultural competence to improve patient–provider communication, patient satisfaction, and health outcomes for diverse populations. Saha and Cooper explored early cultural competence models in detail. They found that these frameworks viewed patients only as members of ethnic or cultural groups rather than as individuals with unique experiences and perspectives [3]. Influenced by cross-cultural medicine and trans-cultural nursing theorist Madeleine Leininger among others, the scope of cultural competence has expanded and encourages "acquiring some background knowledge of the specific cultural groups encountered in clinical practice, and developing attitudes and skills not specific to any particular culture, but universally relevant" [3].

While the expanded approach has improved cultural competence, there still exists a twofold problem. The first issue is that "mastering knowledge of the 'other'" [2] describes an attempt to learn specific values and practices of all groups within any one population. Because the world is rich with ethnic and cultural diversity, this may not be feasible. The second problem is the danger of stereotyping. After attempting to learn about the cultural practices of specific ethnic and cultural groups, healthcare providers may assume that all members of a particular group have similar behaviors and values. Also, focusing solely on race or ethnicity often ignores other aspects of identity, such as gender and sexuality, physical and mental disability, and socioeconomic status.

Race
Race is a social or cultural construct. A social or cultural construct is "an idea or system of thought rooted in culture" and accepted by people in society [4]. Race and ethnicity represent social or cultural constructs for categorizing people based on perceived differences in biology, such as physical appearance and behavior [1]. Essentially, race is not scientifically based. Societies have created and defined race.

As these models continued to evolve, a limitation of cultural competence is highlighted by the landmark Institute of Medicine (IOM), renamed the National Academy of Medicine (NAM), 2003 report. The report found minorities are less likely than whites to receive needed services, including clinically necessary procedures, even after correcting for access-related factors, such as insurance status. Report findings also linked healthcare providers' diagnostic and treatment decisions, as well as their feelings about patients, to stereotypes influenced by patients' race or ethnicity, which resulted in health and healthcare disparities for marginalized populations [5]. Extensive research documents the existence and effect of health and healthcare disparities on racial and ethnic minorities in the United States. Disparities represent a global problem for racial and ethnic minorities and majorities. There is also evidence identifying disparities in countries with government-supported healthcare systems such as Canada, Israel, Sweden, New Zealand, the United Kingdom, and many Latin American countries [6]. Cultural competence models do not address healthcare providers' implicit biases that influence patient interactions, clinical decision-making and contribute to health and healthcare disparities [3].

Implicit Bias

Implicit bias refers to the attitudes or stereotypes that affect our understanding, actions, and decisions unconsciously. These biases are activated involuntarily and without an individual's awareness or intentional control, are different from known biases that individuals may choose to conceal for social or political correctness, and cause us to have feelings and attitudes about other people based on characteristics such as race, ethnicity, age, and appearance. Implicit biases develop throughout a lifetime, beginning at a very early age, through life experiences, direct and indirect messages such as media and news programming [7].

Health Disparities

Health disparities are "a particular type of health difference closely linked with social, economic, and environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health linked to discrimination or exclusion" [8]. In the United States (US), the discussion of disparities has focused primarily on racial and ethnic disparities. More recently and increasingly in the US and international literature, socioeconomic status, gender disparities, disparities between disabled and non-disabled individuals, and disparities by sexual orientation have also been acknowledged [9]. Healthcare disparities differ slightly from health disparities that impact marginalized groups. Healthcare disparities are specifically related to healthcare quality differences that patients receive unrelated to access-related factors such as insurance status.

Social Determinants of Health
Social determinants of health are the circumstances in which people are born, grow, live, work, and age and are shaped by the distribution of money, power, and resources at global, national, and local levels. Social determinants of health are primarily responsible for health inequities, which are the unfair and avoidable differences in health status seen within and between countries [10].

Immigration is a social determinant of health, as are health disparities based on race, ethnicity, and gender, which all extend to the care of women in the menopause transition. A qualitative study of health prioritization in women who immigrated to Canada in midlife found that women perceived their health issues as a lower priority than their families' survival needs [11]. A systematic review focused on the menopausal experiences and perceptions of healthcare of women who migrated from their countries of origin in Turkey, China, Tunisia, South Korea, and India to their host countries in Australia, Israel, Sweden, the United States, or countries in Europe [12]. Of the 19 studies included, only 4 of the studies explored the menopause-specific impact perceived by immigrant women. Women expressed that they received little information and support about the menopause transition, even when receiving care from healthcare providers from the same cultural background. Most women who participated in the studies listed several reasons for their dissatisfaction: a lack of information provided by healthcare providers, treatment recommendations perceived as unnecessary, receiving menopause hormone therapy without sufficient education, inadequate treatment options counseling due to a lack of consultation time, and unfriendly mannerisms exhibited by the healthcare provider. The researchers concluded that dissatisfaction with healthcare services might reduce immigrant women's likelihood of engaging in health-promoting practices [12], and increase the risk for health disparities.

Healthcare providers should acknowledge the significance of these contexts, perspectives, and experiences when providing care relevant to and appropriate for this population of midlife women. Cultural competence frameworks fail to acknowledge social determinants of health, implicit bias of healthcare providers, systemic and institutional factors such as discrimination that all lead to health and healthcare disparities for marginalized groups. This realization by proponents of cultural competence resulted in efforts to incorporate cultural competence training to address these issues on both interpersonal and institutional levels and to accommodate the needs of a cross-cultural healthcare landscape.

Any attempt to define midlife must include considering the diverse contexts in which people live their lives and the values and belief systems that shape them. A shift in midlife perspective viewed as a time of freedom from financial and familial caring has been documented. However, women may not share these perspectives about aging across ethnicities and cultures, which may be influenced by social determinants such as class, access to education, and pay equity. It is these factors

that reduce women's choices and impact women as they grow older. As previously stated, social determinants of health such as immigration, poverty, discrimination, and racism can significantly influence midlife and warrant additional study. Consequently, it may be more beneficial to summarize midlife as a period connected to and formed by the diversity of lived experience [13].

A 2014 clinical practice brief for the North American Menopause Society (NAMS) of women's lived experiences in the menopause transition identified a vast diversity within cultures, ethnicities, religions, and nationalities regarding reported symptoms and healthcare concerns. Social determinants such as education, socioeconomic status, and stressors may also modify the underlying biology of menopause. However, what is less clear is whether learning about cross-cultural variation can inform healthcare providers caring for *individual* women [14]. While it is beyond the scope of this book to provide a comprehensive view of the extensive literature that describes the cultural and ethnic variation in the lived experience of the menopause transition, there have been numerous studies of women's experience with and response to the menopause transition from the perspective of race, ethnicity, and culture. Many studies demonstrate a wide variety as well as the commonality of experiences. Throughout the research, there is a common theme: aging and menopause are often viewed through a "Westernized," Americanized, or Eurocentric lens.

Feminist scholarship has criticized the medicalization of the life stage of menopause [15]. Self-valuation may become a reflection of how society perceives women's value. Often characterized as failing or deficient, women who internalize these messages may feel that as they age, they are no longer valuable, desirable, or capable of significant achievement [16]. The sociocultural devaluation of older women sends the message that a woman's worth is based on youth and fertility rather than on competence and contribution. "Western," defined as American or European, standards of aging often link midlife to the pursuit of youthfulness and a desire to avoid looking and growing older, which may not be a concern of women from other cultures.

A comparison of the cultural values of aging of Western and Eastern (primarily Chinese) cultures found that as people age, they shape their world in ways that maximize their well-being within the confines and definitions of their respective cultures [17]. The United Nations identifies over 40 different countries in Asia, and these countries include a myriad of ethnicities, cultures, and languages. A study of Taiwanese women found that some accepted menopausal effects on their sexual relationships as a reason to transition from a sexual relationship with their partner to one of companionship. In comparison, other women in the study saw their sexual relationship as meaningful enough to their individual or marital role to seek strategies to mitigate or adapt to the menopausal changes [18]. Ultimately, the lived experience and choices of the women studied varied widely.

The lived experience of the menopause transition and even the words used to describe common symptoms such as "hot flushes" are just as diverse. A study of Greek Cypriot women's lived experiences found that women found the menopausal body to be "uncontrollable." As a result, the physical changes associated with the

menopausal transition and aging are interpreted as "distressing" [19]. A study of Turkish women notes that there is no Turkish word to define menopause. However, most of the participants studied referred to the menopause transition as "natural," defined as an inevitable but difficult time for women [20]. Similarly, the term menopause does not exist in many Indigenous languages. The terms "The Change" or "Change of Life" are more common. Freedom, loss of youth and fertility, change in self-perception, and status in society were universal themes found in studies of Yamatji women of Western Australia [21], Movima women of Bolivia, South America [22], and Mi'kmaq women of Northeast Canada [23].

In a suburban resettlement area in Chandigarh, North India, menopause also signals change. A study shows women gain power and prestige in the family and society as they age. Women tend to ignore bothersome menopausal symptoms or tolerate them silently, giving more value to the freedom attained from the end of menses [24]. A study of women in four ethnic groups: Yoruba, Hausa, Igbo, and Ijaw in Nigeria, West Africa, found that menopausal symptoms perceived to be bothersome were less common in societies that view menopause as positive rather than a negative transition. However, the researchers did not find a significant difference in the perception and attitudes about menopause among the ethnic groups [25].

The Study of Women's Health Across the Nation (SWAN) is a multi-center, multi-ethnic longitudinal study designed to evaluate changes during the menopausal transition in the United States. Participants self-identified as Caucasian/white (47%), African-American/Black (28%), Japanese-American (9%), Chinese-American (8%), or Hispanic (8%) [26]. Additional research suggests that African-American women had a more positive attitude toward the menopause transition than Hispanic or non-Hispanic white women; Japanese-Americans and Chinese-Americans expressed the most negative attitudes [27]. While the SWAN study provides essential information about differences in perception of the menopause transition among ethnic populations in the United States, it raises concerns about bias in the study design. Reviewers should interpret conclusions with caution to avoid stereotyping based on race and ethnicity [28, 29].

A literature review explored both heterosexual and lesbian women in midlife transition and how those changes are affected by sexual orientation [16]. Lesbian participants who described sexual dysfunction related to menopause tended to engage in open communication with their partners regarding their sexual needs and preferences. They also expressed a broader, more flexible definition of sex and showed a greater willingness to adapt their sexual activities to accommodate physical changes in sexual response. As a result, the lesbian participants found the sexual changes associated with the menopause transition much less bothersome than heterosexual participants [16, 30]. By embracing an often stigmatized identity based on their sexual orientation, some lesbians may have developed a greater sense of empowerment and personal agency. As a result, they may feel less impacted by older women's negative perceptions and less restricted by the limited expectations placed on older women by society. Furthermore, the coming-out process may help to prepare some, who identify as lesbian, gay, bisexual, transgender, or queer

(LGBTQ), for the losses associated with aging, providing them with more resilience against the negative changes they may experience at midlife [16, 30].

Healthcare providers may consider learning more about the cultural beliefs and practices of the predominant cultural and ethnic groups in the area where they serve. However, clinicians must be careful to remember that the patient is not a representative of their entire race, ethnicity, or culture and that their menopause transition is their own. It is critical to focus on assessing the individual patient and learning about their personal lived experience.

3.2.2 Humility

Research by Tongeren et al. [31] identified personality characteristics associated with humility: acknowledging and owning one's biases and limitations, openness, and prioritizing others' well-being. Humility can be further contextualized through being humble about one's ideas, beliefs, or viewpoints, which involves a willingness to revise one's views in light of solid evidence. It shows that one cares more about learning and preserving relationships than about being "right" or demonstrating intellectual superiority. Through assessing other's perspectives, it is possible to maintain respect for differing viewpoints while holding onto one's beliefs. Cultural humility refers explicitly to humility about one's own cultural beliefs, values, and attitudes [31] (**See** Table 3.1).

3.2.3 Cultural Humility

Cultural humility in the clinical setting is a lifelong commitment to learning, active engagement, self-evaluation, and a critique of healthcare provider practices. The purpose of cultural humility is to rectify power imbalances in the clinician–patient interaction and develop mutually beneficial partnerships with the communities they serve. Intrapersonal cultural humility involves an awareness of the limitations of one's cultural worldview and controlling the natural tendency to view one's values

Table 3.1 Personality characteristics associated with humility

Personality characteristics vs. communicating with patients	
Intrapersonal Humility	Acknowledging and owning one's biases and limitations
Interpersonal humility	Openness and prioritizing others' well-being
Intellectual humility	Willingness to be humble about one's ideas, beliefs, or viewpoints, and to make revisions in light of solid evidence
Cultural Humility	Willingness to be humble about one's own cultural beliefs, values, and attitudes

Adapted from Tongeren et al. [31]

Table 3.2 Competencies for relating to patients with cultural humility

Competencies for relating to patients with cultural humility	
Intrapersonal Cultural Humility: Awareness of the limitations of one's cultural worldview Controlling the tendency to view one's values and culture as superior	**Interpersonal Cultural Humility**: Openness and willingness to learn about the cultural orientation of other people Letting go of the habit of using stereotyping as shorthand
Openness	Healthcare providers must have an open mind, be open to interaction with patients whose race, ethnicity, culture, gender, or sexual identity are different from their own, and be open to exploring new ideas.
Self-awareness	Be aware of one's strengths, limitations, values, beliefs, behavior, and appearance to others.
Egolessness	Be humble, including the ability to see all humans' inherent worth and value equally.
Supportive interaction	Implement methods and actions that result in positive human exchanges
Self-reflection and critique	Engage in a critical process of reflecting on one's thoughts, feelings, and actions, as an endless process of continual reflection and refinement

Adapted from Tervalon and Murray-Garcia [32]

and culture as superior. Interpersonal cultural humility requires openness and willingness to learn about the cultural orientation of other people. This practice includes being humble enough to let go of the false sense of security that stereotyping provides [32]. (**See** Table 3.2).

Much of the research on cultural humility limits the general meaning of the term culture to ethnic and racial diversity. A formal analysis of cultural humility conducted between 2009 and 2014 included 62 studies written in English representing disciplines from medicine, nursing, pharmacy, physical therapy, social work, and others. The review noted that cultural humility was defined in a variety of contexts. The studies reviewed included LGBTQ communities, battered yet economically privileged spouses, faculty–student relationships, minority occupational therapists serving patients in a majority group, nurse–physician relationships, and patient–physician relationships [33]. The groups included in the studies demonstrate how a multitude of cultures and factors influence lived experience and must be considered when interacting with interpersonal and intrapersonal cultural humility.

The concept of cultural humility can be useful when healthcare providers interact with someone different from themselves. Cultural competence implies "I am the expert" versus cultural humility, which acknowledges that "You are the expert" [34]. The practice of cultural humility can improve the experience of patients who may be marginalized based on their race, ethnicity, religion, gender identity or sexual orientation, socioeconomic status, and geographic location [34]. The concept of cultural humility can be applied when caring for patients who do not identify as binary male or female. Because sexual orientation and gender identity are complex, patients who identify as LGBTQ face unique challenges and healthcare disparities [35]. Healthcare providers who commit to the practice of cultural humility and

Table 3.3 Patient-centered care and communication

Patient-Centered Care: Providing care that is respectful of and responsive to individual patient preferences, needs, and values and that ensures patient values guide all clinical decisions and care quality improvement initiatives.	**Patient-Centered Communication**: Approaches that facilitate patients' access to accurate and understandable information to achieve patient understanding.
Care must: Be respectful to patients' values, preferences, and expressed needs Be coordinated and integrated Provide information, communication, and education Ensure physical comfort Relieve fear and anxiety by providing emotional support Involve family and friends	**Communication must**: Include communication about their diagnosis, prognosis, treatments, follow-up, and support services Consider patients' individuality, values, and needs

Adapted from IOM/NAM Report [36], Tzelepis et al. [37], and ISQua Report [38]

remain open to learning about concepts of sexual orientation and gender identity that may be unfamiliar to them will be better able to provide patient-centered care. (**See** Table 3.3).

3.3 Patient-Centered Care and Communication

The development of the patient-centered model is linked to perceived limitations in the "biomedical model" [39, 40]. The biomedical model focuses on signs and symptoms of illness, identifying and treating disease, and accurate diagnosis of pathology so that appropriate treatment can cure the illness. Patient-centeredness expands the view of illness by incorporating the patient's experience.

In the summary of their comprehensive report on the quality of healthcare in America, the Institute of Medicine (IOM), renamed the National Academy of Medicine (NAM), endorsed six domains of patient-centered care [36] and approaches to patient-centered communication [37] (**See** Table 3.3). Recommendations in the IOM/NAM report include redesigning healthcare delivery systems to ensure that patients are fully informed, retain control, and participate in their care delivery whenever possible. Systems must facilitate the application of scientific knowledge to practice and provide healthcare providers with the tools and support necessary to deliver evidence-based care consistently and safely [36]. The International Society for Quality in Healthcare and the International Hospital Federation, organizations who promote worldwide quality and safety in healthcare, echo this guidance in a 2019 joint statement that identifies patient-centered care as the foundation of patient safety and endorse it as essential to the development of all initiatives to improve care [41].

Ultimately, in a multicultural world where power imbalances exist, cultural humility is a process that results in mutual empowerment, respect, partnerships, optimal care, and a commitment to lifelong learning on the part of the healthcare

Table 3.4 The QIAN Healthcare Curriculum Model

Self-**Q**uestioning and critique	Healthcare providers can ask themselves questions such as, "What are assumptions that I make about the world?"
Bi-directional cultural **I**mmersion	Emphasizes a patient–clinician cultural exchange for mutual understanding and awareness of inherent power imbalances
Reciprocal **A**ctive-listening	Expressed and strengthened by stories and narratives shared by the patient and clinician
Flexibility of **N**egotiation	Transforms the clinician–patient encounter into a "therapeutic alliance" through equal information sharing

Adapted from Chang et al. [42]

provider. In general, individuals with cultural humility are more likely to consider the importance of cultural backgrounds, understand their cultural limits and privilege, and take a genuine interest in learning about others' cultures [32]. Most research in this area is centered in Western, educated, industrialized, wealthy, and democratic countries, with nearly all of it in the United States. Further examination of the cross-cultural experiences and effects of humility and research in different cultures and nations must be conducted [31]. Healthcare providers who want to move toward the practice of cultural humility must commit to learning at the highest level: personal transformation. Cultural humility involves a change in one's overall perspective and way of life. Practicing cultural humility means being aware of power imbalances and being humble in every individual interaction [32].

3.4 The QIAN Healthcare Curriculum Model

The **QIAN** healthcare curriculum model emphasizes cultural humility and enhances patient-centered communication skills required for healthcare providers to be effective. The model is also adaptable to cultural groups worldwide by improving cross-cultural communication skills. Qian means "humbleness" in Chinese, is based on ancient Chinese philosophers Laozi (Daoism) and Confucius, and is an acronym that describes key elements of cultural humility. These skills are essential for healthcare providers when communicating with a woman about the menopause transition [42] (**See** Table 3.4).

3.5 Communicating Effectively with Cultural Humility

3.5.1 Establishing a Trusting and Supportive Relationship

Culturally humble, patient-centered communication and care help create a trusting and supportive relationship and an environment that facilitates the patient sharing their own lived experience of health or illness (**See** Tables 3.2 and 3.3). Many women have had exposure to trauma, abuse, and exploitation within their families, intimate relationships, and navigating the healthcare system [43]. A patient's lived experience may influence the acceptance of communication and education about

Table 3.5 Competencies for communicating with patients with cultural Humility

Competency	Example
Openness	"Tell me about how women in your culture/in your family perceive the menopause transition?"
Self-awareness	"I am not as well versed in complementary and alternative medicine (CAM) as I am about conventional therapies, but I am willing to review the available data with you."
Egolessness	"I understand your insurance may not cover the cost of this therapy. You deserve to feel better. Let's explore other therapeutic options that may be a more affordable alternative."
Supportive interaction	"Thank you for your willingness to follow up with me. Please do not hesitate to reach out to me if you have any questions or concerns. We can always discuss the treatment plan at your next visit and make modifications as needed."
Self-reflection and critique	(Ask yourself) "How could that patient encounter have gone better, what style of communication might the patient respond best to, what tools/resources might be used to improve communication and mutual understanding?"

Adapted from Foronda et al. 5 Key Attributes of relating to patients with cultural humility [33]

their health. Their culture may be directly or indirectly associated with health-related priorities, decisions, and behaviors. The effect of communication on health outcomes is often indirect, suggesting that patient-centered care immediate outcomes such as feeling understood, trust, or the motivation for change may increase adherence to the treatment plan and self-care. "I want to make sure that I've provided you with everything you need to understand your symptoms. Patients usually have questions because menopausal symptom management can be complicated. Can you tell me what you understand, and then I can help clarify?" is an example of healthcare provider communication that demonstrates a desire to work toward these outcomes by inviting the patient to be a partner in their care [44]. (**See** Table 3.5).

Complementary and Alternative Medicine (CAM)
Complementary and alternative medicine (CAM) is a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine [45]. CAM practices are dynamic and may include everything from herbs and supplements to acupuncture.

An essential outcome of cultural humility utilized in patient-centered communication and care is the establishment of trust. For example, willingness to discuss CAM in addition to menopause hormone therapy (MHT) may appear less biased against alternative therapies, thereby improving patient trust [46, 47]. Despite the substantial use of CAM to treat menopausal symptoms, women still reported feeling ill-informed about CAM treatment options due to poor communication with their healthcare providers. As a result, they were less likely to disclose their CAM use to their providers [47].

The perceived advantages of CAM use reported by menopausal women were that CAM therapies and products are natural and safe, relieve symptoms, maintain general health, and have no or mild adverse effects. However, negative experiences and poor communication with healthcare providers resulted in insufficient knowledge of safety, efficacy, and potential CAM use risks. This uncertainty did influence some women's decision not to use CAM for their symptoms. Lack of trust may be why some menopausal women preferred to receive CAM information from sources other than their healthcare providers. Some women may not feel comfortable initiating a discussion about CAM. Healthcare providers must make concerted efforts to emphasize their willingness to help, communicate their knowledge of menopause symptom management options, and make their desire to discuss CAM known to the patient [46, 47].

Humility is a prerequisite for patient-centered interaction as the healthcare provider surrenders their authority role in patient interactions. Patient-centered communication focuses on four aspects of the patient experience: their ideas about what is wrong with them; their feelings about their symptoms or illness—especially their fears; the impact of their presenting problem on their quality of life; and their expectation about what should occur to manage or resolve the issue. Acknowledging these aspects, the provider becomes an active learner and enters a partnership with the patient [48]. Healthcare providers must remember that the patient is the expert in their own lived experience. When these factors are incorporated, patients are more likely to feel heard, cared for, and invested in the treatment plan [15, 49].

3.5.2 Gathering Information

When gathering women's health history about their menopausal experience, it is essential to remember that the menopause transition is a phenomenon that women have in common. Still, each woman's journey is unique [48]. The stages of menopause are a normal transition, and women who are experiencing menopausal symptoms are not ill. However, it is common for women to feel unwell or "not like themselves" during this life transition. The amount of distress a woman may experience is influenced by what menopause means to her. Variation in the meaning of menopause and attitudes toward menopausal symptoms may lead to differences in help-seeking behavior and therapeutic choices. When exploring symptom management options, healthcare providers must focus on the "bothersomeness" or the impact on the woman's quality of life and level of functioning rather than only the frequency or severity of symptoms. Because some women do not find hot flushes or other physical symptoms bothersome, help-seeking behaviors vary across cultures [14].

Healthcare providers must practice cultural humility when gathering information about their patients' lived experiences and in understanding their menopausal journey. When completing the health history, questions that are important but follow the typical medical model for obtaining the health history may include: "When did you start your menopausal transition, What are your symptoms, Where are you experiencing pain, How long does your discomfort last?" Asking questions to elicit

information about the patient's lived experience is equally as important: "What are you most concerned about, How do you feel about this life transition, How can I help you through the transition, How are your symptoms impacting your life?" Additional questions may provide a more holistic perspective: "What was your mother's experience with menopause, How have your symptoms impacted your partner/your children, Why do you think this is happening to you now?" Asking specific questions about symptoms is extremely important because many women may not realize that some of their symptoms are related to the menopause transition: "Do you have hot flashes or night sweats, How is your sleep, Do you have mood swings such as easy anger or easy tears, Do you have muscle and joint pain, Do you have leaking urine, vaginal dryness or irritation, or pain with intercourse?" Listening without judgment and/or projection creates space for women to share their experiences with the menopause transition and symptoms.

Practicing cultural humility can facilitate patient-centered communication about important and sensitive subjects. Healthcare providers may find talking about sex and sexuality uncomfortable, which then becomes a barrier to effective communication. Younger healthcare providers or those of a different gender or sexual orientation than their patients going through the menopause transition may find creating space for women to express concerns, ask questions, and discuss symptom management options particularly challenging. Research has identified strategies to help healthcare providers develop and maintain a safe space for women to talk about sex and sexuality aspects of their menopause transition by acknowledging that many women in the menopause transition enjoy active sex lives [50]. Questions specific to sex, sexuality, and intimacy that can elicit information with cultural humility: "Are you experiencing any problems in your intimate relationships? Some people taking certain medications notice sexual problems; often women around the time of menopause experience sexual problems such as vaginal dryness—is that something that is affecting you?" It may be helpful to first ask permission before asking more personal questions. Sex is often defined as intercourse, which may not include lesbians' menopausal and midlife sex experiences [16]. Using more inclusive language such as "intimate relationships," "intimate partner(s)," and "genital contact" may help create a safe space that allows all women to be honest, to open up, and share.

Shared Decision-Making

Shared decision-making is a critical feature of patient-centered communication. It is "the process of negotiation by which [healthcare providers] and patients arrive at a specific course of action, based on a common understanding of the goals of treatment, the risks and benefits of the chosen treatment versus reasonable alternatives, and each other's values and preferences [51]" [52]. Shared decision-making occurs in a participatory, collaborative, open, respectful relationship and directly relates to health-related quality of life [53]. Because the shared decision is not the endpoint but signals the need for ongoing dedicated work and refinement, approaches should be customized and tailored to focus on individual patients' needs and preferences.

3.5.3 Providing Information

The healthcare provider's willingness to identify their strengths, weaknesses, and knowledge base of treatment option information can positively impact communication and patient trust. A study about how trust affects women's information-seeking and decision-making about menopause symptom management found that women utilized three sources of information about menopause therapies: their healthcare provider, the media, and family or friends. Perceived knowledge, helpfulness, and trust played an essential role in women discussing menopausal symptom management options with their healthcare provider. Women who had never used MHT seemed to have lower trust levels in their healthcare provider's information [46].

Communicating the importance of clinical evidence and providing balanced examples of therapeutic options is critical when engaging in shared decision-making [51]. Providing information must be patient-centered, based on medical evidence, the healthcare providers' clinical expertise, and the patient and their family's unique and individual preferences.

Existing data indicate women have novel needs in patient-centered care, although there is little research about applying patient-centered care in women's health. A scoping review of over 9000 studies revealed a dearth of research on patient-centered care specifically focused on women's health. Only 11 studies met the review criteria, and none were based on an existing model or created a unique framework, theory, or approach specific to patient-centered care in women's health. The definition of patient-centered care varied widely throughout the studies. None included all domains of patient-centered care previously identified as critical to achieving high-quality care. This review highlighted the lack of established frameworks specific to patient-centered care for women's health. Although none of the studies included women exclusively, in over half of the studies reviewed, novel elements of patient-centered care desired by women emerged, including timely responses to questions, flexible scheduling, feeling seen and heard as a unique individual, and receiving individualized treatment [15]. These findings disclose vital areas for quality improvement initiatives and further research. Providing patient-centered care to women offers a pathway to reducing gender-related health and healthcare disparities.

Individualized choice, consent, and trust are critical issues in the communication of risk. Mixed messages and negative patient perceptions of the various treatment options for bothersome menopausal symptoms, in particular MHT, have increased the need for healthcare providers to communicate effectively and engage in shared decision-making with patients, especially in circumstances in which a degree of uncertainty exists. Menopause hormone therapy does not have the same risks and benefits for all women. Age, time since menopause, medical, psychiatric, gynecological surgical history, family history of breast cancer are just a few of the factors that influence the risk-benefit profile of menopause symptom management options and must be included in the consultation and treatment plan (See Chap. 6). The IOM/NAM surveyed 1068 nationally representative adults in the United States who had seen at least one healthcare provider in the past year about what they wanted

from their healthcare provider. Results indicated that women most wanted to be listened to, given the truth about their diagnosis, and given information about the risks and quality of life impact of each treatment option [54, 55].

The findings of a qualitative study of the experience of risk communication and decision-making among primary care patients about menopausal symptom management and MHT in the United Kingdom mirrored those of the IOM/NAM survey. The majority of women who participated in the study mentioned the need for accurate, truthful, and individualized risk information. They found that participants rejected generalized advice about risks to inform their decisions about MHT and wanted more personalized risk information. Participants' vision of an effective risk consultation about menopausal symptom management options, including MHT, consisted of interacting with a healthcare provider who used effective communication skills to explain the current best evidence to reach a mutually acceptable treatment decision [55].

3.5.4 Communicating Treatment Decisions

Absolute Risk Reduction
Absolute Risk Reduction (ARR) reflects the total reduction in one's risk of treatment harm versus no treatment at all. ARR is the most helpful way of presenting research results to help patient decision-making. ARR will be most significant in those at the highest baseline risk. The greater the baseline risk, the more the patient stands to gain from the treatment [56, 57]

Relative Risk Reduction
Relative Risk Reduction (RRR) identifies how much a treatment reduces one's risk of poor health outcomes. RRR is often presented as a percentage of whether one's risk of harm is reduced by treatment compared to the control group, who is not treated [56].

Using techniques to facilitate effective communication and shared decision-making is especially important when discussing treatment options' risks and benefits. Visual aids such as infographics and pictures may help visual learners and educate patients about statistical data [39, 57]. When presenting patients with statistics about Relative Risk Reduction, healthcare providers should be aware that data provided in this way may be more persuasive but not necessarily well understood. Discussion and depictions of Absolute Risk Reduction are more intuitive and easier to grasp than other methods of presenting research findings, especially if presented in graphic form. ARR information should be presented with data about the patient's baseline risk to improve accuracy and patient understanding.

Positively framing information and explaining the treatment in a way that helps put health risks into perspective demonstrates patient-centered communication and may require using language that fosters feelings of trust and is grounded in the ideals of cultural humility. Examples such as, "My discussions with you are based on the best medical evidence available. However, research is constantly changing, which means treatment recommendations may change over time. I will always keep the latest data and your specific menopausal symptoms, preferences, and goals in mind as we work together to select the best treatment option for you." And, "There are several treatment options that may work to help alleviate your hot flushes. MHT is considered the most effective of these, but we should talk about whether this is the right option for you [54]". Reflective listening is a tool that fosters effective communication. This technique involves allowing the patient to speak while the healthcare provider actively listens and reflects back to the patient what they have heard. Another strategy is to allow patients 5–10 seconds of silence after asking a question to contemplate a response is an additional tool that fosters effective communication [54]. Prompts such as, "Does what I just explained make sense to you?" can also encourage the patient to think about whether they truly understand or if additional information is needed.

Accurate communication of risks and benefits of interventions to patients is a critical component of shared decision-making. Patients want deep engagement in conversations about their health, including detailed medical evidence. They do not want their provider to make decisions for them or offer only some of the options. Those who experienced effective communication were involved in decisions and felt their goals and concerns were honored uniformly reported being more satisfied with their care [51]. It is incumbent upon providers and institutions to create the environment and provide the tools to make this possible.

Healthcare providers must develop skills to individualize their communication approach by evaluating how much patients prefer choice and shared decision-making. Some women may like more professional guidance and directive communication to assist in deciding on a management plan. It is critical to assess whether patients see themselves as sharing in decision-making or prefer the provider to be the primary decision-maker [39, 58]. The patient's role may change over time; there may be moments when the healthcare providers will lead and other moments when the patient will determine the best next steps. Culture, race, age, sexual identity, other societal factors, and lived experience of trust or mistrust of healthcare systems may influence the process of both sharing of information and decision-making.

3.5.5 Open Door Policy

The open door policy is critical because the experience of the menopause transition is dynamic. Risks and benefits associated with management decisions change at different points throughout the women's menopause transition. The treatment plan that is in place today may not be the best fit tomorrow. Shared decision-making is an ongoing process that does not end with the decision. The healthcare provider's

role is to provide support, guidance, mentoring, coordination, and education to patients throughout the shared decision-making process. It is critically important to communicate to patients that this support will continue after decisions are made [58]. After providing information about the benefits and risks of the management options, healthcare providers must partner with the patient on a plan and review the rationale for the selected management plan. Partnering requires that healthcare providers be proactive and consistent about inviting patients to participate in their care. They should allow the patient to ask questions if they need further explanation and be prepared for ongoing discussion at follow-up visits [54].

There may be times when patients find the management plan challenging or that the outcomes do not meet expectations. After the patient and provider have agreed upon a plan and the patient returns home, they may choose not to initiate the agreed-upon treatment or action plan [58]. Healthcare providers should be careful to avoid giving the impression of being disappointed if patients do not follow their advice [54]. In these situations, the patient may have additional questions, concerns, or unresolved issues that require them to return to the provider to re-evaluate the plan. For example, patients may feel pressured by the perceived power imbalance they experienced with their provider and, as a result, find themselves aligning with a particular decision favored by the provider [58]. Social determinants of health may also influence the patient's ability to adhere to the plan. Factors such as poverty, poor health literacy, or underinsurance make it difficult to adhere to treatment plans. Because these issues may not be shared in the first interaction and arise later, flexibility in the healthcare provider–patient relationship can facilitate communication by alternating who takes the lead during shared decision-making. There may be times when the healthcare provider takes the lead to educate the patient about best practices while considering patient preferences and their response to the information provided. Alternately, there may be times when, as the expert in their lived experience, the patient takes the lead [58].

Patient-centered communication is associated with patient satisfaction, reduced symptom concern, and treatment adherence [48]. Healthcare providers must practice cultural humility and be mindful of the patient's response throughout the shared decision-making process to encourage ongoing connections between the healthcare provider and patient that are consistent, continuous, supportive, and sustaining.

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Physiology of Menopause

4

Patricia Geraghty

4.1 Hypothalamic Pituitary Ovarian Axis and Control of the Menstrual Cycle

Ovarian gamete population peaks before birth when the oocytes number six to seven million [1]. Oocyte loss begins during follicle formation starting at 19 weeks gestation with about 1 in 10 oocytes failing to be incorporated into a follicle. By birth, the population of oocytes numbers 650,000–700,000 [1, 2]. The principle driving force for follicle loss throughout the subsequent years is apoptosis. Puberty, believed to be signaled via central nervous system maturation and triggered by the hypothalamus with regular pulsatile release of gonadotropin releasing hormone (GnRH), begins with an oocyte population of approximately 300,000. There is a subsequent loss of 400–500 follicles each recruitment cycle [1].

Gonadotropin releasing hormone (GnRH) from the hypothalamus and gonadotropin secretion from the pituitary stimulate primordial follicle granulosa and theca cell hormone production in the ovary, making up the hypothalamic pituitary ovarian axis. Once menstrual cycles are established in the early reproductive life stage, and continuing into the peak reproductive life stage, low ovarian steroid levels signal pulsatile release of GnRH from the hypothalamus leading to follicle stimulating hormone (FSH) secretion from the pituitary. This in turn initiates the recruitment of several primordial follicles in the ovary. The menstrual cycle is driven by the granulosa and theca cells of these follicles. The granulosa cells produce Anti-Mullerian hormone (AMH) in the early developmental, pre-antral, stage of follicular development. AMH suppresses further follicular recruitment and growth, preserving the ovarian follicular reserve. Serum AMH levels may represent the remaining available follicle count but do not reflect the quality of the remaining follicles [3]. With

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follicular recruitment, granulosa cells also begin production of inhibin B, and 17β-estradiol. Estradiol further enhances FSH receptor development on the granulosa cell membrane and luteinizing hormone (LH) receptor development on the theca cell. Still in the follicular phase, theca cells begin production of androgens, primarily androstenedione and testosterone, which undergo aromatization to estrogen in the granulosa cells via the action of p450 aromatase, enhancing the estrogen dominant environment. This feedback of increased estradiol leading to increased receptors selects for the dominant follicle. The inhibin and estradiol simultaneously cause atresia of the remaining developing follicles, which have fewer receptors and thus are protected by less FSH support [2].

Follicular estradiol triggers the cessation of bleeding from the previous menstrual cycle and stimulates growth of the endometrial lining in the uterus, the endometrial proliferative phase. A critical level of estradiol signals the release of luteinizing hormone (LH) and a second wave of FSH from the pituitary. This leads to ovulation of the dominant follicle, which then becomes the corpus luteum. The conversion of androgens to progesterone in the theca cells begins with the ovarian luteal phase. Progesterone supports the final maturation of the endothelial lining, stimulating glandular structure but suppressing further growth of lining, the endometrial secretory phase. Under the influence of decreased FSH and estradiol production in the luteal phase, the corpus luteum degenerates and ovarian hormone production further decreases, signaling the sloughing of the endometrial lining as menses and the initiation of the following cycle. See Fig. 4.1.

4.1.1 Influence of Aging on the HPO

In the 1990s, five large-scale longitudinal studies of reproductive aging were initiated; Rotterdam, Melbourne Women's Midlife (MWMHP), Seattle Midlife Women's (SMWHS), Penn Ovarian Aging (POAS), and Study of Women's Health Across the Nation (SWAN). The studies involve a total of more than 17,000 individuals, with study duration ranging from 9 to 30 years. Most of the studies are ongoing. Not all participants in each cohort were involved in hormone studies and the Rotterdam population also included men [9, 10]. The SWAN Daily Hormone Study (SWAN DHS) is the only study to look at daily hormone levels and thus informs most of our understanding of age-related changes in ovulatory patterns and luteal phase [11]. These studies give us the first evidence of hormonal reproductive changes including baseline data and increased diversity in the study populations (POAS and SWAN). Limitations of these studies are the exclusion from most of the studies of women who do not have baseline regular menses. This compromises extrapolation of data to women with polycystic ovarian syndrome (PCOS), women using hormonal contraception, women who have had hysterectomy, women with functional hypothalamic amenorrhea (FHA), and women with primary ovarian insufficiency (POI) (see Chap. 7). Together these conditions potentially exclude more than a third of women [12]. Some of these studies were initiated prior to the STRAW definitions of the stages of menopause and all prior to the STRAW + 10

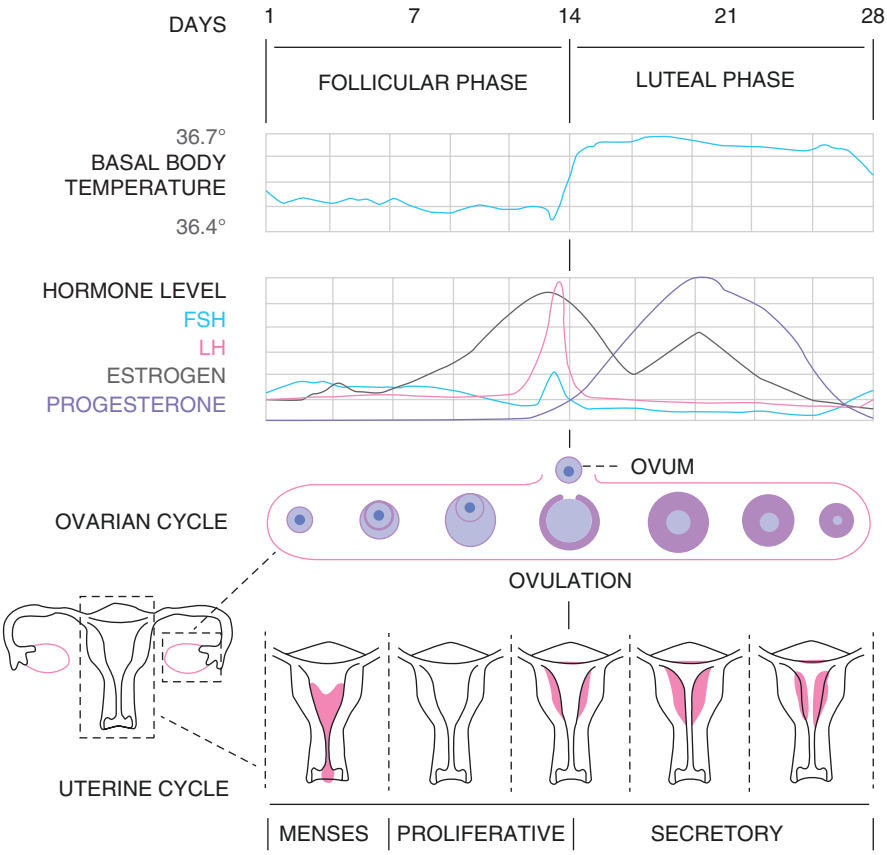

Fig. 4.1 Menstrual cycle. Diagram of hormonal, ovarian, and endometrial menstrual cycle activity, Published under CC BY-SA 3.0. From Isometrik. MenstrualCycle2 en.svg.

revision, making it difficult to link findings to specific timeframes within the menopause transition (See Table 4.1). The POAS independently developed the PENN-5 staging system, roughly comparable to though less specifically defined than STRAW + 10 [4, 11]. These studies have illuminated the trajectory and pattern of hormonal changes, subsequent menstrual cycle changes, and association with possible menopause transition symptoms.

4.1.1.1 Late Reproductive Stage (STRAW + 10 Stages −3b, −3a)

The gradual loss of ovarian follicular mass alters every aspect of cyclical hormone production in the late reproductive and the menopause transition stages. In the late reproductive stage, the FSH level remains low. The MWMHP identified a decrease in inhibin as the first endocrine marker of the menopause transition and most but not all studies indicate the production of inhibin is low in the late reproductive stage [1, 11]. AMH also gradually declines over the reproductive life span. The aging

Table 4.1 Stages of menopause with timeline of HPO and menstrual changes

	Menarche						FMP 0			
Stage	−5	−4	-3b	-3a	−2	−1	+1a	+1b	+1c	+2
	Reproductive				Menopause transition		Postmenopause			
Terminology	Early *begins w/ menarche*	Peak	Late		Early	Late	Early *begins w/ FMP*		Late	
					Perimenopause					
Duration	*Variable*				*Variable*	1–3 years	2 years (1 + 1)		3–6 years	*Remaining lifespan*
STRAW + 10	Variable to regular menses	Regular	Regular	Subtle changes flow/length with shorter cycles [22]	Variable cycle length persistent ≥7-day difference (w/in 10 cycles)	Interval of amenorrhea of >/= 60 days	No cycles			
FSH			Low	Variable	↑variable	↑ >25 IU/L	↑ variable		↑ stabilizes	
AMH			Low	Low	Low	Low	Low		Very low	
Inhibin B				Low	Low	Low	Low		Very low	
AFC			Low	Low	Low	Low	Very low		Very low	

Harlow D, Gass M, et all. Executive Summary of the Stages of Reproductive Aging Workshop 10: Addressing the Unfinished Agenda of Staging Reproductive Aging. J Clin Endocrinol Metab. 2012 Apr;97(4). Used with permission of Oxford University Press.

Timeline of physiological, menstrual, and fertility changes in reproductive aging**.**						
HPO activity	Cyclic FSH stimulates follicle development. Menstrual cycle driven by granulosa and theca cell steroid production. Dominant follicle produces high levels estrogens and inhibins, leading to atresia of remaining growing follicles. ELA cycles 100% 10 years before FMP. Apoptosis, w/loss of 400–500 eggs per follicular recruitment, predominant path of germ cell and follicle atresia.	Compensated follicle failure: Low AMH and inhibin allow diminished follicular reserve to develop and ovulate. Age-related aromatase increase results in mid-reproductive or higher E2 despite oocyte deterioration. At least a decade of rise in FSH, low AMH, low inhibin before cycle changes. Infrequent, but developing reduced sensitivity of hypothalamus with failed LH despite adequate E2. High % ELA (80–87.9%) up to 5 y before FMP followed by rapid decline in the subsequent 5 y.		Uncompensated follicle failure: Decreased follicular reserve w/increase hypothalamus insensitivity. Only 22% cycles w/in 1 year FMP show ELA. Striking rise LH, FSH in non-ELA cycles stage -3 to FMP. More cycles hypoestrogenic	Follicular reserve exhausted. No further ovulation. No P4 with variable E2	Limited reproductive endocrine changes. Somatic aging dominates. Stable, elevated FSH and LH. E2 10–25 pg/mL. Increased aromatization with obesity, E2 30 pg/mL or higher. Ovarian androstenedione and testosterone production continue.
Menstrual, fecundity, fertility change	Fertility declines	Fecundity declines. Flow and length change subtle. Non-ELA cycles longer. ELA cycles heavier bleeding.	LOOP cycle 1:4 accelerated ovulation w/ many small follicles. Follicular stage compressed, luteal stage increase to retain relatively stable cycles. w/ possible link to ↑ PMS.	LOOP cycle 1:3 Fertility possible. Women w/obesity, new shorter cycles stage -1. 44% cycles 36 days, duration bleeding short (1–3 days) in 18%, long bleeding (> 8 days) in 23%.	Fertility possible up to 12 months after FMP	

FSH follicle stimulating hormone, *AMH* anti-mullerian hormone, *AFC* antral follicle count, *HPO* hypothalamus pituitary ovarian axis, *ELA* evidence of luteal activity, *FMP* final menstrual period, *E2* estradiol, *LH* luteinizing hormone, *P4* progesterone, *LOOP* luteal out of phase event, *PMS* premenstrual syndrome
In some, but not all cases, HPO activity, menstrual, and fecundity/fertility events have been identified for the specific reproductive stages. The absence of borders in those timelines reflects the less precise link to reproductive stages. Timeline based on Harlow et al. [4], Pelosi et al. [2], Hale et al. [5], Genazzini et al. [1], Santoro et al. [6], Santoro et al. [7], Van Voorhis et al. [8], Allshouse et al. [9]

follicles in the late reproductive stage become less sensitive to FSH stimulation but the reduction in AMH and inhibin may permit follicles to commence development despite a decreased antral follicle count and accelerating apoptosis [1, 4, 9, 13]. There is an age-related increase in aromatase, maintaining normal 17β-estradiol production, allowing the LH surge [14]. This is considered "compensated follicle failure." Less inhibition of follicle recruitment and enhanced estradiol formation maintain the ovulatory capacity and endometrial development of the menstrual cycle at the expense of accelerated follicle loss. The duration of the late reproductive stage is variable [4].

4.1.1.2 Early to Late Menopause Transition (STRAW + 10 Stages − 2, −1)

With further loss of ovarian reserve and follicular activation, FSH levels begin to vary and to increase during the transition from late reproductive to early menopause stages. The AMH, inhibin B, and antral follicle count remain low. Follicular development also alters. There is more rapid growth of follicles with smaller peak diameter and shortening of the follicular phase [1, 9–13, 15, 16]. Continuing increased aromatization causes increased estradiol levels in some but not all cycles [9].

Hale et al. [5] defined a cycle alteration unique to the menopause transition stages which they named a luteal out of phase (LOOP) event. See Fig. 4.2. The elevated FSH production recruits a second follicle during the luteal phase of cycle one. There is a mild estradiol elevation during luteal phase cycle 1 from the growth of this second follicle. The second, or out of phase cycle, has normal FSH and estradiol levels with 50% of these cycles experiencing an LH surge and ovulation within the first 5 days of follicular recruitment. This early ovulation results in a cycle of less than 21 days. If there is no second ovulation, the estradiol drops and the result is a cycle longer than 36 days. LOOP cycles occur in 1 in 4 cycles in women in the early menopause transition, increasing to 1 in 3 in the late menopause transition [5].

Menopause, like puberty, may also be affected by age-related central nervous system changes. The hypothalamus becomes less sensitive to estrogen due to decrease in neuropeptide and neurochemical molecules [1]. Despite adequate or even increased levels of estradiol, an uncoupling of the GnRH stimulus from pituitary response results in an LH surge inadequate to stimulate ovulation [17, 18]. The first cycles with lack of evidence of luteal activity (ELA), measured by low or absent serum progesterone or the metabolite urinary pregnanediol glucuronide (PdG), due to either anovulation or luteal phase deficiency appear in the late reproductive stage and gradually increase in frequency through the early menopause transition [19]. In the SWAN population, non-ELA cycles were present 8 and 6 years before the FMP, though a high percentage, 88% of cycles, had ELA up to 5 years before FMP [6].

At 5 years before the FMP, a rapid decline in ELA commences so that only 23% of cycles have ELA 1 year before the FMP, the late menopause transition stage [6]. Luteal phase progesterone more sharply declines in the late menopause stage. The hormonal variability cycle to cycle decreases in the last 2 years before the FMP as cycles are more consistently hypoestrogenic with reduced follicular development, and are hypergonadotropic with increased LH and FSH [6, 9, 11]. The largest

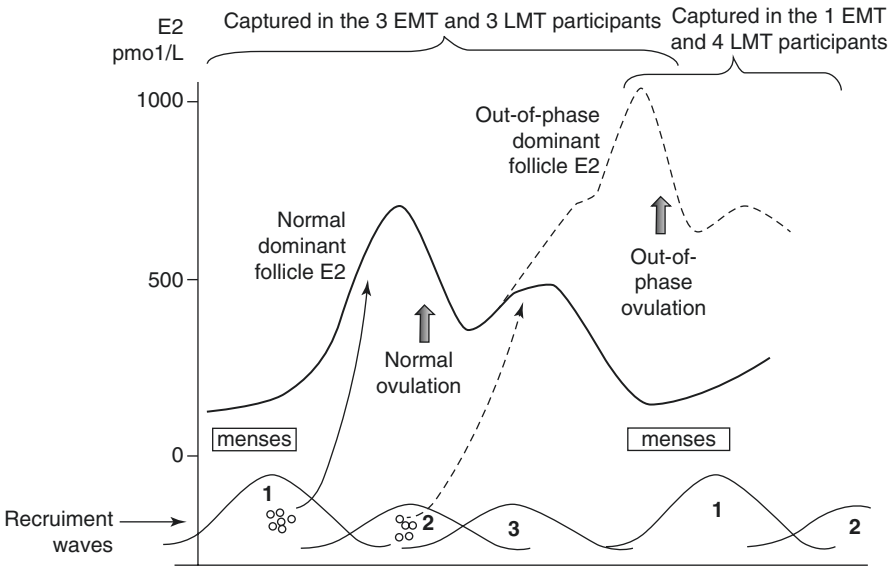

Fig. 4.2 Atypical estradiol secretion and ovulation patterns caused by luteal out-of-phase (LOOP) events underlying irregular ovulatory menstrual cycles in the menopause transition. (Hale G, et al. 2009. Used with permission from the North American Menopause Society). Ovarian follicle recruitment waves 1, 2, and 3 are illustrated at the bottom of the figure, where wave 1 is normally ovulatory and wave 2 and wave 3 do not normally result in ovulation. Wave 1 occurs during the early folliclular phase and normally provides the reservoir of developing antral follicles that result in a dominant follicle, which causes the normal increase in E2 during the follicular phase (solid line) and a normal mid-cycle ovulatory episode. Wave 2 occurs around mid-cycle and may be the source of a dominant follicle that causes the steep increase in E2 during the mid-luteal phase (heralding the onset of the LOOP event, represented by the dotted line) and triggers ovulation early in the subsequent cycle. Wave 3 occurs in some women during the late- luteal phase and may be responsible for the advancement of dominant follicle selection and decreased cycle length observed in late reproductive age. *EMT*-early menopause transition; *LMT*-late menopause transition

variation in FSH levels occurs in the 18 months on either side of the FMP but the elevation is ineffective in stimulating development of the depleted follicular reserve in most cycles [20]. This is considered "uncompensated follicle failure" [9, 11].

The late reproductive and early menopause stages have variable durations. The late menopause transition is 1–3 years before the FMP [4].

4.1.1.3 Postmenopause (STRAW + 10 Stages +1a, +1b, +1c, +2)

There is no hormonal marker for the FMP. Variable amounts of estradiol continue to be produced in the first 1–2 years following the FMP but there is no progesterone production after the final ovulation [11, 13]. Early postmenopause FSH, LH, and estradiol levels are not significantly different than levels found during predominantly anovulatory cycling of the late perimenopause stage [21]. By late postmenopause, STRAW stage +2, estradiol is consistently low and further reproductive endocrine changes are limited with somatic aging dominating the hormone profile [13]. The woman continues to have stable and elevated FSH and LH. Estrone is the

dominant estrogen after menopause, likely due to peripheral aromatization in adipose tissue. Androstenedione and testosterone continue to be produced by ovarian stromal tissue, possibly as a result of the increased LH [11, 13].

4.2 Physiology of Menstrual Changes Prior to FMP

At least a decade of variable and gradual rise in FSH, decrease in AMH, and decrease in inhibin throughout the late reproductive stage precede the first menstrual cycle changes [9]. The first menstrual changes may be related to flow and to subtle cycle length alterations, less than 7 days variability, occurring in the late reproductive stage. With increased aromatization leading to increased estradiol in some but not all cycles, menstrual flow varies from cycle to cycle [3, 8].

Earlier follicle recruitment compresses the follicular phase, extending the luteal phase, possibly increasing symptoms of premenstrual syndrome as women transition into the early menopause stage. Women may experience transient breast tenderness and headaches in cycles with LOOP activity [13, 22]. Heavier menstrual bleeding is associated with the ovulatory cycles [8]. Anovulatory cycles, incidence of about 20% in the early menopause transition, may be associated with both shorter (<21 days) and more commonly longer (>35 days) cycle intervals [8]. This 7-day variation in cycle length, repeated within 10 cycles, establishes the early menopause transition stage [4]. Cycles following anovulation are more likely have either shorter (1–3 days) or longer (≥8 days) flow [8].

In the late perimenopause stage, 1–3 years before the FMP, the follicular depletion leads to a majority of anovulatory cycles with longer periods of amenorrhea [13]. This is more likely to be accompanied by hypoestrogenic symptoms such as vasomotor symptoms. When the follicular mass is exhausted, menses cease. Menopause is defined as 12 months of amenorrhea not due to other causes. Case reports of premenstrual symptoms followed by menstrual-like bleeding after established menopause are not entirely uncommon and may reflect residual follicle activity [3]. These episodes must be evaluated as postmenopause bleeding (see Chap. 7).

4.2.1 Physiological Profiles in Race/Ethnicity, Body Morphology, and Lifestyle Variations

The SWAN study was purposely powered to investigate variation in race/ethnicity in self-identified Caucasian/white, Hispanic, Japanese, Chinese, and African-American women. The POAS population self-identified as 50% white and 50% Black. Both studies were geographically limited to the United States, possibly limiting the definition of cultural diversity. The POAS study found inconsistent relationships between race and menopause-related hormone changes [11]. SWAN found no difference in the probability of ELA adjusted for years before FMP among white, Japanese, and Chinese women. Both Hispanic and African-American women had lower evidence of ELA, possibly indicating more rapid trajectory toward FMP, but

this difference became insignificant when adjusted for social factors of geographic region, smoking, and BMI. The authors concluded that at this time no clear association between race/ethnicity and ELA trajectory can be established [6].

Obesity and BMI consistently demonstrates a complex influence on the menopause transition related hormonal trajectory and on perimenopause menstrual cycles. Both POAS and SWAN demonstrated lower estradiol in premenopausal women with obesity compared to overweight and normal weight. The relationship then reversed and became higher estradiol among women with obesity postmenopause [6, 11]. Increased aromatase activity is associated with obesity. The elevated postmenopause estradiol may be due to peripheral aromatization [3]. A significant reduction in all menstrual hormones (FSH, LH, estradiol, and uPdg) was seen with obesity in the SWAN population. AMH and inhibin B were lower in women with obesity in the POAS population during late reproductive and menopause stages but there was no association with FSH and BMI. However when waist circumference and waist to hip ratio measurements were used in the POAS population, correlations were maintained with the increased body size and decrease of all hormones [6, 11]. As noted above, race/ethnicity correlation to ELA became insignificant when adjusted for BMI in the SWAN data indicating body morphology is the dominant influence [6].

These data generally indicated a lower ovarian reserve and decreased hypothalamic sensitivity in women with obesity although there is either no difference in age of FMP between women with obesity and overweight, or menopause occurs at a later age than for women with normal weight. Menstrual cycle patterns are altered in women with obesity. In late reproductive stage, women with obesity have longer cycles. Cycles then become shortened in the late menopause transition, counter to the pattern of women without obesity [6].

Population studies indicate consistent relationship between smoking and earlier age of FMP [2]. Although the correlation between smoking and earlier age of FMP remained strong in hormonal longitudinal studies, the pattern of the menopause hormonal trajectory did not differ [9].

4.3 Physiology of Fertility Decline

In the late reproductive stage, menstrual cycles remain regular but fecundity, the ability to conceive, and fertility, pregnancy resulting in birth, both decrease. Women begin to experience a decrease in fertility at age 32 years, with steep and rapid decrease after age 37 years despite high incidence of both regular ovulation and regular menstrual cycles as demonstrated in the SWAN DHS [6, 23]. By the age of 40 years, there is also a decrease in fecundity [23, 24]. Menken et al. examined birth records ranging from 1600 to 1930 from 10 communities in Europe, North American, Middle East, and North Africa. These records reflect natural fertility and demonstrate rates of 1–3% of births after age 40 years and 0% rate at 47.5 years [25].

The appearance of decreased fertility prior to the decrease in fecundity may reflect decreasing oocyte quality rather than ovulatory disorder or uterine aging. In the late reproductive stage, less sensitive follicles with decreased peak diameter

achieve dominance and ovulation. The fertilized ovum subsequently undergoes 5–7 days of cleavage before implantation and access to an external blood supply. These developmental steps are dependent on mitochondria within the fertilized ovum. Mitochondria play an essential role both in powering cell function via adenosine tri-phosphate (ATP) and in the initial steps of sex steroid synthesis necessary to support early pregnancy. In addition, meiotic spindles are essential for chromosome allocation in the final stage of oocyte formation and in the initial steps of sex steroid synthesis necessary to support early pregnancy. In addition, meiotic spindles are essential for chromosome allocation in final stages of oocyte formation and the subsequent cell cleavage and development of the zygote. Meiotic spindle abnormalities and loss of mitochondrial DNA accrue with time [26]. Accumulated abnormalities in these structures and changes in mitochondrial DNA lead to truncated development and pregnancy loss [9, 27, 28]. Women over 40 experience similar rates of healthy pregnancy as younger women when donor ovum are used [13]. With the advent of the early menopause transition, increasingly less frequent ovulatory cycles and luteal phase insufficiency initiate changes in menses and a further threat to fecundity and fertility [6].

4.4 Role of Hormone Testing and Predicting FMP

There is very little role for hormone testing to establish menopause stage or predict FMP [29, 30]. The menopause transition stages in STRAW + 10 are defined by menstrual cycle changes, antral follicle count, and day 3–5 FSH. However, FSH is variable from cycle to cycle and from day to day, reducing its usefulness in identifying menopause stage from a single analysis independent of other markers [13]. If any alteration in menstrual cycles has already occurred, timing of FSH and all menstrual hormones within the woman's cycle is less specific. High FSH levels might be useful in identification of approaching menopause but do not indicate completed transition. Low levels are not informative [31].

AMH, a marker of ovarian reserve, has been proposed as a marker for fertility. The biomarker has been used to successfully predict response to exogenous gonadotropic stimulation in women with infertility. However, several studies have shown that low serum AMH levels (0.7 and 1.4 ng/mL) did not distinguish likelihood of pregnancy in the next 6 months from women with normal serum AMH levels in populations without a history of infertility, including a group of women 38–44 years of age [32, 33].

AMH has also been proposed as a measure to predict age of natural menopause (ANM). The Michigan Bone and Health Study found baseline AMH correlated to age of FMP; however, in the study's assay method levels of AMH declined to non-detectible 5 years before FMP [34]. A 20-year longitudinal study of a group of initially normo-ovulating women found that with increasing age AMH became less predictive of ANM and the variation in prediction was too broad for clinical application [35]. This is in agreement with other findings [36]. However, in the Tehran Lipid and Glucose Study, a longitudinal study following AMH and other markers every 3 years over a 9-year span, AMH had a negative predictive value for FMP,

showing an 88% likelihood of not reaching menopause in the next 6 years when repeated measurements of AMH exceeded a threshold of 0.39 ng/mL [37]. The clinical utility of this finding is questionable as superior to predicting menopause based on age or menstrual cycle changes without serum hormone levels.

Clinical use of serum AMH is limited by lack of international assay standards and differing assay methodologies. Traditional radioimmunoassays are not specific or sensitive enough to measure low sex steroid levels during and after menopause. Mass spectrometry, while specific and precise, is costly and difficult to access, limiting clinical utility [38]. AMH is not useful in predicting time to pregnancy in populations with presumed fertility and is not more predictive of FMP than either age or amenorrhea of 60 days [4, 29].

4.5 Intracrinology

Intracrinology, pioneered and named by Labrie, studies the intracellular formation and inactivation of estrogens and androgens from dehydroepiandrosterone (DHEA) and its sulfate conjugate, DHEAS. DHEA is an inactive precursor, transformed via approximately 30 tissue-specific enzymes into active estrogen and androgen molecules [39–41]. The enzymatic pathways are specific to humans and old world large primates, limiting application of other animal studies [38].

Minute forms of estradiol and testosterone are synthesized and metabolized within the cell for intracellular activity in most if not all peripheral tissue and the central nervous system, with the exception of the uterine endometrium. Serum estradiol and testosterone levels do not reflect intracrinology activity. Estrogen metabolites may be reflective of cellular estradiol production. Assays sensitive and specific enough for testosterone metabolites are not yet available [38].

DHEA and DHEAS are produced by the ovaries, the brain, and the adrenal cortex. DHEA and DHEAS serum levels decline starting at age 30, show a transient resurgence in the menopause transition, then continue to decline throughout the lifespan [1, 40, 42, 43]. DHEA and DHEAS did not change relative to FMP in the MWMHP but did demonstrate age-related decline with reduced ovarian contribution. Postmenopause DHEA and DHEAS are reduced by 60% from reproductive stage levels and production is dominated by the adrenal cortex with 20% ovarian contribution [11, 41, 44].

DHEA and DHEAS are not subject to serum level control via feedback mechanisms as are the steroids of the HPO axis. It is hypothesized that age-related reduced DHEA and DHEAS production is reflected in less intracrinology activity; however, DHEA and DHEAS conversion to androgens and estradiol appears self-limiting. Transformation becomes less efficient with increased serum DHEA and DHEAS levels. Labrie et al. showed a reduction of steroidogenesis by 60% when 2% DHEA cream was applied to the skin. DHEA transformation appears to be capped at serum levels of 7.9 ng/mL which is lower than the 95th centile of normal premenopausal women [45].

Highest concentrations of DHEA and DHEAS are found in the brain relative to plasma [46]. In the central nervous system DHEA and DHEAS act as a neurosteroid, demonstrating neuroprotective effects in stimulating neurite growth, neurogenesis and neuronal survival, apoptosis, and catecholamine synthesis and

secretion. A review of cross-sectional placebo controlled studies of DHEA 50 mg supplementation showed conflicting results for measurable cognitive effects in the menopause and postmenopause stages [47]. A 3-month trial showed no benefit in sense of well-being or cognitive function. A 2-week trial showed DHEA supplementation improved selective attention but impaired visual memory in the presence of stress and had no effect without stressor present [48]. A 12-month trial showed decreased depression and increased satisfaction with life in women taking 50 mg DHEA daily but these effects did not persist over time [49]. In menopause symptom management, DHEA 6.5 mg (prasterone) vaginal suppositories improve histology and associated symptoms of genitourinary syndrome of menopause without increasing serum estradiol levels above normal postmenopause range [40] (see Chap. 11).

Labrie hypothesized that as menopause symptoms may be experienced prior to changes in estradiol, age-related changes in intracrinology play a predominant if not exclusive role in the menopause symptoms associated with central nervous system and peripheral tissue activity: vasomotor symptoms, bone loss, loss of muscle mass, urogenital tissue changes, and sexual dysfunction [38]. The exclusive role of intracrinology in menopause symptoms hypothesis is not supported by the SWAN evidence that vasomotor symptoms become more common once menstrual cycle changes occur, and the evidence that vasomotor symptoms are responsive to increased serum levels of estradiol [4, 50, 51]. The evidence for support of other menopause symptoms in relation to DHEA and DHEAS and the relative contribution of the roles of traditional endocrinology and intracrinology is limited.

4.6 Menopause Physiology with Reproductive Endocrine Pathologies

In women younger than 45 years, menstrual cycle alteration from regular to irregular or to amenorrhea in the absence of exogenous hormones such as contraception should be evaluated for pregnancy, thyroid abnormalities, hyperprolactinemia, polycystic ovarian syndrome, functional hypothalamic amenorrhea, and primary ovarian insufficiency (see Chap. 7). The final three etiologies of amenorrhea are more chronic in nature and menopause considerations associated with those diagnoses will be discussed here. Other etiologies of menopause are oophorectomy and certain types and duration of chemotherapy. Increased lifetime health risks related to both the specific etiological disorder and to the premature loss of sex steroids are associated with all causes of menopause occurring prior to 45 years age. The hypoestrogenic environment promotes early development of atherosclerosis, impaired endothelial function and CVD, as well as accelerated bone mineral density loss [52, 53] (see Chap. 5). With the exceptions of breast cancer survivors and individuals with history or risk for thrombosis, women with premature or early cessation of menses should be provided with systemic menopause hormone therapy or combined hormonal contraception up to the age of typical natural menopause (see Chap. 6) [54, 55].

4.6.1 Primary Ovarian Insufficiency

Cessation of menses with consistently elevated FSH (≥30 mIU/mL) and low estradiol (<50 pg/mL) randomly measured at least 1 month apart and prior to age 40 years is highly suggestive of primary ovarian insufficiency (POI), the preferred and more accurate name to premature menopause or primary ovarian failure. POI occurs in 1% of women. [56]. Loss of menses is due to premature depletion of initial follicle cohort, accelerated follicle destruction, or lack of follicular response to gonadotropins. POI may be associated with genetic mutations or deletions, autoimmune disorders, dose, type and timing dependent chemotherapy particularly in childhood cancer, or idiopathic [54]. Women with POI experience a subsequent incidence of infrequent menses in 50% and spontaneous pregnancy of 5–10% [56].

Women under age 30 years presenting with secondary amenorrhea have a 13% incidence of genetic disorders [57]. Turner's syndrome (complete or partial deletion of one X chromosome) is typically associated with other growth abnormalities but may initially present as secondary amenorrhea [54]. Excess trinucleotide copies of CGG sequence greater than 55, but less than 200, in the 5′ area of the Fragile X gene is a FMR1 premutation and is associated with POI and other phenotypic expression. Prevalence is estimated to be between 1 in 148 and 1 in 204 females [58]. Autoimmune disease associated with the adrenal gland or the ovary account for 4–30% of all cases of POI. Approximately 20% of women with POI will develop hypothyroidism. There are no specific guidelines for diagnosing autoimmune POI but testing may include thyroid, adrenal, and ovarian antibodies [56]. Survivors of childhood cancer are at risk for accelerated follicle depletion following certain types of chemotherapeutic agents. Evaluation for POI regardless of suspected etiology should specifically include serial FSH and estradiol levels, karyotype, FMR1 allele testing, and adrenal antibodies in addition to the standard secondary amenorrhea testing profile [54, 59].

There is a paucity of data describing the menopause trajectory for all causes of POI. One study of women with FMR1 mosaicism or FMR1 premutation and a median age of 58 years showed incidence of experiencing vasomotor symptoms consistent with the general population but had no genetically typical control group for comparison. Anxiety and executive function symptoms were also detected but these were not necessarily associated with the menopause transition [60]. Young women with POI of unknown or idiopathic etiology report symptom profiles similar to women who experience menopause at a typical age [56]. The trajectory of hormonal changes has not been described.

4.6.2 Polycystic Ovarian Syndrome

Polycystic Ovarian Syndrome (PCOS) is the most common menstrual endocrinopathy with an international incidence of up to 20% and a population of more than 105 million women worldwide [61]. PCOS is a genetic variant with phenotypic expression starting in utero [62]. PCOS is diagnosed by the presence of any two of the

following: lifelong oligomenorrhea (cycles >35 days) or amenorrhea, clinical or biochemical markers for hyperandrogenism, and increased antral follicle count on ultrasound (≥25 follicles per ovary) and with the exclusion of other endocrinopathies [62, 63]. The 2018 International Guidelines on PCOS support diagnosis with menstrual history starting 2–3 years after menarche, with biochemical liquid chromatography/mass spectrometry or extraction chromatography immunoassays of calculated free testosterone, free androgen index or calculated bioavailable testosterone, and with ultrasound evaluation of follicle count in women over age 20 years. Direct enzymatic assays of testosterone lack accuracy and sensitivity for diagnosis of PCOS. Androstenedione and DHEAS levels may be used if free testosterone is normal but add little to diagnosis. Hormone assays and ovarian follicle counts are not accurate in women on exogenous hormones such as hormonal contraception [64]. Access to sensitive bioassays and to ultrasound is limited worldwide. Clinical markers for hyperandrogenism including cystic acne and darkly pigmented face and body hair growth in midline pattern, hirsutism, and alopecia may be substituted. The addition of ultrasound evaluation with elevated antral follicle count was included in the Rotterdam 2003 criteria for diagnosis of PCOS [62, 63, 65].

The pathophysiology of PCOS is associated with neuroendocrine-related abnormal GnRH pulse activity, leading to low LH and low or low normal FSH. Follicular stimulation with absence of dominant follicle selection or ovulation results in reduced fertility and an unopposed estrogen state leading to risk of endometrial hyperplasia. Increased cortisol activity and abnormal adipose tissue aromatization, combined with increased theca cell androgen production, lead to hyperandrogenism. This causes hyperinsulinemia, circling back to further neuroendocrine disorder and gonadotropin suppression [62, 66]. PCOS is associated with subfertility, with endometrial hyperplasia and increased risk for cancer, with metabolic disorders such as insulin resistance, impaired glucose tolerance, type 2 diabetes, dyslipidemia, and cardiovascular risks, and with psychological issues such as anxiety, depression, and reduced self-esteem. Goals of therapy focus on fertility, endometrial protection, reduction of hirsutism and alopecia, and cardiovascular and metabolic risk reduction [61, 64].

Phenotypic expression of PCOS varies across race/ethnicity and changes over the lifespan, including the menopause transition. Racial/ethnic variation cannot be ascribed as uniquely genetically or culturally influenced. White women with PCOS, especially in North America and Australia, have a higher BMI. Worldwide the majority of women with PCOS are not obese. African women have more metabolic and cardiovascular risk and higher BMI. Middle Eastern, Hispanic, and Mediterranean women demonstrate more severe hirsutism. East Asian women have lower BMI and milder hirsutism, while South East Asian and Indigenous Australian women have increased central adiposity, insulin resistance with acanthosis nigricans and diabetes [64].

Longitudinal studies are rare, and few extend into the menopause transition years. Many of the studies show a normalization of menstrual cycling in women with PCOS as menopause approaches [67–69]. Antral follicle counts are reduced in women with PCOS during the late reproductive and early perimenopause stages [70]. The age-related decline in inhibin B and AMH may allow for dominant follicle

selection and ovulation despite reduced gonadotropins. Androgen levels decrease with age though still remain elevated in women with PCOS over control groups [67–69]. Some women with PCOS have regular cycles for the first time in their lives in the late 30s and 40s and, although age-related fertility is low, they may experience an increase in fertility over their baseline [67]. Women with PCOS may have later menopause [67]. Even with a trend toward normalization of ovulation, metabolic abnormalities persist and waist circumference, an indicator of abdominal adiposity and an independent risk factor for CVD, increases [68]. Metabolic risk in women with PCOS, however, appears to be independent of these markers. In the SWAN population, the initially eumenorrheic women who later developed hyperandrogenism and oligomenorrhea consistent with criteria for PCOS diagnosis did not differ from euandrogenic and eumenorrheic women in incidence of metabolic syndrome [71]. Management of PCOS in the perimenopause and postmenopause stages should focus on metabolic and cardiovascular risk amelioration. Even in the post menopause stage, patient history may uncover evidence of PCOS and direct risk management [61, 64, 66].

4.6.3 Functional Hypothalamic Amenorrhea

Functional hypothalamic amenorrhea (FHA) presents with low FSH (<10 mIU/mL), low LH (<10 mIU/mL), low estrogen (<50 pg/mL), and amenorrhea of at least 3 months after excluding the other causes of amenorrhea listed previously. FHA is responsible for 20–35% of all cases of secondary amenorrhea [53].

Suppressed hypothalamic GnRH release mutes pituitary FSH and LH. In the absence of FSH, the granulosa cells of the follicle do not produce estradiol to stimulate endometrial development and LH secretion, leading to anovulation with suppressed endometrial growth and amenorrhea. This results in infertility and a hypoestrogenic state [53].

FHA development is associated with severe psychological stress, intense exercise, and disordered eating. It is a potentially reversible secondary amenorrhea [53]. A type of FHA is Female Athlete Triad, cessation of menses in young competitive athletes during intense training. Restoration of menses is seen with improved energy balance and increased caloric intake [52]. The HPO axis is closely linked with the hypothalamic pituitary adrenal axis. Stress increases cortisol. Elevated cortisol levels are correlated with suppressed gonadotropins [52]. Hypogonadotropins with amenorrhea has been documented in women with traumatic brain injury both prior to and after menopause. Studies of this population illuminate the link of cortisol production and menstrual cycle. In the premenopause group, menstruation was restored when elevated cortisol levels normalized and in the postmenopause group a decrease in cortisol correlated with resolution of suppressed LH [72]. FHA is managed by correcting the etiological trigger and providing exogenous hormones such as hormonal contraception to prevent long-term consequences of low estrogen [55]. Old studies hypothesize atherosclerosis of uterine arteries and an accelerated trajectory to FMP in the presence of controlled FHA but this theory predates the

more complete understanding of the menopause hormone trajectory [73]. Recent research does not describe links between resolved FHA and ANM.

4.6.4 Induced Menopause

Induced or iatrogenic menopause is caused by the removal of the ovaries, with or without hysterectomy, or the destruction of ovarian function by chemotherapy, pelvic radiation, or other forms of ovarian toxicity. Hysterectomy with ovarian conservation may affect ovarian blood flow. Despite conservation, one cohort demonstrated a doubling of the risk of ovarian insufficiency after hysterectomy compared to women with intact uteri [74]. Measurements of ovarian deterioration after hysterectomy have been documented in other populations [75, 76]. The most common cause of induced menopause is bilateral oophorectomy. The incidence of oophorectomy as part of a hysterectomy for benign disease has decreased in recent years but still remains high, particularly in higher income countries [77]. Differences in reporting make cross-country comparison difficult. In India, the prevalence of hysterectomy 2015–2016, reported without data on concomitant oophorectomy, was 3.59% (3.45,3.74) among women aged 30–39; and 9.20% (8.94,9.46) among women 40–49 years [77]. In the United States, 39% of the 2.25 million women undergoing hysterectomy for benign reasons between 1998 and 2006 had their ovaries removed [78]. In Taiwan, the rate of oophorectomy with hysterectomy decreased by 80% from 22.1% in 2000 to 9.9% in 2010 [79].

Oophorectomy leads to the sudden loss of both follicular/luteal sex steroids and of steroids, primarily androgens, produced by the ovarian stroma. Chemotherapy-induced menopause may be a gradual or a sudden loss of both sources of ovarian hormones. The abrupt loss of hormones has been linked to increased risk of severe vasomotor symptoms (90% vs. 70%) and sleep disruption (OR 2.13) when compared to natural menopause [80] (see Chaps. 8 and 9). Aging is accelerated with increased risk of the 18 common chronic conditions within the first 6 years after oophorectomy [81, 82] (see Chap. 5). The incidence of oophorectomy as prophylactic therapy in women at high risk demonstrates efficacy in reduction of subsequent cancer risk. In women positive for BRCA mutation or other genetic mutations with high risk of ovarian and breast cancer, oophorectomy and salpingectomy reduced risk of ovarian cancer by 72–80% and of breast cancer by 46–48% [83] (see Chap. 14).

4.7 Physiology of Menopause Symptom Profile

Some women experience a final menstrual period and report no symptoms beyond that of menstrual cycle changes for which the physiology has been described. Most women in midlife report some combination of sleep disruption, vasomotor symptoms, depressed mood, libido and urogenital changes, cognitive symptoms, muscle/joint pain, and accelerated bone loss [51, 84]. The physiology underlying these specific symptoms, where known, will be outlined in subsequent chapters.

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The Interaction of Menopause and Chronic Disease

5

Patricia Geraghty

5.1 Chronic Disease Overview

Disability-adjusted life years (DALY) is a globally applied measurement based on expected health in an ideal situation. It combines the measurement of years of life lost (YLL) and years of lived disability (YDL) to give a picture of the burden of disease [1]. As a nation's economic resources improve, maternal-neonatal morbidity and infectious disease play a decreasing role and cardiovascular disease, stroke, and diabetes mellitus appear in the top 20 causes of DALY. In both high middle and high income nations, chronic lung disease, mood disorders, and cancers are added to the picture. Only in high income nations does cognitive impairment become a top cause of disability [2]. However, the disease burden is a dynamic situation. Low and low middle income nations are experiencing the most rapid increase in non-communicable disease burden [3].

Global risk factors in the leading causes of chronic disease are identified by the World Health Organization. Modifiable risk factors are influenced by social determinants of health and include tobacco use, unhealthy diet, lack of physical activity, and the harmful use of alcohol, which in turn lead to overweight and obesity, elevated blood pressure, increased cholesterol, and, if unmanaged, ultimately target organ disease [3]. The presence of risk factors are not equitably distributed across or within nations, races, and ethnicities. Risk factor amelioration plays an important role in disease prevention both in the individual and the society. However, there is no place for incorporating blame for failed risk factor management in the diagnosing and treating of chronic disease in the individual. The impacts of aging and environmental/behavioral risk interact with the gradual loss of sex steroids in the menopause transition. Although multiple risk factors with variable influence may outweigh the influence of sex steroids, the

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roles of estrogen and progesterone production by the ovaries and, less well defined, the role of intracellular sex steroid production, impact lifelong health.

The deleterious effect of early menopause with regard to chronic disease is well documented. Early menopause (younger than 45 years age) and menstrual cessation younger than 40 years age have multiple etiologies including primary ovarian insufficiency, idiopathic disease, genetic disorders, chemotherapy, pelvic radiation, and surgical oophorectomy. Extended hypoestrogenism is linked to increased intraabdominal adiposity in the absence of actual weight gain or changes in physical activity, increase in total cholesterol, and altered endothelial cell function leading to increased vascular inflammation and decreased vascular elasticity [4]. These are risk factors for metabolic diseases and cardiovascular disease. Increased metabolic syndrome and total cholesterol are seen in women who have had risk reducing bilateral salpingo-oophorectomy [5, 6]. Impaired vascular endothelial function is seen in women with primary ovarian insufficiency [7].

The increased risk of chronic disease in early menopause translates to earlier mortality in observational studies. The Nurses' Health Study (NHS) prospectively followed for a duration of 28 years a cohort of over 30,000 women undergoing oophorectomy for benign reasons. Among women with a projected 35-year lifespan at the time of surgery, 1 in 8 women experienced earlier mortality compared to nonsurgical controls. Causes of death included increased cardiovascular disease, cancer, and all-cause mortality [8]. A systematic review and metanalysis of observational studies including over 300,000 women showed increase in coronary heart disease (RR 1.5, 95% CI 1.28–1.76), fatal coronary heart disease (RR 1.11, 95% CI 1.03–1.31), and overall mortality (RR 1.12, 95% CI 1.03–1.21) in women with menopause prior to age 45 years [9]. The interaction of disease and natural age of menopause is more complex and less well defined.

Differences in disease trajectories are also seen with implementation of menopause hormone therapy (MHT). Cardiovascular disease, type 2 diabetes mellitus, decreased bone mass, and chronic lung disease have later onset in women who use menopause hormone therapy close to the time of natural menopause [10–14] (see Chap. 6 for a thorough discussion of menopause hormone therapy).

Professional organizations have contributed to opinion and guidelines on the use of MHT with the intention of chronic disease protection. The United States Preventative Task Force (USPSTF) states that, given adverse events associated with MHT, estrogen plus progestogen, or estrogen alone in women who have had a hysterectomy, should not be used for disease prevention [15]. The USPSTF acknowledges that, although risk of adverse events is small, the limited effect on chronic disease prevention fails to alter the benefit risk profile. Other preventative measures, particularly lifestyle interventions, have much larger effect in chronic disease prevention (see Chap. 12). The indications for MHT in osteoporosis prevention and vaginal dryness in the United States is not altered by this recommendation (see Chaps. 11 and 13). The USPSTF analysis relied heavily on data from the Women's Health Initiative (WHI), a study that represented older women (mean age 63 years), mostly initiating MHT at a time more than 10 years after the final menstrual period, and exclusively using oral conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) [16]. The International Menopause Society (IMS) is both critical of overreliance on a single study of older women and slightly less restrictive in the concept of the role of MHT in chronic disease prevention, stating: "Increasing

data indicate benefits for primary prevention of osteoporotic fractures and coronary artery disease and a reduction in all-cause mortality for women who initiate MHT around the time of menopause" [17].[1]

Concurrent chronic disease may also impact management of menopausal symptoms. Determining the safety of using MHT in the presence of established conditions identifies large gaps in knowledge. Timing and duration of MHT use play roles in safety profiles. While estrogen or estrogen plus progestogen use close to the age of the final menstrual cycle have beneficial effects on CVD risk, initiating estrogen in the presence of existing cardiovascular disease increases incidence of cardiac events in the first year of use [18]. The interaction of menopause on the risk of chronic disease and the potential for altered menopause transition trajectory in the presence of chronic disease are discussed in this chapter. Menopause symptom management in the presence of existing chronic diseases, gynecological cancers, and leading causes of cancer is outlined. Separate chapters cover weight management, musculoskeletal health, urogenital health, breast health, and mood and cognition.

5.2 Cardiovascular Disease

Cardiovascular disease (CVD) is an inclusive term including conditions of hypertension, atherosclerosis, cerebrovascular disease, ischemic heart disease, and cardiac failure. It is the leading non-communicable cause of mortality worldwide, accounting for 17.8 million deaths in 2017, of which greater than 75% were in low and low middle income countries [19]. Genetic, metabolic, social, and environmental factors contribute to risk of CVD. There is little heterogeneity of risk across regions. The major modifiable risk factors identified by the WHO are current cigarette smoking, history of diabetes, hypertension, and elevated cholesterol. It is not clear if obesity is an independent risk factor or is part of risk clustering [20].

Sex steroid influence on cardiovascular function appears to be primarily estrogen mediated. In direct action, vascular endothelial cell ERα receptors, and possibly G protein-coupled estrogen receptors, modulate production of nitric oxide, increasing vasodilation, cell proliferation, and cell migration. This decreases vascular resistance and promotes endothelial regeneration. In indirect action, estrogen targets vasculature smooth muscle to promote vasodilation and reduce cell migration. These actions combine to reduce vascular resistance. Estrogen acts on cardiomyocytes to reduce LDL cholesterol, insulin resistance, ischemia/reperfusion injury, and to limit infarct size, cardiac hypertrophy, atherosclerosis, and arterial thrombosis [4, 21].

Cardiovascular disease predominantly occurs in women following menopause; however, the contribution of risk from diminishment of sex steroids and from age may not be constant. Early menopause and younger age at menopause increase risk of CVD. A multinational longitudinal study of over 300,000 women demonstrated the highest hazard ratio with menopause <40 years age (HR 1.55, CI 1.38–1.78), and

[1] Baber RJ, Panay N, Fenton A; IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric. 2016 Apr;19(2):109–50. Reprinted by permission Taylor & Francis.

diminishing risk as age of menopause approached the mean of 50.2 years age. The risk of experiencing a cardiac disease before the age of 60 was two times higher in women with menses cessation before age 40 years and 1.4 times higher with early menopause, before age 45 years. The contribution of age at menopause as a CVD risk factor attenuated after age 60 years and became insignificant at age 70–79 years [22].

In the first year following menopause, low density lipoprotein cholesterol (LDL-C) and total cholesterol increase. This may be a result of the decreased estrogen to androgen ratio [10]. Prior to midlife, women have lower blood pressure than men, a trend that reverses after menopause, presumably a result of increased vascular resistance [23]. However in the Study of Women's Health Across the Nation (SWAN), a multi-site, multi-ethnic, longitudinal observational study in North America, the trajectory of blood pressure increase and glycated hemoglobin A1c (HgbA1c) increase appear to follow age linearly rather than link to the menopause event [24].

Cardiovascular disease risk factors influence the menopause transition trajectory with earlier age of menopause in current smoking and later age of menopause with increased body mass [25, 26]. The presence of cardiovascular disease itself has not been linked to alterations in the menopause transition trajectory.

MHT for secondary prevention of future CVD events in women with existing CVD demonstrated increased events in the first year of use, a risk that ameliorated with continued use [27]. A systematic review and metanalysis of MHT and cardio protection showed no impact of MHT on CVD mortality in women with pre-existing CVD (Risk 45 per 1000 placebo and MHT) [10]. The International Menopause Society concluded MHT has no role in secondary prevention of CVD [17]. This is in agreement with many regional and national menopause professional associations [28–31].

Initiation of MHT in healthy women conveys no to minimal increased CVD risk. The timing of MHT use in the menopause transition effects MHT and CVD interaction. There are possible beneficial effects when initiated close to the final menstrual period (FMP) and increased risk when initiated more than 10 years from FMP. A large systematic review analyzed the timing hypothesis of MHT and CVD [10]. A collection of observational, case-controlled and epidemiological studies of women using MHT published in the 1990s and involving over 90,000 women followed for a range of 2–16 years indicated a 30–50% reduction in cardiac events with use of MHT when initiated close to the age of FMP [10, 32]. These studies were criticized for healthy bias as women in the studies sought treatment and had resources to do so. The WHI, a randomized controlled trial of CEE alone in women with history of hysterectomy or CEE and MPA in women with intact uterus and with a population mean age of 63 years, an age chosen specifically to identify cardiovascular effects, sought to answer this critique. Subsets of this population demonstrated a reduction of cardiovascular events in women <10 years from FMP and an increase in events in women who had metabolic syndrome at the initiation of the study or were more than 10 years from FMP. All groups demonstrated increased risk of venous thromboembolism [33, 34]. The Danish Osteoporosis Prevention Study (DOPS) included women aged 45–58 years age and within ≤24 months of final menstrual period randomized to oral 2 mg synthetic 17β-estradiol for 12 days, 2 mg 17β-estradiol plus 1 mg norethisterone acetate for 10 days, then 1 mg 17β-estradiol for 6 days. After 10 years treatment and 6 years follow-up, the women randomized to treatment had reduced mortality, heart failure, and myocardial infarction (HR 0.48; 95% CI

0.26 to 0.87, $p = 0.015$) without an increase in stroke or cancer [35, 36]. As in the WHI, DOPS had strong evidence of increased risk of venous thromboembolism in the treatment group.

The International Menopause Society, incorporating this recent data from younger women, stated that MHT has little risk of contributing to CVD and confirmed a window of opportunity for MHT use close to the age of menopause for primary prevention of cardiac disease [17]. The Indian Menopause Society, the Korean Menopause Society, and the North American Menopause Society continue to recommend against the use of MHT solely for primary CVD prevention [28, 29, 31].

5.2.1 Summary

- Management of risk for and of existing cardiovascular disease is most effective if modifiable risk factors are ameliorated. Lifestyle interventions should incorporate tobacco cessation, increased regular physical activity, and weight management (see Chap. 12). Hypertension, hyperlipidemia, and diabetes should be managed pharmacologically if lifestyle interventions are not sufficient [29, 37].
- Women who have undergone early menopause (<45 years age) should use combined hormonal contraception or MHT up to the age of natural menopause to prevent CVD [17, 29, 31].
- MHT has no role in secondary prevention of CVD. Guidelines have slight variations. MHT contributes to primary prevention of CVD in women <10 years from menopause but generally should not be used solely for this purpose.
- MHT use is contraindicated in presence of existing or newly diagnosed cardiovascular disease.
- The clinician and the patient should be aware of small but consistent findings of increased cardiac events shortly after initiation of therapy and the additive risk of venous thromboembolism.
- For women more than 10 years after menopause and for women with CVD, alternatives to MHT should be considered first line for menopause symptom management.

5.3 Thromboembolism

Venous thromboembolism (VTE), including deep vein thrombosis (DVT), and pulmonary embolism (PE) has an incidence of 1:10,000 before age 45 years, then approximately doubles in incidence each decade thereafter. Incidence is higher in men than in women and in individuals of European ancestry than in those of Asian or Hispanic ancestry. In the United States, Black individuals have up to 25% higher risk, mostly of secondary disease, possibly reflecting differences in treatment of associated risks and use of prophylaxis. Risk factors in addition to age include surgery, hospitalization, immobility, trauma, pregnancy/postpartum, cancer, obesity, and inherited and acquired disorders of hypercoagulation [38, 39]. Menopause hormone therapy is also a risk factor for venous thromboembolism (RR 1.92, 95% CI

1.36–2.69; 37,313 participants in 10 studies) and pulmonary embolism (RR 1.81, 95% CI 1.32–2.48; 36,316 participants in 7 studies) [10].

The physiology of thromboembolism is an interaction of vascular endothelial damage, circulatory stasis, and hypercoagulability, known as Virchow's Triad. Most clots form in the calf and many clots appear to be self-limiting. If a clot forms and does not dissolve, it extends proximally into the popliteal and femoral veins within 7 days. Proximal vein DVT are more likely to be symptomatic and to form emboli [40].

Although incidence of thromboembolism increases linearly with age, menopause contributes to a pro-coagulable and pro-embolic environment. The decrease in estrogen associated with menopause leads to reduced endothelial repair, less inhibition of inflammation, increased secretion of pro-atherogenic cytokines, and less stability of the fibrin cap in existing atherosclerotic plaques [21]. Platelet action is also affected with reduced fibrinolysis [32]. The shift from estrogen to androgen dominance may also play a role in coagulable status [10].

MHT was associated with a doubling of risk of DVT (RR 1.92; CI 1.24–2.99. 33,477 in 6 studies). The assumed risk increased to 20:1000 from 10:1000 across all age groups. There was slightly less risk in women less than 10 years from menopause (RR 1.74, CI 1.11–2.73), with increase in assumed risk of 11:1000 from 6:1000. The majority of events occurred in the first 1–2 years of MHT use [10]. Risk factors are additive. Obesity or tobacco use and MHT contribute up to a tripling of risk [38].

Women with a history of VTE who use MHT are at increased risk of recurrence with oral estrogen. A study of women with a history of DVT or superficial venous thrombus (SVT) randomized to 2 mg estradiol/norethisterone or placebo was halted prematurely when women with a history of DVT/SVT had a threefold increased incidence of recurrent thrombosis [41]. Women with disorders of hypercoagulation such as Factor V Leiden (FVL) and prothrombin G20210A mutation have an annual VTE incidence of 0.5% with relative risk in heterozygotes of four to tenfold and in homozygotes of 50–100-fold [38]. A nested case-control study of women with FVL and oral delivery of CEE and MPA demonstrated an increased risk of VTE. In the WHI data, the annual risk was calculated to be 0.8% in women with FVL [42].

Route of delivery of MHT interacts with risk of VTE. Transdermal delivery of estrogen demonstrated no significant increase in VTE in a metanalysis of 7 population-based studies including 26,471 VTE cases [43]. A French multi-site case-control study, the Estrogen and Thromboembolism Study, specifically looked at use of transdermal estrogen in FVL and PT G20210A mutations. Though case numbers were small ($n = 271$), women with a prothrombotic mutation using transdermal estradiol did not differ from non-users in incidence of VTE (OR, 1.2; 95% CI, 0.8–1.7). Women using oral estrogen had a 25-fold increase in incidence [44].

The association of estrogen formulation with CVD and stroke is less robust. In the WHI, there was no increase in risk of VTE on oral CEE when women with CVD and those over age 60 were eliminated from analysis [45]. Confounding variables, including age, risk factors, and treatment adherence, have larger influence than hormone formulation in VTE [46].

The use and the type of progestogen used in women with a uterus may play a role in VTE risk. Estrogen and progestin have higher risk VTE than estrogen alone. Micronized progesterone combined with transdermal estradiol did not show increased risk of VTE [43].

5.3.1 Summary

- A careful assessment of personal and family history should precede initiation of MHT. Screening for thrombophilia is not helpful. The patient should be informed of VTE risks, potential symptoms, and the emergent nature of the condition prior to initiation of MHT.
- Management of modifiable risk factors for VTE should be incorporated into all therapy plans. Weight management, physical activity, and tobacco cessation reduce risk of VTE.
- Women with active thromboembolic disease should not use MHT. Women with a history of VTE may consider transdermal estrogen [17, 28–31, 47].
- Women with associated VTE risk factors such as smoking, obesity, and prothrombotic genetic mutation should use transdermal estrogen over oral delivery route [17].
- The lowest effective dose of estrogen with transdermal route of delivery, combined with micronized progesterone in women with a uterus, ameliorated or eliminated increased risk of VTE.
- As risk of VTE increases with age, continued use of MHT should be routinely assessed.

5.4 Stroke

Worldwide, stroke is the second leading cause of disability [48]. A woman's lifetime risk of stroke from age 25 years is 25.1%. There is geographic variation in the lifetime risk of stroke, with the highest risks in East Asia, Central Europe, and Eastern Europe (31.6–38%) and the lowest risk in eastern sub-Saharan Africa (11.8%) [49]. Stroke occurs 15 years earlier and causes more death in people living in low and middle income countries compared to high income. Hemorrhagic stroke accounts for 36% of strokes in low income countries and only 9% in high income countries [50]. The risk of stroke before the age of 60 years is very rare. Age-stratified data from 19 countries show men age 45–74 have a 45% higher risk of stroke than women. The differential risk narrows with age [51]. Risk factors for ischemic stroke closely follow the risk factors for CVD: current cigarette smoking, low physical activity, abdominal adiposity, history of diabetes, hypertension, elevated cholesterol, and cardiac arrhythmias [50]. As in CVD, depletion of sex steroids impacts ischemia, including ischemic stroke.

Women experiencing early menopause (<42 years) had a doubling of lifetime risk of stroke in the Framingham data [52]. This elevated risk of stroke in early menopause persisted across race and ethnicity (HR 2.19, CI 1.11–4.32) [53].

Any MHT associated increased risk of stroke in women with typical age of menopause appears related to the timing of MHT initiation and the route of delivery. There was increased risk of stroke with MHT across all age groups (RR 1.32, CI 1.12–1.56) in 4 studies involving 29,000 patients [10]. This data is heavily weighted by WHI data, involving older women at MHT initiation. When women initiate MHT within 10 years of menopause, there was no significant increase in stroke in either healthy women (RR 1.37, CI 0.80–2.34) or in secondary prevention (RR 1.09,

CI 0.89–1.33) [10]. A nested case-control population study in the United Kingdom with 15,710 cases of stroke showed no increase in stroke risk with use of transdermal estradiol ≤50 μg compared to non-users (RR 0.81, CI 0.62–1.05). [54].

5.4.1 Summary

- Management of risk for ischemic stroke is most effective if modifiable risk factors are ameliorated. Lifestyle interventions should incorporate tobacco cessation, increased regular physical activity, and weight management. Hypertension, hyperlipidemia, and diabetes should be managed pharmacologically if lifestyle interventions are not sufficient. Prophylaxis should be implemented in the presence of atrial fibrillation after risk of falls and bleeding is considered [29, 55].
- Women who have undergone early menopause (< 45 years age) should use combined hormonal contraception or MHT up to age of natural menopause to prevent increased risk of stroke [17, 29, 31].
- Initiating MHT < 10 years from final menstrual period and selecting transdermal estrogen delivery ameliorate risk of stroke associated with MHT.
- MHT should not be used in women with a history of stroke [17].

5.5 Diabetes and Metabolic Syndrome

Diabetes includes Type 1 diabetes mellitus, with pancreatic beta cell destruction and absolute insulin deficiency, accounting for 10% of all diabetes, and Type 2 diabetes mellitus (T2DM) involving a progressive insulin secretion disorder in the presence of insulin resistance and representing the large majority of diabetes worldwide [12]. Globally the incidence of diabetes is increasing with 471 million affected adults, a more than fourfold increase from 1980 to 2017. The highest numbers are found in China, followed by India and the United States [56, 57]. Risk factors for T2DM include diabetes in first-degree relative, age, abdominal adiposity, sedentary lifestyle, sleep disruption, and history of gestational diabetes [58].

Women with early surgical menopause have increased risk of T2DM. In the National Health and Nutrition Epidemiologic Followup Study (NHEFS), there was a 57% increase in T2DM in the following 9.2 years in women with premenopausal oophorectomy [59]. While many of the risk factors for T2DM increase in midlife, menopause at natural age does not appear to be an independent risk. The European Prospective Investigation in Cancer and Nutrition (EPIC) followed 3691 women with T2DM, mean age 59.2 years, for 11 years. Adjusting for age, BMI, and smoking, there was no independent link to menopause. Data from the US Diabetes Prevention Program, the Spanish Pizarra Study, the Australian Longitudinal Study on Women's Health, the Melbourne Women's Midlife Health Project, and cross sectional data from Latin America, China, Japan, and Italy corroborate these findings [12].

Metabolic Syndrome (MetS), another metabolic disorder prevalent in midlife, is a risk factor for T2DM and for CVD. A diagnosis according to the 2009 International Consensus Statement is indicated when there are three or more of the following characteristics [60]:

- Waist circumference >31 in (88 cm), >31.5 in South Asian.
- Elevated serum triglycerides ≥150 mg/dL (1.70 mmol/L).
- Low serum high density lipoprotein cholesterol <50 mg/dL (1.3 mmol/L).
- Elevated blood pressure (>130/85).
- Fasting plasma glucose level ≥110 mg/dL (6.105 mmol/L).

Incidence of MetS does increase with menopause, largely due to rise in lipids and to alterations in body composition with increased central adiposity (see Chap. 12). MHT use has been shown to have beneficial effects on prevention of abdominal adiposity with lower waist-to-hip ratio and BMI in several populations internationally [61–64].

MHT delayed the onset of T2DM in some studies. The WHI showed a 14% reduction in T2DM in women on CEE and MPA and a 19% reduction in women on CEE alone. This reduction in disease was not maintained after MHT was discontinued. During treatment there was a reduction of 16 cases/10,000 person-years and post-intervention follow-up had an increase of 20 cases/10,000 person-years in the CEE + MPA group [65]. Several other RCTs using various forms of estrogen and progestogen reported either neutral or positive effects on fasting glucose [66–68]. Two systematic reviews and metanalyses concluded that the effect of estrogen alone or of estrogen and progestogen is either advantageous when the administered orally, or neutral in both oral and transdermal administration [12].

5.5.1 Summary

- Management of risk factors for diabetes and MetS with lifestyle intervention is the first-line treatment. If nutritional management and increased physical activity are insufficient to control blood sugar, pharmacological management of blood sugar and lipids is indicated [17, 29].
- Do not use MHT solely for primary prevention of diabetes [17].
- MHT may be used for menopause symptom management in women with diabetes after assessing for co-morbidity of CVD.
- MHT may have a positive effect attenuating increase in abdominal adiposity associated with menopause and with MetS [29, 31].

5.6 Chronic Lung Disease

Asthma and chronic obstructive pulmonary disease (COPD) are the most common inflammatory lung diseases. They are both contributing risk factors for lower respiratory infection. COPD and lower respiratory infection are in the top 20 causes of shortened healthy lifespan across all nations and economic rankings [2]. The major risk factors for chronic lung disease are tobacco smoke exposure, age, female gender, cooking fuel exposure, and air pollution. Excess weight and genetically and environmentally mediated allergens are additional risk factors [69, 70]. There are gender differences in lung disease across all age spans. Women have increased incidence of asthma, more sensitivity to carcinogens, and experience unique lung disease [71]. Asthma, commonly thought a childhood disease, may develop at any age.

The incidence of asthma is increasing in the population over age 65, the postmenopause stage of life, and is subject to misdiagnosis [72].

ERα, ERβ, and progesterone receptors and aromatase are present in the lung tissue of both women and men though the hormone effect is not well defined. Low estrogen levels appear to provide resistance to bronchoconstriction while high levels of estrogen increase sensitivity to vasoconstrictive stimuli [73]. Multiple animal studies identified an estrogen anti-inflammatory effect on lung tissue which is enhanced at puberty and reduced with menopause [74–77]. This is not in concordance with the epidemiology of asthma, where incidence in females surpasses that in males at puberty. Endogenous and environmental estrogens have been implicated in immune activity allergy reactions [78]. Progesterone is a powerful vasodilator, increases relaxation of bronchial smooth muscle, and has anti-inflammatory effect through stimulation of helper-T cells and cytokines with a potential positive effect on pulmonary function [79].

The loss of sex steroids in the menopause transition is associated with more rapid decline in lung function [79]. When women in the menopause transition were compared to an age-controlled population of women in premenopause, there were significant differences in decline of pulmonary function (Forced vital capacity [FVC] −10.2 mL/year, CI −13.1 to −7.2, perimenopause and −12.9 mL/year, CI −16.2 to −8.9, postmenopause, forced expiratory volume at 1 s [FEV1] −3.8 mL/year perimenopause and −5.8 mL/year postmenopause) [14]. This is in agreement with data from the ECRHS II study [80].

MHT may have a beneficial effect in the health of women with chronic lung disease. Hospitalizations for COPD were reduced in a prospective cohort in the United Kingdom [13]. One metanalysis of 2 studies involving 998 women reported increased asthma like symptoms but not diagnosis of asthma or use of asthma medications in women using MHT compared to women not using MHT (RR 1.32, CI 1.01–1.74) [81]. A study of 50 women with asthma had spirometry measurements before and after 6 months of treatment of transdermal 17β-estradiol and MPA. When using both MHT and inhaled glucocorticoids, asthma exacerbations and glucocorticoid use decreased while spirometry parameters improved following 6 months of MHT [82].

5.6.1 Summary

- The international guidelines and various regional and national guidelines do not address chronic lung disease [17, 28–31].
- MHT use in women with chronic lung disease is not harmful and may be beneficial based on evidence from a limited number of studies [13, 81, 82].

5.7 Chronic Kidney Disease

Chronic kidney disease (CKD) in its milder stage affects 5–7% of the world's population. It is a reversible disease when detected and managed early. The major causes of CKD are hypertension and diabetes. Men are more likely to progress to end stage renal disease (ESRD) than women. The presence of CKD is a risk

multiplier, associated with an eight- to tenfold increase in CVD [83]. A questionnaire administered by the International Kidney Society in 2016 demonstrated wide variation in resources for screening and care. Availability of CKD monitoring (estimated glomerular filtration rate (eGFR), urine protein, albumin, and creatinine) at the primary care level was described as always available in 73.5% of upper and high middle income nations but always available in only 48% of low and low middle income nations. Access to end stage renal disease care including nephrology specialty care, hemodialysis, and transplant are most limited in Africa, followed by South Asia [84].

Menopause does not appear to affect the progress of CKD. Decline in eGFR is linear, consistent with age, rather than the menopause transition. Serum levels of sex hormones, estradiol, testosterone, free androgen and the testosterone to estradiol ratio were not associated with eGFR [85].

Women with mild to moderate CKD and women on dialysis experience menopause earlier than women without CKD. In the WHI cohort, women with mild to moderate CKD (mean eGFR 50.7 mL/min/1.73 m^2) had a 26% vs. 23% incidence of menopause at <45 years age ($p = 0.02$). Among women in dialysis, an anovulatory profile was observed in the majority of patients [86]. Early menopause may subsequently exacerbate risks associated with CKD, specifically bone and cardiovascular health and sexual function.

The experience of the menopause transition also appears altered by the presence of CKD. Women with mild CKD were less likely to experience vasomotor symptoms than women without CKD (38% vs. 46%, $p < 0.001$). The physiology supporting this difference is unclear. It is possible impaired vascular endothelial function may prevent vasodilation. Central nervous system control of body temperature regulation may also be impaired even in early CKD [86] (see Chap. 8).

Management of menopausal symptoms in women with CKD is not mentioned in either international or regional guideline [17, 28, 29, 31]. Women with CKD are at increased risk of co-morbid CVD. Women with CVD face increased risk of cardiac events shortly after MHT initiation [17, 29, 31]. There are no studies of CVD mortality and use of MHT in women with CKD. Measurement of CVD surrogate markers show improved lipid profile (decreased LDL −13.2 mg/dL, CI −23.32 to −3.00 mg/dL, increased HDL 8.73 mg/dL, CI 4.72–12.73 mg/dL) and no association with triglycerides or blood pressure in women using MHT compared to placebo [87]. The population with early menopause is at increased risk of osteoporosis (see Chap. 13). For women with CKD and early menopause, MHT may be beneficial close to the age of final menstrual period.

5.7.1 Summary

- Women with CKD experience menopause at a younger age and are less likely to have vasomotor symptoms.
- In the absence of guidelines, co-morbidities and the age of menopause in women with CKD should dictate use of MHT to manage menopausal symptoms.

5.8 Gallbladder Disease

Gallstones are predominantly a disease of higher income regions, affecting up to 10–15% of individuals in Europe, North America, and northern India. Also at increased risk are individuals of North and South American native ancestry [88, 89]. Epidemiological survey relies on abdominal ultrasound for case detection and may underestimate prevalence in low and low middle income regions [90]. Most cases of gallstones are without symptoms and only 35% of incidentally detected stones later require surgery [88]. The major risk factors are female gender, age, obesity, sedentary lifestyle, diabetes mellitus, rapid weight loss, and some drug interactions [88–90]. Mortality rate from gallstones is low (0.6%) and decreasing; however, the condition is associated with increased mortality in CVD and cancer, possibly due to overlapping risk factors [90]. Large stones, >2.5 cm, and high volume and mass of stones, are linked to a 5- to 11-fold increased risk of gallbladder dysplasia and gallbladder cancer, also of highest incidence in Native North and South Americans [90, 91].

Most gallstones are composed of cholesterol. Estrogen increases the hepatic secretion of biliary cholesterol, leading to cholesterol saturation in bile and formation of precipitate and stones. Estrogen also slows motility of bile, further enhancing stone formation [92]. Tibolone has been shown to have similar effect in studies on rats [93].

The development of gallstones is linearly related to age rather than the menopause event. The female to male ratio of disease, 4:1 during the reproductive stage of life, equalizes after menopause due to a steep increase in disease in males though incidence continues to increase in both genders [88]. MHT is associated with an up to 50% increased risk of gallbladder disease [17]. In the WHI and the Heart and Estrogen/progesterone Replacement Study (HERS) cohorts, using oral CEE and MPA, the hazard ratio was 1.57, CI 1.36–1.80, and 1.38, CI 1.00–1.92 respectively with similar increased risk in the CEE only arm of the WHI [65, 94]. Risk increased with more than 5 years duration of use [95]. Transdermal delivery of estrogen ameliorated increased risk of gallbladder disease in the large observational Million Women Study (RR 1.17, CI 1.10–1.24 vs. 1.74, CI 1.68–1.80). Conjugated equine estrogen was higher risk than estradiol (RR 1.79, CI 1.72–1.87 vs. 1.62, CI 1.54–1.70) [96]. A large prospective French cohort with more heterogeneity of estrogen formulations found less substantial increased risk of gallbladder disease associated with oral estrogen only (RR 1.10, CI 1.01–1.20) and no increased risk of gallbladder disease with transdermal delivery of estrogen [97].

5.8.1 Summary

- Oral delivery of estrogen is associated with increased risk of gallbladder disease after 5 years use.
- Transdermal delivery of estrogen ameliorates or eliminates increased risk of gallbladder disease.
- Use oral estrogen with caution in women with current or history of gallbladder disease.

5.9 Cancer

The incidence and mortality rates of all cancers are highest in upper middle and high income regions, though rates are decreasing in these regions while increasing in low and low middle income regions [98]. Cancer profiles differ among countries. Breast cancer is the most common cancer among females in North America, Europe, and Oceania. Breast and cervical cancer are most frequent cancer diagnoses in Central/South America, the Caribbean, Africa, and most of Asia though lung cancer is the most frequent female cancer in China and North Korea [98]. Chap. 14 of this volume covers breast health and menopause.

The gynecological cancers: endometrial, ovarian, and breast, and colorectal cancers share risk factors. Non-modifiable risks of age and genetics, and modifiable risks of body weight, activity, and alcohol intake and the presence of diabetes mellitus have stronger influence than menopause on the development of disease in these cancer profiles.

Obesity increases peripheral cell aromatization, increasing sex steroids. Risk of the gynecological and colon cancers doubles with a BMI > 25 and triples with BMI > 30 in postmenopause women [99]. Metanalysis have reported an approximate 30% increased risk of breast cancer recurrence or breast cancer death in women with obesity vs. women without [100]. Early adult weight gain and subsequent maintenance appear to convey the highest weight related risk of endometrial cancer [101, 102]. The incidence of overweight (BMI > 25) or obesity (BMI > 30) was significantly higher in colon adenoma positive but not colon adenocarcinoma patients than in normal weight controls (49.9% and 0.9% respectively, $p = 0.04$). The adenocarcinoma group were older individuals than the non-adenocarcinoma group [103].

An international systematic review and metanalysis of very high activity (≥8000 MET min/week, the rough equivalent of jogging at 11 km/h for 12 h weekly) compared to lower than recommended activity levels (<600 MET min/week, the rough equivalent of jogging at 11 km/h for less than 1 h weekly) demonstrated risk reduction in the very high activity group of 14% for breast cancer (RR 0.863, UI 0.829–0.900) and 21% for colon cancer (RR 0.722, 0.678–0.768) [104, 105]. High versus low physical activity reduced risk of endometrial cancer 20% overall with general recreational, occupational, and household activity all affecting risk reductions of 6–30% dependent on intensity of activity. Activity was protective for postmenopausal women but not premenopause and for overweight or obese but not normal weight [106].

Alcohol has a clear and consistent link to increased risk of breast cancer, with an increase in risk of 7–10% per number of drinks consumed daily. The link to breast cancer was evident at levels of alcohol intake not associated with cancer risk in other body organs [107]. Alcohol intake had inconsistent findings in risk of endometrial cancer. The Nurses' Health Study, a prospective cohort of 60,867 women aged 34–59 years followed for 30 years, showed an inverse association with 0.5 up to 2 drinks/day reducing endometrial cancer risk compared to non-drinkers (RR 0.81, CI 0.68–0.96) [108]. A prospective multi-ethnic cohort of 41,574 postmenopausal women followed for 8 years showed increased risk with more than 2 drinks per day (RR 2.01, CI 1.30–3.11) but no association in 0.5 drinks to less than 2

drinks/day [109]. This was confirmed in a systematic review and metanalysis, with a J-shaped relationship of no endometrial cancer risk associated with 0.5 up to 2 drinks/day [110]. A similar J-shaped relationship was seen with colorectal cancer and alcohol consumption. A metanalysis of case-controlled and nested case-control studies with over 14,000 cases of colorectal cancer demonstrated a reduced risk with 0.5 drinks up to 2 drinks/day compared to non/occasional alcohol (OR 0.92, CI 0.88–0.98, $p = 0.005$), no relationship with 2–3 drinks/day and increased risk with very heavy drinking >3 drinks/day (OR 1.25, CI 1.11–1.40, $p < 0.001$) [111].

Diabetes increases insulin-like growth factor and decreases sex hormone binding globulin leading to small increase in circulating free sex steroids. There was both increased risk of endometrial cancer (RR 1.72, CI 1.48–2.01) and breast cancer (RR 1.20, CI 1.12–1.28) in women with diabetes compared to women without [112, 113]. There was increased risk of an adenomatous colon polyp (RR 1.831, CI 1.058–3.169, $p = 0.023$) but not adenocarcinoma in individuals with diabetes. The adenocarcinoma cohort was significantly older [103].

A first-degree relative with a history of breast cancer imparts a 30% increased individual risk of disease [114]. In endometrial cancer, there is a doubling of risk with a first-degree relative [115]. Thirty-five percent of colorectal cancer patients have a positive family history of disease [116]. However, identified genetic markers account for only 10% of all endometrial cancers, 10–15% of ovarian cancers and breast cancers, and 5–10% of colorectal cancers [114–116]. A shared genetic marker in all of these types of cancer is hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome. HNPCC involves a mutation in the mismatch repair genes in multiple loci and has an estimated general population prevalence of 1 in 279 [117]. HNPCC imparts a 40–60% individual risk of endometrial cancer, a 52–82% individual risk of colorectal cancer with younger age of diagnosis, and approximately 8% risk of ovarian cancer of which more than half of patients are diagnosed at stage I or II [117–119]. The PMS2 mutation of HNPCC imparts a higher risk of breast cancer and a younger age at diagnosis than mutations at other loci, 27% compared to 3–9% [120].

Together, the predominant genetic markers for breast and ovarian cancer, BRCA1 and BRCA2, have variable population prevalence. Combined prevalence of 1:265 in a random Mexican population, combined prevalence of 1:365–1:1000 in the US population, and 1:40 in the Ashkenazi Jewish population [121, 122]. A metanalysis of 10 studies calculated cumulative risks by age 70 years as follows: breast cancer risk of 55% (95% CI, 50–59%) for *BRCA1* and 47% (95% CI, 42–51%) for *BRCA2* mutation carriers; and ovarian cancer risk of 39% (95% CI,34–45%) for *BRCA1* and 17% (95% CI, 13–21%) for *BRCA2* mutation carriers [123]. See Chap. 8 for more discussion of genetic risk and assessment in breast cancer.

5.9.1 Endometrial Cancer

Endometrial cancer is the most common gynecological cancer worldwide. Type 1 results from an environment of unopposed estrogen, accounts for approximately 80% of all endometrial cancers, and is more likely to be diagnosed at an earlier stage with an 85% 5-year survival. Endometrial cancer is rarely seen in women younger than 45 years age [124, 125]. ERα activity stimulates endometrial cell

proliferation, inhibits apoptosis, and promotes angiogenesis, all leading to endometrial hyperplasia [126]. Among women with biopsy proven complex hyperplasia with atypia, 15–50% have carcinoma at hysterectomy and 29% progress to carcinoma if left untreated [124, 127]. Women with simple atypical hyperplasia at biopsy have a subsequent 8% risk of endometrial cancer [128].

The anovulatory cycles of early perimenopause result in an unopposed estrogen environment; however, it is not clear if early perimenopause is an independent risk factor for development of complex hyperplasia. Lifelong decreased ovulation as in polycystic ovarian syndrome, as well as the risk factors listed above, may be principle contributors to risk [129]. Systemic estrogen only hormone therapy in women with an intact uterus for 1 year resulted in 20% incidence of hyperplasia [130]. Systemic, oral, unopposed estrogen was associated with endometrial hyperplasia at all doses, and duration of therapy between 1 and 3 years [131]. Topical vaginal estrogen for treatment of genitourinary syndrome of menopause is not associated with endometrial stimulation and hyperplasia but no data for use beyond 1 year has been reported [132]. The dose, type, and pattern of progesterone influences the suppression of the estrogen-dependent development of hyperplasia. Progestogen used in continuous combined delivery is rarely associated with hyperplasia. For women with a uterus using continuous estrogen and a progestin, the risk of endometrial hyperplasia was not different from placebo (1 mg NETA: OR 0.04; 95% CI 0–2.8; 1.5 mg MPA: no hyperplasia events) [131]. The WHI had a non-significant 19% reduction of endometrial cancer with continuous combined CEE/MPA compared to placebo [133]. Sequential systemic progestogen use has been associated with increased endometrial cancer compared to continuous progestogen (HR 2.42, CI 1.53–3.83). Difficulty adhering to treatment protocol may influence this [126] (see Chap. 6).

5.9.1.1 Summary

- Encourage use of a menstrual calendar in women in perimenopause to assess risk of unopposed estrogen, particularly in women with increased baseline risk. [134].
- Women with a uterus should always use progestogen with estrogen at any stage of the menopause transition. [135].
- Postmenopause bleeding should be thoroughly assessed for endometrial cancer. (See Chap. 7 of this volume.).

5.9.2 Breast Cancer

Although breast cancer is not among the top ten causes of death or DALY in women in all income regions worldwide, breast cancer is the leading cause of cancer mortality in women [136, 137]. Breast cancer survival has improved in some groups but the incidence of breast cancer is increasing globally. The large majority of breast cancer occurs in women in postmenopause. However the incidence in women prior to menopause is increasing more rapidly in high resource regions [138]. An entire chapter of this volume, Chap. 14, has been devoted to breast cancer in women.

Breast cancer risk factors of alcohol, obesity, sedentary lifestyle, and family history are discussed in Sect. 5.9, with additional information in Chap. 14. Women with earlier menopause have a reduced breast cancer risk. The risk of ER+ breast

cancer increases by 2.9–4% with each year menopause is delayed [139]. Screening, diagnosis, genetic screening, and the criteria for chemoprevention of breast cancer are discussed in detail in Chap. 14.

The interaction of menopause hormone therapy and increased risk of breast cancer, with prolonged duration of use of estrogen and progestin as the dominant influence, and with less increased risk in use of estrogen alone or estrogen with micronized progesterone, is discussed in depth in Chaps. 6 and 14. Breast cancer survivors should not use menopause hormone therapy due to increased risk of recurrent disease. The cumulative incidence of breast cancer in the HABITS study MHT arm at 5 years was 22.2% versus 8.0% in the non-MHT arm [140]. Menopause symptoms may be more severe in breast cancer survivors with chemotherapy-induced menopause and women using selective estrogen receptor modulators and aromatase inhibitors [141, 142]. Effective symptom management, particularly of vasomotor symptoms and genitourinary symptoms, is achievable with methods other than exogenous hormones, as discussed in Chaps. 8 and 11.

5.9.3 Ovarian Cancer

Epithelial ovarian cancer (EOC) is the seventh most common type of cancer in women worldwide with an incidence tenfold lower than breast cancer, but is the most common cause of gynecological cancer death. Five year survival rates fall below 45% [143]. The age-standardized rates (ASR; a method for comparing rates in populations of different size and age-distribution) range from 7.0 to 11.6 per 100,000 in the Americas, Europe, and Oceania. In Asia, the ASR in Israel (Ashkenazi Jewish) is the highest at 8.1 per 100,000 and range from 6.2 per 100,000 in China (Hong Kong) to 7.9 per 100,000 in Japan (Osaka Prefecture) [144]. Rates are stable or falling in upper middle and high income countries and increasing in low and middle low income countries [143, 145]. There are four subtypes of EOC, of which high grade serous comprises the large majority of cases, is the most aggressive subtype, and may be associated with BRCA1 and BRCA2 mutations [146]. Many of these tumors develop from tubal neoplasms [147]. The seromucinous endometroid and the clear cell subtypes may be associated with atypical endometriosis and the clear cell subtype is associated with Lynch Syndrome [114, 148]. The final subtype, mucinous, is very rare and must be distinguished from metastases of extragenital malignancy.

Risk factors associated with ovarian cancer include nonparity, smoking, obesity, and genetics. MHT as a risk factor is analyzed more thoroughly below. Protective factors include hormonal contraceptive use, salpingectomy and/or oophorectomy [149, 150].

There are no adequate ovarian cancer screening methods for average risk individuals. Tumor markers such as CA-125 may be associated with other cancers and with inflammatory or benign gynecological conditions [151]. Ovarian cancer has no specific symptoms. Early stage disease may be associated with abdominal bloating, dyspareunia, and change in bowel or bladder. Ascites, bowel obstruction, and pleural effusion are typically associated with late stage disease [146]. Diagnostic workup begins with tumor marker and imaging, initially ultrasound followed by CT or MRI as indicated.

Cases of ovarian cancer increase linearly with age. The menopause transition does not appear to influence this trend. Analyses of ovarian cancer risk associated with MHT

have inconsistent findings. The rarity of the disease must be considered when analyzing the clinical impact of relative risk. Observational studies have indicated an increased risk of ovarian cancer with menopause estrogen use: the Nurses' Health Study reported RR 1.41, CI 1.07–1.86 when using estrogen for more than 5 years and the NIH-AARP Diet and Health Study reported RR 2.15, CI 1.30–3.57 when using ET for more than 10 years and RR 1.68 (95% CI, 1.13–2.49) when using EPT for more than 10 years. A metanalysis combination of 52 retrospective and prospective cohorts, including both of the previous studies and relying heavily on data from the MWS, identified increase risk of ovarian cancer RR 1.37 (95% CI 1.29–1.46; $p < 0.0001$) with current use, with recent use (discontinued <5 years) and with short duration of use (< 5 years using). The increased risks were confined to serous and endometroid tumor subtypes [152]. This study has come under critique for the absence of population data on oophorectomy and hysterectomy/salpingectomy, absence of dose or duration related information, possible loss to follow up of non-MHT users, and the wide disparity of risk among the studies. Gompel and Burger calculated the absolute excess risk for a 50-year-old United Kingdom woman using MHT for 5 years from this metanalysis to be 1:10,000 per year use [143]. The only randomized controlled trial was the WHI using CEE and MPA or CEE alone which found no increased risk after 5.6 years intervention and 13 years follow-up [65]. Very limited data on BRCA mutation carriers using estrogen and progesterone following risk reducing salpingo/oophorectomy reported no increased risk but the sample size was very small ($n = 1100$) [153].

5.9.3.1 Summary

- The International Menopause Society states that the risk of ovarian cancer associated with MHT use is unclear [17]. The North American Menopause Society states that if an association between MHT and ovarian cancer exists, the absolute risk is likely to be rare (< 1:10,000) or very rare (<0.01:10,000) [31].
- Potential prevention of ovarian cancer with use of hormonal contraceptives, tubal sterilization, salpingectomy performed with other invasive gynecological procedures after childbearing, and risk reducing salpingectomy/oophorectomy in BRCA mutation carriers should be considered [154–156].

5.9.4 Colorectal Cancer

Worldwide the incidence of colorectal cancer is decreasing in high income countries and increasing in low income countries. This trend is largely attributable to access to screening, with removal of precancerous lesions, and increases or decreases in risk factors such as smoking. Mortality rates follow curves similar to incidence [98]. Risk factors have the largest impact on disease development. There is no evidence of sex steroid impact or the menopause transition on colorectal cancer risk.

The Nurses' Health Study showed reduced risk of colorectal cancer in current users of MHT when hormones were started close to the age of menopause [157]. A metanalysis of 18 studies showed a risk reduction in colorectal cancer for ever-use of MHT (RR 0.80, 95% CI 0.74–0.86) [158]. In the WHI randomized trial, there was slight risk reduction for $E + P$ (RR 0.63, CI 0.43–0.92), but not for estrogen alone [16]. This reduction was not seen in post-hoc analysis of combined WHI data

[65]. Tibolone is indicated for use in Europe for prevention of colorectal cancer in women at increased risk (HR 0.31, CI 0.10–0.96) [17].

5.9.4.1 Summary

- The International Menopause Society acknowledges a beneficial impact of MHT on colorectal cancer but states MHT should not be used solely for colorectal cancer prevention [17]. The North American Menopause Society states there is no strong protective effect for MHT on colorectal cancer [31].
- Reduction of modifiable risk factors, obesity, inactivity, alcohol intake, smoking, and diets high in red meat should be reinforced.
- Consider rectal bleeding when assessing report of postmenopausal bleeding. It is an opportunity to evaluate screening currency.
- With a diagnosis of colorectal cancer, family history should be assessed and genetic counseling considered [117].

5.9.5 Lung Cancer

Lung cancer is the second leading cause of cancer in women worldwide and is the leading cause of cancer death. It is a disease of upper middle and high income countries. The incidence of lung cancer is declining across all races/ethnicities in high resource countries. Between 2000 and 2016, lung cancer dropped out of the top 20 causes of shortened healthy lifespan worldwide, but still exceeds that of the combined incidence of colon, breast, and prostate cancers [2]. The disease decline has been less steep in women so that the incidence of lung cancer in non-Hispanic white women in the USA born in the 1960s now exceeds the incidence of disease in men, an excess in incidence not explained by smoking risk [159]. Direct and indirect exposure to smoking is the main risk factor in middle and high resource communities, accounting for 90% of lung cancers [160]. Women appear more susceptible to the carcinogenic effect of smoking for which there is no underlying physiological explanation [161]. In low resource communities, exposure to solid cooking fuels is a major source of lung cancer risk, as well as asbestos, air pollution and hazardous occupational exposure [160, 162].

There is evidence for interaction of lung cancer with sex steroids but the effect is not strong. Reproductive life stage events alter risk, but findings are mixed. A population based case-control study, the Environment and Genetics in Lung Cancer Etiology (EAGLE), found reduced risk of lung cancer among women with menopause after age 51 years (OR 0.49, CI 0.31–0.79) [163]. In the International Lung Cancer Consortium, premenopausal women showed increased risk with high parity (>3 children) and with breastfeeding but no strong association with age at menopause [164]. The effect of MHT, estrogen and progestogen, used for less than 5 years showed a slight protective effect for all lung cancers in the combined WHI data (HR 0.84, CI 0.72–0.98) and a similar slight protection for non-small cell lung cancer with previous use of any MHT for 5–10 years [165]. The EAGLE cohort demonstrated a reduced risk for estrogen only users (OR 0.63, CI 0.42–0.95) [163]. A metanalysis of 18 studies including RCT, case-control, cohort, and cancer registry, showed an overall benefit for estrogen only users (RR 0.80, CI 0.72–0.89).

5.9.5.1 Summary

- Tobacco use is the predominant risk factor for lung cancer. Encourage smoking cessation and avoidance of second-hand smoke exposure.
- The International Menopause Society concludes there is a slight lung cancer risk reduction with menopause hormone use and the North American Menopause Society states the effect of MHT on lung cancer risk is neutral [17, 31].
- In the absence of guidelines, MHT use is neutral in women at high risk for lung cancer. Consider discontinuance of MHT use in the presence of a new diagnosis of lung cancer due to the additive risk of VTE.

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Menopause Hormone Therapy

6

Patricia Geraghty

6.1 Introduction

There are more than 100 years of history of providing supplemental hormones to women in the menopause transition. Given the early and ongoing assumptions, then the limited data, then a plethora of data, it is not surprising that many women and many clinicians remain either confused or overwhelmed by the nuances of menopause hormone therapy (MHT). Estrogen, and estrogen with a progestogen in women with a uterus, are indicated for relief of vasomotor symptoms and vaginal dryness, and for osteoporosis prevention [1]. Other menopausal symptoms benefit from MHT. In this volume, chapters on each menopause transition experience provide the specifics of estrogen and progestogen application and benefits if any for that symptom. This chapter summarizes international and regional guidelines and analyzes the data regarding important differences in patient profile, hormone formulation, and delivery route which impact the benefits and risk profile.

6.2 Estrogen

6.2.1 Type and Delivery Methods of Estrogen Therapy

Oral estradiol is poorly absorbed in the gastrointestinal tract. It is rapidly converted to estrone in the intestinal mucosa, then extensively metabolized in the first pass through the liver. Less than 5% of the original dose of estradiol is available unchanged in circulation. For clinical use, estradiol absorption is enhanced by micronizing. Estrogens are stabilized by conjugating or adding piperazine or an

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Table 6.1 Oral estrogens available for menopausal use. Not all doses are available in all regions

Estrogen	Low dose (mg/day)	Moderate dose (mg/day)	High dose (mg/day)
Conjugated equine estrogen (CEE)	0.3, 0.4, 0.45	0.625	1.25
Conjugated estrogen (CE)	0.15, 0.3, 0.4, 0.45	0.625	
Piperazine estrone	0.3, 0.625	1.25, 1.5	2.5
Ethinyl estradiol (EE)	<0.010	0.010	>0.010
17beta-estradiol (E2)	0.5, 1.0	1.5, 2	4
Estradiol valerate (EV)	0.5	1	2
Esterified estrogen (ESE)	0.3	0.625	1.25

Classification of orally delivered estrogen doses based on Furness et al. [5]

ester group. Addition of an ethinyl group decreases liver metabolism, increasing potency [2].

Conjugated equine estrogen (CEE) was made available as Premarin® in North America in the 1940s. With development of more sensitive assays it became clear that CEE contains at least ten equine estrogens, all of which are biologically active, with 17beta-estradiol dominant [3]. Subsequently, synthesized conjugated estrogen, micronized estradiol, and esterified estrogen became pharmaceutically available. Conjugated estrogen and 17beta-estradiol are available in oral products or topical vaginal creams from regulatory bodies. Other estrogens are available in oral and in transdermal forms as adhesive patches, creams, gels and sprays, as well as topical vaginal cream [4]. See Table 6.1. These estrogens have unique absorption and first-pass hepatic metabolism when delivered orally and unique absorption profiles dependent on the delivery matrix when used topically [5, 6]. Transdermal delivery avoids hepatic first-pass effect on lipid profile and achieves a steady state serum level. There are differences in risk profile between transdermal and oral delivery, discussed in that section.

6.3 Progesterone

Micronized progesterone, medroxyprogesterone acetate, dydrogesterone (a stereoisomer of progesterone, not available in North America) and progestins, synthetic compounds with progestational activity, are pharmaceutically available for use in MHT. Collectively all progestational activity compounds, including progesterone, are termed progestogens [7]. Progestogen dose is determined by ability to inhibit endometrial development. There are limited studies comparing progestogen side effect profiles. Differences in risk profile are discussed in that section.

The biological activity, including pharmacokinetics, potency, and efficacy are dependent upon structure. Synthetic progestins are classified as having structure similar to testosterone or structure similar to progesterone, a classification unrelated

Table 6.2 Bioavailability and half-life of progestogens

Micronized progesterone	Progesterone similar molecular structure	Testosterone similar molecular structure		Spironolactone similar molecular structure
Low <5% bioavailable Half-life oral with food 5–10 h, vaginal 14–50 h	*Medroxyprogesterone* High >90% bioavailable Half-life oral 40–60 h *Dydrogesterone* Moderate 28% bioavailable Half-life 8 h	*Norethindrone/ norethisterone family* Prodrugs norethindrone acetate, ethynodiol diacetate, lynestrenol Moderate 62–76% bioavailable Half-life 8 h	*Levonorgestrel family* Etonogestrel, Desogestrel Prodrug norgestimate to norelgestromin High >90% bioavailable Intermediate half-life	*Drosperinone* Moderate 66% bioavailable Half-life 31–32 h

to source or molecular precursor [8]. Drospirenone is structurally similar to spironolactone and synthesized to exhibit progestogenic activity. See Table 6.2. Some progestogens of the norethindrone family (norethindrone acetate, ethynodiol diacetate, and lynestrenol) and of the levonorgestrel family (desogestrel and norgestimate) are prodrugs and require hepatic metabolism into the biologically active form. Metabolism of norethindrone also results in ethinyl estradiol (EE). It is estimated that a dose of 0.5–1 mg oral norethindrone may result in an increase of 2–10 μg of EE [8].

6.3.1 Clinical Use of Progesterone in the Menopause Transition

Progesterone may be used alone for treatment of VMS in women who cannot use estrogen, but is most commonly used in combination with an estrogen for endometrial protection [6]. Progesterone improves sleep and has beneficial effects on endothelial function, a marker for cardiovascular risk [9]. Used alone, progestogens demonstrate limited ability to manage VMS. In small studies, progesterone at 150% of standard dose independently alleviated VMS. A systematic review of progestogen only therapy identified seven RCT with a total of 601 women using varied forms and doses of progestogen, with both oral and transdermal administration, with durations of treatment from 21 days to 12 weeks [10]. A trial of 300 mg micronized progesterone reported the most robust findings. Women within 10 years of menopause randomized to either 300 mg of micronized progesterone or placebo demonstrated improvement of VMS frequency and overall VMS score (58.9% improvement progesterone, 23.5% improvement placebo) but not in VMS severity [11]. Side effects including headaches and vaginal bleeding were significant in five of seven trials and led to discontinuation of treatment in 6–21% of participants.

None of the studies were of sufficient power or duration to identify risks in progestogen only therapy [10].

6.3.2 Type and Delivery Methods of Progesterone and Progestins

Oral Delivery Progestogen
Given significant differences in progestogens, oral delivery results in considerable variability, up to fivefold, of circulating active drug and intracellular progesterone activity. Further, in a not yet completely defined manner, dependent upon the particular progestogen-receptor combination, the bioactivity may range from partially to fully either agonistic or antagonistic within the same cell [8].

Transdermal Delivery
Two transdermal progestins, levonorgestrel and norethindrone acetate, are available as patches in combination with estradiol for use in menopause symptom management. There are no transdermal topical progesterone cream or gel products approved for menopausal use.

Intravaginal Delivery
Intravaginal progestogen delivery has been studied but is not approved for use in menopause symptom management. Compared to intramuscular, intravaginal delivery of 200 mg micronized progesterone gel (compounded, off-label) resulted in relatively low circulating progesterone (7 ng/mL vs. 16 ng/mL) but still exhibited increased progestational endometrial activity, the target organ of progestogen therapy [12]. Micronized progesterone gel 4% (45 mg/day) is available in pharmaceutical grade with regulatory body approval for uses other than menopause symptom management. This delivery method was not represented in the 2020 systematic review [10].

6.4 Combined Estrogen and Progestogen in Women with a Uterus

6.4.1 Endometrial Suppression

In women with a uterus, a progestogen or bazedoxifene, a selective estrogen receptor molecule with endometrial suppression activity, must be used in conjunction with estrogen in all stages of the menopause transition to protect from endometrial hyperplasia, atypia, and possible carcinoma [1, 6, 13–16]. Systemic oral delivery of estrogen alone in women with a uterus is associated with endometrial hyperplasia at all doses and duration of therapy between 1 and 3 years [5].

6.4.2 Combined Hormone Regimens

Continuous combined regimens use an estrogen with a progestogen (E + P) on a daily basis. The continuous combined regimen avoids withdrawal bleeding and allows for smaller though more frequent doses of progestogen than sequential regimens. Continuous combined E + P is associated with more frequent unscheduled uterine bleeding, up to 40% in the first several months after initiation, but most women (75–89%) become amenorrheic within a year due to progressive progestogen induced endometrial suppression [17].

Sequential, also known as cyclic, estrogen and progestogen regimens use daily estrogen with the addition of progestogen at an increased dose for 12–14 days each month. This is likely to be followed by monthly withdrawal uterine bleeding. Long cycle regimens, with a progestogen every 2–6 months, have insufficient evidence of endometrial safety. Long cycle regimens are not recommended in international or regional menopause symptom management guidelines [1, 6, 13–16].

Delivery of oral micronized progesterone 200 mg was shown efficacious in endometrial protection for up to 5 years when used cyclically for 12–14 days each month [18]. Maximum endometrial protection was seen in the continuous combined delivery regimen. For women with an intact uterus using continuous combined estrogen and oral progestogen, the risk of endometrial hyperplasia was not different from placebo (1 mg NETA: OR 0.04; 95% CI 0–2.8 and 1.5 mg MPA: no hyperplasia events) [5]. The recommended dose of oral progestogen for endometrial protection is based on potency studies of endometrial tissue relative to norethindrone/norethisterone dose as value of 1 [19]. See Table 6.3.

Though off-label, use of the 52 mg levonorgestrel intrauterine system (LNG-IUS) as a menopause progestogen to suppress estrogen effect on the uterine endothelium is included in the recommended options of the Korean Society of Menopause, North American Menopause Association clinical care guidelines, the Society of Obstetricians and Gynecologists of Canada and the Indian Menopause Society Guidelines [6, 13, 14, 16]. The 52 mg, 20 μg/day, LNG-IUS used with various estrogen types and doses demonstrated strong endometrial suppression in clinical trials and observational studies of women in postmenopause followed for 5 and 10 years [20–23]. There was no difference in intrauterine and systemic progestin in symptom relief in a 2011 systematic review of the LNG-IUS that included six trials with 518 participants. Intrauterine progestin had less endometrial proliferation than sequential oral MPA [24].

Vaginal micronized progesterone gel 4% (45 mg/day) used sequentially at least 10 days/month or every other day at 100 mg/day for up to 3–5 years provided endometrial protection [18]. This indication is not approved by pharmaceutical regulatory bodies.

Table 6.3 Minimum progestogen dosing for endometrial suppression when used with standard dose of estrogen

	Continuous combined mg/day	Sequential (12–14 days/month progestogen with daily estrogen) mg/dose
Oral		
Micronized progesterone	100 mg	200 mg
Medroxyprogesterone acetate	2.5 mg	5 mg
Norethindrone/norethisterone	0.35 mg	0.35–0.7 mg
Norethindrone/norethisterone acetate	0.5–1 mg	2.5 mg
Dydrogesterone	5 mg	10 mg
Transdermal (available only as patches in combination with estrogen)		
Norethindrone/norethisterone acetate	0.14–0.25 mg	
Levonorgestrel	0.015 mg	
Dienogest	2 mg	
Vaginal		
Progesterone gel[a]	45–100 mg twice to three times weekly	45–200 mg
Intrauterine system		
Levonorgestrel[a]	20 μg/day or 52 mg device	

[a]Not approved for endometrial suppression in MHT. Based on Pinkerton [17], Meeta et al. [14], Mueck and Römer [20]

6.5 Bioidentical Estrogen and Progesterone

The definition of bioidentical hormone therapy (BHT) is "having the same molecular structure as a substance produced in the body" with a first known use of the term in 1997 [25, 26]. Sometimes the term body-identical is substituted. All hormone products are synthesized or changed in some manner with the exception of the Class A steroid conjugated equine estrogens, which while native to the horse, are not to the woman. Although technically of questionable accuracy, bioidentical terminology has slowly become accepted in the scientific realm and typically applies to estradiol and micronized progesterone. Many BHTs are available via approved regulatory bodies. Thus bioidentical is a distinct concept from custom compounded hormone therapy.

Superiority of Micronized Progesterone Micronized progesterone (MP) is available from regulated pharmaceutical sources. Evidence for the superiority, if any, of MP over synthetic progestins is limited to observational studies and physiological data. Micronized progesterone may provide a clinical benefit beyond endometrial protection with a mild sedative effect in women with sleep issues [27, 28].

Micronized progesterone appears to convey the best safety profile in breast cancer risk as seen in the E3N longitudinal observational study [29]. Physiological data demonstrate that MP with transdermal estradiol is less mitogenic in breast tissue than CEE with MPA [30]. Medroxyprogesterone acetate and androgenic progestins negated the endothelial cell protection, improved lipid profile, and improved glucose metabolism imparted by estrogen while MP and drospirenone (available in one combination estrogen/progestin product for menopause therapy use) did not [31–34]. The American Association of Clinical Endocrinologists and American College of Endocrinology guidelines call for preferential use of micronized progesterone over progestins [35].

Superiority of Estradiol Estradiol is available from regulated pharmaceutical sources. There are very few comparison studies of different estrogens' efficacy. There is no strong evidence of estradiol superiority over CEE in management of VMS [36]. The increase in hepatic stimulation with oral dosing, indicated by increase in sex hormone binding globulin, is twofold for oral CEE over oral estradiol [37]. Oral estrogens are largely converted to estrone via hepatic metabolism. CEE, composed of many estrogens, contains a higher dose of estrone via the tablet and as a result of metabolism than estradiol. Estrone is the most prothrombotic of the three adult human estrogens [27, 28, 38]. The effect of this in outcome studies is difficult to determine. Risk of estradiol and CEE have been assessed in large population studies and smaller nested case control designs, but there are few direct comparisons. CEE studies report either no higher rate or an increased rate of CVD over reports in estradiol studies [39, 40].

Estradiol use may be cardioprotective in specific groups (see Chap. 5). Age of initiation and the type of progestogen used affected outcome. Stronger CVD protection was seen with initiation close to the age of menopause, use of estrogen alone in women without a uterus, or with use of estradiol but not CEE combined with micronized progesterone or NETA rather than MPA [27, 28]. In a direct observational study, comparison of CEE current users showed a doubling of risk of thromboembolic events over current estradiol use (RR 2.08, 95% CI 1.02–4.07) [41]. As discussed later in this chapter, transdermal delivery of estradiol does not appear to convey risk of increased gallbladder disease, thromboembolic events, stroke, or of CVD when used close to the age of menopause. The American Association of Clinical Endocrinologists and American College of Endocrinology guidelines call for preferential use of transdermal estrogen delivery but do not stipulate a preference for either CEE or estradiol in other routes of administration [35].

6.5.1 Compounded Bioidentical Hormone Therapy

Compounding is the process of mixing, combining, or altering ingredients to create a medication tailored to the needs of a patient [42]. Compounding is initiated by a health care clinician's order, then fulfilled by a licensed clinician, most often a

pharmacist, who may or may not have special training and certification [43]. Compounding plays a role in menopause hormone therapy but there is confusion in terminology. In this chapter, bioidentical hormones, as already defined, are hormones having molecular structure the same as the human body. Compounded bioidentical hormones (cBHT) meet bioidentical criteria, but are obtained from a compounder rather than a pharmaceutical manufactured source. The term *natural*, employed in popular literature, is without scientific precision or accuracy.

Following the publication of the Women's Health Initiative study of CEE with or without MPA, there was a popular push away from synthesized hormones and toward cBHT worldwide, with the largest impact in the United States. Tracking of compounded prescriptions and post-marketing is done on a state level, making it difficult to determine the impact and safety of cBHT use [44]. In the USA, an estimated 1–2.5 million women aged 40 years or older use cBHT, accounting for 28–68% of all hormone use. Of women using cBHT, 86% of women were unaware that the products are not FDA approved [45]. In an internet survey of women ages 40–84 years, 28% of responders were ever-users of MHT with cBHT representing 31% of all ever-users and an even higher 41% of ever-users among the younger women aged 40–49 years [44]. In contrast, in Australia, data published in 2016 showed current use of MHT in a population survey of women age 50–69 years was 13%, similar to the number reported in 2004–2005 following the 55% decrease in use seen after publication of the WHI. The estimated population weighted prevalence of ever use cBHT in Australia was 6% and was 2% for use at the time of the survey [46].

A qualitative analysis identified women's decision-making process in choosing a cBHT over an approved product. Themes of fear of the safety of FDA-approved hormone products, aversion to CEE specifically, and distrust of the medical and pharmaceutical industries emerged. In contrast, women were attracted by a belief of superior safety and efficacy in cBHT, as well as cBHT being more tailored to an individual's needs while accompanied by enhanced clinical care and attention [47]. Analysis of the regulatory gaps in cBHT with in the United States can identify fallacies in these beliefs.

Compounded products are not tested for safety or efficacy or required to be labeled with the warnings imposed on regulatory approved medications using the same active ingredients. The lack of data and labeling do not imply safety, though the public may be led to believe it does so. Compounding pharmacies have much less stringent regulatory supervision. They are not required to report adverse drug events [43]. Pharmacies, regardless of size, that do not provide more than 5% of their product across state lines are exempt from registration, from new drug applications including the standard process of dose determination, efficacy and safety, from providing medication labels with instructions for use, and from current good manufacturing practice procedures, all of which create challenges in patient understanding of cBHT use [43].

The National Academy of Science, Engineering, and Medicine (NASEM) of the United States released a comprehensive report on the Clinical Utility of Compounded Bio-identical Hormones in 2020. Large gaps in data were identified. Their report states that the absence of data does not imply safety [43].

- There were no studies of compounded progesterone with estrogen related to risk of endometrial cancer.
- In assessing effectiveness of cBHT in meeting the approved indications for MHT, studies of estradiol were largely limited to manufactured products sponsored by pharmaceutical companies rather than individually compounded products.
- There were no studies of osteoporosis prevention (see Chap. 13).
- Only one study of compounded progesterone cream was identified, indicating effectiveness in managing VMS but limited by difficulty in replication of the product studied [48].
- Data on estriol, limited to approved manufactured products from outside the United States rather than compounded products, failed to demonstrate superiority to estradiol in meeting MHT indications.
- There were no studies on effectiveness of compounded estradiol, estriol, or progesterone in improving symptoms associated with genitourinary syndrome of menopause (see Chap. 11).
- There were no studies allowing conclusions on the safety, either superior or inferior, of cBHT products compared to BHT products approved by regulatory bodies.

Endometrial cancer protection using compounded progesterone is reliant on the least bioavailable of the progestogens, and a form possibly ineffective in transdermal but not transvaginal delivery. There is no identified safe and effective dosage of topical progesterone cream or gel. There is no long-term data demonstrating lasting suppression or prevention of endometrial neoplasia [8, 18].

In multiple studies, pharmaceutical grade progesterone cream at doses of 30–80 mg/day applied to keratinized skin and administered with estrogen, found serum levels of progesterone remained very low (>4 ng/mL) though with evidence of endometrial suppression and high salivary levels of progesterone. However at 20 mg/day dose, endometrial suppression was seen in only a limited number of participants. Efficacy of topical progesterone cream in endometrial suppression cannot be based on serum progesterone level but must rely on endometrial evidence of suppression [49].

Further compromising patient safety, prescriptions for combined estradiol progesterone capsules and creams from 15 compounding pharmacies showed up to 27% and 35% variation in dose for capsules and up to 14% and 18% in creams [50]. Many creams available over the counter and labeled progesterone did not actually contain progesterone but rather contained wild yam extract. Diosgenin, a precursor for progesterone, is present in wild yam extract but the necessary conversion to an active ingredient is not possible in vivo [8]. Cases of endometrial cancer have been reported in women taking cBHT [51].

The National Academy of Science, Medicine and Engineering concluded that the majority of marketing claims about the safety and effectiveness of cBHT preparations are not supported by evidence from well-designed, properly controlled studies [43]. The International Menopause Society, the American College of Obstetricians and Gynecologists, the Endocrine Society, the North American Menopause Society

(NAMS), the United States Food and Drug Administration, the American College of Clinical Pharmacology, the Society of Obstetricians and Gynaecologists of Canada, and the Australian Menopause Society have all released statements advising against the use of compounded therapy until evidence is produced with regard to efficacy and safety. As the Australian Menopause Society statement acknowledges, "with such diverse content mix, production sites and methods, that is unlikely to be forthcoming" [1, 6, 16, 26, 42, 52–54].

A role for compounding menopause hormone therapy continues in the provision of products addressing dose and allergies, particularly peanut allergy. In most of the world except the USA, peanut oil in micronized progesterone capsules has been replaced by safflower oil. Safflower oil is not a registered drug component in the USA [28]. Women allergic to peanuts require a compounded product to use oral micronized progesterone.

6.6 Risks in Estrogen Only and Estrogen with Progestogen Menopause Hormone Therapy

The most common therapy associated risks for MHT use are venous thromboembolism (VTE) and gallbladder disease. There is a less robust but consistent risk of stroke within specific patient profiles. There is some increase in risk of breast cancer with long duration estrogen and progestin use and much less to no increase in breast cancer with estrogen alone. The type of estrogen, the delivery route, and the timing and duration of use impact risk. See Table 6.4.

6.6.1 Venous Thromboembolism

Estrogen plus progestogen menopause therapy is associated with a doubling of risk of VTE across all age groups (RR 1.92; CI 1.24–2.99. 33,477 in six studies). The assumed risk increased from 10:1000 to 20:1000 users. There is slightly less risk in women less than 10 years from menopause (RR 1.74, CI 1.11–2.73), with an increase in assumed risk from 6:1000 to 11:1000 users. The majority of events occur in the first 1–2 years of MHT use [55].

Route of delivery affects the increase in risk of VTE. Estrogen delivered orally causes significant hepatic stimulation [56]. Transdermal delivery, avoiding first-pass liver metabolism, has decreased risk of VTE over oral delivery of estrogen. Transdermal delivery of estrogen demonstrated no significant increase in VTE in a meta-analysis of seven population-based studies including 26,471 VTE cases [57].

6.6.2 Gallbladder Disease

Estrogen alone and estrogen with progestogen increased risk of gallbladder disease measured as occurrence of cholecystectomy (HR 1.10, 95% CI 1.01–1.20)

Table 6.4 Summary of hormonal management of VMS

	Indications	Contraindications and cautions	Risk → Risk amelioration
			Absolute Risk Uncommon 1/100–1/1000[a]
Estrogen and progestogen (E+P) Estrogen alone in women w/o a uterus (E)	Moderate to severe VMS Osteoporosis prevention GSM	*Contraindications*: History CVD Hormone-dependent cancer Active or history of thromboembolic event Severe active liver disease w/abnormal LFT Undiagnosed vaginal bleeding History of breast cancer *Cautions* History of gallbladder disease Prothrombotic mutations	VTE across all age groups → No increase risk with transdermal estrogen Gallbladder disease Risk E > E+P → Less increase risk with transdermal estrogen Dementia *only when initiated 65+ years age.* Risk E+P > E → No increase risk initiated close to age of FMP Consider nonhormonal management options 65+ years age
			Absolute Risk Rare 1/1000–1/10,000
			Stroke, CVD *when initiated 60+ years age* → No increase risk initiated close to age of FMP No increase risk with transdermal estrogen Less increase risk with estrogen dose <oral estradiol 1 mg, CEE 0.0625 mg, transdermal estradiol 0.05 mg Less increase risk with micronized progesterone Increased incidence breast cancer *when initiated close to FMP and used for long duration.* Risk E+P > E → Less increase risk with micronized progesterone Assess use regularly Consider nonhormonal management after long duration of use
CEE and bazedoxifene	Moderate to severe VMS Osteoporosis prevention	Same as E/E+P with addition of Contraindicated Prothrombotic mutations	Limited data. Unable to draw conclusions
Tibolone		Same as E/E+P	

VMS vasomotor symptoms, *GSM* genitourinary syndrome of menopause, *CVD* cardiovascular disease, *VTE* venous thromboembolic event, *E* estrogen, *P* progestogen, *LFT* liver function tests, *FMP* final menstrual period, *CEE* conjugated equine estrogen

[a]Definitions of frequency of adverse drug reactions (CIOMS): uncommon (infrequent) ≥1/1000 and <1/100, rare ≥1/10,000, and <1/1000 from World Health Organization definitions https://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf

in the French E3N observational study of 70,928 women. The largest increase in risk was seen in the estrogen only group. When adjusted for age, body mass index, parity, diabetes, and hypercholesterolemia, the oral estrogen only group demonstrated an increase in risk (HR 1.16, 95% CI 1.06–1.21) with an assumed risk of 1:150 incidence of cholecystectomy over 5 years of oral estrogen only use [58].

As in VTE, transdermal, rather than oral, delivery of estrogen ameliorates increased risk of gallbladder disease. In a prospective review of hospital records in women in the United Kingdom, the Million Women Study, current users of oral estrogen had increased risk of gallbladder disease (RR 1.64, 95% CI 1.58–1.69) which decreased after discontinuing estrogen (RR 1.27, 95% CI 1.22–1.32) compared to never users. Current transdermal estrogen therapy was associated with significantly lower increase in risk of gallbladder disease (RR 1.17, 95% CI 1.10–1.24) [59].

6.6.3 Stroke and Cardiovascular Disease

Dose of estrogen, timing of MHT initiation, and delivery method influence risk of stroke. Women in the Women's Health Initiative (WHI) with and without modifying risk factors such as hypertension, history of CVD, previous hormone use, statin use, and aspirin use had increased risk of ischemic stroke in the CEE plus MPA group (RR 1.49, 95% CI 1.02–1.90) and the CEE group (RR 1.39, 95% CI 1.10–1.77) with MHT initiation mean 12 years postmenopause. The risk is categorized as rare with an absolute risk of 0.8:1000 and 1.2:1000, respectively [60, 61]. In large epidemiological studies and in the WHI observational trial there was no increased risk of stroke when MHT was initiated close to the age of menopause [60, 62]. Doses of estrogen lower than 1 mg estradiol and 0.625 mg CEE were not associated with increased risk of stroke [60]. Transdermal delivery of estrogen, with and without progestin, at doses 50 mcg and lower did not have any increased risk of stroke in a nested case control study of over 15,000 women (RR 0.95, 95% CI 0.75–1.20) [63].

Initiation of MHT in healthy women conveys no to minimal increased CVD risk. The timing of MHT use in the menopause transition effects MHT and CVD interaction. A large systematic review analyzed the timing hypothesis of MHT and CVD [55]. A collection of observational, case-controlled, and epidemiological studies of women using MHT published in the 1990s and involving over 90,000 women followed for a range of 2–16 years indicated a 30–50% reduction in cardiac events with use of MHT when initiated close to the age of final menstrual period [55, 64]. These findings were in agreement with the WHI analysis of women starting MHT <10 years after the final menstrual period and with the Danish Osteoporosis Prevention Study (DOPS) which included women aged 45–58 years age within ≤24 months of final menstrual period [65–68].

MHT for secondary prevention of future CVD events in women with existing CVD demonstrated increased events in the first year of use, a risk that ameliorated with continued use [69]. A systematic review and meta-analysis of MHT and cardioprotection shows no impact of MHT on CVD mortality in women with preexisting CVD (Risk 45 per 1000 placebo and MHT) [55]. The International Menopause Society along with regional menopause societies state that MHT has no role in secondary prevention of CVD. Nonhormonal methods should be used for VMS management in women with existing CVD [6, 13–16, 70].

6.6.4 Breast Cancer

Summary of risk The Revised Global Consensus statement representing multiple regional scientific societies concluded that the increased risk of breast cancer associated with MHT in women over 50 years age is complex, and seems to be primarily, but not exclusively, associated with the use of estrogen with progestin. The increased incidence of <1.0 case of breast cancer per 1000 women per year of E + P use meets the definition of a rare event. Further, the consensus statement points out that the relative risk of breast cancer with MHT use is akin to that of the risk of breast cancer from sedentary lifestyle, obesity, and alcohol consumption [1].

Concern arose regarding the effect of combined E + P in menopause treatment from the WHI. The study demonstrated increased risk of breast cancer with use of CEE and MPA (RR 1.26; 1.0–1.59 later revised to RR 1.24; 1.01–1.53) but not CEE used alone in women without a uterus [71]. Risk was primarily in women who initiated MHT close to the final menstrual period and continued for prolonged duration. Risk of breast cancer with use of CEE + MPA for this group has an estimated hazard ratio of 1.64 (95% CI 1.00–2.68) with 5 years use and 2.19 (95% CI 1.56–3.08) with 10 years use [72].

6.6.4.1 Effect of Progestogen Formation on Breast Cancer Risk

No studies of progestogens alone at power sufficient to detect breast cancer and other risks have been done. Progesterone and progestins have differential affinity for PR-A and PR-B receptors in breast tissue, raising the question of a possible differential breast cancer risk [8]. There are no sufficiently powered RCTs of any progestin with estrogen other than CEE/MPA use in the WHI. A meta-analysis of observational studies including 86,881 women in postmenopause with a mean age of 59 years and followed for a range from 3 to 20 years compared cancer risk in MP and synthetic progestins. Micronized progesterone with estrogen was associated with lower breast cancer risk compared to progestin and estrogen use (RR 0.67, 95% CI 0.55–0.81) [73].

A subsequent systematic review of MP and breast cancer risk concluded that estrogens combined with oral MP or vaginal MP (off-label) do not increase breast cancer risk for up to 5 years of use. Further, there is very limited evidence that oral MP combined with estrogens for more than 5 years of use is associated with increased breast cancer risk.

The review identified 19 studies of varied design, type of estrogen, inclusion of progestins as well as use of MP, duration of follow-up (4.0–11.2 years), and sample size (643–80,391) [74]. Findings in the studies ranged from that of no difference in breast cancer risk among E + P use regardless of progestogen [75] to the Etude Epidemiologique de femmes e la Mutuelle Generale d l'education Nationale E3N report of 2354 cases of breast cancer among 80,377 women in postmenopause with no increase in risk of breast cancer in less than 6 years use of estradiol with MP (RR 0.9; 95% CI 0.7–1.2) while use of estradiol with

synthetic progestins did incur risk (RR 1.4; 95% CI 1.2–1.7) [76, 77]. The third report of the E3N demonstrated increased breast cancer risk with MP use mean 6.1 years (RR 1.22; 95% CI 1.11–1.35) and increased risk using synthetic progestins for more than 5 years (RR 1.98; 95% CI 1.73–2.26) [29]. This increase risk of breast cancer dissipated after discontinuation of MP (3 months to 5 years since last use, RR 1.15; 95% CI 0.93–1.42) but remained elevated 5–10 years after discontinuation when synthetic progestins were used for at least 5 years (RR 1.34; 95% CI 1.04–1.73) [29]. That said, counseling on breast cancer risk with use of E + P should be provided to all women regardless of progestogen used [74].

6.6.5 Dementia

The interaction of MHT use with cognitive function and with risk of Alzheimer's disease appears to differ between the cognitive condition investigated, the type of estrogen used, the type of progestogen used, and the use of unopposed estrogen [78]. Multiple national and international guidelines caution against MHT initiation in women over age 65 years due to risk of Alzheimer's disease but do not generalize this increased risk to younger women. No guidelines support the use of MHT for prevention of dementia [1, 13–16].

A meta-analyses of observational studies prior to 2001 linked MHT use to reduced risk of Alzheimer's disease. These primarily included younger women, close to the age of menopause, and identified a larger benefit from 17beta-estradiol than from CEE [79]. The WHI Memory Study (WHIMS), a randomized trial of CEE + MPA or CEE alone, found increased risk of probable dementia but not minor cognitive impairment (MCI) in women starting MHT after age 65. Probable dementia was determined by universal screening for cognitive function, followed by neuropsychological testing and diagnostic procedures. The small number of identified cases limited statistical power. The CEE + MPA active treatment group demonstrated doubling of risk, with an absolute risk of 12 additional dementia cases for 1000 treated women over 5 years. The CEE alone group had a relative risk of 1.5 that was not statistically significant [80, 81]. Observational data has also looked into the effect of current use compared to past use and the age and timing of use. Younger women who used hormone therapy were at reduced risk of Alzheimer's disease. Current users were at higher risk than past users. These findings may be subject to unidentified variables including a health bias [78].

The risk of a deleterious MHT effect on cognitive function has not been widely analyzed. The WHI Study of Cognitive Aging (WHISCA) explored the effect on cognitive functioning measured by standardized tests with current use of MHT in women with a mean age of 74 years. Current use of CEE + MPA but not of CEE alone worsened verbal memory over placebo and the effect was not age dependent [78].

6.7 Discontinuation of Menopause Hormone Therapy

Guidelines do not stipulate an age at which hormone therapy should be discontinued [6, 13–16]. As menopause symptoms are largely transitional, and as underlying health risks and some risks associated with use of MHT increase with age and duration of use, women should be assessed and educated regularly to share in decision-making regarding continuation of therapy. Women tolerated MHT discontinuation equally well when hormones were either stopped abruptly or tapered over 4 weeks to 6 months [82, 83]. There is limited data and a lack of consistency in stage of menopause, age of participants, and duration of therapy among hormone discontinuation studies [84–86]. In a follow-up of women with mean age at discontinuation of 56.8 ± 3.7 years and mean duration of use of 6.9 ± 2.3 years using the Menopause Rating Scale (MRS), a large number were lost to follow up (23%) and 93% of remaining women experienced recurrence of symptoms, including vaginal dryness. Twenty-three percent resumed systemic hormone use and 62% initiated vaginal estrogen [87]. Inclusion of vulvovaginal symptoms in the MRS likely contributed to the high rate of symptom recurrence. Separate data on VMS was not reported. Resumption of systemic hormones in 23% of women concurs with other observational studies [88].

6.8 Tibolone

Tibolone is a product with both estrogenic and progestogenic activity but is supported by less extensive research than estrogens and progestogens. It is available in Europe, Korea, Australia, and India, but not approved in the United States or Canada. Recommended dose is 2.5 mg orally. Tibolone has been shown effective in managing VMS, reducing bone fracture, and improving sexual dysfunction related to the menopause transition [89–92]. Tibolone may have an improved breast cancer and endometrial cancer risk profile over E + P [93]. As breast cancer is a rare to infrequent event after prolonged duration of exposure to E + P, the small sample sizes and limited duration of tibolone studies make interpretation of actual risk difficult. In women with a history of breast cancer, use of tibolone was associated with increased risk of recurrence [90].

Tibolone is a progestogen of the norethindrone family with low affinity to the progesterone and androgen receptors in its own form. Tibolone is metabolized rapidly into three metabolites, two of which bind to estrogen receptors, and the third of which binds to progesterone receptors [8].

In a small trial (n = 140 in 3 arms), tibolone was equally effective as CEE with MPA except in the Female Sexual Function Index, where tibolone demonstrated superiority [92]. In a systematic review of use of tibolone in Asian women, combined MHT was more effective in VMS management than tibolone in nine RCTs with 1336 women. When studies with a high risk of attrition bias were eliminated, the resulting effect was if 7% of women taking MHT experience VMS,

8–14% of women taking tibolone will do so. Unscheduled bleeding was more likely on MHT than tibolone, with a suggested comparison of unscheduled bleeding in 47% of women taking MHT to 18–27% of women taking tibolone [91]. See Table 6.4.

A Cochrane Database systematic review included 46 RCTs comparing tibolone to placebo, estrogens, or combined estrogen and progestogen (E + P), and involved almost 20,000 women. In the placebo comparison group, fewer women continued to experience VMS, 35–45% tibolone versus 67% placebo, and more women experienced unscheduled bleeding, 31–44% tibolone versus 18% placebo. Among women with no history of breast cancer, there was no increased risk of new onset breast cancer in follow-up ranging from 3 months to 3 years (OR 0.52, 95% CI 0.21–1.25; four RCTs; 5500 women; very low-quality evidence). Among women with history of breast cancer, there was increased risk of recurrence with tibolone (OR 1.5; 95% CI 1.21–1.85; 2 RCTs; 3165 women; moderate quality evidence). There was no difference in cerebrovascular events, endometrial cancer, cardiovascular events, VTE, or mortality from any cause [90].

6.9 Tissue Selective Estrogen Complex: Conjugated Estrogen and Bazedoxifene

The revised global consensus statement on menopausal hormone therapy (2016) places the tissue selective estrogen complex (TSEC) product of conjugated estrogen (CE) 0.045 mg and selective estrogen receptor modulator (SERM) bazedoxifene 20 mg with estrogen and progestogen as first line therapies for VMS [1]. Conjugated estrogen with bazedoxifene is approved worldwide. Each SERM product has unique tissue selection and activity. Bazedoxifene is used in MHT because of the anabolic action on bone tissue while having an antagonistic action in the breast and endometrium. It is effective in reducing VMS, relieving genitourinary syndrome of menopause, increasing bone mass, and improving sleep disruption [94–99]. Though the physiologic activity and the mammographic evidence of no increase in breast density may indicate protective breast action, it is important to note that there is not yet any breast cancer outcome data [100, 101]. See Table 6.4.

6.10 Conclusion

Counseling patients on the use of menopause hormone therapy in symptom management requires an understanding of the importance of analyzing individual benefits and risks. A patient health history is a critical indicator for risk. Age of initiation, duration of use, and specific hormone formulation and delivery route complete the profile necessary for action. Further, the clinician must clearly communicate these concepts to each individual patient so that shared decision-making may take place.

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Part II

Menopause Symptom Management

Abnormal Uterine Bleeding

7

Patricia Geraghty

7.1 Normal Menstrual Parameters and Abnormal Uterine Bleeding (AUB) Overview

The International Federation of Gynecology and Obstetrics (FIGO) has defined two systems, System 1 for the nomenclature of symptoms of normal and abnormal bleeding (AUB), and System 2 for the classification of the etiologies of abnormal bleeding [1]. The revision of previous menstrual terminology, first introduced in 2007, and revised in 2018, has increased the precision and uniformity of assessment of AUB across the lifespan for use in clinical practice and research (Table 7.1). Menses are assessed on the dimensions of regularity, frequency, duration, and volume. Regular or normal is roughly defined by the menstrual pattern experienced by 90% of the population, similar to the definition of norms in other health parameters. Despite the elegance of this system, adoption has been slow in many diagnostic compendiums [2, 3].

It is likely to be the first change in cycles, not necessarily the most dramatic change, that leads a woman to seek advice and treatment. The clinician must be aware of the possibility of other causes of HMB superimposed on the expected age-related cycle changes. Women in the LRS often report menstrual patterns outside of the norms for regularity, frequency, duration, and volume and these women should be evaluated. The clinician must be alert to differentiating patterns of menstrual and anovulatory bleeding. Women may consider all vaginal bleeding a menstrual period and report it as such, but a true menstrual bleed implies follicular development and ovulation, followed by menstrual flow. Heavy menstrual bleeding is no longer

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Table 7.1 International Federation of Gynecology and Obstetrics (FIGO) menstrual cycle terminology. (Based on Fraser et al. 2007 [2], Munro et al. [1]. Used with permission of John Wiley and Sons Publishing)

Dimension	Descriptive categories			
Regularity cycle-to-cycle over 12 months	***Regular***		***Irregular*** (typical variation >7–9 days between longest/shortest interval)	
Frequency	***Absent***	***Infrequent*** (>38 days)	***Normal***	***Frequent*** (<24 days)
Duration			***Normal***	***Prolonged*** (>8 days)
Volume (patient determined)	***Light***		***Normal***	***Heavy*** (interferes w/ activity)
Intermenstrual	***Random***			
	Cyclic		***Early Cycle Intermenstrual*** ***Mid Cycle Intermenstrual*** ***Late Cycle Intermenstrual***	
Unscheduled bleeding on gonadal steroids (hormonal contraception)	***Not applicable***		Not on gonadal steroids	
	None		Using gonadal steroids and having no bleeding	
	Present			

defined quantitatively, which was difficult to implement in the clinical setting, but as bleeding that interferes with the women's physical, emotional, and material quality of life. The NICE Guidelines also state that any woman who perceives her cycles to interfere with daily activity or to deviate from her established pattern should be evaluated. All assessments of menstrual bleeding should include a discussion on the impact of bleeding on a woman's life [4–6].

The second FIGO system organizes the approach to diagnosis of AUB. Even though pregnancy is an increasingly unlikely etiology for AUB in the fifth decade, complications of pregnancy should always be considered and eliminated as a first step to diagnosis. Remaining etiologies are organized into the PALM-COEIN classifications [5] (see Fig. 7.1). The PALM categories are structural or neoplastic in nature, including AUB-P endometrial or cervical polyps, AUB-A adenomyosis or endometriosis, AUB-L leiomyoma, and AUB-M malignancy and hyperplasia. The COEIN categories are systemic or endocrinological, including AUB-C coagulopathy, AUB-O ovulatory dysfunction, AUB-E endometrial, AUB-I iatrogenic due to a medication including anti-coagulation therapy, medical device, or medical procedure, and AUB-N not otherwise classified [1]. Systemic or endocrinological conditions associated with AUB may become apparent for the first time in the late reproductive and perimenopause stages or may be superimposed on the cycle changes expected in these life stages. The very nature of the menopause transition is increasing irregular anovulation. Otherwise, neoplastic etiologies are the more likely sources of abnormal bleeding in the late reproductive to perimenopause stage.

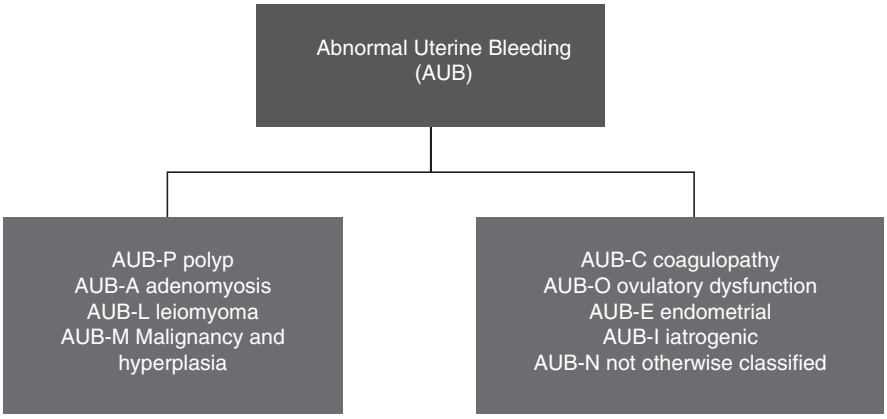

Fig. 7.1 FIGO PALM-COIEN classification of abnormal uterine bleeding. (Based on Munro et al. [1]. Used with permission of John Wiley and Sons Publishing)

7.1.1 Epidemiology of AUB

AUB is a common presentation in the clinical setting, accounting for 30% of gynecological visits in the United States. The reported population incidence worldwide varies from 3% to 30% of women. As many as 50% of women with AUB do not seek treatment, regardless of access to care, with a resulting lack of precision in epidemiological estimates [1, 7]. A study in rural India comparing women's reports of menstrual disorders to the incidence detected upon examination found that only 5% of women reported heavy menstrual bleeding with an examination detected incidence three times higher [8]. Menstrual disorders are not included in the global burden of disease. Most surveys in low and middle low resource countries, dating back to the 1970s through 2002, are hampered by lack of definitions, varied interpretations of menstrual disorders, and methodological inconsistencies [9].

Conditions such as leiomyomata and coagulation disorders demonstrate variable racial/ethnic and geographic patterns of distribution. This variability stems from the combined influences of genetics, consanguineous cultural marriage patterns, modifiable risks, and gaps in data. One classification of AUB may not be independent of other classifications.

Twin studies of uterine leiomyomata (UL) indicate heritability [10]. A genome-wide association scan (GWAS) of 35,474 UL cases and 267,505 controls in females of European ancestry identified numerous loci associated with risk of UL, with four loci specifically associated with HMB and four loci overlapping with risk of endometriosis. An epidemiological meta-analysis across 402,868 women suggests at least a doubling of risk for UL diagnosis among women with a history of endometriosis [11]. Women of African ancestry in the United States report 2–3 times more

diagnosed leiomyomata, experience onset at a younger age, and are more likely to undergo surgery than women of European ancestry. In a prospective universal ultrasound screening of premenopausal women, the difference in prevalence narrowed, while still remaining significantly higher in women of African ancestry [cumulative incidence of tumors by age 50 >80% Black and almost 70% white] [12]. A GWAS identified unique loci of heritability among women of African ancestry. The attempt to replicate a dense set of tag single nucleotide polymorphisms at different loci associated with UL in Japanese women failed to replicate the associations in women of African ancestry. This indicates that genetic variation for heritability of UL may differ among populations [13]. Differential exposure to epigenetic triggers must also be considered.

Von Willebrand Disease (VWD) is the most common inherited coagulation disorder with a general population prevalence estimated to be 1% and with a prevalence of 11–16% among women with HMB [14]. The incidence of VWD appears to be underreported in low resource regions based on the increased percentage of the severe form identified and the low ratio of the less severe VWD to Hemophilia A prevalence. Heritability appears influenced by culture with an increased incidence of VWD in cultures with high prevalence of consanguineous marriage [15]. This pattern is similar to the prevalence of the more rare autosomal recessive bleeding disorders such as combined Factor V and Factor VIII deficiency [16]. In summary, the varied influences of culture and care resources, or lack thereof, lead to gaps in our understanding of the epidemiology and impact of AUB.

7.2 Management of Acute Heavy Bleeding

Acute heavy bleeding is an episode of bleeding requiring management of bleeding before considering management of the underlying etiology [1]. Assessment of hemodynamic stability and possible pregnancy determine initial triage. A hemodynamically unstable woman should be seen in an acute care setting. Management of acute HMB in the hemodynamically stable woman may occur in the outpatient or ambulatory setting. Women should be evaluated with a complete blood count. When possible, the investigation of acute heavy uterine bleeding starts with a transvaginal ultrasound to assess the endometrial thickness.

7.2.1 Combined Estrogen and Progestin in Acute HMB

In the presence of a normal endometrial thickness, proceed with an oral monophasic combined hormonal contraceptive (CHC) formulation of 20–25 μg ethinyl estradiol (EE) and progestin in a multi-dose regimen. See Table 7.2. The initial dose is one tablet four times daily. This serves to reduce bleeding, typically within

Table 7.2 Management of acute heavy menstrual bleeding in the hemodynamically stable woman

Protocol	Initial management	After bleeding subsides
Estrogen and Progestin with Transvaginal ultrasound to assess endometrium prior to management	**Normal endometrial thickness**: Monophasic oral **CHC 20–25 mg EE/progestin** 4 times daily	**CHC** 3 times daily for 7 days then **CHC** 2 times daily for 7 days then **CHC** daily for 7 days Expect withdrawal bleeding after completion
	Thin endometrium: Oral **CEE** 2.5 mg 4 times daily	**CEE** 2.5 mg/day plus **MPA** 5–10 mg/day for 7–10 days
Progestin	**MPA** 20 mg 3 times daily for 7 days	**MPA** 20 mg/day for 21days
Anti-fibrinolytic	**Tranexamic acid** 1.3 g orally 3 times daily for 5 days	

EE ethinyl estradiol, *CHC* combined hormonal contraceptive, *CEE* conjugated equine estrogen, *MPA* medroxyprogesterone acetate
Based on Taylor et al. [17], James et al. [18], American College of Obstetricians and Gynecologist [4]

48 h. Once a reduction of bleeding has occurred, continue the CHC three times daily for a week, tapering to twice daily for a week and then once daily for a week. The CHC should be continued for 1 week after bleeding stops. The patient may need an anti-emetic at the higher dose and she should be counseled that bleeding is likely to return after completion of the protocol [17].

In the denuded endometrium, start with conjugated equine estrogen (CEE) 2.5 mg four times daily to restore epithelium and stabilize lysosomal enzymes [17]. Administer an anti-emetic with the CEE. Consider the woman's risk of venous thromboembolism (VTE) with this regimen. Pulmonary embolus has been reported in high dose intravenous estrogen [19]. Once bleeding has tapered, proceed with tapering the CEE to 2.5 mg/day and adding a progestin such as medroxyprogesterone acetate (MPA) 5–10 mg/day for 7–10 days [17].

7.2.2 Progestin Only in Acute HMB

Management with high dose progestin is appropriate, particularly when there are concerns for VTE such as a history of VTE, obesity, or reduced activity. Women with migraine with aura are advised against use of estrogen containing contraceptives [20]. There are no guidelines regarding emergency use of estrogen as in this scenario. Inability to access sonographic evaluation of the endometrium in a timely manner may also influence management decisions. The clinician may use expert judgement and shared decision making with the individual woman in determining treatment protocol. MPA 20 mg is given three times daily for 7 days, then daily for 3 weeks. See Table 7.2. A trial of EE with norethindrone acetate (NETA) compared to MPA alone demonstrated equal median days to bleeding cessation (3 days), with 76% cessation of bleeding and 100% avoidance of surgery in the MPA group and

88% cessation of bleeding and 95% avoidance of surgery in the EE/NETA group. Satisfaction was equal and high in both groups [21].

7.2.3 Antifibrinolytics in Acute HMB

Antifibrinolytics block lysine sites on plasminogen, preventing degradation of fibrin, and reducing bleeding. Tranexamic acid is widely used in Europe and is approved for use in the United States for HMB. Use has been adopted for acute bleeding due to trauma and postpartum hemorrhage [22, 23]. Tranexamic acid meets the European and ACOG guidelines for acute HMB [4, 18]. Treatment is 1.3 g orally every 8 h for 5 days. See Table 7.2. There is concern about risk of VTE due to the mechanism of action of tranexamic acid. The actual risk of VTE is controversial. An observational population based study over a 19-year period with 238,000 women-years treatment with tranexamic acid had no occurrence of VTE [24]. A nested case-control study in Sweden found increased risk for VTE with tranexamic acid that failed to reach statistical significance, partially due to the low overall incidence of VTE and to the presence of VTE in other treatment groups for HMB. The authors concluded that anemia, as a proxy for HMB, may be an independent risk for VTE [25]. Use of tranexamic acid is contraindicated with acquired impaired color vision impairment and current thrombotic or thromboembolic disease. Caution should be used with history of thrombosis and with concurrent combined hormonal contraceptive (CHC) use [26].

7.3 Chronic Heavy Menstrual Bleeding Presentations in Midlife

Chronic HMB is defined as heavy bleeding that most often occurs in the preceding 6 months or cycles [1]. Many women experience heavy menstrual bleeding for the first time or an exacerbation of previously moderately heavy flow in the transition from late reproductive stage to early perimenopause. The first changes may be related to flow and to subtle, less than 7 days variability, cycle length alterations. With increased aromatization leading to increased estradiol in some but not all cycles, menstrual flow varies from cycle to cycle [27] (see Chap. 4). Hale et al. measured blood loss in ovulatory and anovulatory cycles across mid-reproductive to late perimenopause stages. In ovulatory cycles, blood loss increased only slightly from mid to late reproductive age, then almost doubled in early perimenopause. The heaviest blood flow occurred in the rare ovulatory cycles of late perimenopause [28]. Life stage is the most common contributing factor to ovulatory dysfunction, possibly resulting in HMB. This may occur as much as a decade prior to the final menses [27].

7.3.1 AUB-O: Ovulatory Dysfunction

Polycystic ovarian syndrome (PCOS) is the most common menstrual endocrinopathy with an international incidence of up to 20% and a population of more than 10 B women worldwide [29]. Geographical prevalence varies widely, reported as low as 3% in some areas. Lack of surveillance, inadequate diagnosis, and challenges in resources to achieve diagnosis contribute to gaps in epidemiological data by race and region [30].

Chronic ovulatory dysfunction, as in PCOS, is characterized by irregular bleeding with heavy or variable flow. With PCOS, there is increased peripheral aromatization of androgens to estrogen, decreased SHBG with increased free testosterone and estrogen, and increased peripheral insulin resistance leading to increased insulin and increased ovarian production of androgens. This contributes to an estrogen/androgen dominant physiology. The unopposed estrogen and hyperandrogenism cause heavy but unstable endometrium. Bleeding may be heavy without typical premenstrual symptoms, mixed with light bleeding or spotting due to partial endometrial sloughing [17, 29, 31].

There is no single diagnostic measurement to identify PCOS. The international consensus of the Rotterdam criteria identify four phenotypes of PCOS. Phenotype A, representing 75% of the population with PCOS, includes clinical and/or biochemical hyperandrogenism (HA), oligomenorrhea/infrequent menses (OA), and polycystic ovarian morphology (PCOM) on ultrasound (ovarian volume >10 mL or ≥25 follicles of 2–9 mm size). The remaining phenotypes involve any combination of two of these findings. Phenotype B (HA, OA) along with phenotype A is considered "classic" PCOS, while phenotype C (HA, PCOM) is sometimes called "ovulatory" PCOS, and phenotype D (OA, PCOM) is "nonhyperandrogenic" PCOS [31, 32]. Many studies show a normalization of menstrual cycling in women with PCOS as menopause approaches [33–35]. The age-related decline in inhibin B and AMH may allow for dominant follicle selection and ovulation in the woman with PCOS despite reduced gonadotropins [33–35].

7.3.2 AUB-A: Adenomyosis

Endometriosis, the implantation of endometrial tissue external to the endometrial lining, and the subtype adenomyosis, the presence of endometrial tissue within the uterine wall, is a disease of estrogen dependent inflammation typically presenting with some combination of heavy painful menses, pain with intercourse, and nonmenstrual pelvic pain. The clinical course is variable with symptoms worsening with time, spontaneous remission of symptoms, or late onset of symptoms. There is little to no correlation between the extent of endometrial implants identified surgically and symptom profile. Women with endometriosis and adenomyosis typically have symptoms for many years prior to diagnosis. It is feasible that a woman with

AUB-A may first present with new or worsening painful and heavy menses in the late reproductive stage [17, 36]. In a recent shift from the reliance on invasive uterine biopsy or costly imaging, two-dimensional ultrasonography has been shown to be as sensitive as MRI for detecting adenomyosis. The exact criteria of ultrasound detected morphological findings for a diagnosis are in development [1].

7.3.3 AUB-L: Leiomyoma/Uterine Fibroids

Uterine leiomyomata (UL), commonly called "fibroids," are benign neoplasms of fibrous connective tissue. FIGO has classified leiomyomata according to location. Most leiomyomata are without symptoms and most are discovered incidentally. Ultrasound evidence of UL was detected in 51% of perimenopausal women without a previous clinical diagnosis [12]. Actual prevalence is difficult to assess without universal ultrasound screening [37]. Symptoms, when present, may include infertility, heavy menstrual bleeding, and "bulk" symptoms such as pain, abdominal distention, and urinary or bowel changes. Presence and severity of symptoms is correlated to tumor size and uterine mass rather than leiomyoma location [37]. A 25 year review of hospitalizations for UL in South Nigeria found the women treated had a median uterine size 15 ± 9.7 weeks. Presenting complaints were menstrual irregularities (47.7%), abdominal swelling (39.1%), and infertility (31.9%) [38]. Similar presentations were seen in a second review, demonstrating that Nigerian leiomyomata data follows patterns similar to other parts of the world [39]. Uterine mass due to leiomyomata increases over the reproductive life stages under the influence of reproductive hormones. Heavy bleeding may require attention only in the late reproductive or early perimenopause stages. In the United States, peak hospitalization for UL occurs in the fifth decade [40].

7.3.4 AUB-I: Iatrogenic

Iatrogenic heavy menstrual bleeding is caused directly or indirectly by a medication or medical device. The copper IUD initially increases menstrual blood flow duration and volume by up to 50% over baseline though flow may return to baseline with continued use [41, 42]. The number of medical diagnoses increases with age. Women in late reproductive and perimenopause stages are more likely to be using medications that can influence menstrual bleeding. Women on anti-coagulant therapy who are still menstruating experience HMB. In one study, rivaroxaban demonstrated a twofold increase in HMB over vitamin K antagonist anticoagulants. There were more interruptions in therapy in the rivaroxaban group, possibly related to bleeding events, and a subsequent increased incidence of recurrent VTE [43]. Selective serotonin reuptake inhibitors (SSRIs) interact with gonadal steroids and are associated with increased gastrointestinal bleeds. A review found scant data on the interaction with menstrual bleeding [44].

Table 7.3 Screening for inherited coagulopathy in heavy menstrual bleeding

Presence of:	Heavy menstrual bleeding since menarche			
Presence of one of:	History postpartum hemorrhage	Surgery-related bleeding	Bleeding associated with dental work	
Presence of two or more:	Bruising 1–2 times monthly	Epistaxis 1–2 times monthly	Frequent gum bleeding	Family history of bleeding symptoms

Based on Kouides et al. [46]

7.3.5 AUB-C: Coagulopathy

Inherited coagulopathy presents with a lifelong history of HMB. It would seem feasible that the diagnosis of AUB-C would then occur in adolescence or early adulthood. However, 47% of women presenting with HMB were found to have a hemostatic disorder and the prevalence of new diagnosis of AUB-C did not vary by age groups of <20 years, 21–44 years, and >44 years [45]. An international collaboration of professional hematological societies are developing guidelines on detection and management of the most common bleeding disorder, Von Willebrand disease. Currently appropriate screening using a structured history accurately identifies 90% of women with AUB-C and directs further investigation. See Table 7.3 [46]

7.3.6 AUB-E: Endometrial

AUB-E is indicated in regular heavy menses with a structurally normal uterus and exclusion of coagulopathy and ovulatory dysfunction. The events leading to endometrial sloughing, repair, and regrowth are triggered by hormonal changes and mediated via prostaglandins, plasminogen hypoxia-inducible factor 1, and local glucocorticoid metabolism, all of which have been implicated in AUB-E [47]. There are no clinical tests for AUB-E at this time so it remains a useful category in research and a diagnosis of exclusion in the clinical setting [48].

7.4 Approach to the Assessment of Chronic Heavy Menstrual Bleeding

The approach to the investigation of chronic heavy menstrual bleeding in the late reproductive stage starts with a structured history and physical examination. The history will identify related medical disorders, medications, and lifestyle influences and dictate the need for inherited coagulopathy screening [1]. All women should have a complete blood count (CBC). Further laboratory assessment may include thyroid studies in the presence of infrequent heavy menses. Hormone studies are not helpful in determining AUB-O in the late reproductive stage or perimenopause stage woman outside of an infertility assessment. A single lab value does not

adequately reflect the highly variable state of reproductive hormone levels in this age group [1, 17, 49]. The European and FIGO guidelines do not recommend serum ferritin in the initial workup [1, 6]. If she is screen positive for hemostatic disorder, first-level laboratory investigation of suspected coagulopathy includes CBC with platelets, ferritin, partial thromboplastin time and prothrombin time as well as ristocetine cofactor activity and antigen (Von Willebrand Factor) and factor VIII [50].

Following the initial clinical assessment, the most productive direction is to rule out neoplasms with a uterine assessment. Transvaginal ultrasound is first-line imaging for UL. If obtaining the imaging via a separate institution, making specific requests for noting endometrial thickness, ovarian size and morphology, and uterine wall texture assists both referring and imaging clinicians in achieving a proper diagnosis. In the absence of other clear etiologies, the diagnosis of HMB is related to AUB-O or AUB-E [1].

7.4.1 Medical Management of Chronic Heavy Menstrual Bleeding

Empiric treatment should begin based on the index of suspicion even while waiting for pending test results. Many treatment modalities achieve similar results regardless of etiology. Most national guidelines consider medical management as first-line therapy [51]. The clinician should discuss all available options with the individual woman, considering her desire for future fertility and her cultural concerns [52].

7.4.1.1 Estrogen and Progestogen or Progestogen Alone in Chronic HMB

Although widely used for reducing menstrual blood flow, there is little empirical evidence that combined hormonal contraception is effective for this purpose. A trial of two combined hormonal agents and two prostaglandin inhibiting agents demonstrated a 40% reduction in blood flow with the EE and progestin [53]. Combined hormonal agents have the additional benefit of providing high quality contraception and bleeding regularity. Midlife women are more likely to have medical conditions such as hypertension or tobacco use, precluding use of estrogen containing contraceptives [20].

Progesterone or a progestin alone was once the most common medical treatment for HMB. Anti-estrogenic activity suppresses blood volume, but increases irregularity of bleeding. Depot medroxyprogesterone acetate (DMPA) provides contraceptive benefits but short and long course cyclic progestin do not. Short course (MPA or norethisterone for 7–10 days, starting cycle Day 15 or 19 of cycle) was inferior to other medical treatments in measures of reduction in blood flow and number of days bleeding. Long course (MPA 10 mg - 20 mg or norethisterone 5 mg three times/day) daily from Day 5 to Day 26 of the menstrual cycle was inferior to LNG-IUS or tranexamic acid and equal to combined hormonal vaginal ring in reduction of bleeding. Patient satisfaction was equal to the combined hormonal vaginal ring. There is no patient satisfaction comparison data for LNG-IUS or tranexamic acid [54].

7.4.1.2 Nonsteroidal Anti-inflammatory in Chronic HMB (NSAID)

Prostaglandins control the volume of menstrual flow. PGE2 causes vasodilation and inhibits platelet aggregation while PGE2α stimulates vasoconstriction and, with thromboxane, promotes platelet aggregation [17]. Both prostaglandins increase near menses with the ratio of PGE2α:PGE2 increasing with menstrual flow, stimulating tapering and cessation of flow. Women with HMB have both increased levels of prostaglandin and prostacyclin in menstrual flow and more PG receptors in the endometrium [17]. NSAID initiation prior to onset of menstrual flow and used continuously to maintain serum levels for 3–5 days reduces menstrual blood flow by 30%. No single NSAID regimen is superior to any other. This management has the advantage of no exposure to exogenous hormones but does not provide contraception for the woman desiring fertility control. NSAIDs are less effective to treat HMB than antifibrinolytics or LNG-IUS [55].

7.4.1.3 Levonorgestrel Intrauterine System (LNG-IUS) in Chronic HMB

The LNG-IUS suppresses endometrial development via progestin action and provides ongoing highly reliable contraception for the woman who desires fertility control. The 52 mg levonorgestrel intrauterine system is the most effective medical management for heavy menstrual bleeding. Not all doses or brands of LNG-IUS have been evaluated or approved for this use. Menstrual pain and menstrual blood loss are reduced by 97% in 6 months of use. Patient satisfaction is superior to any other medical management for HMB and is equal to satisfaction in endometrial ablation [56]. HMB in the presence of leiomyomata requires special consideration. Distortion of the uterine cavity may preclude device placement. Efficacy of blood loss reduction has been demonstrated in small studies, but may be hampered by fibroid mass interference with the uterine muscle contracture involved in menstrual flow tapering and cessation [57].

7.4.1.4 Antifibrinolytics in Chronic HMB

Antifibrinolytics inhibit plasminogen activator with a 40–60% reduction in menstrual blood loss [56]. Tranexamic acid 1.3 g orally three times daily for up to 5 days during menses is approved for this use. Tranexamic acid, due to its mechanism of action, is contraindicated for use in the patient with a history of VTE and with concomitant use of CHC. See further discussion under management of acute HMB [26].

7.4.1.5 GnRH Modulation for HMB

First-line medical management of HMB in the presence of leiomyoma includes the potential benefits and limitations of the methods previously discussed. GnRH analogs have been used as second-level intervention to reduce fibroid size but the hypoestrogenic bone loss limits treatment to 6 months. These medications are typically used prior to surgery or adjuvant with surgery [58]. A GnRH antagonist elagolix with add back estrogen and progestin, is indicated for HMB associated with fibroids. Elagolix rapidly and dose dependently reduces gonadal steroid production via competitive binding with GnRH receptors of the pituitary leading to inhibition

of release of follicle stimulating hormone and luteinizing hormone. The approved protocol for management of HMB in the presence of UL is 300 mg elagolix twice daily with add back hormones (1 mg estradiol/0.5 mg norethindrone acetate) once daily for up to 12 months. In clinical trials, elagolix compared to placebo demonstrated reduced blood loss volume to ≤80 mL (72.2% vs. 9.3%), mean change in menstrual blood loss (−172.5 mL vs. −0.8 mL), amenorrhea (50.4% vs. 4.5%), reduced symptom severity (−37.1 vs. −9.2), and improved health-related quality of life score (39.9 vs. 8.9) [59]. A second GnRH antagonist, relugolix, combined with estradiol and norethindrone acetate is also approved for this indication. Elagolix is effective for alleviation of endometrial pain using 150 mg daily for 24 months or 200 mg twice daily for six months. While clinical trials in this population also demonstrated reductions in menstrual bleeding, this was not a study endpoint and reduction of HMB is not the approved indication in endometriosis [60]. Elagolix and relugolix are contraindicated for use in severe liver dysfunction. They must be used with contraception and hormonal contraception may interfere with therapeutic results. Hypoestrogenic side effects include vasomotor symptoms (6.9% hot flush and 3.2% night sweats) along with headache (5.5%) and nausea (4.1%) in elagolix clinical trials. Treatment duration is limited by bone mineral density decrease [61].

7.4.1.6 Selective Progesterone Receptor Modulation for HMB in Uterine Leiomyoma

Selective progesterone receptor modulators (SPRM) act to suppress the progesterone receptor gene, counteracting the progesterone and estrogen growth promoting effects upon leiomyoma. Several SPRM products have been developed. Dosing and regimens vary widely with no clear superiority of any product or protocol [58]. Ulipristal 5 mg, approved in Europe in 2012, but not in the United States, is the most widely used. Ulipristal was studied in women with UL with HMB as a series of 5 and 10 mg oral daily doses for 12 weeks, followed by a drug holiday to induce menses and then repeated for up to eight consecutive courses of treatment. Reduction in pain, bleeding, and tumor size were significant [62]. Benign endometrial changes occurred with a trend toward resolution at completion of therapy [63]. In 2018 reports of liver failure and death in women using ulipristal acetate 5 mg resulted in the European Medicines Agency reviewing the medication, with the conclusion that causal relationship could not be established but also limiting use to 3 months duration as adjuvant to surgery [64–66].

7.4.2 Minimally Invasive Procedural and Surgical Options in Chronic HMB

Endometrial ablation is indicated for women with a normal endometrial cavity who have not had satisfactory outcome using medical therapy, have no desire for future fertility, and have highly reliable contraception. In women with high risk factors for endometrial carcinoma such as obesity, complex atypical endometrial hyperplasia, diabetes, and hypertension, strongly consider establishing normal endometrial

histology prior to the procedure or select a different treatment method [52]. The procedure may be performed in an office setting with minimal analgesia and has shorter recovery time than hysterectomy. Endometrial ablation has been widely adopted in middle and high resource countries. Currently there are five methods of endometrial ablation utilizing techniques of thermal balloon, heated free fluid, cryoablation, radio-frequency, and two microwave devices.

Compared to hysterectomy, only 11% fewer women with endometrial ablation perceived improved bleeding symptoms at 1 year (RR 0.89, CI 0.85–0.93; four studies, 650 women). This gap persisted but narrowed over 4 years follow-up. Compared to LNG-IUS, endometrial ablation had equal patient satisfaction, quality of life, and treatment failure in 8-year follow-up [67]. Younger women (mean age ≤42 years) who received endometrial ablation were more likely to experience subsequent need for hysterectomy than women who received LNG-IUS (RR = 5.26, 95% CI 1.21–22.91, $p = 0.03$, I2 = 0%, three studies, 189 women) [68].

Late onset endometrial ablation failure (LOEAF) presents with persistent or recurrent vaginal bleeding, cyclic pelvic pain, or the inability to assess the endometrium as needed. Etiology of intractable bleeding involves both insufficient initial ablation and endometrial regrowth. Unsuspected adenomyosis and intrauterine scarring contribute both to bleeding and pain [69]. Of a group of 377 women undergoing endometrial resection, 22% had diagnosis of adenomyosis following the procedure [69]. Age at initial procedure is the predominant risk for LOEAF, as well as uterine anatomical distortion including leiomyomata and septum. Women under age 45 years at time of ablation are 2 times more likely and women under age 36 years are 3 times more likely to require subsequent hysterectomy [69, 70].

Two minimally invasive procedures, uterine artery embolization (UAE) and MRI guided high-frequency ultrasound, to reduce tumor bulk and decrease HMB are available for HMB with UL. Uterine artery embolization (UAE) is a minimally invasive interventional radiology procedure performed via femoral artery catheterization and embolization of the bilateral uterine arteries. This leads to necrosis of the leiomyoma while preserving the uterus. The first large trial of 305 women with uterine fibroids undergoing selective uterine artery embolization (UAE) demonstrated satisfactory control of HMB of 86% at 3 months post-procedure and 92% at 12 months [71]. Outcomes with UAE are similar to those obtained following myomectomy, with a subsequent intervention rate at 5 years of 20–30% [72]. A Cochrane Review found no difference in UAE patient satisfaction when compared to hysterectomy and to myomectomy at 2 and 5 years post-procedure. Post-procedure risk of major complications was equal in all procedures with a slightly higher risk of minor complications in UAE and more likelihood of subsequent surgery in UAE (15–32% vs. 7%) [73]. Though healthy pregnancies have occurred after UAE, effects on fertility and subsequent adverse events are not well defined [74].

MRI guided focused ultrasound thermal ablation technique results in coagulative necrosis at the target site [58]. Damage to surrounding tissue has been documented and future fertility may be compromised. Cost may be prohibitive. There is, as yet, no large body of outcome data [62].

7.5 Infrequent Bleeding

Infrequent bleeding is an expected bleeding pattern of the menopause transition. It is a defining criteria of the late perimenopause stage [75]. The gradual age-related loss of ovarian follicular mass and reduced follicular sensitivity to follicle stimulating hormone (FSH) are initially compensated by the gradual decline in Antimullerian hormone (AMH), decrease in inhibin, and age-related increase in aromatase, maintaining normal 17β-estradiol and ovulation [76 77]. With transition into the late perimenopause stage, a critically low threshold of follicles leads to decreased folliculogenesis and decreased follicular size when ovulation does occur, resulting in limited progesterone production. Cycles are irregular and interspersed with durations of ≥60 days without bleeding. Estrogen dominance may lead to endometrial hyperplasia [78] (see Chap. 4).

Infrequent bleeding at an age not within the norm for the menopause transition should be evaluated as an endocrinopathy (see Chap. 4). Health conditions developed in midlife may directly affect menstrual pattern. Thyroid, liver, and chronic kidney disease are all associated with infrequent menses [17]. There may also be increased health conditions with treatment induced menstrual changes. The most frequent source of iatrogenic (AUB-I) infrequent menses is exogenous hormone use [48]. Drug induced hyperprolactinemia and infrequent or absent menses may result from multiple classes of frequently used pharmaceuticals: anti-psychotics, antidepressants including tri-cyclic antidepressants, SSRI, SNRI, and MAO-I, as well as antihypertensives verapamil, α-methlydopa, reserpine, and labetolol (intravenous only) and the pro-kinetic agents metoclopramide and domperidone. There is question if H2-receptor blockers cimetidine and ranitidine contribute to hyperprolactinemic infrequent menses. Finally recreational drugs have been implemented in hyperprolactinemic infrequent menses including marijuana, heroin, methadone, cocaine, and alcohol [79].

To protect from endometrial hyperplasia, women who have a uterus must always be prescribed with a progestogen when estrogen is initiated, regardless of menstrual status [80]. Numerous studies have compared protocols for progestogen. Continuous use of 100 mg oral daily micronized progesterone, 1 mg norethisterone, or 1.5 mg MPA or sequential use 10–14 days per month of 200 mg oral daily micronized progesterone are effective for preventing endometrial hyperplasia in the presence of exogenous estrogen [81, 82]. Bjarnason et al. [83] comparing long cycle sequential progesterone (10 days every 12 weeks) to monthly sequential progesterone demonstrated increase in neoplasia in the long cycle group (see Chap. 6). In another study, the LNG-IUS was more effective in endometrial suppression than sequential MPA, but was comparable to other forms of systemic progestogen [84].

The clinical challenge is to determine which women in the perimenopause stages with infrequent bleeding require further investigation into endometrial status. A careful history is necessary to uncover iatrogenic and health-related causes beyond the expected age-related changes in menstrual pattern. Consider ultrasound evaluation for women with:

- Atypical age for perimenopause
- Symptoms or signs consistent with acquired comorbidity: thyroid endocrinopathy, liver and kidney disease
- Use of drug-inducing hyperprolactinemic agents
- Presence of additional risk factors for complex hyperplasia and endometrial carcinoma: obesity, PCOS, family history of endometrial cancer or genetic cancer syndrome such as HNPCC [85]

Management of an ultrasound measured endometrial stripe that is >4 mm or of irregular profile follows the assessment protocol as in postmenopause bleeding. A woman presenting with infrequent menses and <6 months without bleeding, may be considered for a progestogen withdrawal in the presence of a uniform endometrial stripe of >4 mm on ultrasound. Micronized progesterone 200 mg/day or MPA 10 mg/day for 10–12 days should stimulate a sloughing of the endometrium. Ultrasound re-assessment of the endometrial stripe should be done on Day 3–7 of withdrawal bleeding. If the endometrium remains >4 mm, endometrial sampling is warranted [17, 86].

Management of infrequent bleeding in the absence of endometrial hyperplasia in perimenopause is largely expectant. Ongoing management of the woman with infrequent menses and no additional risk factors for endometrial hyperplasia and carcinoma is directed at protection from the influence of unopposed estrogen in anovulatory cycles. She may use continuous low dose 1.5 mg MPA or 100 mg micronized progesterone, or cyclic progestogen for 12–15 days of 10–15 mg MPA or 200 mg micronized progesterone, or combined hormonal contraception, particularly if contraception is desired [17].

7.6 Postmenopause Bleeding

The largest risk for endometrial hyperplasia is exposure to unopposed estrogen. The time frame of exposure typically occurs in the ages of the early 50s, with progression to endometrial atypia in the early 60s, and peak incidence of carcinoma in the 70s [87]. Postmenopause bleeding may be a result of exogenous hormone use, benign neoplasms such as endometrial or endocervical polyps, endometrial atrophy, or endometrial hyperplasia or carcinoma [88]. Selective estrogen receptor modulators (SERMs), particularly tamoxifen, demonstrate endometrial activity and stimulation leading to risk of endometrial hyperplasia. Raloxifene, bazedoxifene, and ospemifene show no increase in endometrial activity over placebo [81].

There is only very limited evidence of endometrial safety for women using compounded bioidentical progesterone (cBHT). The National Academies of Sciences, Engineering, and Medicine [89], in a report on cBHT focusing on the United States, included only three studies of compounded progesterone cream, two of which were pharmaceutically formulated products. None of the studies were of sufficient power

or duration to determine long-term endometrial safety. Additionally cBHT products typically lack oversight in production ensuring uniformity of dosage and delivery. Many women may be unsure of formulations in current or previous use (see Chap. 6).

Any patient with postmenopause bleeding, whether on MHT, SERM, or no medication, and regardless of flow volume or duration, requires investigation. Even though only 1–14% of such patients will actually prove to have endometrial cancer, with peak age of incidence over 60 years, the clinician must assume an etiology of endometrial carcinoma until proven otherwise [90]. The initial step in evaluation is ultrasound imaging [88]. A uniform endometrial thickness of ≤4 mm has a greater than 99% negative predictive value for endometrial carcinoma [91].

In the presence of thickened endometrium, blind endometrial sampling is an appropriate next step and may be accomplished as an office procedure. With an irregular endometrial profile on ultrasound or persistent bleeding despite normal endometrial stripe and negative blind sampling, hysteroscopy and targeted biopsy is indicated [86, 88, 91]. This woman, and any woman with endometrial atypia or carcinoma on blind endometrial sampling, should be referred to gynecological oncology specialty if available or to gynecology for management.

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Vasomotor Symptoms

8

Patricia Geraghty

8.1 Epidemiology of Vasomotor Symptoms (VMS)

Menopausal symptoms are experienced by 70–85% of women worldwide with geographic and cultural variations (see Chap. 1). Along with myalgia/arthralgia and sleep disruption, VMS are the most commonly experienced symptoms [1, 2] (see Chap. 1). Vasomotor symptoms include a mild feeling of heat, or a moderate to severe feeling of heat with flushing, cold sweats, and night sweats. The sensation may be limited to a consistent body region such as the chest and face or the legs. There is sometimes a detectible prodrome. A woman may first awaken during the night with a feeling of dread or increased heart rate, and a subsequent sensation of hot flush or sweating. Women describe VMS differently and the nature of VMS may vary over the course of the menopause transition [3, 4].

An interplay of social and genetic variables illustrate the complex influences that result in the lived experience of the individual woman. Among women in North America and Europe, VMS are the most common menopausal experience, while women in Japan report a "chilliness" but have no word for "hot flashes" in the Japanese language [5, 6]. Within geographic regions, the experience of VMS is influenced by the interplay of race/ethnicity and socioeconomic factors. In the United States culture, the incidence and severity of clustered VMS, sleep disruption, and psychological distress were correlated with lower educational level and African American race [2]. The reporting of vasomotor and other symptoms within populations also varies over time. The incidence of VMS in a review of five studies from multiple countries within the African continent increased from 39% of women surveyed in 2009 to 77% of women in 2012 [1].

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Existing health issues may influence the presence, severity, and frequency of VMS. In the Study of Women's Health Across the Nation (SWAN), a prospective multisite, multiethnic observational study in the United States, higher body mass (OR 1.03 per unit of increase, 95% CI 1.01–1.04), smoking (OR 1.63, 95% CI 125–2.12), and anxiety symptoms at baseline (OR 3.10, 95% CI 2.33–4.12) were associated with increased reporting of VMS [7]. Body fat gain during the menopause transition was associated with greater hot flash reporting in the same population [8]. Women with sleep disruption and longer duration of VMS are more likely to report bothersome VMS [9]. Women with insulin resistance experienced increased VMS frequency (≥6/day) [10] (see Chaps. 9 and 12).

8.2 Duration and Trajectory of Vasomotor Symptoms

The most common time within the STRAW + 10 stages of menopause to experience hot flushes and night sweats is the early postmenopause stage, 0–3 years after the final menstrual period [11]. The duration of moderate to severe symptoms is much longer than previously thought, a median of 7.4 years in the SWAN cohort [12] and 10.4 years in the Penn Ovarian Aging Study (POAS) [13]. Women in both cohorts who experienced hot flushes early in the menopause transition had more than 11 years duration of VMS.

Health and social conditions also influence the VMS trajectory. The SWAN data identified four distinct trajectories for VMS (see Table 8.1). Women with more psychosocial and health problems were more likely to be in the early onset or high frequency groups than in low frequency. Women with obesity were not likely to fall into the late onset group [14]. A significant number of women experience prolonged VMS. The POAS cohort found 42% of women ages 60–65 years continue to experience moderate to severe VMS [12].

It is plausible that VMS have a role in other symptoms associated with the menopause transition, such as sleep disruption and cognitive or memory function (see Chaps. 9 and 10). Support comes from the clustering of symptoms linking the severity and frequency of VMS to sleep disruption and quality of life measures [15] and of VMS to sleep disruption and depressed mood but not VMS directly to depressed mood [16]. However, this theory is challenged by evidence that other symptoms may occur in the absence of moderate or severe VMS [2].

Table 8.1 Trajectories of VMS in the menopause transition from the SWAN population

Group	Percentage of population	Characteristics
Early onset	18.4	Initial VMS up to 11 years before FMP
Late onset	29	Initial VMS near FMP and later decline
High frequency early onset	25.6	
Low frequency	27	

VMS vasomotor symptoms, *FMP* final menstrual period
Based on Tepper et al. [14]

8.3 Vasomotor Symptoms Impact on Women's Lives

Exploration of links between the experience of VMS to increased risk of chronic disease yielded mixed results. Women reporting frequent VMS had more than twice the probability of coronary heart disease in a prospective study in the United Kingdom [17]. No or minimal association was found in the Australian Longitudinal Study on Women's Health [18]. Pooled data from the International Collaboration for a Life Course Approach to Women's Reproductive Health and Chronic Disease Events consortium found increased risk of cardiovascular disease related to severity rather than frequency of VMS (HR 1.83, 95% CI 1.22–2.73) and to women with both early onset VMS (HR 1.38, 95% CI 1.10–1.75) and late onset VMS (1.69, 95% CI 1.32–2.16) [19]. However, a systematic review and meta-analysis including 213,976 women with 10,037 CVD outcomes found the increased risk of CVD was mainly explained by CVD risk factors (smoking, body mass index, hypertension) [20] (see Chap. 5).

Failure to Treat VMS Failure to treat moderate or severe VMS may result in increased negative health outcomes and health expenses. Tang et al. prospectively followed women with VMS who were or were not treated with conjugated estrogen. When adjusting for age and co-morbidity, the treatment group had significantly lower 1-year total healthcare costs (−$1601 vs. −$503; $p = 0.044$) and inpatient costs (−$1431 vs. −$28; $p < 0.0001$) than the untreated group [21]. Women may neglect other health care or experience increased risk when menopause symptom management is missing. An example of the consequences of failure treat vulnerable populations may be seen in Duff et al. who evaluated women living with HIV where a minority (17%) received menopause symptom management. Untreated severe symptoms were positively correlated with less use of retroviral medication and increased injection drug use and sexual/physical violence [22].

8.4 Physiology of VMS

The decrease in estradiol alone is not sufficient to trigger VMS. Not all women report VMS while all women do experience loss of ovarian estrogen. The subjective report of VMS may be independent of measurable body temperature changes. American women of Japanese descent living in Hilo, Hawaii reported fewer VMS subjectively but had no difference in the number of episodes of elevated body temperature measured objectively via nuchal skin probes than did American women of European descent in the same community [23].

A reduced thermoneutral zone can be measured in women with VMS compared to asymptomatic women. In women with a reduced thermoneutral zone, even small changes in core body temperature can trigger shivering and sweating [24]. Control of the thermoneutral zone is located in the infundibular nucleus of the

hypothalamus. The role of the kisspeptin, neurokinin B, and dynorphin neurons (KNDy) of the hypothalamus, which control body temperature as well as part of the pituitary-hypothalamic-ovarian axis, is becoming more clear in VMS. KNDy neurons appear to respond to cyclical increased estradiol through negative feedback to act as the GnRH pulse generator, regulating the release of FSH. The KNDy neurons also project to the neurokinin 3 receptors (NK3R), which in turn project to heat dissipation effectors. The ligand for NK3R is the neuropeptide neurokinin B (NKB). With menopause, the decrease in estradiol, and/or possibly the increase in FSH, lead to KNDy neuron hypertrophy. Levels of NKB increase, increasing activation of receptors, resulting in rapid heat dissipation [25].

8.5 Assessing Vasomotor Symptoms

Grading of VMS serves both as an indication for therapy and as a baseline for measuring management efficacy. The clinical interview should cover parameters of frequency, severity, and impact on quality of life. Consistent patient assessment is important in the clinical setting to evaluate therapeutic success. A large number of validated tools to assess VMS are available [26, 27]. One such tool, the Menopause Rating Scale II, assesses multiple menopause transition symptoms. It was initially developed in Germany and has been validated across many languages and cultures [28]. See Table 8.2.

Menopause Rating Scale (MRS)

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply. please mark 'none'.

Symptoms:	none	mild	moderate	severe	very severe
Score =	0	1	2	3	4
1. Hot flushes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3. Sleep problems (difficully in falling asleep, diffcully in sleeping through, waking up early)	☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5. Irrtabilty (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6. Anxiety (inner restessness, feelling panicky)	☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burrning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

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Table 8.2 Menopause rating scale II

Item	Description
1	Hot flushes, sweating (episodic sweating)
2	Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, and chest tightness)
3	Sleep problems (difficulty falling asleep, difficulty in sleeping through the night, and waking up too early)
4	Depressive mood (feeling "down," sad, on the verge of tears, lack of drive, and mood swings)
5	Irritability (feeling nervous, inner tension, and feeling aggressive)
6	Anxiety (inner restlessness, feeling "panicky")
7	Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness, fatigue, headache, and dizziness)
8	Sexual problems (change in sexual desire, in sexual activity, and satisfaction)
9	Bladder problems (difficulty in urinating, increased need to urinate, and bladder incontinence)
10	Dryness of the vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)
11	Joint and muscular discomfort (joint pain, muscle pain, and backache)

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8.6 Management of Vasomotor Symptoms

There are multiple options for managing all symptoms of menopause, including VMS. No single option is best for every woman and many women transition among and between treatment modalities at different stages of menopause. Large numbers of women, particularly with mild to moderate symptoms, manage the transition with behavioral changes. Many women with moderate to severe VMS require additional choices. Individualization is an important component of menopause symptom management. Established trust and shared decision-making in the clinician–patient interaction provide each woman with the best care.

8.6.1 Hormonal Products

Menopause hormone therapy (MHT), low doses of estrogen or estrogen with a progestogen in women who have a uterus, is considered the most effective treatment for moderate to severe vasomotor symptoms [29]. Women with an intact uterus using estrogen need progestogen as part of therapy at every stage of pre- and postmenopause. There are different doses and formulations of estrogen and progestogens, with different delivery routes, as well as variations in dosing regimen. These differences, interacting with the woman's personal health history, significantly impact benefit and risk profiles. Molecules having the same structure as endogenous hormones, imprecisely called bio-identical hormones, are available in approved medications as estradiol and micronized progesterone. These demonstrate some superiority to conjugated estrogen and progestins in population studies.

Compounding of hormones is very popular in some regions but without the same evidence of efficacy or safety and associated with incorrect patient assumptions. Tibolone, a medication with both estrogenic and progestogenic activity, is also available in Europe, Australia, and Asia but not in the United States. Chapter 6 of this volume covers the complexity of MHT.

The Revised Global Consensus Statement on Menopause Hormone Therapy is endorsed by the International Menopause Society, the North American Menopause Society, the Endocrine Society, the European Menopause and Andropause Society, the Asia Pacific Menopause Federation, the International Osteoporosis Foundation, and the Federation of Latin American Menopause Societies. The consensus states the clinician should provide up to date and accurate information on benefits and risk tailored to the woman's lifestyle and health profile, including age since menopause, and risk of VTE, stroke, cardiovascular disease and breast cancer [29]. Further, decisions regarding estrogen and progestogen formulation, dose, and delivery route should be determined to optimize treatment and minimize risk. Approved indications for systemic MHT include treatment of VMS, prevention of postmenopause osteoporosis (see Chap. 12), and treatment of genitourinary syndrome of menopause (GSM) (see Chap. 10). Use of estrogen alone, or estrogen with progestogen in women with an intact uterus, is cautioned in women with a history of gallbladder disease and prothrombotic mutations, and contraindicated in women with a history of CVD, hormone dependent cancers, active thromboembolic event, severe active liver disease with abnormal liver function tests, and undiagnosed vaginal bleeding (see Chap. 5 chronic disease and Chap. 7 vaginal bleeding).

8.6.2 Management of VMS with Nonhormonal Methods

Many women are not candidates for MHT, particularly those with a history of hormone dependent cancers, and history of CVD or VTE. Some women choose to use nonhormonal management. Interventions include nonhormonal medications, botanicals and supplements, acupuncture, and lifestyle changes. Demonstrating the superiority of these interventions over placebo is challenging because of the robust placebo effect (20–60%), strongest in women with associated anxiety and stronger baseline symptoms, found in all studies of VMS treatments [30–32].

8.6.2.1 Nonhormonal Medications

The revised global consensus statement of 2016 states that antidepressants in the selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) classes have been shown to be more effective than placebo in RCT and, along with gabapentin, may be considered when MHT is contraindicated or not desired [29]. SSRIs and SNRIs, gabapentin, and clonidine have approved indications for management of VMS that vary across regions.

Antidepressant Protocols

SSRIs and SNRIs have been studied against placebo with efficacy in reducing VMS. The proposed physiologic pathway is the restoration of serotonin and norepinephrine levels altered by reduced estrogen and endorphins. Symptom relief is

Table 8.3 Suggested dosing ranges for nonhormonal prescription therapies

SSRIs		
Paroxetine salt	7.5 mg	
Paroxetine	10–25 mg/day	Single dose, no titration needed
Citalopram	10–20 mg/day	Start with 10 mg/day
Escitalopram	10–20 mg/day	Start with 10 mg/day (for sensitive older women start with 5 mg/day for titration, but this dose has not been tested for efficacy)
SNRIs		
Desvenlafaxine	100–150 mg/day	Start with 25–50 mg/day and titrate up by that amount each day
Venlafaxine	37.5–150 mg/day	Start with 37.5 mg/day
Gabapentinoids		
Gabapentin	900–2400 mg/day	Start with 300 mg/day at night, then add an additional 300 mg/day at night, then a separate dose of 300 mg in the morning (Start with 100 mg if worried about sensitivity)
Pregabalin	150–300 mg/day	

SSRIs selective serotonin reuptake inhibitors, *SNRIs* serotonin-norepinephrine reuptake inhibitors
North American Menopause Society. Menopause. 2015; 22(11): 1155–1172. Used with permission

typically within 1–2 weeks with venlafaxine; other agent's effects were studied in 12-week or longer trials [33, 34]. Doses studied were lower than or were in the lowest range of doses considered efficacious for depression and anxiety. See Table 8.3. Timed release 7.5 mg paroxetine salt in the United States is the only regulatory approved product. Although international and regional guidelines state that MHT is first-line therapy for VMS, there are few head-to-head comparisons. The SSRIs paroxetine salt, paroxetine, citalopram, and escitalopram, and SNRIs desvenlafaxine and venlafaxine demonstrate 25–69% reduction in VMS over placebo. Sertraline and fluoxetine demonstrate minimal VMS reduction or are ineffective [33].

There is known interaction of tamoxifen and SSRIs via CYP2D6 inhibition leading to the subsequent reduction of tamoxifen conversion to its active metabolite. The most potent inhibition is from paroxetine. Women taking tamoxifen should use one of the SNRIs or a less potent CYP2D6 inhibitor such as citalopram or escitalopram (see Chap. 14). The VMS improvement may be a dose dependent effect and there is no data on the efficacy of SSRI or SRNI at higher doses or the addition of a SSRI/SRNI in women currently in treatment for depression/anxiety on another therapy (see Chap. 10). Use of SSRI/SNRI with a monoamine oxidase inhibitor is contraindicated due to potentially fatal serotonin toxicity [35].

Gabapentinoids

Gabapentin is a neuroleptic, with additional indications for neuralgia and restless leg syndrome. Gabapentin 900 mg/day divided doses has demonstrated efficacy in reduction of VMS frequency and VMS composite score standardized mean differences across placebo trials. A meta-analysis of seven placebo RCTs demonstrated a dose-dependent effect on VMS frequency and composite score improvement with limited efficacy at doses as low as 300 mg/day. All doses reported side effects of

dizziness and somnolence which may limit therapeutic benefits but did not affect drop-out rates. These symptoms are more transient at lower doses [36]. The side effect of somnolence may have benefits for women with sleep disruption [34] (see Chap. 9). Two RCTs comparing 100 mg/day or 300 mg/day gabapentin to 0.625 mg/day conjugated estrogen and 600 mg/day gabapentin to transdermal estradiol 0.025 mg/day respectively demonstrated significant improvement in frequency and intensity of VMS in all arms, with the 300 mg/day dose being as effective as the conjugated estrogen [37, 38]. A gabapentin extended release and pregabalin demonstrated efficacy for VMS improvement but did not get FDA approval for VMS management indication in the United States. The clinical trials had very robust 50% placebo effect [39].

Clonidine

Clonidine, an antihypertensive central α-adrenergic receptor agonist, is approved in Canada for treatment of VMS. In an 8-week RCT, clonidine was slightly more effective in reducing VMS than placebo (38% vs. 30%) but was less effective than SSRIs, SNRIs, or gabapentin [40]. Adverse effects including dry mouth, dizziness and risk for falls, headache, sedation, constipation, and hypotension or rebound hypertension when discontinued limit use.

8.6.2.2 Management with Non-prescription Botanicals and Supplements

Products that are generally available without prescription and purport to improve health but cannot legally claim to prevent, treat, or cure a disease are marketed worldwide. Clinicians trained in allopathic medical theory face challenges in evaluating supplements with their patients. The concerns in evaluating any supplement use are threefold: safety, efficacy, and does the product actually contain the ingredients listed?

Regulation of Supplements

Dietary or food supplement are the legal terms used for these products in the United States, the European Union, India, and Australasia. In Canada, the term natural health product is used and includes the addition of homeopathic medicines and traditional Chinese medicine (TCM). The term nutraceuticals may also be used in some regions [41–44].

There is good harmonization of the definition of supplement across regions. Definitions typically include products such as vitamins, minerals, proteins, amino acids, enzymes, plants or botanicals or their parts, in the delivery forms of powder, concentrate, or extract. The USA Food Safety and Standards Act of 2004 goes a step further, stating supplements “shall not contain drugs, hormones, steroids, or psychotropic substances” [41, 45]. Manufacturing and marketing regulation varies among regions. The international CODEX Alimentarius guidelines of the United Nations and World Health Organization places supplements for groups of individuals who require specific nutrition under the auspice of food regulation rather than of drugs. This concept was codified into law in the USA and has been adopted in similar form by the EU and most countries [42, 46].

In 2007 in the USA and in 2018 in the EU, rules were established for good manufacturing processes to ensure that labeling accurately represents contents and that products are free from contaminants or impurities. The EU goes a step further, evaluating bioavailability of supplements. Products produced in the United States under this regulation may be labeled USP or NSP. In Canada, the products are labeled with a NPN (Natural Product Number) or DIN-HM (Drug Identification Number for homeopathic medicines) when they have obtained the required product license [44].

Thus supplements are removed from drug regulatory bodies evaluation and supervision. The supplement manufacturer is responsible for ensuring that package labels are not misleading. Claims for alleviating so-called natural conditions may be made without new drug trials, peer review, or providing documentation to regulatory bodies. Regulatory bodies may only evaluate safety of products after concerns are raised, not prior to marketing. This leaves management of menopausal symptoms, and the women who need such treatment, particularly vulnerable to products without evidence of safety and efficacy [44]. Even with established safety, choosing an ineffective product may delay effective necessary therapy [34].

Botanicals

In this chapter, "botanicals" are defined as plant products purported to alleviate symptoms. Botanical common names vary widely. Combination products may not indicate which ingredients are the most bioactive and manufacturers change product content at will. Yet the concerns for safety and efficacy can also be evaluated within the context of many areas of the world that have traditionally used botanicals for management of health issues. Analyzing efficacy of a single botanical, when Traditional Chinese Medicine (TCM) typically uses combination products has been criticized [47]. Clinicians rely on resources from professional society guidelines and from meta-analyses of studies using established scientific technique to apply allopathic medical theory to the traditional knowledge. The goal is to avoid harm and maximize therapeutic benefits.

A Cochrane review evaluated the efficacy of TCM compared to placebo or MHT. Only 22 RCTs with small sample sizes (2902 women) met inclusion criteria. Imprecise estimates of effects resulted in an outcome of inconclusive evidence. The authors concluded that data showed little to no evidence of improvement in VMS. Adverse events reported in the TCM group included diarrhea, breast tenderness, gastric discomfort, and unpleasant taste [48].

The North American Menopause Society (NAMS) 2015 position statement on management of menopause-associated VMS analyzed evidence for use of over-the-counter supplements and herbal therapies in single product and combined preparations. NAMS does not recommend use of any botanicals as they are unlikely to be beneficial in alleviating VMS. Other meta-analyses have concluded there is positive effect with botanicals containing phytoestrogens but these reviews include soy isoflavones, which are discussed separately [49]. See Table 8.4. This list is not exhaustive. The International Menopause Society, Korean Menopause Society, and Indian Menopause Society have not addressed botanicals in position statements.

Table 8.4 Analysis of botanicals commonly used for relief of menopause-associated VMS

Common name(s)	Scientific name	Specifics
Black Cohosh	*Actaea racemosa*	• Active ingredient and method of action unknown • Most commonly purchased botanical • Possible hepatotoxicity • Ineffective
Crinum lily	*Crinum asiaticum*	• No studies
Dioscorea aka Wild Yam	*Dioscorea barbasco*, *D Mexicana*, *D villosa*	• In vitro but not in vivo conversion to progesterone • Possible DHEA activity • Evidence of adulteration in marketed products • Ineffective
Dong quai aka Dang gui, Tang kuei	*Angelica sinensis*, *Angelica polymorpha*	• Contains (Z)-ligustilide with possible anti-inflammatory and neuroprotective activity • Very unstable to light • Possible photosensitization, anticoagulation, and carcinogenicity • Ineffective alone or in combination
Evening Primrose	*Oenothera biennis*	• Contains linoleic acid and ϒ-linoleic acid anti-inflammatory • Ineffective
Flaxseed	*Linum usitatissimum*	• Lignans converted by gut microbiota to weak estrogenic sterols • Must be crushed or milled and not present in oils • Ineffective
Ginseng	*Panax ginseng* (Asian, Korean, or Chinese red ginseng) *Panax quinquefolius* (American white ginseng) *Acanthopanax senticosus* (Siberian "ginseng")	• Estrogenic activity in rats but not humans • Ineffective
Hops	*Humulus lupulus*	• Flavonoid 8-prenylnaringenin phytoestrogen • Ineffective in RCT and crossover studies
Maca aka "Peruvian ginseng"	*Lepidium meyenii*, *Lepidium peruvianum*	• Uncertain method of action, possible modulation of sex steroid-receptor • Methodological problems in studies prevent support
Omega-3 fatty acids		• Purported anti-oxidant and anti-inflammatory activity • Inconsistent results

Table 8.4 (continued)

Common name(s)	Scientific name	Specifics
Pine bark	*Pinus pinaster*	• Proanthocyanidin source, a phytoestrogen • Effective in small trials of insufficient size and number to warrant recommendation
Pollen extract (proprietary) aka Relizen ©, Serelys ©, Femal ©, Femalen ©	*Pinaceae* cytoplasmic pollen and pistil extracts	• No estrogenic activity. Active ingredient and method of action unknown • Single small study effective in VMS but insufficient number to warrant recommendation
Peurpuria aka kwao krua	*Puerpuria mirifica*	• Phytoestrogen • No significant adverse effects in limited data • Reduced VMS but without placebo control in one study and results reported without sufficient detail in study comparing 0.0625 CEE ± MPA
Red Clover	*Trifolium pratense*	• Contains genistein and daidzein, phytoestrogens • Effective at 3–4 months but not at 12 months • Ineffective in meta-analysis of five placebo trials
Siberian rhubarb	*Rheum rhaponticum*	• Contains hydrostilbenes with ERα weak and ERβ stronger affinity • Strong laxative effects • Inability to form conclusion due to poor subject retention in trials

*Ba*sed on The North American Menopause Society [31], Gartoulla and Han [46], Ghazanfarpour [47], Myers and Vigar [48], Duric et al. [49], Johnson [43]

Soy Foods and Soy Extracts

Efficacy of soy in menopause symptom management is subject to both the manufacturing process of the product and the ability of the recipient to metabolize the isoflavone daidzein into the nonsteroidal estrogen receptor beta (ER-β) agonist S-equol. The NAMS 2015 position statement recommends with caution the use of S-equol supplementation as a second-line management of VMS in women without allergy or sensitivity to soy. If there is no response to S-equol within 12 weeks, other treatment options should be considered [34].

Soy contains isoflavones genistein and daidzein in high quantities. Isoflavones are phytochemicals with weak affinity for estrogen receptor alpha (ER-α) and stronger affinity for ER-β. Thus they operate similarly to a selective estrogen receptor modulator. Epidemiological studies demonstrate high consumption of soy products may reduce breast cancer risk [54]. Therapeutic efficacy of soy may vary dependent on

the part of the soybean used. Daidzein is metabolized to the active product S-equol by gut bacteria. Ability to metabolize S-equol varies with populations and appears to be dependent on diets that support the necessary gut microbiome. Typically women in Asia metabolize S-equol more readily than women in Europe or North America.

The differential ability to produce S-equol illuminates the inconsistent results in placebo controlled trials. Soy isoflavinoids in their natural form demonstrate no difference from placebo in relief of menopausal symptoms [49, 55–59]. Trials of women who metabolize S-equol and of non-metabolizers using S-equol supplements demonstrate cardioprotective effects [60], decreased fat mass accumulation, decreased bone resorption [61, 62], relief of VMS, cognitive function preservation [63, 64], and trends toward improvement in skin measurements [65]. A combination daidzein, genistein, and S-equol 50 mg tablet is in phase II clinical trials. As clinical trials are not required for supplements, it is not clear if this product will be marketed as a drug or as a supplement [66].

8.6.2.3 Acupuncture

Acupuncture is a part of TCM and involves the placing of thin needles in specific body locations by a trained clinician. TCM theory states that acupuncture alters body energy qi (chi). Allopathic medical theory accepts acupuncture efficacy in pain management. Acupuncture for relief of VMS and other menopausal symptoms has been widely studied. In comparison to no treatment or wait list control, acupuncture was effective in reducing frequency and severity of symptoms [34]. When acupuncture was compared to sham acupuncture involving light touch or placing needles in non-acupuncture locations, the results were inconsistent with most studies finding no difference between groups [67, 68]. Discussion continues as to the appropriate control for acupuncture studies. A potential benefit of light touch is consistent with both TCM theory and allopathic medical theory [69]. Additionally, as the causes of natural menopause and medically induced menopause differ, practitioners of acupuncture argue that studies should be done separately on the two groups. A review of acupuncture with both no treatment and sham control groups in women experiencing natural menopause concluded that acupuncture is effective for reducing hot flash frequency and severity and improving quality of life [70].

8.6.2.4 Lifestyle Management

Women who are distressed by VMS spontaneously attempt relief with changes in behavior. This typically involves clothing that is lightweight or layered, use of fans, having cool drinks nearby, and identifying and avoiding triggers. Heat dissipation devices as simple as wicking night clothes or as elaborate as water cooled bedding are available. While there is no clinical evidence supporting these interventions, such data may be unnecessary [34]. The woman who is able to manage menopause-related VMS with these behavior changes does not need clinical attention. Rather it is the clinician's imperative to identify women for whom these and the following lifestyle management techniques do not meet their needs and to ensure that they are educated enough in management options to fully share in decision-making. While lifestyle management has many benefits for health and well-being, this section focuses on the efficacy of lifestyle management in alleviating VMS.

Weight Loss

Increased BMI, percentage body fat, and increase in body fat over time have been associated with increased reporting of VMS [9, 71, 72]. Observational data from the Study of Women's Health Across the Nation reported increased VMS positively correlated with increase in BMI and waist circumference in early menopause transition but not in late menopause [73]. There are now a number of intervention trials of planned weight loss and VMS. In a study of urinary incontinence with weight loss as a secondary end point and in another study of weight management in women with breast cancer, women who lost weight were less likely to report moderate to severe VMS [74, 75]. In the Women's Health Initiative Dietary Modification trial, women who lost 10 lb or more were 23% more likely, and women who lost 10% or more of body weight were 56% more likely to eliminate VMS at 1 year. However, only 8% and 2% of participants in this study reported moderate or severe VMS respectively at baseline [76]. A small ($n = 40$) behavioral weight loss intervention RCT found greater weight loss and a correlated reduction in reported VMS with the intervention group [77]. Although weight loss as an intervention has challenges, it has potential to be efficacious in decreasing or eliminating VMS [34].

Exercise

A Cochrane review of exercise and vasomotor symptom management [78] including a total of seven studies concluded that exercise does not positively impact VMS. A subsequent scoping review of walking programs and menopausal health included 96 studies with 7456 women mean age 56.8 ± 5.0 years of whom 3686 completed walking programs of duration ranging from 12 to 24 weeks. Many of the studies included women with sedentary lifestyles, overweight or obesity, or specific health conditions. Only 4 of the 96 studies reported on VMS. Studies comparing exercise to no exercise or to wait groups showed no improvement of VMS with walking. Two studies comparing walking exercise to MHT demonstrated superior efficacy of MHT [79]. NAMS and other regional menopause societies concluded that although there are many health benefits for women from exercise, randomized control trials do not support it as an intervention for VMS [34, 80].

Mind-Body Therapies

Many mind-body therapies incorporate multiple modalities making distinction among techniques difficult and perhaps unnecessary. Yoga has diverse practices but typically involves physical work as well as breath control and meditation. Yoga has consistently been shown ineffective in reducing VMS [81–83]. Paced breathing, as an individual modality, is not effective in RCT of VMS. Mindfulness-based therapy, focusing on awareness and acceptance of the present, showed a trend of improvement in VMS that was not statistically significant [84]. Cognitive behavioral therapy (CBT), however, which incorporates many of these modalities along with education and counseling about a condition, in this case menopausal symptoms, has been shown effective both in group and guided individual programs. Women with breast cancer and women without breast cancer reported less bother from VMS despite few changes in severity or frequency. The NAMS considers CBT an effective intervention for VMS [34].

8.7 Emerging Vasomotor Symptom Management

8.7.1 Neurokinin 3 Receptor Antagonist

Neurokinin 3 receptor antagonists have potential for controlling VMS without exogenous hormone administration. Changes in sex steroids in the menopause transition cause hypertrophy of the KNDy neurons of the hypothalamus and increase in the neuropeptide neurokinin B (NKB) which acts on the neurokinin 3 receptor (NK3R). This neuroendocrine pathway moderates heat dissipation as well as crucial roles in GnRH secretion and regulation of human reproduction (see physiology in this chapter) [85]. Several NK3R antagonist products have been developed and tested in small, short-term (4 weeks) trials. NK3R antagonism appears to have a rapid onset reduction in VMS. In one trial, VMS were reduced by 73% and 45% above placebo [86]. There were three episodes of elevated alanine aminotransferase (4.5–5.9 times normal) out of 28 participants completing the trial. Safety and efficacy in long-term use must still be established [85, 87].

8.7.2 Estetrol

Estetrol (E4) is a native estrogen produced only in the fetal liver. It has a unique relationship to estrogen receptors, binding with nuclear but not membrane ER-α. This results in a profile of action with minimal hepatic stimulation, possibly conferring a safer thrombotic and cardiovascular risk profile. Estetrol with drospirenone is available as a contraceptive [88]. In rat models, there were positive effects on both hot flushes and bone loss with minimal stimulation of liver or breast tissue [89]. There was both significant reduction in VMS and endometrial activity at doses of 2 mg and above when tested in the absence of controls. In placebo control phase 2b trials, there was 75% reduction of VMS in 80% of participants at 15 mg but not 10 mg with the presence of a strong placebo effect (65% reduction VMS over baseline by 12 weeks) [90]. Multi-center (Europe, Russia, South America, North America) phase 3 trials are currently underway [88].

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Sleep Disruption

9

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9.1 Introduction

Sleep disturbance is one of the most commonly reported and most bothersome symptoms of the menopausal transition [1, 2]. Although changes in sleep occur with aging [3], and female gender is a risk factor for poor sleep [4], the menopause transition is a unique contributor to the greater prevalence of sleep disorders and general sleep dissatisfaction in midlife women. Despite the high prevalence of sleep disturbance during the menopause transition, sleep remains critical for physical, mental, and social well-being in midlife women. Therefore, there is a need to better understand sleep disruption in the menopause transition. Sleep is a complex process affected by physiological, psychological, social, and cultural factors. The unique challenges and benefits associated with pre-, peri-, and postmenopause status affect the sleep experience in midlife women. The purpose of this chapter is to describe the consequences and characteristics of sleep in the menopause transition—the quantity, quality, and prevalence of disorders. Additionally, we will consider the broader biopsychosocial context affecting sleep peri- and postmenopause. Lastly, we end with a discussion of the assessment and treatment of sleep disturbance.

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9.2 Mental and Physical Consequences of Disrupted Sleep

The menopause transition is associated with a myriad of sleep difficulties ranging from transient disturbances to severe and chronic poor sleep [5]. Sleep is recognized as the fourth pillar of health, and accordingly, disturbed sleep in the general population is tied to adverse mental and physical conditions including cardiovascular disease, depression, cognitive impairment, and metabolic syndrome among other outcomes [5, 6]. Cross-sectional and longitudinal studies show an association between short sleep duration and hypertension, particularly in middle-aged adults and in women [7]. A meta-analysis of studies investigating hypertension and short sleep duration found that short sleep duration, more so than insomnia, significantly predicted hypertension [6]. Short sleep duration has also been associated with the risk for type 2 diabetes in numerous studies [8]. Similarly, a meta-analysis of studies investigating type 2 diabetes and short sleep duration found that short sleep duration, not insomnia, was associated with increased risk for diabetes [6]. Finally, short sleep duration has been associated with increased BMI [9]; however, a meta-analysis found that BMI was not different between groups with insomnia and adequate sleep duration or insomnia with short sleep duration [6].

Although sleep difficulties can both emerge or worsen during the menopause transition [5], sleep disturbance is associated with severe mental and physical outcomes [5]. In a clinical trial with postmenopausal women, women with insomnia were twice as likely to show physical impairments and 3–4 times as likely to show mental impairments [10]. These insomnia symptoms at baseline predicted impairments at 1- and 3-year follow-up, even if the insomnia had resolved [10]. Other studies support these findings for mental health with women with sleep problems early in the menopause transition at greater risk for persistent/recurrent depression over and above the increased risk from a lifetime history of depression compared to those without sleep problems [11] (see Chap. 10). Sleep changes that occur during the menopause transition have additionally been linked to physical health problems such as cardiovascular risk and metabolic syndrome in midlife women. Poor sleep quality and shorter sleep duration have been tied to increased carotid atherosclerosis in peri/postmenopausal women [12]. Accordingly, women in midlife show a more rapid increase in the severity of metabolic syndrome during the years leading up to menopause compared to the postmenopausal period [13] (see Chap. 5). In longitudinal and experimental studies investigating adult men and women, sleep deprivation or curtailment, sleep fragmentation, selective restriction of slow wave sleep, and sleep-disordered breathing are causally linked to key components of the metabolic syndrome including increased blood pressure, glucose dysregulation, and changes in metabolism that favor weight gain [14] (see Chap. 12). In research specific to women in midlife, objective measures of sleep continuity, sleep depth, and sleep-disordered breathing have significantly correlated with metabolic syndrome in midlife women [15]. Short sleep duration has been linked to metabolic syndrome and higher weight outcomes in midlife women [14]. Similarly, women who reported sleeping less than 6 h per night were significantly more likely to experience metabolic disturbances and have higher weight outcomes than those who reported more

sleep [16]. Poor sleep efficiency is associated with an increased risk for poor weight outcomes and metabolic disturbances including increases in central adiposity in this population [14].

9.3 Characteristics of Sleep During the Menopause Transition

Sleep is primarily driven by homeostatic, circadian, and ultradian processes [17]. The homeostatic process of sleep describes "sleep need" as dependent on previous amounts of sleep. As more time is spent awake and a person is temporally further from their last sleep episode, the homeostatic drive for sleep increases. Conversely, the homeostatic drive for sleep is at its lowest when someone has just finished a sleep episode. The circadian process of sleep refers to the regulation of the sleep cycle by a master biological clock called the superchiasmatic nucleus (SCN; [18]). The SCN controls numerous rhythms, such as feeding rhythms and sleep/wake rhythms. The two-process model of sleep regulation explains how the homeostatic and circadian processes work in concert [19]. Across the day, the drive to sleep increases. This homeostatic process would result in greater sleepiness as the day continues. However, the circadian process works in opposition to the homeostatic process with the body clock promoting alertness during the day and sleepiness at night. Therefore, although sleep needs get met during the night, we do not become progressively less sleepy as the night continues. Rather, the circadian process ensures we remain sleepy during the night and alert during the day. Finally, the ultradian process describes how non-rapid eye movement (NREM) and rapid eye movement (REM) sleep states alternate within a sleep episode [17]. Sleep traditionally follows a predictable pattern of a three-stage non-rapid eye movement (NREM) sleep cycle followed by a rapid eye movement cycle (REM). Sleep begins with NREM sleep, Stage 1, which is a very light transition to sleep state. Stage 2 includes light sleep that helps to prepare the body for entering deep sleep. Stage 3 begins when a person enters deep, or slow-wave sleep which serves a restorative function. These three NREM sleep stages are followed by rapid eye movement sleep, which helps with consolidation of emotional and cognitive functioning [20]. Throughout the night, a person repeats this cycle around five times and spends the majority of the night in the first three stages of sleep [21].

Neurotransmitters also play a role in the sleep/wake cycle. The neurotransmitter GABA helps to induce sleep and is most active during lighter stages of sleep such as NREM sleep [22]. Histamine helps to maintain wakefulness; however, when histamine is inhibited, sleep is induced [22]. Norepinephrine and serotonin are additional neurotransmitters that encourage sleep when inhibited. The inhibition of norepinephrine or serotonin relaxes muscle tone and promotes sleep maintenance [22]. The circadian system contributes to the consolidation of sleep/wake periods by controlling the secretion of melatonin. Light enters the retina and is absorbed by melanopsin, a photopigment located in retinal ganglion cells [23]. These ganglion cells project to the SCN which sends cues for the release or suppression of

Table 9.1 Stages of sleep [20]

NREM sleep			
Stage 1 (N1)	Stage 2 (N2)	Stage 3 (N3)	REM sleep
Transition to sleep	Light sleep	Deep sleep Slow wave sleep	Rapid eye movement sleep, increased brain activity
1–5 min	10–60 min	20–40 min	10–60 min

melatonin by the pineal gland [23]. With increasing levels of darkness, the SCN cues greater release of melatonin which, in turn, cues sleepiness [23] (Table 9.1).

Throughout the menopause transition, there are numerous changes to sleep architecture. Research on sleep architecture utilizes objective measures such as polysomnography (PSG) to capture sleep data, typically in a laboratory setting. Studies using PSG show mixed findings for samples of women in various stages of menopause, and many are based on one night of sleep data, are observational, and do not control for confounding factors [5]. However, two large cohort studies—the SWAN and Wisconsin Sleep Cohort—addressed these limitations. The SWAN study found no differences in PSG-assessed sleep across menopause status [24] and the Wisconsin Sleep Cohort study found that peri- and postmenopausal women had better PSG sleep (more slow wave sleep) than premenopausal women [25]. Within the SWAN study, late-perimenopausal stage and postmenopausal women had greater cortical hyperarousal during sleep than pre- and early-perimenopausal women which was partially explained by more hot flashes [24].

However, these objective findings using PSG do not capture the sleep complaints and sleep difficulties reported by perimenopausal and postmenopausal women and suggest that other measures of sleep may be necessary to fully understand the sleep experiences of women in the menopause transition. Subjective measures of sleep are usually administered through self-report retrospective questionnaires such as the Pittsburgh Sleep Quality Index (PSQI) or daily sleep diaries. Sleep troubles and complaints are influenced by menopause status, with sleep problems being more common for women in the transition to menopause and throughout postmenopause [26–28]. Overall, sleep problems are more common for perimenopausal and postmenopausal women, with 40–64% of all perimenopausal and postmenopausal women reporting sleep disturbances [26–28]. Using the Pittsburgh Sleep Quality Index to measure subjective sleep quality, 39% of premenopausal women, 52% of perimenopausal women [29], and 59.7% of postmenopausal women reported poor sleep quality [30]. Postmenopausal women also seem to have worse subjective sleep quality in comparison to premenopausal controls [31]. Postmenopausal women subjectively report more restless sleep, more nocturnal awakenings [31], and more time needed to fall asleep compared to premenopausal and perimenopausal women [32].

Women also report sleep disturbances as one of the most bothersome menopausal symptoms, therefore making sleep complaints a core component of the menopausal transition [33]. The SWAN study found perimenopausal women were more likely to have trouble sleeping compared to premenopausal women [34], and other research suggests that trouble sleeping increases as women progress through

the menopause transition [35]. Specific examples of sleep problems include increased intermittent awakenings [36]. Intermittent awakenings are not only the most common sleep complaint for perimenopausal and postmenopausal women [37], these awakenings are also reported as the most bothersome sleep complaint [38]. Other common sleep complaints during the menopausal transition include difficulty falling asleep, staying asleep, and not feeling refreshed and rested after a night of sleep [5, 39]. Overall, these findings suggest that sleep problems are numerous, varied, and bothersome throughout and following the menopausal transition.

9.4 Sleep Disorders in the Menopause Transition

While the incidence of sleep disorders increases with age, it is likely that menopause status contributes to the increase of sleep disorders in midlife women [40]. Sleep disorders commonly reported in perimenopausal and postmenopausal women include insomnia, sleep-disordered breathing, and restless leg syndrome. Although restless leg syndrome is reported to worsen after menopause [41], it is unclear as to whether restless leg syndrome is truly influenced by the menopausal transition or is simply age-related [42, 43]. This chapter focuses on the two most prevalent sleep disorders in the menopause transition—insomnia and sleep-disordered breathing.

9.4.1 Insomnia

Insomnia is characterized by difficulty initiating or maintaining sleep or by obtaining sleep that is of poor quality (see Table 9.2). Incidence of insomnia peaks during the menopausal transition. Symptoms of insomnia such as chronic difficulty initiating sleep, nonrestorative sleep, and global sleep dissatisfaction are all more commonly reported among perimenopausal women compared to premenopausal and postmenopausal women [45]. In a large multinational cohort study, 39.5% of premenopausal women and 46.3% of postmenopausal women had insomnia [46]. Additionally, the menopause transition appears to have the highest rates of insomnia, as 36.5% of premenopausal women, 56.6% of perimenopausal women, and 50.7% of postmenopausal women had insomnia [45]. Perimenopausal symptoms such as vasomotor symptoms are highly associated with insomnia [45] and contribute to the elevated rates of insomnia during the transition, although this association is complex (see Chap. 8).

9.4.2 Sleep-Disordered Breathing

Sleep-disordered breathing (SDB) is defined as abnormal breathing that occurs during sleep. It can range from having increased breathing effort caused by airflow resistance, reduced airflow, or repeated pauses in breathing (i.e., apnea; [47]).

Table 9.2 Sleep disorder diagnostic criteria included in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; [44])

Diagnosis (ICD-9 code)	Diagnostic criteria
Insomnia Disorder (307.42)	1. A predominant complaint of dissatisfaction with sleep quantity or quality associated with one (or more) of the following symptoms: (a) Difficulty initiating sleep. (b) Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (c) Early morning awakening with inability to return to sleep. 2. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning. 3. The sleep difficulty occurs at least 3 nights per week. 4. The sleep difficulty is present for at least 3 months. 5. The sleep difficulty occurs despite adequate opportunity for sleep. 6. The insomnia is not better explained by and does not occur exclusively during the course of another sleep–wake disorder. 7. The insomnia is not attributable to the physiological effects of a substance. 8. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia
Obstructive Sleep Apnea Hypopnea (327.23)	1. Either (a) or (b): (a) Evidence by polysomnography of at least five obstructive apneas or hypopneas per hour of sleep and either of the following sleep symptoms: • Nocturnal breathing disturbances: snoring, snorting/gasping, or breathing pauses during sleep. • Daytime sleepiness, fatigue, or unrefreshing sleep despite sufficient opportunities to sleep that is not better explained by another mental disorder (including a sleep disorder) and is not attributable to another medical condition. (b) Evidence by polysomnography of 15 or more obstructive apneas and/or hypopneas per hour of sleep regardless of accompanying symptoms
Restless Legs Syndrome (333.94)	1. An urge to move the legs, usually accompanied by or in response to an uncomfortable and unpleasant sensations in the legs, characterized by all of the following: (a) The urge to move the legs begins or worsens during periods of rest or inactivity. (b) The urge to move the legs is partially or totally relieved by movement. (c) The urge to move the legs is worse in the evening or at night than during the day or occurs only in the evening or at night. 2. The symptoms in Criterion A occur at least three times per week and have persisted for at least 3 months. 3. The symptoms in Criterion A are accompanied by significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning. 4. The symptoms in Criterion A are not attributable to another mental disorder or medical condition and are not better explained by a behavioral condition. 5. The symptoms are not attributable to the physiological effects of a drug of abuse or medication

Although SDB was thought to largely impact men compared to women, evidence suggests that menopause changes the prevalence and risk for sleep-disordered breathing. Multiple studies have found that postmenopause women not using menopause hormone therapy had significantly higher prevalence of sleep-disordered breathing compared to premenopausal women [25, 48]. In addition, postmenopausal women were 2.6 times more likely than premenopausal women to have mild sleep-disordered breathing, and 3.5 times more likely to have more severe sleep-disordered breathing compared to premenopausal women [25]. Lastly, a study of sleep-disordered breathing in postmenopause found that 82% postmenopausal women with chronic insomnia in the study had clinically significant SDB [49].

Although increased body weight and visceral adiposity (increased abdominal fat) can increase risk for SDB, menopausal status remains a significant independent risk factor for SDB after adjusting for age, body mass index, waist circumference, or waist-to-hip ratio [25, 48]. Anovulatory cycles and subsequently decreased progesterone levels are increasingly more frequent in the 5 years prior to the final menstrual period [50] (see Chap. 4). As such, endogenous hormone reduction is likely a factor increasing risk of SDB in this population.

9.5 Biopsychosocial Etiology and Context for Sleep Disruption During the Menopause Transition

Many biopsychosocial factors have been investigated in their association with sleep disturbances in the menopause transition. Biologically, vasomotor symptoms (i.e., hot flashes and night sweats), changes in reproductive hormones, and metabolic changes influence sleep during this time period [28]. Psychological and social factors including mood disorders, stress, and lifestyle can also influence sleep in this population [28]. Although biological, psychological, and social factors are discussed separately in this section, these factors overlap and have bidirectional influences on sleep. For example, women in the menopause transition often attribute negative mood (e.g., daytime irritability) to nighttime awakenings [51]. In addition, poor mood has been associated with the experience of nighttime vasomotor symptoms which then impact sleep and lead to nighttime awakenings [52, 53].

9.5.1 Biological Factors

9.5.1.1 Vasomotor Symptoms

Vasomotor symptoms, also known as hot flashes and night sweats, are significantly associated with increased sleep disturbances in midlife women [34, 54, 55]. Kravitz et al. [34] and Polo-Kantola et al. [56] independently found that the experience of vasomotor symptoms doubles the risk of sleep disturbance in women in the menopause transition. It is generally believed that vasomotor symptoms produce arousals and awakenings from sleep, leading to fatigue, and, possibly, impaired performance [57]. As such, vasomotor symptoms have been strongly negatively associated with

sleep constructs including sleep efficiency, sleep quality, and nighttime awakenings. Women experiencing vasomotor symptoms also have a greater likelihood of receiving an insomnia diagnoses compared to women without vasomotor symptoms [45, 58, 59].

The investigation of vasomotor symptoms and sleep has used self-report methods (e.g., self-report questionnaires, interviews) as well as objective measures of vasomotor symptoms (physiological monitoring; [60, 61]. A number of epidemiologic studies have shown self-reported sleep disturbance including reduced sleep quality, unrefreshing sleep, and nighttime awakenings, to be associated with self-reported vasomotor symptoms [34, 54, 55, 62]. Research investigating sleep using objective measurement of vasomotor symptoms is more limited and has produced discrepant findings. Although vasomotor symptoms have been significantly correlated with increased objectively assessed waking episodes throughout the night [60], additional work has not replicated this finding. Additional research has found that vasomotor symptoms in the evening can impact sleep both positively and negatively [63], while other research has found no association between objective or subjective sleep and physiologically measured hot flashes [64]. A study by Thurston et al. [65] found that sleep disturbance in peri- and postmenopausal women was not significantly related to physiologically measured vasomotor symptoms. However, the study did find that more self-reported sleep hot flashes were associated with increased self-reported acute sleep problems [65].

Factors such as mood/affect, sensitivity to menopausal symptoms, and general health can impact the perception and reporting of vasomotor symptoms [66]. In addition, subjective reporting of hot flash quantity was unrelated to the number of hot flashes detected through objective measurement [66]. As such, subjective and objective measurement of vasomotor symptoms are interconnected, yet distinct measurements. Not all women who experience vasomotor symptoms will be bothered by or report them, highlighting the need to further understand the association between vasomotor symptoms and sleep. Importantly, subjective and objective measures of both vasomotor symptoms and sleep may provide distinct yet complementary information about women's sleep during the menopause transition.

9.5.1.2 Reproductive Hormones and Menopause Hormone Therapy

The female reproductive hormones estrogen and progesterone fluctuate during perimenopause with direct impact on sleep [42]. Receptors for these hormones are located in the multiple areas of the brain involved in sleep regulation: the cortex, hippocampus, hypothalamus, amygdala, basal forebrain, midbrain raphe nuclei, pituitary gland, locus coeruleus, and cerebellum [67, 68]. Sex steroids have also been found to influence the neurotransmitters that influence sleep [68]. Mechanisms linking hormone levels to sleep in the menopause transition include the influence of menopause hormone therapy on vasomotor symptoms, stress reactivity, and mood, as both estrogen and progesterone have been shown to influence regulation of body temperature, mood, and stress hormones [69].

Menopause hormone therapy has been shown to positively improve sleep disturbance when the disturbance is associated with vasomotor symptoms [70]. In

particular, a network meta-analysis including 43 randomized controlled trials with 32,271 women in the menopause transition from North America, Europe, South America, Iran, Central America, New Zealand, and Australia found significant associations between menopause hormone therapy and reduced sleep disturbance [70]. For participants with vasomotor symptoms, oral gabapentin showed the best effects on sleep disturbance followed by oral combined menopause hormone therapy, and bazedoxifene plus-conjugated estrogens. However, further research is needed to validate the benefits of oral combined menopause hormone therapy as the most effective approach as only one study to date has investigated this association [71]. The precise mechanism underlying this effect of oral gabapentin remains unknown. However, it is hypothesized that gabapentin may affect the thermoregulatory center in the hypothalamus and may possess nociceptive properties [72]. Regardless, the benefits of menopause hormone therapy for sleep in women experiencing vasomotor symptoms have led some organizations such as the Italian Association of Sleep Medicine to recommend menopause hormone therapy as a preventative as well as treatment approach to the management of menopausal-related sleep disorders [73] (see Chap. 6).

9.5.2 Psychological Factors

9.5.2.1 Mood/Mood Disorders

Mood disorders are also common in the menopause transition (see Chap. 10). Cross-sectional analyses demonstrate that up to 70% of perimenopausal women endorse depressive symptoms compared to 30% of premenopausal women [74]. Longitudinal studies also highlight an increased risk for depressive symptoms during the menopause transition [74, 75]. Women with a history of depression are almost five times more likely to have a diagnosis of major depression during the menopausal transition compared to premenopause [74]. In addition, women with no history of major depression are two to four times more likely to report depressed mood in the menopausal transition compared with those in the premenopausal stage [74, 76].

Women in midlife are also at increased risk for anxiety with 67% of women reporting feeling tense or nervous daily [52]. Peri- and postmenopausal women are at greater risk for anxiety compared to premenopausal women [77] with the menopause transition increasing the risk for onset or worsening of anxiety symptomatology [78]. A qualitative study of anxiety in the menopause transition found that anxiety during this period is a unique experience with variability in the onset, timing, and severity of symptoms [79].

An association between mood disorders and sleep problems has been demonstrated in midlife women. Sleep and mood demonstrate a bidirectional relation, whereas poor sleep can impact mood and vice versa [69, 80]. Poor sleep has been associated with higher levels of both anxiety and depression in this population [55, 74] with previous work highlighting that mental health concerns are often the most significant predisposing factors for sleep-related problems for midlife women [81].

9.5.2.2 Stress Reactivity

Stress is also associated with poor sleep in the menopause transition. Both high levels of stress and acute and mild stressors are associated with sleep disruption. In particular, high levels of stress have been associated with decreased sleep quality, and acute, mild stressors (e.g., daily hassles, mild psychological distress) are associated with increased arousal and subjective ratings of sleep disturbance [82]. Research suggests that low levels of estrogen characteristic of the peri- and postmenopause transition are associated with increased cardiovascular and hormonal responses to stress. In comparison, women treated with menopause hormone therapy have demonstrated reduced stress reactivity [83, 84]. In studies investigating sleep in the menopause transition, postmenopausal women had increased heart rate and blood pressure responses to stress compared with age-matched premenopausal women [85–87]. In addition, menopause hormone therapy significantly reduced cardiovascular and hormonal responses to psychological stress in postmenopausal women and was associated with better objective sleep quality (e.g., increased total sleep time, shorter time to fall asleep, and more slow-wave sleep) compared with postmenopausal women who were not taking menopause hormone therapy [86, 87].

9.5.3 Social Factors Influencing Sleep in the Menopause Transition

The menopause transition represents a biopsychosocial cultural transition, whereby women can experience a questioning and redefinition of *self*, through which they can evaluate past intra- and inter-relational self-concepts and find meaning in new ones [88–90]. Women's perceptions of the menopausal transition are largely shaped by their sociocultural background and contexts. For example, in the USA, the menopause transition is largely medicalized and marginalized, meaning that the focus is often on the treatment of physical symptoms rather than psychosocial experiences [91]. Internalization of societal stigma is associated with women's experiences of shame and silencing surrounding the menopause transition and menopausal symptoms [90]. Fueled by internalized social stigma and societal expectations of women, women in the menopause transition may choose to forego treatments such as menopause hormone therapy out of concerns informed by: menopause-informed discrepant self-images; internalized ageism and sexism; and upholding attractiveness and social status standards tied to maintaining a youthful appearance [88, 92, 93]. Alongside the impact of sociocultural factors on menopausal experiences, research suggests that women's prospective expectations of menopause directly influence psychological and physiological outcomes. Women in the menopause transition who hold expectations that it will be a negative event and/or experience higher levels of stress have been shown to be more likely to undergo a negative experience characterized by worse symptomatology [94, 95].

In addition to biological and psychological factors, there are notable social factors associated with midlife that may have a meaningful impact on sleep outcomes in women in the menopause transition. Indeed, one important social factor that may influence sleep for women experiencing menopausal changes is stress. Stress is a known contributor to a wide array of health outcomes such as slowed wound healing [96] and increased susceptibility to viral infections [97–99]. Among midlife women specifically, stress is shown to contribute to decreased health-related quality of life [100]. One form of psychosocial stress particularly relevant to the experiences of many women in the menopause transition is role stress. Role stress can be defined as stress that occurs as a result of maintaining multiple competing daily social roles and often results in poor overall wellness [101]. Women in midlife hold multiple roles, such as spouse and worker, simultaneously. Stress normally associated with holding such roles is amplified by the experience of menopausal symptoms. On top of multiple life demands, women in the menopause transition must work harder in order to ensure that their job performance is not impacted by symptoms such as hot flashes [102]. Alongside managing career and spousal roles, many women in midlife are in a generational stage characterized by multigenerational caregiving obligations. They must balance caring for their own parental figures as well as their children. This dual caregiving role has been associated with poor subjective health ratings [89]. Although there is limited research on the impact of psychosocial stress on health behavior outcomes specifically among women in the menopause transition, an emerging body of research suggests that role stress has important implications for sleep outcomes among women in midlife. In a longitudinal study of midlife women conducted over a 9-year period, higher levels of chronic stress (characterized by burden and acute experiences of distress) were associated with lower self-reported sleep quality, increased insomnia symptomatology reporting, and increased polysomnography-measured nighttime awakenings [103].

Race, ethnicity, and socioeconomic status are additional social factors that are meaningfully associated with sleep outcomes for women in midlife. Indeed, although role stress alone has been shown to influence sleep, race, ethnicity, and financial strain have surfaced as stronger risk factors for poor sleep outcomes. Marital satisfaction was strongly associated with better sleep outcomes for white women, with a weaker association for African American women [104]. Race or ethnicity differences may be partially accounted for due to additional allostatic load (chronic and repeated stress) associated with African American women's experiences of racial microaggressions and discrimination [105]. In a cross-sectional study of sleep in midlife women, African American women evidenced worse subjectively and objectively measured sleep compared with white women. Further, financial strain contributed to worse sleep quality and decreased sleep efficiency above race/ethnicity in the same sample [106]. Sleep health can serve as a universal target for intervention with the aim to improve overall quality of life for women in the menopause transition.

9.6 Assessment and Interventions for Sleep Disruption During the Menopause Transition

9.6.1 Assessment

It is important that sleep disruption be assessed beyond menopausal symptoms. Although vasomotor symptoms are readily established as both primary contributing and mediating factors of poor sleep in the menopause transition, sleep disorders such as insomnia, sleep-disordered breathing, and restless legs syndrome are similarly or, in the case of sleep-disordered breathing, more prevalent in women in the menopause transition compared with the general population [42, 48, 107, 108]. Notably these disorders are classified identically by both the *International Classification of Sleep Disorders* (*ICSD*) and American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*; see Table 9.2 for diagnostic criteria for these diagnoses). Best practice guidelines for the assessment of disordered sleep include a combination of polysomnography, actigraphy, and validated self-report measures [109]. Patients are evaluated clinically including obtaining a detailed sleep, medical, substance, and psychiatric history (see Table 9.3 for specific measures that are applicable for the assessment of insomnia).

Table 9.3 Assessment of insomnia based on Schutte-Rodin et al. [109]

Measure	Description
General medical/psychiatric questionnaire	Used to identify comorbid disorders
Epworth Sleepiness Scale or other sleepiness assessment Shaver and Woods 2015 [5, 39]	Identify daytime consequences of poor sleep and other comorbid disorders of sleepiness
Sleep Diary (see [110])	Daily sleep diary data should be collected prior to (e.g., for 2 weeks) and during the course of active treatment
Dysfunctional Beliefs and Attitudes about Sleep [111]	Evaluates sleep-disruptive cognitions such as "I must get 8 h of sleep to function well the next day"
Polysomnography (PSG)	PSG is typically done in a sleep lab or through at home testing. PSG records brain waves, oxygen blood levels, heart rate, breathing, and eye and leg movements. PSG is indicated when there is reasonable clinical suspicion of breathing or movement disorders, when initial diagnosis is uncertain, treatment fails, or violent or injurious behavior occurs with arousals
Actigraphy	Actigraphy is a wristwatch-like device that uses a built-in accelerometer to detect movements. Based on arm movements, sleep and wake periods can be identified to provide data on sleep, wakefulness, and activity patterns across the night or day. Used to characterize circadian rhythm patterns or sleep disturbances (optional)

9.6.2 Cognitive Behavioral Therapy for Insomnia

A number of interventions for improving sleep have been identified as efficacious for the treatment of menopause-related sleep disturbance. Cognitive behavioral therapy for insomnia (CBTi) is an intervention focused on sleep-related behaviors and cognitions. This psychobehavioral intervention is evidenced-based and is considered a gold standard for the treatment of sleep disturbance across many patient populations ([112, 113], a foundational article; [114]). CBTi is typically delivered by trained providers, such as psychologists and other mental health practitioners trained and experienced in administering CBTi (see the Society for Behavioral Sleep Medicine and World Sleep Society for examples), via in-person, telehealth, or online platforms. Additionally, Brief Behavioral Treatments for Insomnia (BBTi; [115]) and self-guided treatments (https://www.sleepio.com/) exist.

Often conducted face-to-face over four to eight weekly sessions approximating 60–90 min in duration, CBTi is a multicomponent treatment approach composed of psychoeducation on sleep hygiene, sleep scheduling interventions (e.g., sleep restriction and stimulus control), and cognitive restructuring often in conjunction with relaxation exercises (e.g., progressive muscle relaxation, imagery, meditation; [116]). Psychoeducation related to sleep hygiene commonly includes discussion of sleep disrupting and promoting bedroom factors, use and timing of substances (e.g., caffeine, nicotine, alcohol), exercise, and the timing and portions of evening meals [116, 117]. Stimulus control refers to associating the bed and bedroom with sleep and relaxation. Individuals experiencing insomnia often associate the bed and bedroom with an inability to sleep and non-sleep producing activities (e.g., watching tv, reading, worrying). As such, stimulus control procedures, such as getting out of bed if you cannot sleep within 15 min and only returning to bed when sleepy, are implemented in order to associate the known stimulus (bed or bedroom) with a new response (relaxation and sleep; [113]). Sleep restriction is a method geared toward limiting an individual's time in bed initially to reduce waketime so that the time in bed reflects actual time asleep [118]. Cognitive restructuring involves identifying, challenging, and changing maladaptive sleep and insomnia beliefs [117]. The five primary aims of the cognitive restructuring component of CBTi include: (1) addressing a misattribution of daytime consequences of insomnia; (2) correcting unrealistic sleep expectations; (3) decreasing performance anxiety and learned helplessness; (4) uncovering faulty beliefs about sleep-promoting practices; and (5) correcting misconceptions about the causes of insomnia [116, 117].

CBTi has shown efficacy in improving sleep-disrupting symptomatology in women experiencing the menopause transition. The use of CBTi in the treatment of menopause-related sleep disturbance is aligned with the best practice guidelines. Both the World Sleep Society and American Academy of Sleep Medicine (AASM) recommend that clinicians utilize "multicomponent cognitive behavioral therapy," or CBTi, alongside consideration given to an individual's preferences, for the treatment of insomnia in adults [119, 120]. Guthrie et al. [121] employed a 12-week

CBTi-Meno(pause) intervention characterized by provision of psychoeducation on menopausal symptomatology, depression, sleep, anxiety, sexual concerns, and relapse prevention as well as related cognitive and behavioral strategies. Their study focused on women actively experiencing insomnia tied to vasomotor symptoms. CBTi produced the greatest reduction in insomnia symptom reporting compared to yoga, antidepressant, and menopause hormone therapy treatment methods. CBTi has further been shown to produce the greatest decrease in insomnia symptomatology above yoga, escitalopram, exercise, estradiol, and venlafaxine among women in the menopause transition actively experiencing vasomotor symptoms [121].

9.6.3 Mindfulness

Mindfulness is an additional approach that has shown efficacy in ameliorating menopause-related sleep disruption. Mindfulness, employed solely or as a key component of CBTi, encourages attention to the present moment through bodily introspection. In a study of 110 women in the menopause transition, Carmody et al. [122] utilized an 8-week mindfulness-based stress reduction intervention designed to reduce how much women were bothered by hot flash symptoms and symptom intensity. The intervention trained women to engage in body scan, sitting, and stretching mindfulness exercises to improve bodily sensation awareness. Women in the intervention group showed significantly improved subjective sleep quality, among other outcomes of interest, compared to women in the control group [122]. See Tables 9.4 and 9.5 for examples of mindfulness exercises.

9.6.4 Pharmacotherapy

Both the World Sleep Society and AASM guidelines suggest that pharmacotherapy be considered for chronic insomnia only when patients are unable to participate in CBTi, symptoms remain despite CBTi, or as a temporary adjunct to CBTi [123].

Table 9.4 Mindfulness breathing practice provided by Rebecca Berke BCH

Step by step instructions:
• To begin, sit still and tall somewhere comfortably. Sit erect yet not stiff. Close your eyes and begin breathing through your nose. If more comfortable, then let the out breath go through your mouth, with soft lips.
• Then, inhale for a count of two, hold the breath in for a count of one, exhale gently, counting out for four, and finish by holding the breath out for a count of one. Keep your breathing even and smooth.
• If the 2–4 count feels too short, try increasing the breath lengths to four in and six out, or six in and eight out, and so on. But if longer breaths create any anxiety, there is no need to push yourself. The most important thing is that the exhale is longer than the inhale, not the absolute length of the breath.
• Set a timer and breathe this way for at least 4 min You will see a difference in your mood and how your body feels.

Table 9.5 Ocean mindfulness exercise provided by Rebecca Berke BCH

Script:
• Settle into nice seated position. Notice where you are being supported.
• Mind is linked to the ocean …. It is deep below the ocean's surface where it is calm and clear from this place below the surface.
• Whatever may be happening on the surface of the ocean
• It is calm, clear, and peaceful below.
• Notice the deep place below the surface … calm, clear peaceful.
• Notice the conditions of the surface whatever that may be choppy, storming, pounding of the waves …. Remaining in the place of calm below.
• Staying with the breath …. The mind deep beneath the surface …. In the mind is clarity … feeling calm beneath the surface.
• Enjoy the sensation of just riding the breath in and out … calm and peaceful below the surface.
• Waves and turbulence are like the activities of life.
• Below the surface of the ocean is calm.
• The mind is calm.

When utilizing pharmacologic agents to treat insomnia, it is important to achieve and maintain a balance between therapeutic effects and side effects. Indeed, choices regarding pharmacological treatment for insomnia should be made with attention to the following: symptom pattern, treatment goals, past treatment response(s), patient preference, cost, treatment availability, comorbid conditions, contraindications, concurrent medication interactions, and side effects. Further, the recommended sequence of medication trials for the treatment of insomnia is as follows: (1) short- or intermediate-acting benzodiazepine receptor agonists (BzRAs) or ramelteon, a melatonin agonist; (2) alternate short- or intermediate-acting BzRAs; (3) sedating antidepressants (e.g., trazodone, amitriptyline, doxepin, or mirtazapine); (4) a combination of BzRA or ramelteon and a sedating antidepressant; (5) other sedating agents such as anticonvulsant (e.g., gabapentin) or atypical antipsychotic medications [109, 124] (see Table 9.6). Although benzodiazepines such as temazepam have regulatory approval for insomnia, use is cautioned due to rapid development of tolerance and dependence and associated deleterious psychomotor, memory, and mood effects [124].

Hypocretin/orexin antagonists (e.g., suvorexant) is an additional pharmacological agent showing efficacy supported by European and World Sleep Society guidelines. Medications approved for sleep including benzodiazepines, BzRAs, barbituates, and suvorexant have possible rebound insomnia upon discontinuation and potential for abuse. They are subject to increased regulation in many countries. Notably, melatonin, valerian, phytotherapeutic substances (e.g., valerian and medicinal cannabis), trazodone, and antihistaminergic agents are not recommended for the treatment of insomnia due to low-quality evidence of safety and/or efficacy [109, 120, 123, 125].

The AASM makes pharmacological recommendations based upon whether a provider is treating sleep maintenance insomnia or sleep onset insomnia. For sleep

Table 9.6 Agents and sequence of pharmacotherapy for insomnia

Agent	Dosing considerations	Metabolism/ interactions	Common side effects	Insomnia-related information
Step 1. Short- or intermediate-acting benzodiazepine receptor agonists ("Z-drugs") or melatonin agonist (ramelteon)				
Zolpidem BzRa Immediate-release half-life 2.5–3.1 h AASM recommended sleep onset and sleep maintenance	Immediate- and modified-release Sublingual Oral spray	Drug interactions CYP3A4 metabolism. CYP3A4 inhibitors, e.g., impramine, rifampin, chlorpromazine, ketoconazole increase CNS effects	Next day drowsiness, nausea, dizziness Nightmares and agitation Anterograde amnesia in modified-release Abuse potential	Lower doses in women (5 mg orally immediate release, 6.25 mg orally modified-release)
Zaleplon BzRa Half-life 1 h AASM recommended sleep onset and sleep maintenance	Delayed absorption (2 h) and reduced exposure with high-fat or heavy meal	Aldehyde oxidase metabolism (fewer drug interactions)	Headache and dizziness Less residual sedation than zolpidem Abuse potential	Shorter half-life advantage in wakening after sleep In a single 6-week trial, no rebound insomnia
Eszoplicone BzRa Half-life 6 h AASM recommended sleep onset	Delayed absorption and reduced exposure with high-fat or heavy meal	CYP3A4 metabolism. Reduce dose in people using CYP3A4 inhibitors	Unpleasant taste, headache, somnolence, dizziness Abuse potential	Use only if 7 h sleep time available
Ramelteon Melatonin agonist Half-life 1–2.6 h parent drug, 2–5 h metabolite AASM recommended sleep onset	Delayed and reduced absorption if taken with food	Multiple metabolic enzyme pathways but use with caution in potent CYP3A4 inhibitors (ketoconazole) and CYP2C9 inhibitors (fluconazole)	Dizziness, nausea, fatigue No effect on balance; reduced risk of falls No cognitive or psychomotor effects	Rapid metabolism, not recommended for sleep maintenance

Table 9.6 (continued)

Agent	Dosing considerations	Metabolism/ interactions	Common side effects	Insomnia-related information
Step 2. Alternate agent from step 1				
Step 3. Sedating antidepressants, tricyclics with histamine (H1) antagonism; Serotonin modulators				
Amitriptyline TCA Half-life 10–26 h Not AASM recommended		Multiple metabolic enzymes, CYP450, 2C19, and 2D6	Drowsiness, dizziness, impaired coordination	Potentially inappropriate for use in older adults
Doxepine TCA Half-life 15.3 h parent drug, 31 h metabolite AASM recommended sleep maintenance	Increased absorption with delayed peak concentration with high-fat meal	Multiple metabolic enzymes, CYP450, 2C19, and 2D6	Headache and somnolence Anticholinergic effects Orthostatic hypotension	Minimal to no adverse effects with doses lower than depression treatment (3–6 mg) Long half-life with active metabolite may see increased next day effects with higher doses
Mirtazapine TCA with H1 antagonism Half-life 20–40 h Not AASM recommended		Multiple metabolic enzymes, CYP450, 1A2, 2D6, 3A4; active metabolite	Drowsiness, dizziness Anticholinergic effects	Most effective for insomnia at low dose 30 mg/day Long half-life with active metabolite may see increased next day effects with higher doses
Trazodone Serotonin modulator Half-life 3–6 h first phase 5–9 h second phase Not AASM recommended		CYP450, 3A4; active metabolite	Drowsiness, headache, dizziness Anticholinergic effects Orthostatic hypotension	Start at dose of 25–50 mg

(continued)

Table 9.6 (continued)

Agent	Dosing considerations	Metabolism/ interactions	Common side effects	Insomnia-related information
Step 4. Combination of a step 1 agent and sedating antidepressant				
Step 5. Anticonvulsant or atypical antipsychotic				
Gabapentin Neuroleptic Half-life 5–7 h		Excreted unchanged in urine	Drowsiness, dizziness, ataxia, peripheral edema	Start with low dose, 100–300 mg and titrate up if necessary Evidence supporting amelioration of vasomotor symptoms
Quetiapine Atypical antipsychotic, non-benzodiazepine Half-life 6–7 h		CYP450, 3A4 metabolism	Drowsiness, dizziness	
Olanzapine Atypical antipsychotic Half-life 21–54 h		Multiple metabolic enzymes; CYP450, 1A2, 2D6	Drowsiness, weight gain, hyperprolactinemia, extrapyramidal sx	Long half-life Lower doses in females, starting 2.5 mg/day

BzRa benzodiazepine receptor agonists, *AASM* American Academy of Sleep Medicine, *TCA* tricyclic antidepressant, *H1* histamine 1 receptor
Based on Lie JD, Tu KN, Shen DD, Wong BM. Pharmacological Treatment of Insomnia. P T. 2015;40(11):759–771

maintenance insomnia, the AASM recommends suvorexant, eszopiclone, zolpidem, temazepam, or doxepin. For sleep onset insomnia, the AASM recommends eszopiclone, zaleplon, zolpidem, triazolam, temazepam, or ramelteon. Pharmacologic treatments should be utilized with attention to outcome expectancies and appropriateness on a patient-by-patient basis [123].

9.6.5 Alternative and Complementary Treatment Approaches

Complementary and alternative medicine (CAM) approaches have shown limited efficacy in the treatment of menopausal sleep disruption, although they are not recommended by the World Sleep Society or AASM in light of low-quality evidence. Specific CAM approaches include herbal remedies, melatonin, acupuncture, and yoga [120, 126–128].

Approximately one in four individuals experiencing insomnia symptoms use CAMs [129]. Herbal remedies for insomnia including valerian, chamomile, kava, and wuling, while popular, have been shown to perform no better than placebo

[130]. Melatonin, a hormone produced by the pineal gland which facilitates sleep onset and regulation [124, 131], has been shown to decrease sleep onset latency, improve sleep quality, and increase self-reported morning alertness and overall sleep quality in individuals experiencing primary insomnia. As such, the French Medical and Research Sleep Society recommends a melatonin dosage of 2 mg, 1–2 h before bedtime, for a duration of 3 weeks to 3 months for primary, non-comorbid insomnia. Melatonin is advised to be used with caution in individuals with medical comorbidities such as autoimmune or liver disorders [132]. Acupuncture is believed to improve sleep quality through interaction with GABA pathways, increased melatonin production, and reduced heart rate variability and blood pressure via the autonomic nervous system. In a review of randomized controlled trials derived from both Eastern and Western databases Complementary and alternative medicine (CAM) acupuncture improved sleep quality compared to both pharmacologic treatments and placebo groups [133]. Efficacy of yoga as a treatment approach for insomnia is mixed. The effect of yoga on sleep quality ranges from no effect to significant positive changes in sleep quality among women experiencing insomnia when compared to controls [134, 135].

In a recent systematic review and network meta-analysis on CAM insomnia treatment approaches, although melatonin and meditative movement therapies (e.g., yoga) showed efficacy in improving sleep-onset insomnia, no CAM intervention included in the study (melatonin, light exposure, or exercise) outperformed CBTi [136]. Although CAM approaches have evidenced limited efficacy in ameliorating insomnia symptoms, for many these approaches are not enough. As such, these complementary approaches may be best used as add-ons to evidence-based practices for sleep disruption. A best practice integrative approach for addressing sleep concerns in women in the menopause transition includes proper assessment of underlying factors contributing to sleep disruption (e.g., sleep disorders, vasomotor symptoms, or psychosocial factors), employment of CBTi, and use of pharmacological agents, such as antidepressants and menopause hormone therapy, as indicated [137].

9.7 Conclusion

During the menopause transition, women experience worsened subjectively reported sleep and an increased risk for sleep disorders such as insomnia and sleep-disordered breathing. Sleep disruption in the menopause transition is multifactorial in origin—affected by biopsychosocial factors as well as differences across menopause stages. Although broader social expectations and systemic issues contribute to sleep disruption in the menopause transition, there are highly efficacious individual-level treatments for sleep during this period. The gold-standard treatment for insomnia is cognitive behavioral therapy for insomnia. Given the multiplicative and long-ranging consequences of poor sleep in midlife women, there is a need to better understand this experience and deliver efficacious treatment interventions to combat poor sleep.

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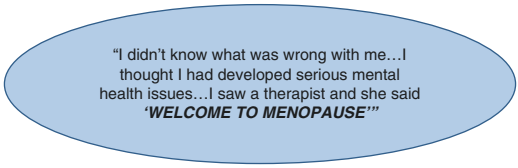
Mood and Cognition

10

Eleanor S. Bremer



10.1 Introduction

The menopausal transition typically consists of a variety of physical and emotional symptoms associated with the decline in ovarian hormones. Perimenopause has been identified as the period where women become vulnerable to psychological symptoms [1]. Many women report distressing symptoms including feelings of sadness, irritability, tearfulness, insomnia, fatigue, decreased memory and concentration, depression, anxiety, stress, and an overall decreased sense of well-being [2] (Table 10.1). Because these symptoms may be subtle and may begin long before the final menstrual period is anticipated, women may not be able to articulate what they are experiencing; they just know they "don't feel right."

Many of the epidemiologic studies of the menopause transition are limited to Western cultures and samples of white women which may limit generalizability to non-Western and non-white women [3]. Studies carried out in other cultures have used different measures, varied sampling methodologies, and varied population

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Table 10.1 Mood symptoms associated with the menopausal transition

• Feelings of sadness
• Irritability
• Tearfulness
• Insomnia
• Fatigue
• Decreased memory and concentration
• Depression
• Anxiety
• Stress
• An overall decreased sense of well-being

North American Menopause Society [2]

compositions in age and menopausal status resulting in inconsistent findings [3]. Without the use of consistent and comparable measures in cross-cultural comparisons of studies, interpreting, and comparing results is difficult [3, 4].

While we continue to look for similarities and consistencies across studies and populations, the vast array of differences and variances in menopausal symptoms brings us back to what we know. ***All women will experience the menopause transition in a unique way***. Some women will manage the transition with little or no symptoms while others will have a more challenging time [2]. Healthcare providers are uniquely positioned to help alleviate and avoid minor psychological symptoms through early education and by alerting women on what to expect during the menopause transition [2].

10.2 History of Mood Disturbance Related to the Female Endocrine Events

The lifetime prevalence of mood disorders in women has been reported to be at least twice that of men [5]. It has been suggested that the higher prevalence in women may be related to a number of factors including genetic propensity, exposure to stressful life events, hormonal fluctuations, or a combination of these factors [5]. Hormone fluctuations, especially periods of low estrogen, have long been associated with mood disturbance and are encountered over a woman's life in many stages including the menstrual cycle, pregnancy, lactation, postpartum, and perimenopause [6, 7]. It has been suggested that women may become vulnerable for depression beginning as early as puberty with the onset of cycling levels of estradiol and the effect it has on neurotransmitter and mood regulating systems [8, 9].

10.2.1 Menstruation

The menstrual cycle (Fig. 10.1) consists of two stages: the follicular and the luteal phases. On Day 1 of the cycle which is the onset of menstruation, the ovarian hormones estradiol and progesterone are both low, but estradiol levels begin to rise and

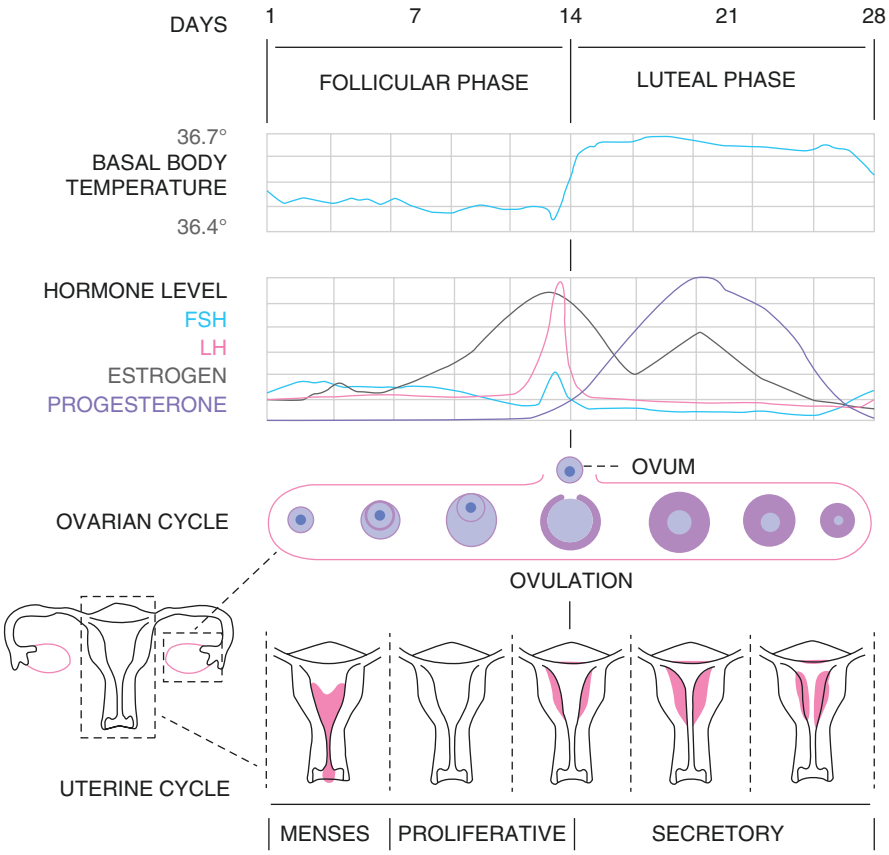


Fig. 10.1 Menstrual cycle. (Published under CC BY-SA 3.0. From Isometrik. Diagram of the menstrual cycle. MenstrualCycle2 en.svg. Used with permission)

peak just before ovulation. After ovulation, progesterone levels begin to rise and increase over the course of the luteal phase. Estradiol levels dip immediately with ovulation and then rise again with the midluteal phase progesterone. During the late luteal phase, progesterone and estradiol levels drop if pregnancy has not occurred and menses occurs followed by the next cycle [10] (see Chap. 4).

Many women experience premenstrual syndrome (PMS) defined as a combination of psychologic and physical symptoms occurring during the second half of the menstrual cycle (luteal phase) consistent with the lowest hormone levels prior to onset of bleeding [11]. As many as 40% of women will present with symptoms of PMS, and 5–8% of women will have extreme PMS symptoms [12]. Symptoms may include breast tenderness, abdominal bloating, edema of lower extremities, fatigue, mood swings, depression, and headache [11] (Table 10.2). The association with mood swings and low hormone levels has been confirmed by the use of hormone-free interval (HFI) combined contraception [13]. The more severe symptoms of PMS have been shown to be associated with *increased* levels of estrogen and

Table 10.2 PMS symptoms

• Breast tenderness
• Abdominal bloating
• Edema of lower extremities
• Fatigue
• Mood swings
• Depression
• Headache

Petraglia et al. [11]

decreased levels of progesterone (estrogen dominance) in the luteal phase of the menstrual cycle [11].

10.2.2 Pregnancy/Postpartum

Pregnancy and childbirth have a substantial impact on a woman's body and mind [5]. During pregnancy, estrogen and progesterone levels increase exponentially and then drop rapidly after delivery [7]. As a result, women may experience mood disturbance known as postpartum blues, characterized by symptoms of dysphoria, mood lability, crying, anxiety, insomnia, poor appetite, and irritability [5]. The peak in mood disturbance associated with postpartum blues usually occurs around the fifth day postpartum coinciding with the extreme hormonal fluctuations accompanying childbirth [5].

While episodic blues are common, more severe symptoms may develop and present as postpartum depression (PPD). The symptom profile of PPD resembles that of a major depressive episode experience (Table 10.3) [5]. In a recent systematic review and meta-analysis, Shorey and colleagues [14] examined the prevalence and incidence of postpartum depression among healthy mothers without prior history of depression [14]. All geographic regions were represented in the review with 13 studies reporting prevalence in Asia, six in Europe, nine in the Middle East, 13 in North America, five in South America, seven in Australia, and three in Africa. The overall results suggested that the incidence of PPD was 12% while the overall prevalence of PPD was 17% [14].

10.2.3 Perimenopause/Menopause

The menopause transition is a major hormonal event which includes both physical and psychological symptoms [5]. During the menopausal transition, ovarian hormones begin to fluctuate erratically which may contribute to a variety of mood symptoms such as irritability, fatigue, depressive, and anxiety symptoms [2, 7]. Women may also be experiencing physical symptoms such as hot flashes and insomnia that may exacerbate mood symptoms [7]. While estrogen levels are declining in

Table 10.3 *DSM-5* diagnostic criteria for major depression

The *DSM-5* outlines the following criteria to make a diagnosis of depression. The individual must be experiencing five or more symptoms during the same 2-week period and at least one of the symptoms should be either (1) depressed mood or (2) loss of interest or pleasure.
1. Depressed mood most of the day, nearly every day.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.
4. Agitation or slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).
5. Fatigue or loss of energy nearly every day.
6. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
7. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
8. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
To receive a diagnosis of depression, these symptoms must cause the individual clinically significant distress or impairment in social, occupational, or other important areas of functioning. The symptoms must also not be a result of substance abuse or another medical condition.

American Psychiatric Association [15]

perimenopause, progesterone levels are dropping at a disproportional rate, and by the time women reach menopause, progesterone levels are virtually undetectable (see Chap. 4). Progesterone and its metabolites have been recognized as playing a significant role in alleviating anxiety symptoms through the action at GABA-A receptors, producing an effect that is similar to those of anxiolytics [16]. It is hypothesized that this low progesterone-to-estrogen ratio may be associated with the development of anxiety symptoms.

If menopausal symptoms were solely based on the biologic decline of hormone levels, it would be reasonable to assume that some sort of a menopausal syndrome would be seen in most women and that menopause hormone therapy (MHT) would reverse the symptoms when they occur. However, menopausal symptoms are not universal which suggests that there is some other dynamic that is not yet well understood [17]. Mood symptoms experienced during the menopause transition are most likely the combination of interrelated psychosocial and biologic factors resulting in an experience that will be unique to each woman.

10.3 Timeline of Menopause Transition

The Stages of Reproductive Aging Workshop 10 (STRAW + 10) (Fig. 10.2) was developed to provide a system to offer consistency in identifying the stages of reproductive aging in women. The system suggests that perimenopause involves two phases: the early stage characterized by changes in menstrual cycle length of 7 days or more and the late stage characterized by the occurrence of amenorrhea for

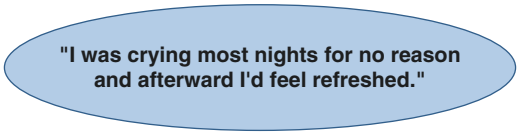
Menarche — FMP (O)

Stage	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	**REPRODUCTIVE**				**MENOPAUSE 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										
Menstural Cycle	Variable to regular	Regular	Regular	Subtle changes 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[67-69]

Fig. 10.2 STRAW + 10 staging system for reproductive aging in women. (Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ; STRAW + 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab. 2012 Apr;97(4):1159–68. Used with permission Oxford University Press)

60 days or longer [18]. Both the early and late stages of the menopausal transition are considered the perimenopause period which ends 12 months after the final menstrual period (FMP) [18]. Several studies have suggested that the perimenopausal stage is when women are most vulnerable to mood disturbance [19, 20]. During this transition phase, the associated hormone fluctuations may be responsible for mood symptoms such as irritability, fatigue, depressive, and anxiety symptoms [2, 21]. Toward the end of the late reproductive stage (LRS) and very early in the perimenopausal transition, many women may first begin to complain of worsening PMS symptoms [2]. Symptoms can begin in the LRS as early as age 35 years [2], and the perimenopausal period can last for an indefinite amount of time; however, the median time is 4 years [22].



10.4 Depression

The existence of a menopause-associated depression has been the focus of clinical and scientific debates for years [23]. Depressive symptoms can be described as psychological, physical, and/or social. The psychological symptoms may include feelings of low mood, sadness, hopelessness, low self-esteem, feelings of guilt, irritability, lack of motivation or interest, difficulty in making decisions, and thoughts of self-harm or suicide [24]. Physical symptoms may include changes in sleep, weight, and appetite, unexplained aches and pains, decreased energy, and loss of interest in sex. Social symptoms may include a decrease in productivity at work and a decrease in social activities and contact with friends [24]. Because there is no *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (*DSM-5*) definition of perimenopausal depression and terms such as psychological distress, stress, depressive symptoms, and clinical depression are often used interchangeably, it creates confusion and difficulty in making specific clinical and research assumptions [23]. Despite this confusion, there is substantial evidence supporting the view that depressive symptoms increase immediately before and during perimenopause [25].

The *DSM-5* Diagnostic Criteria for Major Depression (Table 10.3) may be a useful starting point in the evaluation process. The *DSM-5* is available in other languages as detailed in Table 10.4 below.

Depression in midlife is a complex phenomenon that may be influenced by a myriad of factors including vasomotor symptoms, sleep changes, age, ethnicity, lifestyle behaviors, and stressful life events [26]. Evaluating psychological symptoms across different cultures remains challenging because different instruments are used to measure symptoms, and the results are often varied and conflicting [27]. Also, at midlife, many women experience increased stressors such as caring for aging parents, children leaving home, changes in marital status, and medical illness often without support. The combination of mid-life stressors coupled with the menopausal transition may exacerbate depressive symptoms [2].

It has been well established that women with a previous history of depression are at higher risk for developing depressive symptoms during the menopause transition [23, 28]. However, for women with no history of depression, the risk of developing

Table 10.4 Availability of *DSM-5* in other languages

• According to the American Psychiatric Association, translations for the *DSM-5* collection are currently underway in 18 languages, including Chinese (Classical and Simplified), Croatian, Czech, Danish, Dutch, French, German, Greek, Hungarian, Italian, Japanese, Korean, Portuguese (Brazil and Portugal), Romanian, Serbian, Spanish, Swedish, and Turkish. https://appi.org/Products/dsm
• The International Statistical Classification of Diseases and Related Health Problems (ICD) developed by the World Health Organization covers a variety of medical conditions, not only psychological ones. https://www.who.int/standards/classifications/classification-of-diseases

depressive symptoms has been shown to be increased fourfold during perimenopause compared with her risk when she was premenopausal [25, 29]. In the Study of Women's Health Across the Nation (SWAN), Bromberger et al. [25] assessed major depression in midlife African American and white women transitioning through perimenopause and menopause and found that age, history of major depression, use of psychotropic medications, upsetting life events, higher body mass index, and frequent vasomotor symptoms were significant factors for experiencing major depression episodes [25].

In a similar study, Avis et al. [3] examined the diversity of the menopause transition experience by comparing symptom reporting in a large cross-sectional survey of women 40–55 years among racial/ethnic groups of women in the United States (white, African American, Chinese, Japanese, and Hispanic). Results demonstrated consistency suggesting a highly similar factor structure of symptoms across all racial/ethnic groups. They found psychological symptoms (feeling tense, depressed, and irritable) and psychosomatic symptoms (headache and stiffness) were all frequently reported symptoms. Japanese and Chinese women were less likely than the other groups to report symptoms. Age and educational level had a small negative association with psychosomatic symptoms, and women reporting better health and low economic strain (how hard it was to pay for basics) had lower symptoms levels.

Symptoms associated with perimenopausal depression may also present in combination with other menopausal-specific symptoms such as vasomotor symptoms (VMS) and sleep disturbance [26, 30]. To further complicate the issue, anxiety symptoms are common in women with depression [31] and anxiety is often associated with other adverse symptoms such as stress, depressive symptoms, and sleep disturbance [23, 31–34]. The "domino theory" hypothesizes that VMS and night sweats cause sleep disturbance which in turn may affect mood and cause psychological symptoms [28] (see Chap. 1). With the similarity and overlap of anxiety, depressive, and menopausal symptoms, it becomes clinically challenging to determine which symptoms are attributable to the menopause transition or which may be related to a psychological disorder [20, 23, 35].

The fluctuation in estradiol during the LRS and the menopause transition is strongly associated with the new onset of depressed mood in women with no history of previous depression [29, 36]. It has also been suggested that the fluctuation in hormone levels rather than absolute hormone levels may be a trigger for depressive symptoms in vulnerable women [23]. Furthermore, there seems to be a subset of women who have an increased sensitivity to the hormone fluctuation which makes them extremely vulnerable to experience symptoms related to the hormonal changes associated with perimenopause [37]. Studies have provided good evidence that there is a close reciprocal relationship between estrogen and serotonin neurotransmission, and the effect of estrogen on serotonin and noradrenaline neurotransmission has been linked to the development of depressive symptoms [9].

More recently, it has been suggested that perimenopausal depression may have a unique symptom profile with symptoms of depression presenting differently as compared to the premenopausal years [38]. Perimenopausal depressive symptoms

have been described as an "on/off" phenomenon characterized by periods of sadness or irritability that may last for a few minutes to hours and then spontaneously resolve, somewhat similar to premenstrual syndrome [28]. Gibbs et al. [38] conducted a study to explore whether mood and depressive symptoms differed during perimenopause compared to those in premenopause. The results revealed a significant difference in depressive symptoms between the two different life stages based on levels of depression, tension-anxiety, anger, fatigue-hostility, fatigue-inertia, and sleep disturbance. The perimenopausal group was found to have lower levels of depression and anxiety (milder mood presentation), but higher levels of anger-hostility (irritability) and higher levels of fatigue. The results support the existence of a unique perimenopausal depressive symptom profile [38]. The authors conclude that the identification of a unique mood symptom profile may help to gain a better understanding of perimenopausal depression and provide different targets for intervention to help improve quality of life for perimenopausal women.

10.5 Evaluation and Treatment

The North American Menopause Society (NAMS) and the National Network of Depression Centers Women and Mood Disorders Task Group (NNDC) collaborated and convened an 11-member expert panel in 2019 to review the literature on depressive disorders and depressive symptoms in perimenopausal and postmenopausal women [26]. The panel developed recommendations for the evaluation and treatment of depression during the menopausal transition which is discussed below in Sect. 10.6 of this chapter. The European Menopause and Androgen Society (EMAS) similarly reviewed the literature and developed a management/position statement for the management of depressive symptoms in peri and postmenopausal women which is outlined in Fig. 10.3 [39].

10.6 Evaluation

Evaluation should consist of identification of the reproductive stage, assessing for concurrent and overlapping menopausal symptoms such as hot flashes, night sweats, sleep disturbance, weight/energy changes, sexual disturbances, cognitive shifts; psychiatric symptoms (e.g., anxiety), and psychological risk factors (e.g., history of prior depressive episode, socioeconomic factors, psychosocial factors) [26] (Table 10.5). Currently, no menopause-specific mood disorder scale exists; however, there are several general validated depression screening tools such as the Patient Health Questionnaire-9 (PHQ-9) [40] which may be used to diagnose depression and grade the severity. Validated menopause symptom and health-related quality of life scales such as the Menopause Rating Scale (MRS) [41], Menopause-Specific Quality of Life Questionnaire (MENQOL) [42], Greene Climacteric Scale [43], and the Utian Quality of Life Scale [44] include mood items and may be useful

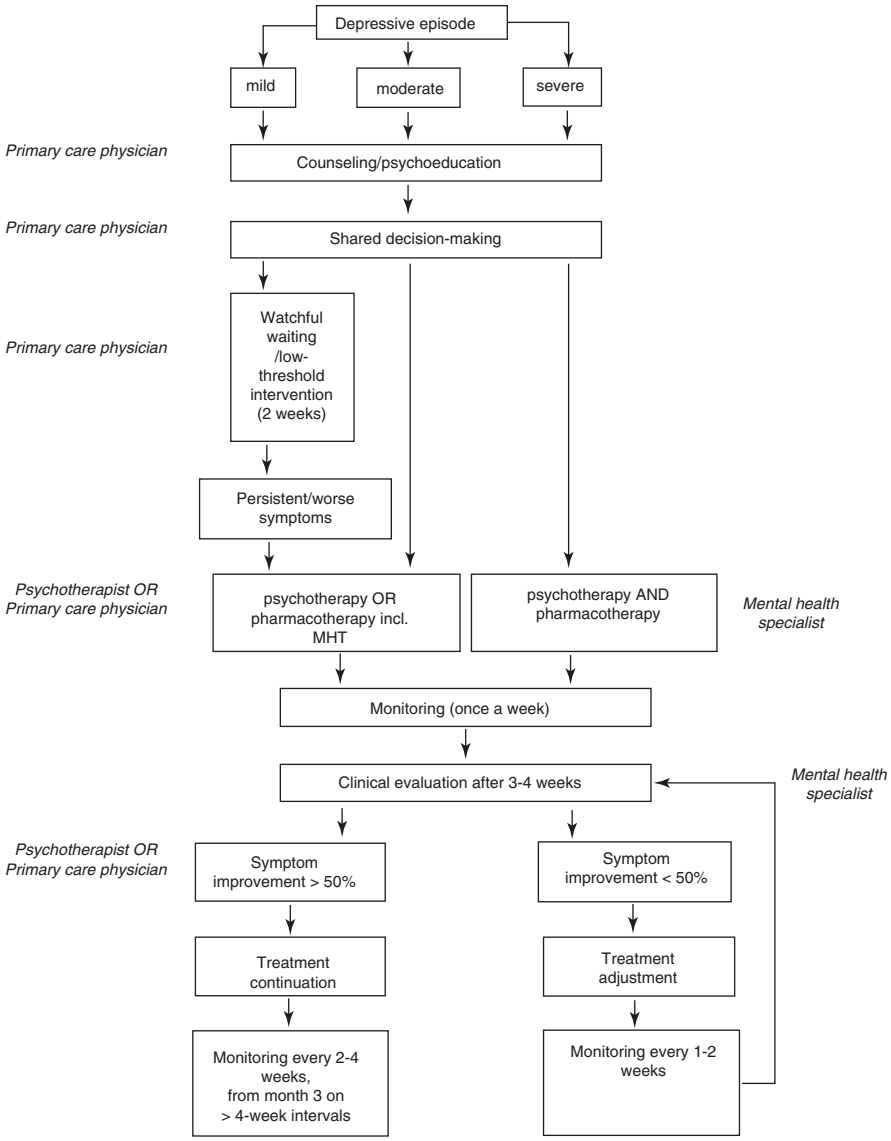


Fig. 10.3 EMAS algorithm for depression management in peri and postmenopausal women [39]

in helping to differentiate the contribution of menopause-related symptoms. Many of these validated tools are available in a variety of languages and are used internationally. Differential diagnoses should be considered during evaluation (Table 10.6), and women with severe depressive symptoms and/or suicidal ideations should urgently be referred and evaluated for a mood disorder [2].

Table 10.5 Evaluation of Depressive Symptoms (NAMS and NNDC Collaborative Group)

• Identification of the reproductive stage
• Assess for concurrent and overlapping menopausal symptoms (hot flashes, night sweats, sleep disturbance, weight/energy changes, sexual disturbances, cognitive shifts)
• Assess for psychiatric symptoms (e.g., anxiety)
• Evaluate psychological risk factors (i.e., prior MDD, socioeconomic factors, psychosocial factors)
• Use validated screening tools (e.g., PHQ-9) may provide a starting point for screening
• Use validated menopause symptom and health-related quality of life scales (e.g., MRS, MENQOL, Green Climacteric Scale Utian Quality of Life Scale); these tools include mood items and may be useful in clarifying the contribution of menopause-related symptoms
• Women with severe depressive symptoms and/or suicidal ideations should always be evaluated for a mood disorder

Maki et al. [26]

Table 10.6 Differential diagnoses of depression during the menopause transition

• Major depressive disorder (MDD)
• Subsyndromal depression
• Adjustment disorder
• Psychological distress
• Bereavement
• Depressive episodes associated with bipolar disorder
• General medical causes of depression

Maki et al. [26]

10.7 Treatment Options

Studies on treatment options for managing depression during the menopausal transition are scarce [9]. Treatment strategies should be multi-targeted considering all potential contributing factors, especially anxiety and sleep disturbance which are frequently associated with depression. Recommendations for treating depression include antidepressants, cognitive behavioral therapies (CBT), and psychotherapies [45] (Table 10.7).

10.7.1 Antidepressants

Existing data suggests selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) (including citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, and venlafaxine) are highly effective in treating depression in perimenopausal and postmenopausal women [2]. While SSRIs are considered first-line treatment for depression, many women may not respond or will discontinue therapy due to side effects such as sexual dysfunction, fatigue, and weight gain [2, 46, 47].

In a review of the literature on antidepressant medication nonadherence, Sansone and Sansone [48] reviewed five studies conducted in various countries (one in the

Table 10.7 Treatment options for depression in the menopause transition

Antidepressants (SSRIs/SNRIs)
• Citalopram
• Sertraline
• Fluoxetine
• Escitalopram
• Desvenlafaxine
• Duloxetine
• Venlafaxine
Estrogen-based therapy (not FDA approved to treat mood disturbance) may be considered as alternative or adjunct to antidepressant (especially if treating concurrent vasomotor symptoms)
• Extended cycle combined hormonal contraception may be used in the late reproductive stage (LRS)
Behavioral
• Cognitive behavioral therapies
• Psychotherapy

North American Menopause Society [2]

United States, one in Taiwan, two in Japan, and one in Korea) and found nonadherence rates for antidepressant medications in the psychiatric population ranged anywhere from 13% to 55.7% [48]. The authors similarly reviewed the literature on antidepressant adherence in primary care populations, and out of 13 studies (seven in the United States, one in Belgium, two in Denmark, one in France, one in Canada, and one in Spain), overall adherence rates ranged from 5.4% to 87.6%. After study limitations were acknowledged, including variations in methodology, the authors compared 6-month antidepressant nonadherence rates between the psychiatric populations (52%) and the primary care populations (46.2%), finding the percentages were very close [48].

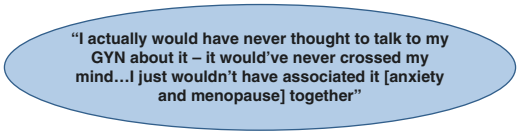
Determining the right medication for patients can be challenging. With recent advances and a push for precision and personalized medicine approaches, pharmacogenomic testing has become available in high-resource settings as a tool to help guide clinicians in prescribing medication that is unique to the patient's genetic profile [49]. Pharmacogenomic testing evaluates multiple genes and can provide a prediction of which medication(s) are most likely to be effective and/or carry the lowest risk of adverse effects, specific to the individual [50]. While more research is needed to assess the clinical benefit and cost effectiveness, pharmacogenetic testing is becoming increasingly less expensive and more readily available for use [50].

10.7.2 Menopause Hormone Therapy (MHT)

While there is evidence that estrogen therapy has antidepressive effects in perimenopausal women (with or without VMS); it should be noted that estrogen is not FDA approved to treat mood disturbance. Hormone therapy may be considered as an alternative or an adjunct to conventional antidepressants for the treatment of

perimenopausal depression, to effectively manage both VMS and depression with a single medication [28] and to augment a clinical response to antidepressants [26]. A progestin/progesterone should always be included with estrogen when a woman has an intact uterus [2]. Hormonal contraceptives in extended cycles may be useful for mood regulation as well as preventing unwanted pregnancy in women who are approaching the transition to menopause [26].

Behavioral treatment options include cognitive behavioral therapies (CBT) and psychotherapy which are discussed later in the chapter. The available evidence is insufficient for recommending botanical or complementary and alternative interventions for treatment depression related to perimenopause [2]. These treatments are discussed in more detail later in the chapter under Sect. 10.14.



10.8 Anxiety

As with menopausal depression, there is also debate on the existence of menopausal anxiety [23]. Even though anxiety is a mood symptom commonly experienced by menopausal women negatively impacting quality of life [19, 23], it has received far less attention in the research compared to depression. The term anxiety is used to describe a wide variety of symptoms. It may be used to describe features of panic (e.g., suddenly feeling fearful for no reason) or overall generalized anxiety (e.g., excessive worry or intense irritability) [19] or physical symptoms such as shortness of breath, tightness in the chest, racing heart. Because symptoms are so diverse and the terms anxiety, anxiety symptoms, and anxiety disorders are often used interchangeably, it increases the difficulty in drawing conclusions both clinically and in research [19].

Many of the validated tools used to measure anxiety are designed to measure generalized anxiety disorders in the general population such as the Hospital Anxiety and Depression Scale (HAD) [51], State-Trait Anxiety Inventory (STAI) [52], and the Generalized Anxiety Disorder 7 (GAD-7) [53]. Because these tools have not been designed to assess anxiety specifically related to the menopause transition, the interpretation may be somewhat limited [54]. Most of these tools are available in a variety of languages and are used internationally in research studies; however, they have not been validated for specific use in the menopausal population.

The *DSM-5* provides criteria for generalized anxiety disorder (Table 10.8) and may be a useful starting point in the evaluation process. As with depression, evaluation of anxiety symptoms should include identification of the reproductive stage, assess for concurrent and overlapping menopausal symptoms (hot flashes, night sweats, sleep disturbance, weight/energy changes, sexual disturbances, cognitive

Table 10.8 *DSM-5* criteria for generalized anxiety disorder

1. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
2. The individual finds it difficult to control the worry.
3. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):
   (a) Restlessness or feeling keyed up or on edge.
   (b) Being easily fatigued.
   (c) Difficulty concentrating or mind going blank.
   (d) Irritability.
   (e) Muscle tension.
   (f) Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
4. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
5. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
6. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance of flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

https://dsm.psychiatryonline.org/doi/full/10.1176/appi.books.9780890425596.dsm05

shifts), assess for psychiatric symptoms (excessive worry, panic, obsessive-compulsive symptoms), identify psychological risk factors (i.e., prior hx of depression or other psychiatric disorders, substance abuse, socioeconomic factors, psychosocial factors). Use validated screening tools (e.g., GAD-7) which may provide a starting point for screening and validated menopausal symptom and health-related quality of life scales (e.g., MRS, MENQOL, Green Climacteric Scale Utian Quality of Life Scale). These scales include mood items and may be useful in clarifying the contribution of menopause-related symptoms. Women with severe anxiety symptoms and/or suicidal ideations should always be referred to a mental health professional for evaluation (Table 10.9). Differential diagnoses for consideration are outlined in Table 10.10.

There are many hypotheses for causes of anxiety in menopausal women. Research has suggested there may be a role for age [55, 56], stress [8, 57, 58], depressive symptoms [29, 36], and sleep disturbance [23, 32, 59]. The prominence of VMS in the menopausal transition makes it difficult to determine whether there is an association with VMS and anxiety; however, several studies have found a strong association between hot flashes and anxiety, especially in women who were in the early menopausal transition [19, 60]. While several studies have found that anxiety symptoms are high in the perimenopausal period [19, 61], a more recent

Table 10.9 Evaluation of menopausal anxiety symptoms (NAMS and NNDC Collaborative Group)

• Identification of the reproductive stage
• Assess for concurrent and overlapping menopausal symptoms (hot flashes, night sweats, sleep disturbance, weight/energy changes, sexual disturbances, cognitive shifts)
• Assess for psychiatric symptoms (excessive worry, panic, obsessive-compulsive symptoms)
• Identify psychological risk factors (i.e., prior hx of depression or other psychiatric disorders, substance abuse, socioeconomic factors, psychosocial factors)
• Use validated screening tools (e.g., GAD-7) which may provide a starting point for screening
• Use validated menopause symptom and health-related quality of life scales (e.g., MRS, MENQOL, Green Climacteric Scale, Utian Quality of Life Scale). These scales include mood items and may be useful in clarifying the contribution of menopause related symptoms
• Women with severe anxiety symptoms and/or suicidal ideations should always be referred to a mental health professional for evaluation

North American Menopause Society [2]

Table 10.10 Differential diagnoses for anxiety symptoms during the menopause transition

• Anxiety disorder due to another medical condition
• Substance/medication-induced anxiety disorder
• Panic disorder
• Social anxiety disorder (social phobia)
• Somatic symptom disorder or illness anxiety disorder
• Separation anxiety disorder
• Posttraumatic stress disorder or acute stress disorder
• Anorexia nervosa or bulimia nervosa
• Obsessive-compulsive disorder
• Adjustment disorder with anxiety
• Bipolar disorders, depressive disorders, and schizophrenia spectrum and other psychotic disorder
• Nonpathological anxiety (characterized by worries that are more controllable or are not severe enough to cause clinically significant distress or impairment in functioning)

https://dsm.psychiatryonline.org/doi/full/10.1176/appi.books.9781585629992.mf03

study suggests there is a greater likelihood of increased symptoms of depression during perimenopause and increased symptoms of anxiety during postmenopause [21]. Nonetheless, in women without a history of depression or anxiety, the perimenopause and postmenopausal stages are associated with increased risk of greater symptoms of anxiety and depression compared to premenopause [7, 21].

10.9 Symptom Description

In a recent qualitative study, Bremer and colleagues [62] explored anxiety in menopause with a group of postmenopausal women in an effort to obtain a detailed description of the experience. A small sample of 20 women comprised of mostly white and African American women shared their experiences with anxiety. A

Table 10.11 Qualitative descriptions of anxiety symptoms in the menopause transition

"… you know the first awareness would be … not that I'm awake … it would be something's wrong and … feeling a little short of breath, having my heart beat too fast, being all sweaty and then becoming aware of what I was thinking … then that would cycle into stupid things, like … did I pick the right color to paint the living room … but that would seem like a life-threatening issue at 3:00 in the morning."
"a sudden creepy feeling … a distinct feeling that comes on suddenly like going from 0 to 60, feeling like something horrible has happened".
"You can't really put your finger on when, why, where, how or who … none of that … it just happens."
"… things were definitely different. I got very reactionary … when it … came … to my kids … I started thinking about worst-case scenarios … and end up getting all worked up over nothing … it's kind of like … a shock just going through my body that starts with this burning, tense, tightening sensation that starts in … my gut. I just kind of know something's wrong … you can feel the adrenaline just going right up into my head and by the time it got to my head, I'm like, 'something horrible has happened.' When it was done, it was all of a sudden, everything … it was like putting the genie back in the bottle."
"… right as I'm about to fall asleep, it's like I am struck with this … panicky … overwhelming dread."
"it's like your mind just won't turn off and then it's like oh wait … what if and what if and what if …."

Bremer et al. [62]

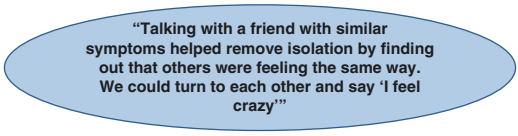
nuanced symptom profile was described with varied descriptions of anxiety symptoms that were new-onset in the menopause transition. Symptom descriptions included an exaggerated, over-reaction type of response to stressful situations which lasted from minutes to hours; some participants identified anxiety as a constant low-level background type of anxiety (feeling uneasy) that is present all of the time but is exacerbated by stressful situations. Severity of symptoms varied considerably from a sudden overwhelming, debilitating experience to a mild, annoying but manageable experience (Table 10.11).

Many experienced anxiety symptoms before going to bed or waking up in the middle of the night (many reporting waking up between 2:00 and 3:00 am) with racing thoughts, worries that included feeling a sense of loss of control and an overwhelming sense of dread or uneasiness. Most reported they could not identify a cause for the anxiety, and the unpredictable onset created the feeling of being out of control. Several participants described an exaggerated, over-reaction type of response to stress while others reported a stress response that was associated with conjuring unrealistic fears. Most of the women reported associated symptoms occurring with or triggering the anxiety including insomnia, hot flashes, night sweats, and stress.

In the Study of Women's Health Across the Nation (SWAN) [19], Bromberger et al. [19] examined the risk of anxiety during the menopausal transition. Pre and early perimenopausal women ($N = 2956$) of various race/ethnic groups living in the United States including white, African American, Chinese, Hispanic, and Japanese

were assessed over 10 years using a cluster of four symptoms of anxiety: irritability, nervousness or tension, feeling fearful for no reason, and heart pounding or racing. They found that women with high anxiety at baseline continued to have high anxiety through the menopausal transition; whereas, women with low anxiety at baseline were more likely to report high-anxiety symptoms at early-late perimenopause or postmenopause [19] Interestingly, women reporting frequent VMS had nearly triple the odds of anxiety compared with women reporting less frequent VMS. African American and Chinese women were significantly less likely than white women to have high anxiety symptoms. The researchers found that menopausal stage was significantly associated with high anxiety with symptoms peaking in late perimenopause but remaining elevated in postmenopause (with and without MHT use) [19].

Avis and colleagues [3] examined the menopause transition experience to determine the existence of a "universal menopausal syndrome." While there are a variety of symptoms commonly reported by menopausal women, the researchers questioned whether there is a single universal syndrome experienced by women. This cross-sectional survey of women aged 40–55 years included racial/ethnic groups of women in the United States (white, African American, Chinese, Japanese, and Hispanic) [3]. The authors looked at a grouping of symptoms (night sweats; stiffness or soreness in joints, neck or shoulders; headaches; hot flashes or flushes; forgetfulness; feeling tense or nervous; feeling blue or depressed; vaginal dryness; irritability or grouchiness; and heart pounding or racing) experienced by women as they progressed from premenopause to postmenopause. They aimed to evaluate the diversity of the menopause transition experience by comparing symptom reporting across various racial/ethnic groups. Results showed that across all five racial/ethnic groups, two consistent factors emerged. One of menopausal symptoms included hot flashes and night sweats and the other consisting of psychological and psychosomatic symptoms. Racial/ethnic differences in symptoms reporting showed white women reported significantly more psychosomatic symptoms (tense, blue or depressed, irritable, forgetfulness, and headaches) than other racial/ethnic groups. African American women reported significantly more vasomotor symptoms, and Japanese and Chinese differed the most from white women in that they were less likely to report symptoms. The authors concluded that these results support there is no universal symptom experience and that all women experience a variety of symptoms, and those symptoms are associated with individual and cultural influences (see Chap. 1).



10.10 Impact on Women, Their Partners and Families

The menopausal transition can be a stressful time for many women. It is important to remember that menopause is also a culture-related phenomenon. Different cultures will have differing attitudes toward menopause which may result in different psychological symptoms [63]. Healthcare providers will often focus on physical symptoms, such as hot flashes and genitourinary symptoms, overlooking the psychological symptoms and the emotional strain that may accompany the hormonal changes. Qualitative research is the ideal methodology to explore the complex phenomenon of the menopause transition. This methodology allows for the development of a more holistic, rich description of the phenomenon and will provide a greater understanding of the experience [64].

A recent meta-synthesis explored the qualitative menopausal experiences of Asian women and looked at possible differences in the experiences that may be related to acculturation in Asian women living in Western countries [65]. This analysis included 17 qualitative studies which included the United States ($n = 5$), India ($n = 2$), Iran ($n = 3$), Jordan ($n = 1$), Korea ($n = 2$), Singapore ($n = 1$), Taiwan ($n = 1$), Thailand ($n = 1$), and Turkey ($n = 1$). The inclusion criteria for eligible qualitative studies were study samples of women aged 40 years and above who were undergoing or had undergone natural menopause. Exclusion criteria were: (1) study samples of women who experienced premature menopause or underwent surgical menopause (i.e., hysterectomy, oophorectomy), (2) study samples of premenopausal women. The results provided insight into Asian women's attitudes and perceptions toward menopause, including emotional and physical experiences and how it affected their daily lives [65]. Five themes emerged: (1) perceptions and attitudes toward menopause, (2) physical and emotional experiences during the menopause transition, (3) changes in life and relationships, (4) needs and coping strategies, and (5) unique Asian experiences in Western societies.

The analysis revealed a wide diversity in perceptions and attitudes ranging from a neutral and accepting attitude, to a positive view looking forward to this new stage in life, to a negative perception viewing it as an illness or sign of aging. Interestingly, while the perceptions and attitudes of women were varied, physical and emotional symptoms were similar across most of the women's experiences. The commonly reported physical symptoms included hot flashes, vaginal dryness, headaches, fatigue, incontinence, insomnia, poor memory, body aches, feeling weak, decreased sexual desire, and declining physical appearance. In 82% of the studies, emotional symptoms reported included depression, worried and fearful of aging, disability, loneliness, loss of autonomy and increased dependence on others, irrational irritability, aggressiveness, and being short-tempered. The women felt that the emotional symptoms were amplified by insensitive and inconsiderate family members, including a lack of understanding and social support by their partners. Conversely, some of the women felt more relieved, relaxed, cleaner (not menstruating), and healthier during the menopausal period feeling that menopause brough maturity, wisdom, and experience, and it helped to improve the way they handled situations and accentuated their femininity.

Table 10.12 Qualitative descriptions of changes in life and relationships in menopausal women

"It is something very emotional, as if my brain commands me to fight with somebody. Actually, there is no reason to fight."
"My family was insensitive and inconsiderate. Although he is a teacher, my husband was insensitive too. That was distressing to me. For example, they were not considerate when I was irritable. They could not adjust to this period. When I spoke about this, they told me that everyone goes through this, it is not only you."
"Yes, I lost my sexual interest and I don't care. Just my husband's disappointment makes me stressed and I force myself …"
"That's why you hear many women saying that their husbands have extramarital affairs. I think part of it also has something to do with this."
"We're living like brother and sister now but this is not a problem for us."
"I am anxious; I can't stand my children and grandchildren when they visit,"
"I have no memory of anything to be able to talk with people, and I can't hold a conversation anymore."
"I forget everything; I even forget the order (Rakat) of my prayer" and "I can't pray because I'm unclean and impure (due to incontinence)."

Shorey and Ny [65]

In 65% of the papers, women expressed that physical and emotional changes had taken a toll on marital and family relationships (Table 10.12). Because of uncontrollable and increased irritability, it was reported that mothers scolded their children more frequently, and wives reported picking unnecessary fights with their husbands. Women employed outside of the home described being lethargic and tired, not having enough energy to manage their workload. On the other hand, in certain Asian cultures, the change in familial roles associated with menopause was viewed as an elevation of status and respect. With the freedom from heavy family responsibilities of tending to children and elders, women had more time for self-care and self-reflection.

In recent qualitative work with menopausal women in the United States, Bremer et al. [62] found similar results among women when they were asked how anxiety in the menopause transition had affected their lives (Table 10.13). The impact of menopausal experiences on women's lives highlights the need for the support of women during the menopause transition. Both individual and cultural differences create the need for individualized treatment approaches. By helping women through education, providing coping strategies and support, we can help to increase quality of life during the menopause transition [62, 65].

10.11 Spousal Support

Spousal support during the menopause transition may play a huge role in improving quality of life for menopausal women. A recent clinical trial conducted in Yazd, Iran, showed that educating men on menopause health not only promoted knowledge about menopause but demonstrated significant improvement in their wives' quality of life during the menopausal transition [66]. The authors further suggested

Table 10.13 Qualitative descriptions: how has anxiety in the menopause transition affected your life: a change of self

"I started noticing I just felt so full of fatigue and anxiety all the time for no reason—I would cry about night sweats—I would cry about weight gain."
"I wondered 'is this the new normal' 'is this the new me'? That would make the background anxiety ramp up."
"Prior to menopause, I was not anxious. My memory is worthless compared to the way it was before. This causes anxiety if I have to give a talk. Being anxious all of the time has created a sense of doubt—doubts I've never had before. It doesn't feel like me to be anxious."
"Being in menopause I feel am I attractive? Am I valuable to society? There's a feeling of being invisible to a certain degree."
"It was like I was a different person in how I reacted to things."
"I'm more abrupt with my children—my children interpret my anxiety as anger. I'm more short-tempered."
"I isolated myself a lot because I didn't want to have hot flashes (break out in sweat) around other people."
"It affected my desire to be around a lot of people because if I was too stimulated that made the anxiety worse—I'm a pretty social person. It was more I had no energy left for a meaningful conversation. It took extra energy to do basic things so I would often have nothing left over for leisure or enjoyable activities."
"If I know a situation is going to be anxiety producing … I will now purposely choose not to engage in the situation … I think I'm coming to a place where I know my threshold is. I wouldn't have done this in the past."
"Normal daily activities have become monumental requiring mindful attention instead of being able to multitask or be on autopilot like before menopause."
"… I don't know what to do with it [anxiety] once it comes on … I don't want to be like this … This is not who I am and I don't want this to be how people see me."
"It doesn't feel like me to be anxious … I'm not a worrier—so when I find myself worrying, I start thinking 'that's not me', 'that's not how I handle stuff' … I don't want to become an anxious person."

Bremer et al. [62]

that during a woman's menopausal transition, her spouse should be able to provide her with emotional support, exercise with her, learn relaxation techniques for serenity, prepare suitable foods based on her needs, accompany and encourage her to receive professional menopause symptom management, and establish a more intimate relationship and spend more time with her. They further concluded that the more support a woman receives from her spouse can help her better adapt to and deal with the changes caused by menopause [63] and spouses who have adequate knowledge about menopause-related health will be uniquely positioned to improve their partners' quality of life during this period [66].

A qualitative study on menopause described from the man's perspective was done in Istanbul, Turkey [67]. The aim of the study was to look at menopause from men's point of view to ascertain a better understanding of their perspective in an effort to improve care and support provided to menopausal women. The results of the study showed that men lacked basic knowledge of both menstruation and menopause. Most of the participants defined menopause as loss of fertility, increased weight, and loss of beauty. The most important concern voiced was the men's own

Table 10.14 Treatment options of anxiety in the menopause transition

- SSRIs, SNRIs, and anxiolytics are first-line medications used in the treatment of anxiety disorders.
- There is limited information on the efficacy of menopausal hormone therapy to treat anxiety in menopause [68, 69].
- Psychotherapy including cognitive behavioral therapy, mindfulness-based stress reduction, and relaxation and stress reduction therapies have been identified as therapeutic options for treating psychological symptoms associated with menopause including anxiety [2].
- There is no recommendation for herbs, vitamins, or supplements for the treatment of anxiety symptoms in menopausal women [70].
- Treatment options should be tailored around women's symptoms and treatment preferences.

sexual life. None of the men had heard of treatment for menopause symptoms and perceived any treatment as an effort for women to have children and continue to menstruate. The authors concluded that these results underscored the need to increase men's awareness of common physiologic and psychologic disturbances during the menopausal transition in order to create a more supportive environment for menopausal women.

10.12 Treatment

10.12.1 Anxiolytics

Treatment of anxiety disorders usually involves psychotherapy, medication, or a combination of therapies [2, 47] (Table 10.14). SSRIs, SNRIs, and anxiolytics are the first-line medications used in treatment of anxiety disorders [2, 47]. Although pharmacologic treatment for mood disturbances in menopausal women is common [2], there have been no placebo-controlled clinical trials specifically assessing the efficacy of SSRIs or SNRIs for the treatment of mood symptoms associated with the menopause transition as primary outcomes [71]. While SSRIs and SNRIs have been reported to provide limited symptom relief, they carry an extensive side effect profile, including sexual dysfunction, fatigue, and weight gain, which may actually exacerbate other menopausal symptoms [2, 47].

10.12.2 Menopause Hormone Therapy (MHT)

There is limited information available on the use of MHT in treating anxiety. To date, there are no studies that have evaluated the effect of MHT on anxiety symptoms in the menopause transition as a primary outcome [23]. In a double-blind, placebo-controlled randomized trial, Caan et al. [68] explored the efficacy of estrogen and venlafaxine on menopause-related quality of life and associated symptoms in white and African American postmenopausal women [68]. The study evaluated the effect of low-dose oral 17-β estradiol 0.5 mg/day and venlafaxine XR 75 mg/day

vs. placebo. The primary outcome in the study was the frequency of VMS and secondary outcomes included menopause-related quality of life, pain, depression, anxiety, and perceived stress. Results of the study showed neither treatment group (estradiol or venlafaxine) showed improvement compared with placebo with respect to changes in pain, depressive symptoms, or anxiety.

In an earlier trial, Demetrio et al. [69] investigated the efficacy of estrogen therapy for improving mood and anxiety in postmenopausal women and found that estrogen therapy was not associated with improvements in mood or anxiety symptoms [69]. Bremer et al. [62] interviewed two participants who were using MHT, and the participants reported that while the MHT provided improvement in vasomotor symptoms, their anxiety symptoms were still present. This experience is further supported in the literature by the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) [72]. Results showed vasomotor symptom relief resulting from treatment in each of the three estrogen-progestin treatment regimens versus placebo; however, postmenopausal hormone therapy did not affect self-reported anxiety symptoms.

10.13 Psychotherapy for Depression and Anxiety

Cognitive behavioral therapy (CBT), mindfulness-based therapy (MBT), and other types of supportive psychotherapy have been successful in treating several menopausal symptoms including anxiety [2, 47, 73–75]. It is well established that stress reduction is beneficial in managing mood symptoms associated with the menopause transition [57], and relaxation and stress reduction therapies have been identified as therapeutic options for treating psychological symptoms associated with the menopause transition including anxiety [2, 31].

10.13.1 Cognitive Behavioral Therapy (CBT)

Cognitive behavioral therapy (CBT) is a type of psychotherapy that helps patients assess and modify distorted, depression-promoting thoughts about themselves, their current situation, and their futures [26]. CBT is a psychological intervention that has been used to treat hot flashes, depression, and other menopausal symptoms [70]. Much of the research on CBT is focused on treating hot flashes; however, in a recent review, Johnson et al. [70] did find a small study assessing depression among Iranian women that provided some evidence to suggest that CBT may reduce mild depression in the menopause transtion [76].

Green and colleagues constructed a randomized controlled trial with 71 perimenopausal or postmenopausal women assessing the effects of CBT on menopausal symptoms which included depression and anxiety as secondary outcomes [74]. The results showed an improvement in depressive symptoms and sleep which indicates the use of CBT may be a safe and effective, nonpharmacologic intervention for menopausal women.

10.13.2 Mindfulness-Based Stress Reduction

Mindfulness-based stress reduction (MBSR) is a modality that uses a variety of exercises including acceptance and mindfulness meditation to develop awareness and acceptance of the present moment [70]. MBSR typically involves 8 weekly group classes, an all-day weekend retreat, followed by daily at-home practice [70] or individual training sessions. Much of the research with MBSR in the menopausal population is focused on VMS; however, a recent study in China examined the effect of MBSR on anxiety, depression, and sleep quality in perimenopausal women. The findings indicated that MBSR can effectively alleviate symptoms of anxiety and depression in perimenopausal women [77].

In another comprehensive meta-analysis, Khoury et al. [75] found MBSR is an effective treatment for a variety of psychological problems including reducing anxiety, depression, and stress; however, it was not specifically studied in the menopausal population [75]. Overall, the recommendation is that MBSR is generally safe and may reduce stress and anxiety and improve quality of life for menopausal women [70].

10.14 Complementary and Alternative Medicine for Menopausal Mood Symptoms

Many women seek complementary and alternative medicine (CAM) for the management of menopausal symptoms. There is some confusion with the terms "complementary," "alternative," and "integrative," and they are often used interchangeably. According to the National Center for Complementary and Integrative Health [78], if a non-mainstream practice is used together with conventional medicine, is it considered complementary; if a non-mainstream practice is used in place of conventional medicine, it is considered alternative. Integrative health care brings conventional and complementary approaches together emphasizing a holistic, patient-focused approach to health care and wellness.

Complementary health approaches include products such as herbs (botanicals), vitamins and minerals, and mind/body practices which include a large number of procedures or techniques administered or taught by a trained practitioner or teacher, including yoga, meditation, acupuncture, relaxation techniques, and hypnotherapy [78]. Johnson and colleagues [70] critically reviewed the most popular CAM interventions for menopausal symptoms. The review included randomized controlled trials (RCT) or systematic reviews, published in English, in peer-reviewed journals on or before March 31, 2017. The CAM interventions for menopause symptoms are divided into two broad categories: mind–body practices (e.g., cognitive behavioral therapy, relaxation, meditation) and natural products (e.g., herbs, vitamins, minerals, and dietary supplements) [70].

10.14.1 Acupuncture

Acupuncture techniques come from traditional Chinese medicine and involve insertion of small needles into the skin at certain points on the body, which are called acupoints. The foundation of acupuncture is a belief that diseases and symptoms occur because of disruptions in an individual's qi (or chi), or life force energy [70]. It has been difficult to compare results in studies on acupuncture because many use sham acupuncture as a control. An increasing number of studies show that the "sham" acupuncture does have some therapeutic effects; therefore, it cannot be considered useful as a placebo control [2]. Many of the studies using acupuncture in menopausal women are aimed at addressing VMS, leaving a paucity of research addressing acupuncture and mood symptoms in menopausal women.

Li and colleagues [79] systematically evaluated meta-analyses and systematic reviews of acupuncture as a treatment for anxiety [79]. They concluded that while most of the reviews suggested the acupuncture group was more effective than the control group in treating anxiety, the methodological quality of the reviews and the quality of evidence were low [79]. In an integrative review [80], it was concluded that acupuncture may be a promising treatment for anxiety; however, it was also noted that there needs to be improvement in the methodological quality of the research. In a recent randomized controlled trial evaluating acupuncture in menopause symptom management, Avis et al. [81] found that acupuncture was effective on VMS and quality of life-related measures such as sleep, anxiety, and depressive symptoms [81]. In comparing their results to studies using SSRIs and SNRIs, they concluded that while the SSRIs and SNRIs may be effective, they can have adverse side effects and further concluded that acupuncture use can have a positive benefit on reducing VMS and improving sleep and other symptoms related to quality of life [81].

10.14.2 Yoga

Yoga originated from Hindu disciplines, but many forms of yoga have emerged as its popularity has grown [70]. In research studies, it has become difficult to draw conclusions about the efficacy of yoga due to the high variability of use of yoga for various symptoms and inconsistencies between the types of yoga being used [70]. A systematic review and meta-analysis on yoga for menopausal symptoms found that yoga compared to no treatment was effective in reducing menopausal symptoms, including psychological symptoms [82]. The review included 13 RTCs including USA, Brazil, Germany, Indian, China, and Korea. The results of both of these reviews recommend that yoga has been determined safe and effective for psychological symptoms and may be recommended as an adjunct intervention for menopausal women [70, 82].

10.14.3 Daily Exercise

The benefits of physical exercise for overall well-being are well established, in terms of both improving health and reducing stress. A review evaluating CAM treatment for menopausal symptoms found that current research results on exercise are conflicting largely due to low quality of evidence [83]. Stojanovska et al. [84] reviewed the use of exercise as an alternative treatment for menopausal symptoms and found exercise as an intervention has been shown to have a positive impact on menopausal symptoms, depression, and quality of life. A recent study conducted in Iran found that nutrition education and aerobic exercise demonstrated an improved quality of life in menopausal women [85]. Regular exercise during the menopause transition and in postmenopause can help with preventing weight gain, strengthen bones, alleviate stress, decrease the risks of disease, and improve quality of life [84]. More importantly, exercise is safe, inexpensive, and readily available (see Chap. 13).

10.14.4 Herbs, Vitamins, and Supplements

Many herbal products, vitamins, and supplements are used for the purpose of reducing vasomotor symptoms associated with the menopause transition; however, there are a few herbal supplements that have been investigated for the treatment of mood and anxiety symptoms in perimenopausal and postmenopausal women [70, 83, 86, 87]. While herbal products are frequently used, there is no consistent evidence supporting efficacy and safety [70]. Johnson et al. [70] found that the evidence is mixed regarding the efficacy of these products, and there are some safety concerns with use. Inconsistencies in results are attributed to the small number of well-conducted studies, poor methodologies, and the heterogeneity of studies which limits interpretation [86]. Additionally, there are some studies demonstrating effects similar to placebo, meaning that there is unclear or conflicting evidence for the effectiveness of most of these treatments [83]. In summary, there is insufficient evidence of safety and efficacy to recommend most forms of herbs, vitamins, and supplements. It is extremely important that healthcare providers make sure that patients are provided with information about the risks and benefits of using these products to treat menopausal symptoms [70] (see Chap. 8).

Kava rhizome (Piper methysticum) is an herb that is used to treat anxiety, hot flashes, and sleep disturbance [2]. While kava has been shown to be effective in reducing anxiety [86, 87], there are significant safety concerns. Kava has been linked with cases of severe hepatotoxicity, including active liver failure, cholestatic hepatitis, and cirrhosis of the liver. As a result, some countries (Canada, United Kingdom, Germany, Australia) have banned kava supplements; however, kava is still available in the United States. Given the safety concerns, the North American Menopause Society suggests it may be advisable to avoid use of kava altogether [2].

St. John's wort (Hypericum perforatum) has demonstrated efficacy for mild depression and has been utilized for depressive symptoms associated with the menopause transition [2, 83]. In a meta-analysis, Liu et al. [88] found a significant difference in depressive symptoms following treatment with St. John's wort. While there is evidence of efficacy, there is also significant concern about the safety of St. John's wort especially concerning herb–drug interactions. St. John's wort may interact with some prescription medications, especially with antidepressant drugs, producing serotonin syndrome [83] and should be used with caution. There is also a strong interaction with combined hormonal contraceptives [89] and cyclosporine, digoxin, indinavir, and warfarin [90].

Valerian (Valeriana officinalis) is an herb that is primarily used to treat nervousness and insomnia and is recognized by the German health authorities and the World Health Organization [2]. It is suggested that valerian acts by modulating gamma-aminobutyric acid (GABA) neurotransmission, giving it sedative, anxiolytic, and antidepressant properties [83]. In a recent review, Moore et al. [83] found insufficient evidence for valerian use in treating insomnia or VMS. In a unique Internet-based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia, respectively, Jacobs et al. [91] recruited participants from 45 states within the United States and found that neither kava nor valerian relieved anxiety or insomnia more than placebo [91].

10.15 Association of Cognitive Changes and Dementia with Menopause

According to the Alzheimer's Association, in the United States 13.8 million people aged 65 years and older are projected to have Alzheimer's dementia by 2050 and almost two-thirds of Americans with Alzheimer's disease are women [92]. A gradual decline in some cognitive functions is expected to occur with linear aging beginning midlife, around the age of 50 years [93, 94]; however, more subtle changes may begin as early as the third decade of life [93]. Some cognitive changes that are commonly associated with aging include increased difficulty recalling newly learned lists, names, and other verbal information; slower rate of learning, decreased ability to perform newly learned complex taxes and shortened attention span [94].

Modest changes in memory, processing speed, and organizational skills begin well before midlife; however, they can become more pronounced during the menopause transition [93]. The Penn Ovarian Aging Study [95] and the SWAN Study [96] both found a modest verbal and memory decline supporting the view that some of the cognitive problems that women experience at midlife may be attributable to the menopause transition [93]. Many women complain of cognitive changes during the menopause transition including "brain fog" that involves difficulty remembering and concentrating [93]. It remains unclear whether women who have cognitive difficulties during the menopause transition are at greater risk for cognitive

impairment later in life [94]. For most women, it is not likely that cognitive function will worsen in postmenopause beyond what is expected with normal aging [94].

In the Study of Women's Health across the Nation (SWAN), Gold et al. [97] found complaints of forgetfulness were at rates of 42.0% in postmenopausal women, 44.8% in late perimenopausal women, 44.0% in early perimenopausal women, and 31.2% in premenopausal women. Additionally, forgetfulness was highest in Hispanic women (46.0%), African American women (43.0%), and Chinese women (40.5%) and lower in white (35.2%) and Japanese (33.0%) women [97]. Many women will be concerned as to whether these changes are related to aging or menopause or whether they may be associated symptoms of Alzheimer disease or other cognitive disorders. Because of the overlap with linear aging and menopause, it remains unclear whether menopause-related cognitive changes are transitional or may persist or worsen in the menopause transition.

Mosconi and colleagues [98] used a multi-modal neuroimaging study to evaluate 182 women; 40–65 years old to look at the effects of the menopause transition on the brain. The study used an age-matched male group to ascertain whether the effects were potentially related to the menopause transition vs. chronological aging. The findings demonstrated that the various menopausal transition stages (premenopause, perimenopause, postmenopause) had differing effects on brain structure, connectivity, and energy structure involving brain regions responsible for higher-order cognitive processes, concluding that these effects were specific to menopausal endocrine aging rather than chronological aging. It was suggested that brain biomarker stabilization in postmenopause was potentially an adaptive compensatory process. It was noted that amyloid-beta deposition was more pronounced in perimenopausal and postmenopausal women carrying apolipoprotein E-4 (APOE04) genotype, which is the major genetic risk factor for late-onset Alzheimer's disease. This study supports that the menopause transition is a dynamic neurological transition as well as a reproductive transition that significantly impacts structure, connectivity, and metabolic biomarkers in the brain [98].

In 2014, the World Dementia Council (WDC) requested the Alzheimer's Association evaluate and report on the state of the evidence regarding modifiable risk factors for cognitive decline and dementia [99]. The WDC is comprised of experts from a wide range of disciplines around the world (Canada, France, Germany, Italy, Japan, Russia, the United Kingdom, and the United States) to provide global leadership on dementia. The Alzheimer's Association evaluated previous reviews, meta-analyses, as well as assessing the types, numbers, and strength of individual studies. The Association concluded there is sufficiently strong evidence to support regular physical activity and management of cardiovascular risk factors to reduce the risk of cognitive decline and risk of dementia. Additionally, evidence suggests a healthy diet, and lifelong learning/cognitive training may reduce the risk of cognitive decline [99].

In 2004, the Women's Health Initiative Memory Study (WHIMS), a large, randomized, double-blind, placebo-controlled clinical trial examined whether postmenopausal hormone therapy (estrogen alone or estrogen plus progestin) would reduce the risk of dementia in healthy women aged 65–79 years [100]. Findings of

this study showed an increased risk of dementia and mild cognitive impairment (MCI) with MHT, concluding that the use of MHT to prevent dementia or MCI in women 65 years and older is not recommended [100]. A review of nine randomized clinical trials (United States, Taiwan, France, China, and Norway) of estrogen-containing MHT in Alzheimer's disease patients suggest that MHT does not improve cognitive symptoms of women with Alzheimer's disease [101].

A recent study by Rahman et al. [102] investigated sex differences in late-onset Alzheimer disease (AD) [102]. The study examined multiple variables including age, education, apolipoprotein E (APOE) status, family history, depression, diabetes, hyperlipidemia, thyroid disease, menopause, and lifestyle risk factors which included smoking, diet, exercise, and intellectual activity. Results showed that second to female sex, menopausal status was the predictor most consistent and strongly associated with observed brain biomarker differences.

Further, a regression analysis showed that the menopause transition was the strongest predictor of the observed sex-related brain AD abnormalities. The AD biomarkers were influenced by MHT use with generally more favorable biomarker outcomes in the MHT users compared to nonusers. The authors concluded that their findings support the idea that the optimal window of opportunity for the prevention of Alzheimer disease in women is early in the endocrine aging process [102]. The authors further acknowledged that the effects of MHT on dementia risk remain controversial, and more research in this area is needed.

The "timing" or "critical window" theory that suggests MHT initiated at a younger age (perimenopausal or early postmenopausal period) may be neurocognitive protective and may reduce the risk of Alzheimer's disease. This hypothesis is supported by observational research but is not addressed by clinical trial data [101, 103]. A large prospective cohort study conducted in Finland found no strong evidence for an association between post MHT use and AD or dementia, although a protective association between long-term (>10 years) self-reported use of MHT and AD was observed. This finding indirectly favors the effectiveness of MHT if started in the early postmenopausal period (critical window theory) [104].

Henderson et al. [105] conducted the Early vs. Late Intervention Trial with Estradiol (ELITE) to test the timing hypothesis. The primary research question for the cognitive assessment was whether estradiol initiated within 6 years of menopause affected verbal memory differently than estradiol initiated 10 or more years after menopause [105]. The authors hypothesized there would be a change in verbal episodic memory that would differ between groups, with a better performance predicted for women in early postmenopause using estradiol but not for women in the late postmenopause group. The results failed to confirm the timing hypothesis; reporting estradiol initiated within 6 years of menopause did not affect verbal memory, executive function, or global cognition differently than estradiol begun 10 or more years after menopause. The study included Asian, white, Black and Hispanic women, and the authors did not identify any subgroups of women in which the estradiol improved or impaired cognitive function.

Table 10.15 Evaluation of cognitive complaints

• Are complaints associated with normal aging process?
• Interview a family member, friend, spouse
• Obtain a detailed history assessing for functional impairment/evidence of memory loss
• Investigate family history of dementia beginning before age 60 years
• Assess cognitive function (e.g., Mini-Mental State Exam)
• Assess alcohol, substance abuse, medications (e.g., sleeping pills, sedatives, antidepressants, anxiolytics, antihistamines)
• Is there a history of sleep apnea?

Maki and Henderson [93]

10.16 Evaluation

Evaluation begins with ruling out whether cognitive complaints are associated with the normal aging process or signify a different etiology. Other factors such as alcohol, substance abuse, medications (e.g., sedatives, antidepressants, anxiolytics, antihistamines) should be assessed. Obstructive sleep apnea is also associated with cognitive difficulties and, if suspected, should be evaluated at a specialized sleep center [93] (see Chap. 9).

The evaluation may include interviewing a family member, friend or caretaker; a detailed history assessing for functional impairment and evidence of memory loss. It should be noted that typical cognitive aging does not impair one's ability to function adequately at work and home. Memory loss is a hallmark feature of Alzheimer disease. A family history of dementia beginning before age 60 should also raise suspicion for Alzheimer disease [93]. There are several tools available to assess cognitive function, one of the most common is the Mini-Mental State Exam. This test can easily be administered in the clinician's office, and if there is a concern of cognitive decline, more comprehensive testing can be performed with referral to a neuropsychologist [93] (Table 10.15).

In summary, healthcare providers should be aware that memory, processing speed, and organizational skills may modestly decline with normal aging [93]. In the absence of concerning findings in the history and physical examination, clinicians can reassure patients that cognitive symptoms are common and may be associated with the menopause transition, are self-limiting, and are not known to lead to dementia in later life [93].

10.17 Treatment

Prevention All patients should be advised to stay physically and mentally active; maintain a healthy social network; reduce and treat cardiovascular risk factors (e.g., hypertension, diabetes, hyperlipidemia), stop smoking, improve nutrition (e.g., Mediterranean diet), and consume alcohol in moderation [2, 93] (Table 10.16).

Table 10.16 Treatment of cognitive complaints

• Stay physically and mentally active
• Maintain a healthy social network
• Reduce and treat cardiovascular risk factors (e.g., hypertension, diabetes, hyperlipidemia)
• Stop smoking
• Improve nutrition (e.g., Mediterranean diet)
• Moderate alcohol consumption
• Menopause hormone therapy is not approved nor recommended for the prevention or treatment of age-related cognitive decline or dementia

Maki and Henderson [93], North American Menopause Society [2]

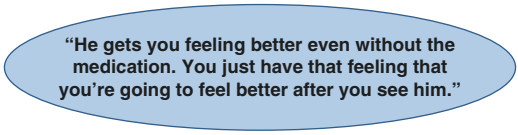
Menopause Hormone Therapy Menopause hormone therapy (MHT) is neither approved nor recommended for the prevention or treatment of age-related cognitive decline or dementia [2, 93].

In its 2017 position statement on the use of hormone therapy[1], The North American Menopause Society confirms that MHT is not recommended at any age to prevent or treat a decline in cognitive function or dementia; caution should be taken initiating continuous combined CEE and MPA in women >65 years old; MHT in the early natural postmenopause period has neutral effects on current cognitive function, and only limited information (observational studies) is available for support of the critical window hypothesis of MHT in Alzheimer disease prevention [106].

Ginkgo (Ginkgo biloba) is an herb that has been used primarily to treat cerebral function disorder, including cognitive decline and slow the process of neurodegenerative disorders including Alzheimer's Disease [2]. It is hypothesized that Ginkgo acts by dilating blood vessels, reducing blood viscosity, and modifying neurotransmitters and acts as a potent antioxidant [2]. A recent systematic review and meta-

[1] This NAMS position statement has been endorsed by Academy of Women's Health, American Association of Clinical Endocrinologists, American Association of Nurse Practitioners, American Medical Women's Association, American Society for Reproductive Medicine, Asociacion Mexicana para el Estudio del Climaterio, Association of Reproductive Health Professionals, Australasian Menopause Society, Chinese Menopause Society, Colegio Mexicano de Especialistas en Ginecologia y Obstetricia, Czech Menopause and Andropause Society, Dominican Menopause Society, European Menopause and Andropause Society, German Menopause Society, Groupe d'etudes de la menopause et du vieillissement Hormonal, Healthy Women, Indian Menopause Society, International Menopause Society, International Osteoporosis Foundation, International Society for the Study of Women's Sexual Health, Israeli Menopause Society, Japan Society of Menopause and Women's Health, Korean Society of Menopause, Menopause Research Society of Singapore, National Association of Nurse Practitioners in Women's Health, SOBRAC and FEBRASGO, SIGMA Canadian Menopause Society, Societa Italiana della Menopausa, Society of Obstetricians and Gynaecologists of Canada, South African Menopause Society, Taiwanese Menopause Society, and the Thai Menopause Society. The American College of Obstetricians and Gynecologists supports the value of this clinical document as an educational tool, June 2017. The British Menopause Society supports this Position Statement.

analysis of randomized controlled trials explored the effectiveness and safety of Ginkgo biloba in treating mild cognitive impairment and Alzheimer's disease [107]. After critical review, the authors found inconsistent findings attributed to limited sample sizes and methodological quality of the trials and concluded that while Ginkgo biloba maybe potentially beneficial for the improvement of cognitive function for patients with mild cognitive impairment or Alzheimer's disease more research is needed to confirm efficacy and safety [107]. Another review by Roland and Nergard [108] found that there is no convincing evidence that ginkgo is effective for treating cognitive impairment or dementia, and there is some concern that the ginkgo leaf extract may increase the risk of bruising and bleeding through potential interactions with anticoagulants and antiplatelet drugs [108].



10.18 Role of the Healthcare Provider

It is so important for clinicians to understand the complexity of menopausal symptoms and to take the time to adequately assess all symptoms, provide individualized treatment options, and recognize when further intervention is necessary [109]. Primary care clinicians and associated allied healthcare clinicians may be frontline providers positioned to initiate care in treating mood disorders experienced by menopausal women.

It is extremely important for healthcare providers to remember the value and the power of the patient–provider relationship [110]. The relationship between a woman and her healthcare provider can create a powerful healing connection [110]. Menopausal women will benefit from reassurance and emotional support, and education and anticipatory guidance should be considered as first-line interventions. Not only can education alert patients to the potential symptom experience, but it can empower patients and engage them as partners in their care (see Chap. 2).

As women move through the menopausal transition, regular visits to a healthcare provider can provide opportunities to educate and reassure patients which may help to decrease anxiety and fears associated with the menopause transition [2]. These visits should encompass a detailed medical history, physical examination, laboratory testing (when indicated), and other age appropriate testing and screening [2]. The examination should be tailored to the individual woman and her individual experience of the menopause transition, including physical and psychological changes she may be experiencing.

Ashkenazy and Peterson [111] developed a patient-centric tool to encourage discussion of symptoms encountered with the menopause transition (Fig. 10.4). PAUSE

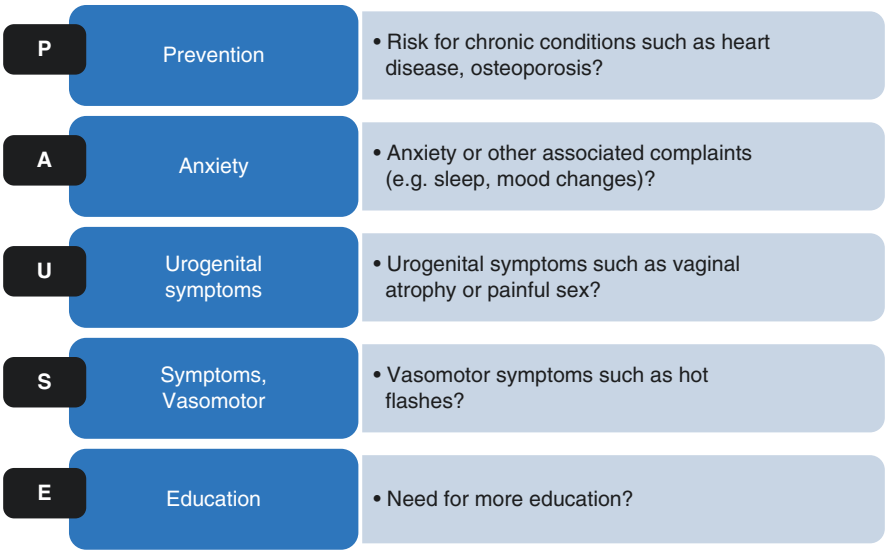


Fig. 10.4 PAUSE: a patient-centric tool to support patient–provider engagement on menopause [111]

represents an acronym to remind providers to focus on symptoms associated with the transition. Because the emphasis is so often placed on physical symptoms, the "A" serves to remind clinicians to ask about anxiety and other psychiatric symptoms associated with mood disorder.

A recent study conducted in Sri Lanka assessed the impact of a health-promoting lifestyle education intervention on quality of life in postmenopausal women [112]. The foundation of the study was centered around health education as a primary strategy for health promotion. The intervention consisted of health education in eight sessions focused on lifestyle modifications with a group of experts including a gynecologist, physician, nutritionist, and sport physician. The intervention included menopausal symptom management, healthy diet, physical exercises, and spiritual support, individualized for each participant. The researchers found that enhanced knowledge and understanding of menopause contributed to an increase in quality of life, and reducing menopausal symptoms and improving health status created a sense of happiness and well-being. This study underscores the importance of a multidisciplinary and holistic approach to effectively manage menopausal health.

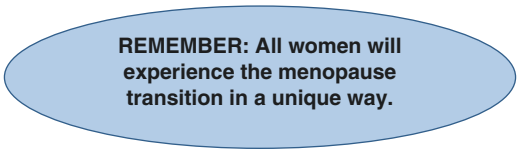
10.19 Summary

Each woman will have a unique symptom experience in the menopause transition and will need to manage symptoms differently. Depression and anxiety symptoms may have a unique and subtle presentation. Clinicians need to take time to discuss these symptoms and develop an effective treatment plan. Education and anticipatory

guidance should be the foundation and first-line treatment for women in the menopausal transition, and the education should begin well before symptoms develop (mid 30s). The wide variety of treatment options including pharmacologic and non-pharmacologic interventions should be tailored to the woman and to her treatment preferences. It is important to remember that menopause is a culture-related phenomenon. Different cultures will have differing attitudes toward menopause which may result in different psychological symptoms and treatment preferences. Understanding the complexity of menopausal mood symptoms will allow health-care providers and menopausal women to work together, in partnership, to develop individualized treatment plans to achieve optimal quality of life.

Key Points

- **Menopause is a complex phenomenon characterized by a combination of physical and psychological symptoms**
- **Perimenopause is the period where women are most vulnerable to psychological symptoms**
- **Symptoms (e.g., depression and anxiety) may be very subtle and unique in presentation**
- **Remember to ask about mood symptoms at the patient encounter**
- **Treatment should be individualized and tailored around patient preferences**
- **A multidisciplinary approach can help provide comprehensive care**
- **Education and anticipatory guidance should be considered first-line interventions**
- **Initiate education before symptoms begin—early 30s**



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Genitourinary and Sexual Health

11

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11.1 Introduction

Perimenopause and postmenopause are common times for women to experience changes in sexual and urinary function. The Global Study of Sexual Attitudes and Behaviors investigators group surveyed almost 14,000 women over the age of 40 years from 29 countries. About 40% of mid-life women worldwide reported sexual concerns, including low desire, inability to reach orgasm, and difficulty with lubrication [1]. These sexual concerns can be multifactorial, with a large contribution from decreasing levels of estrogens during the menopausal transition and beyond, resulting in the vulvovaginal atrophy and urinary symptoms, called genitourinary syndrome of menopause (GSM) [2].

Studies have shown that up to 84% of postmenopausal women show symptoms and/or signs of GSM [3]. Vulvovaginal atrophy is often described as a "silent symptom" of menopause because most women do not seek medical attention for these changes. Unlike vasomotor symptoms of menopause, which commonly decrease with time, genitourinary symptoms are typically progressive and are unlikely to resolve without effective treatment [4]. GSM can have a large impact on quality of life, self-perception, and sexual function [5]. This chapter will review the genital, urinary, and resulting sexual changes that occur with the menopausal transition, as well as safe and effective treatment options.

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11.2 Common Urogenital and Sexual Health Concerns in Menopause

11.2.1 Vulvovaginal Symptoms

Historically, vulvovaginal symptoms associated with lack of estrogen in peri- and postmenopausal women were called vulvovaginal atrophy and/or atrophic vaginitis. Although these symptoms are often described as vaginal dryness, burning, and dyspareunia, urinary frequency and recurrent urinary tract infections are also very common [6]. In 2014, the International Society for the Study of Women's Sexual Health (ISSWSH) and the North American Menopause Society (NAMS) introduced a new, inclusive term, genitourinary syndrome of menopause (GSM). The new terminology highlights the effects of hypoestrogenism on not only the vagina and vulva but also on the bladder and urethra [2]. Vulvovaginal atrophy (VVA) and atrophic vaginitis are considered components of GSM [5, 7]. Atrophic vaginitis describes a purulent vaginal discharge associated with vulvovaginal atrophy. Symptoms of atrophic vaginitis may be very similar to the symptoms of desquamative inflammatory vaginitis (DIV) or to those associated with erosive lichen planus. Vulvar dermatoses, including vulvar lichen sclerosus and lichen planus, are more prevalent in menopause. Vulvar signs and symptoms of lichen sclerosus may mimic or be present with GSM. These symptoms may independently lead to dyspareunia or coexist with vulvodynia. Vulvodynia is defined as vulvar pain of at least 3 months duration, without clear identifiable cause, but may have associated factors [8]. According to the International Society for the Study of Vulvovaginal Disease (ISSVD), ISSWSH, and the International Pelvic Pain Society (IPPS) 2015 consensus document, dyspareunia associated with GSM is characterized as vulvar pain caused by a specific disorder, in this case, a hormonal deficiency [8].

11.2.2 Urinary Symptoms

Urogenital atrophy results in various urinary symptoms that can be simply bothersome or can significantly impact a woman's health and quality of life. These symptoms can include the involuntary loss of urine (urinary incontinence), urinary frequency during the day and night, and recurring urinary tract infections. Urinary incontinence (UI) refers to unwanted loss of urine and this can include stress urinary incontinence (SUI), urge urinary incontinence (UUI), or mixed urinary incontinence (MUI). SUI is urine leakage that occurs during activities (coughing, sneezing, or exercising) that put a sudden increase in pressure on the bladder, urethra, and pelvic floor muscles. With UUI, a sudden and strong urge to urinate is followed by involuntary leakage and can often be referred to as having an overactive bladder. MUI is a combination of stress and urge incontinence.

11.2.3 Pelvic Organ Prolapse

Menopause and a sudden drop in estrogen lead to connective tissue atrophy and pelvic floor muscle weakness, and ultimately evacuation disorders. Pelvic organ prolapse (POP) is a supportive dysfunction and occurs when structures of the pelvis (connective tissue, ligaments, and muscles) are unable to adequately support the pelvic organs in their normal anatomic position. As a result, any of these organs (i.e., the bladder, urethra, uterus, rectum, intestines, vagina, cervix) can descend or herniate into the vagina in relation to the hymen or outside the rectum.

11.2.4 Low Sexual Desire

Sexual desire is comprised of cultural, psychological, and physiological factors. There are excitatory and inhibitory neurochemical systems that control sexual response, which are influenced by steroid hormones, changes in gene expression, and neurochemical function [9]. In the sexual tipping point model, these factors tip the balance toward either excitation or inhibition. Those with decreased sexual desire are tipped toward inhibition based on hypofunctional excitation and/or hyperfunctional inhibition [10] (see Fig. 11.1).

Lower levels of estradiol and testosterone have been associated with decreased sexual desire (Dennerstein 2016; [11]). When decreased sexual desire leads to personal distress and is not related to a psychological disorder, medication, or medical condition, it meets the criteria for diagnosis of hypoactive sexual desire disorder (HSDD). If low desire is related to sexual pain disorder, such as dyspareunia due to

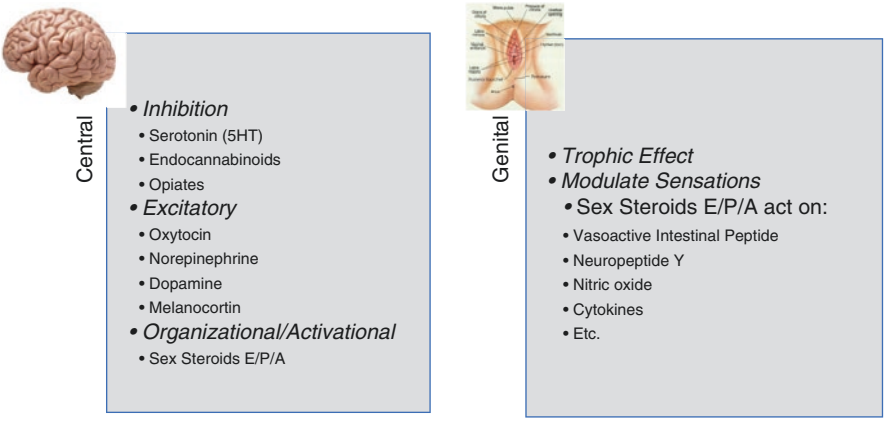

Fig. 11.1 Neuroendocrine influences on sexual function. *E* estrogen, *P* progesterone, *A* androgen. (Based on Kingsberg SA, Althof S, Simon JA et al. *J Sex Med*. 2017;14:1463–1491. Images public domain)

GSM, it is not labeled as HSDD, and underlying pain conditions should first be addressed [11]. Sexual dysfunction associated with psychoactive substance use is coded separately.

11.3 Impact of Genitourinary and Sexual Health Concerns Internationally

There are cultural, behavioral, and social aspects evident when interpreting results from surveys on GSM and sexual activity [12]. Most of the robust studies on GSM and VVA surveyed women in Europe and North America, although there have been smaller studies on this topic conducted throughout the world. Sexual issues in midlife are very common. The Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) Study evaluated sexual health of more than 31,000 women in the United States. Prevalence of any sexual problem was found to be 44.2% and increased with age. Report of any sexual problem not associated with distress was 44.6% in women aged 45–64 years and rose to 80.1% in women 65 years and older [13].

Up to 52% of postmenopausal women report reduced sexual desire [14, 15]; however, postmenopausal women also report lower rates of distress associated with decreased desire (Dennerstein 2016). Supporting this, two Australian studies found that low sexual desire associated with distress was 32.2% among women aged 40–64 years and decreased to 13.6% in women aged 65–79 years [16, 17]. Levels of decreased desire with distress (HSDD) in the aforementioned PRESIDE Study found rates of 12.3% in ages 45–64 years and 7.4% in over 65 years [13]. Arousal problems that are associated with distress follow a similar pattern in mid-life and older women [18, 19].

In a United States-based study of 94,000 postmenopausal women of age 50–79 years, over half (52%) remained sexually active following menopause [20]. Almost a quarter (22%) of women aged 70–79 continued to have sexual intercourse [21]. Many women would like to remain sexually active but are limited by vaginal dryness and dyspareunia. GSM is very prevalent, with 84% of women showing signs of vulvovaginal atrophy during a routine pelvic examination 6 years following menopause. Symptoms of GSM often have significant effects on sexual well-being and quality of life [22, 23]. In the Vaginal Health: Insights, Views & Attitudes (VIVA) study, an online survey of over 3500 postmenopausal women from six countries (Great Britain, the United States, Canada, Sweden, Denmark, Finland, and Norway), 75% felt that their GSM symptoms had a negative effect on their lives [24].

The largest study evaluating VVA among Asian women involved data collection through face-to-face interviews. This study included almost 6000 women, aged 45–75 years, from Indonesia, Malaysia, Singapore, Taiwan, and Thailand. Interestingly, only 11% of those interviewed reported VVA symptoms [25]. A systematic review of 34 articles including 24,743 women found that VVA symptoms are common after menopause in some Asian countries, but are either

under-reported or less common than rates reported in other areas of the world. There is an overall lack of studies utilizing validated questionnaires to assess sexual function in Asian postmenopausal women, which increases risk of bias and decreases external validity [26].

In the Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) study, which surveyed 4100 females and 4100 males from the United Kingdom, Finland, Norway, Sweden Denmark, Italy, France, Canada, and the United States, over a quarter of postmenopausal women did not tell their partners when they initially felt vaginal discomfort. Over 50% of women felt that it was embarrassing or "it was just a natural part of growing older." However, 82% of males indicated that they were open to discussing their partner's vaginal atrophy. Most often, vaginal atrophy led to avoiding intimacy, which was mainly attributed to sexual pain and decreased sexual desire [27–29].

Studies show differences in when women discontinue sexual activity based upon symptoms of vulvovaginal atrophy, with rates lowest in Southern Europe (18%), followed by Northern Europe (22%), the United Kingdom (27%), and highest in North America (29%) [27, 30, 31]. Sexual satisfaction is intertwined with many psychosocial aspects related with well-being and linked to other effects of the menopause transition, including weight, physical activity, sleep, anxiety, and depression [32, 33]. In addition, personality traits and behavioral profiles have been shown to play a role in reporting symptoms of GSM and seeking treatment [34].

A study of over 4200 postmenopausal women from Sweden, Finland, the United Kingdom, the United States, and Canada found that up to 70% of women with symptoms of vaginal atrophy do not raise their concerns with their doctor [35]. This may be because many women believe these symptoms are an expected part of the normal aging process, are uncomfortable discussing vaginal atrophy with their healthcare provider, and are unaware that treatment options are available. About 50% of women in the United Kingdom, Canada, and the United States were unaware that local treatment for vulvovaginal atrophy was available [35].

11.4 Effects of Hormonal Changes in the Menopause Transition

Most genital and urinary changes in the menopausal transition are caused by a loss of estrogen production. This may occur naturally around the average age of 51–52 years, with surgical menopause due to removal of the ovaries, or earlier with premature ovarian insufficiency. There has been documented a 95% decline in serum estradiol levels from premenopausal to postmenopausal states [36]. A 7-year longitudinal, population-based study of 438 perimenopausal Australian women showed that decreasing levels of serum estrogen were associated with vaginal dryness and pain with intercourse [37]. The genital and lower urinary tract are both derived from the primitive urogenital sinus. There are estrogen receptors in the vagina, vulva, urethra, and bladder trigone, with the highest estrogen-receptor density found in the vagina [5, 22, 34, 38, 39]. The pelvic floor musculature and

endopelvic fascia are also affected by lack of estrogen [40]. The pelvic floor muscles (PFM) span from the pubic bone to the tailbone and have superficial and deep layers. The superficial layer aids in sexual function and sphincter control for continence of bladder and bowel. The deeper layer offers dynamic support of the pelvic organs and provides core stabilization of the spine and pelvis.

Decreased estrogen leads to decreased collagen, hyaluronic acid, and elastin in the superficial urogenital tissue. This results in thinning of the epithelium, changes to the smooth muscle cells, increased connective tissue density, and a reduction in vaginal blood flow [2, 22, 38, 39]. These changes occur in the vaginal epithelium, as well as in tissue of the urinary tract.

Lack of estrogen at the level of the vaginal epithelium results in decreased glycogen content in the superficial cells, which results in loss of Lactobacillus species and changes in the vaginal microbiota [39, 41, 42]. The vaginal pH rises due to lack of lactobacilli, which normally keep the vaginal pH in the range of 4.0–4.8 through the production of lactic acid and hydrogen peroxide [42, 43]. This predisposes menopausal women to overgrowth of skin and rectal species within the vagina, including streptococci, staphylococci, coliforms, and diphtheroids, which can lead to an inflammatory discharge [36, 44]. Inflammatory vaginal discharge related to decreased estrogen in the menopause transition was previously termed atrophic vaginitis, but is now included in the diagnosis of GSM. Similar changes in the urinary tract may increase risk of urinary tract infection, as well as stress urinary incontinence [2].

The vulvar vestibule, tissue extending from the medial aspect of the labia minora to the hymenal ring, is also affected by decreased estrogens, as well as decreased androgens [45]. The vulvar vestibule includes the ostia of the Bartholin's, Skene's, and minor vestibular glands, which play an important role in lubrication, arousal, and prevention of dyspareunia.

11.5 Medical Evaluation

Sexual health is often a sensitive topic, especially in the case of sexual pain. Women may feel embarrassment, shame, guilt, frustration, or loss of confidence concerning their symptoms, and many women do not bring these symptoms to the attention of their healthcare provider [32]. Women with conditions that cause hypoestrogenism, such as menopause, should be screened for symptoms of urogenital atrophy, urinary dysfunction and distress from reduced sexual desire or responsiveness during routine visits. An evaluation of sexual health in the menopause transition includes medical history, physical examination, and possibly laboratory testing. It is essential to create an open and trusting relationship to allow for the discussion of sensitive topics concerning sexual health and pain conditions. If ample time is not possible in an initial visit, it may be necessary to reschedule an appointment devoted to addressing sexual health concerns alone.

11.5.1 Medical History

Proactive assessment of women in the menopause transition includes asking about symptoms of GSM, whether they are bothersome, and how they affect quality of life and sexual well-being [5]. It is often most effective to allow the patient to describe her symptoms, providing detail and a timeline when possible. Symptoms of GSM include vaginal and vulvar dryness, burning, irritation, decreased natural lubrication, decreased arousal, pain with vaginal insertion, as well as urinary urgency, pain with urination, and recurrent urinary tract infections. Both vulvovaginal and urinary symptoms may affect sexual activity. A sexual history includes asking about the level and types of sexual activities and relationship with partner(s), as well as effects of GSM symptoms on these factors [5].

The medical history includes medical and surgical history, as well as specific obstetric, gynecologic, and sexual history. Menstrual history, including regularity of menses and last documented menstrual period should be noted. Other causes of hypoestrogenism should be identified, including previous oophorectomy, prolactinemia, and certain medications that could affect estrogen and androgens. In women with a history of cancer, age at diagnosis, site, type, hormone receptor status, and previous treatments are necessary for full evaluation. Certain cancer treatments, such as surgery, radiation, and endocrine therapies, can change anatomy of the vaginal canal, vaginal epithelium, vascular supply, and have hormonal effects on the urogenital tissue (see Chap. 14). These changes may lead to pain with pelvic examinations and intercourse, as well as recurrent urinary tract and vaginal infections [46, 47].

A complete review of systems should be done to determine other causes for urogenital symptoms. Symptoms related to infectious or inflammatory etiologies should be determined, as well as use of products that could be irritants or allergies in the urogenital area. These include powders, panty liners, soaps, douches, spermicides, lubricants, toileting wipes, and tight clothing [48]. It is essential to ask about quality-of-life concerns, including impact of symptoms of activities of daily living, sexual activity, and relationships [48].

11.5.2 Physical Examination

Reported symptoms (or lack thereof) and clinical findings are not always congruent, necessitating both a history and physical examination in evaluation. Visual examination of the vulva involves noting signs of inflammation, lichenification, changes in pigmentation, loss of architecture, scarring, fissures, or ulceration. Signs of vulvar atrophy include thinness and regression of the labia minora, retraction of the vaginal introitus, and involution of hymenal tissue. The clitoris may recede and appear flush with the surrounding tissue. The vulvar vestibule may appear pale and

thin with redness associated with the greater vestibular gland ostia. The urethral meatus may appear prominent related to the surrounding vulvar tissue [22, 38, 39]. A urethral caruncle, which is a benign growth of inflammatory tissue from the urethral meatus, may be present.

In order to evaluate sexual pain related to GSM, a small moistened cotton swab is used to perform a sensory examination of the vulva, including the vulvar vestibule. The cotton swab is gently brushed on the medial thigh, mons pubis, and labia majora, before proceeding to the clitoral prepuce, interlabial sulci, and perineum. Then the labia minora are palpated lateral, then medial to Hart's line, which is the lateral border of the vulvar vestibule. Within the vestibule, the ostia of the Skene's glands (2 and 10 o'clock on the vulvar vestibule), the ostia of the Bartholin's glands (4 and 8 o'clock on the vulvar vestibule), as well as the posterior aspect of the vestibule. In a postmenopausal woman, pain throughout the vulvar vestibule and associated with the ostia of the greater vestibular glands, accompanied by signs of vulvar atrophy, is consistent with sexual pain related to GSM.

A speculum examination of the vagina is then performed. The vaginal introitus may be narrowed and require the use of a narrow pediatric speculum with lubricant for examination. Petechiae or friability may be present, resulting in spotting or bleeding with insertion. Signs of vaginal atrophy include thinning of the vaginal walls with loss of rugae and shortening and narrowing of the vaginal vault. A cotton swab may be used to collect vaginal discharge for pH testing, wet mount, and KOH preparation. A vaginal culture may be sent specifically requesting speciation and sensitivity. A manual examination is then performed to evaluate the urethra, bladder trigone, cervix, uterus, and adnexa. The levator ani pelvic floor muscles are palpated for hypertonicity, tenderness, weakness, and trigger points.

Brown or yellow vaginal discharge, which may be malodorous, and an increase in vaginal pH above 5.0 are consistent with atrophic vaginitis. In the setting of atrophic vaginitis, saline microscopy shows immature vaginal epithelial cells with large nuclei (called parabasal cells), reduced or absent lactobacilli, and white blood cells. Vaginal culture may show enteric organisms, such as gram-negative rods, which are commonly associated with urinary tract infections.

Physical examination and evaluation in pelvic health physical therapy (PHPT) is similar to the gynecologic examination without the use of a speculum, but rather consists of a digital examination of the external perineum, dermatomes, introital and vaginal tissues, pelvic floor muscle tone, strength, relaxation and descent, presence or absence of tender points or trigger points, scar tissue and myofascial restrictions, and degree of a pelvic organ prolapse. In addition, the PHPT examination includes orthopedic assessment of the lumbopelvic spine, skeletal asymmetries, postural assessment, movement tests of the sacro–iliac junction and spine, lower extremity alignment and gait evaluation, abdominal wall assessment, and visceral mobility/adhesions. Physical examination must include the awareness of biopsychosocial factors of pelvic health and pelvic symptoms.

11.5.3 Laboratory Testing

GSM is typically a clinical diagnosis and laboratory testing is often not necessary. However, in the case of vaginitis, saline microscopy should be performed and vaginal culture may be considered. If a urinary infection is suspected, appropriate testing is necessary for evaluation, including a urinalysis and urine culture. Sex steroid serum levels do not correlate with sexual function and have little role in diagnosis.

11.6 A Multidisciplinary Treatment Approach

A comprehensive approach in addressing these common genitourinary and sexual health conditions in the menopause transition is key to achieving long-term results. This is particularly important as multiple symptoms can present in a single patient. Interventions include hormonal and nonhormonal treatments, pelvic floor physical therapy, lifestyle changes, and support for pelvic organ prolapse.

11.6.1 Non-hormonal Options

First-line treatment for GSM is often nonhormonal personal moisturizers and lubricants. Vaginal and vulvar moisturizers are bioadhesive products that are used routinely, anywhere from daily to twice weekly, as maintenance therapy. The goal of vulvovaginal moisturizers is to decrease daily dryness symptoms of GSM, as well as improve comfort with sexual activity. Data showing improvement of GSM symptoms with vaginal moisturizers is limited. There is one randomized, placebo-controlled study showing effectiveness of a pH-balanced vaginal gel in women treated for breast cancer [49]. In a randomized, placebo-controlled 12-week trial of 300 postmenopausal women comparing vaginal moisturizer to vaginal estradiol tablet to placebo, improvements in GSM symptoms are seen in all three experimental arms with no significant difference between groups, indicating the placebo gel likely provided lubrication [50].

Personal lubricants, on the other hand, are often utilized with vaginal insertion, including sexual intercourse, as well as insertion of toys or vaginal trainers and dilators [51, 52]. The goal of personal lubricants is to decrease discomfort due to friction during vaginal insertion. A meta-analysis showed a slight increased efficacy in hormone-based therapies compared to lubricants in restoring sexual function [53]. There may be benefit of silicone-based lubricants compared with water-based in postmenopausal women and survivors of breast cancer with GSM [54].

Osmolarity is an important consideration with vaginal moisturizers and lubricants. The World Health Organization (WHO) recommends an osmolarity of less than 1200 mOsm/kg. Products that are hyperosmolar may be associated with

epithelial cell toxicity. Petroleum jelly-based products have been associated with an increased risk of bacterial vaginosis and oil-based products have been associated with increased colonization of candida species [55]. In addition, oil-based lubricants may degrade latex condoms. In general, iso-osmolar, propylene glycol-free water-based or silicone-based products are most well-tolerated [56].

Hyaluronic acid is a biopolymer that releases water molecules into the tissue. There have been four small randomized trials comparing hyaluronic acid to vaginal estradiol, estriol, genistein (an isoflavone), and/or placebo, with decreased severity of dryness and dyspareunia in hyaluronic acid use in all of the studies. Efficacy of hyaluronic acid was not different from genistein and inferior to estradiol but not estriol [57–60]. The findings are limited by the duration of the studies, ranging from 8 to 12 weeks to unspecified durations. More data is needed to determine if these products are superior to other lubricants or moisturizers [5].

11.6.2 Hormonal Options

11.6.2.1 Systemic Estrogen Therapy

Systemic estrogen therapy is indicated for GSM when menopausal vasomotor symptoms are also present (see Chap. 6) Hormone therapy includes topical or oral estradiol, as well as a progestogen in women with an intact uterus to reduce risk of endometrial cancer associated with unopposed systemic estrogen [61]. Despite efficacy in decreasing vasomotor symptoms of menopause, 40% of women using systemic hormone therapy will still experience persistent vulvovaginal symptoms, including vaginal dryness [62]. Oftentimes, a local low-dose estrogen is utilized in conjunction with systemic treatment to adequately address genitourinary symptoms [5].

11.6.2.2 Local Estrogen

Local low-dose estrogen therapy is the treatment of choice for women with GSM [5]. Vaginal estrogen promotes revascularization and thickening of the vaginal epithelium and lower urinary tract, leading to increased tissue elasticity and lubrication, and decreasing symptoms of vaginal dryness, irritation, pruritis, dyspareunia, and urinary urgency [18, 19, 63, 64]. Limited evidence indicates decreased frequency in urinary tract infections and improvement in overactive bladder symptoms [64]. Increased blood flow and lubrication may also improve arousal, orgasmic function, and sexual desire [65].

Local estrogens, including estradiol, estriol, and conjugated estrogens, are considered safe and effective treatments for GSM. Currently, two vaginal estrogens, estradiol and conjugated estrogens, are approved in the United States for treatment of vaginal atrophy, vaginal dryness, and dyspareunia. Estriol and estriol with probiotic lactobacilli are available in Europe, Australia, and other parts of the world. Various formulations for vaginal estrogen use include creams, tablets, and hormone-releasing rings. A Cochrane meta-analysis, which analyzed 30 randomized trials with 6235 women, found that creams, pessaries, tablets, and the estradiol vaginal ring appeared to be equally effective in relieving symptoms associated with vaginal

atrophy when compared to placebo [66]. A survey of 423 postmenopausal Swedish women indicated the preference for using disposable applicators with small tablets as opposed to dosing syringes with vaginal cream to deliver local estrogen [67]. Women were more likely to continue treatment with vaginal tablets at 1 year compared with those who used vaginal cream [68].

Present consensus is that the smallest effective dose of estrogen should be utilized for long-term therapy, with eventual tapering of estrogen to maintenance dosing once urogenital function has improved. Although it is believed to be acceptable to continue treatment indefinitely, safety data beyond 1 year has not yet been reported [5, 61]. The principle concern with the use of unopposed estrogen in a woman with an intact uterus is endometrial hyperplasia; however, low-dose estrogen formulations have not been shown to increase the incidence of proliferative endometrium when compared with placebo [5]. Furthermore, the North American Menopause Society (NAMS) states that endometrial surveillance and progestin therapy is not indicated in asymptomatic, low-risk women receiving low-dose vaginal estrogen [5]. Nevertheless, it is important to note that although local estrogen therapies may not significantly stimulate the endometrium, all cases of postmenopausal bleeding warrant evaluation with ultrasound examination of endometrial thickness and endometrial sampling [5] (see Chap. 7).

11.6.2.3 Hormone Modulators

Ospemifene, a selective estrogen receptor modulator (SERM), was initially developed as a treatment for postmenopausal osteoporosis, but was found to have favorable estrogenic effects on the vaginal epithelium in clinical trials. This daily oral pill is a systemic nonhormonal therapy approved in the United States and Europe for treatment of moderate to severe dyspareunia due to vulvovaginal atrophy. Studies show improvement in GSM symptoms, clinical improvement of the vulva and vagina, as well as sexual dysfunction scores [69]. The most frequently reported adverse event was hot flushes, found in 8–9% of women taking ospemifene and 3% of women in the placebo group. There was no proliferative effect on endometrial tissue noted [70]. Ospemifene's antiestrogenic activity in several preclinical models of breast cancer piqued interest in this SERM as a possible treatment option for women with breast cancer suffering from vulvovaginal atrophy; however, studies have not demonstrated decreases in breast cancer risk. Based on lack of evidence, ospemifene is not approved in the United States for use in women with a history of breast cancer [71]. Ospemifene is not contraindicated in Europe for women with a history of breast cancer who have completed breast cancer treatment.

11.6.2.4 Dehydroepiandrosterone (DHEA)

Like estrogen, levels of dehydroepiandrosterone (DHEA) decline with age. DHEA, a sex steroid precursor, converts to estrogens and androgens via enzymes in the vulva, vestibule, and vagina, without affecting endometrial tissue in the uterus. In postmenopausal women, vaginal DHEA has been shown to improve the vaginal epithelial thickness, increase vaginal secretions, and decrease vaginal pH, without significantly elevating circulating levels of estrogen. Intravaginal DHEA applied

daily led to improvements in sexual desire/interest, arousal, orgasm, and pain with sexual activity [72]. Vaginal DHEA inserts are approved in multiple regions for treatment of GSM.

11.6.2.5 Local Androgen Therapy

Androgen receptors and aromatase have been identified with immunohistochemistry in vaginal epithelium, suggesting both direct and indirect effects of testosterone on vaginal tissue. There have been several small studies examining the effects of local vaginal testosterone in the treatment of GSM, focusing on postmenopausal women using aromatase inhibitor therapy for breast cancer, where estrogen therapy is contraindicated. Daily vaginal testosterone cream improved vaginal atrophy symptoms of dryness and dyspareunia, increased vaginal tissue integrity, lowered vaginal pH, and increased sexual satisfaction [18, 19, 73–75]. There was no significant difference in estradiol levels before and after treatment [73]. Vaginal testosterone cream is approved in Australia, but there are no approved testosterone products for women in other regions.

11.6.3 Pelvic Floor Physical Therapy

In addition to hormonal and non-hormonal treatment options, pelvic floor physical therapy (PFPT), sometimes called pelvic health physical therapy (PHPT) or pelvic floor muscle training (PFMT), is also considered a minimally invasive, first-line treatment for many of the GSM symptoms. This includes dyspareunia, urinary incontinence, overactive bladder syndrome (OAB), and painful urination. It has also been shown to benefit menopausal women with pelvic organ prolapse (POP) [76].

Treatments conducted by trained pelvic floor physical therapists (PFPT) include manual therapy techniques, biofeedback, therapeutic exercise, neuromuscular re-education, electric stimulation, and various behavioral modification strategies. All of these modalities have been found to improve the symptoms common with GSM listed above.

As mentioned earlier in this chapter, timely management of dyspareunia (pain before, during, or after sex) can be challenging given that over 70% of postmenopausal women do not raise this as a concern with their clinicians [35]. Cultural practices, religious beliefs, and intergenerational sexual attitudes may view painful sex as a "rite of passage," and may prevent referral to PFPT despite the numerous benefits cited by current research. A 2019 study published in the *International Urogynecology Journal* evaluating the various PT modalities such as myofascial release, intravaginal massage, biofeedback, and PFM exercises to improve awareness and release trigger and tender points in the PFM documented benefits in sexual dysfunction [77]. A comprehensive treatment of dyspareunia includes the care of highly educated, and culturally sensitive PHPTs to address the biopsychosocial needs of each individual patient.

A 2018 Cochrane review examined the effectiveness of PFMT in the treatment of incontinence by reviewing 31 studies involving 1817 women from 14 countries.

They concluded with confidence that PFMT can resolve or improve symptoms of SUI and all other types of UI by reducing the number of leakage episodes, and the quantity of leakage [78].

Pelvic floor exercises are recommended for women in the menopause transition and postmenopause with symptoms of POP, and women who wish to avoid surgery. A meta-analysis of 13 studies, where 2340 patients were included, found that women receiving PFMT gained greater subjective improvement in prolapse symptoms and an objective improvement in POP severity than the control groups [79].

The mechanism of how PFMT helps to address GSM symptoms has been shown to be impactful in the following ways: improves vulvoginal blood flow, enhances tissue elasticity, and restores pelvic floor muscle coordination and function [80].

With PFM activation, the internal pudendal artery is able to provide more blood flow to the vagina, vulva, clitoris, PFM, and the perineum [80]. The improvement in blood flow to these structures facilitates an increase in the production of vaginal secretions and improves thickness of the vaginal mucosa.

Poor tissue elasticity along with vaginal dryness can cause tissue friction and vulvovaginal pain. A 12-week study on the impact of PFMT on GSM symptoms by Mercier et al. [80] showed that effective training of these muscles improved tissue elasticity and relaxation capacity. There was also a significant increase in vaginal mucosal thickness and the introital width. This led the authors to conclude that contraction and relaxation exercises of the PFM may help reduce vulvovaginal tissue friction and dyspareunia during intercourse [80].

PFM function (strength, coordination, and endurance) has also been shown to improve with PFMT. In a systematic review published in the *South African Journal for Physiotherapy*, the authors made positive correlations using the International Continence Foundation (ICF) framework between movement impairments of these muscles and management of pelvic organ prolapse. They also relied upon trained physiotherapists to identify the movement impairments contributing to these functional impairments. They concluded that women with pelvic organ prolapse presented with imbalances in local and global stability function of muscles of the pelvic floor, pelvis, and spine [81].

Improved breathing patterns during menopause can improve coordination with the pelvic diaphragm for stability and toileting as well as facilitate relaxation response or parasympathetic nervous system for hot flash management [49]. Diane Lee introduced the concept of the torso as a cylinder, or "soda can," providing both dynamic and postural support: the vocal folds/glottis form the top of the can, the thoracic cavity is the upper half of the can with the diaphragm separating it from the abdominal cavity or lower half of the can, the pelvic floor serves as the base of the can and the abdominal and multifidi muscles comprise the sides of the can. The inverse relationship between the glottis/diaphragm and the abdominals/PFM is essential for understanding changes in intra-abdominal pressure, the coordination of breath with the abdominal and PFM muscles for optimal core support, and the relaxation of these muscles for functional evacuation of the bladder and bowel [49]. Learning to isolate the PFM and deep transverse abdominals can restore PFM

strength, reduce symptoms of SUI and POP. Learning to properly relax and lengthen the abdominals and PFM facilitates proper toileting behavior (without straining), reduces PFM pain due to hypertonia and muscle guarding behavior, and improves blood and lymph circulation via the diaphragmatic/abdominal/PFM pumping mechanism [49].

PFM strengthening and core stabilization exercises are called Kegel exercises and may be combined with various interventions such as manual biofeedback (BF), use of mechanical BF units with external or internal sensors, electrical (Estim) or vibrational stimulation, internal pelvic weights, or vaginal cones [82–87]. Functional Kegels are core strengthening exercises which are integrated into everyday movement patterns or activities of daily living (ADLs). When functional Kegels are coordinated with diaphragmatic breathing, a newfound sensibility of 'moving from one's core' is facilitated, creating new habitual movement patterns and preventatively reducing symptoms of PFM weakness, SUI, POP, and pain [78, 88].

The Knack technique involves activating the core muscle group comprised of the PFM, deep transverse abdominis, internal oblique abdominals, and the multifidi. The technique consists of squeezing "in and up" while maintaining "neutral spine" to facilitate the deep spinal support of the multifidi muscles [89–92]. This "pelvic brace" is performed just prior to a stressful movement or action such as landing from a jump or sneezing to prevent stress urinary incontinence and mechanical stress to the pelvic organs and PFM. When intra-abdominal pressure exceeds PFM strength, leakage and prolapse may ensue. Conversely, when adequate PFM and core stability are present, sphincter activation prevents leakage and inhibits bladder contraction due to frontal lobe voluntary urinary inhibition reflex [91, 92].

The opposite of low-tone PFM disorders is abnormally high muscle tone wherein a muscle that does not relax readily may be comprised of short, tight, and often weak fibers, with possible symptoms of pelvic pain, dyspareunia, or painful sexual intercourse, including vaginismus and vulvodynia [93]. High-tone muscle tissue may exhibit decreased circulation and oxygenation, which may in turn contribute to the pain–spasm cycle, myofascial trigger points, and tender points [94]. High-tone pelvic floor muscles may be addressed by PFM relaxation exercises including diaphragmatic breathing, guided imagery, desensitization techniques, therapeutic stretches, use of mechanical devices such as pelvic dilators, wands and vibrators, and self-manual therapy instruction [95]. Manual therapy release of myofascial pain is considered the first-line treatment of musculoskeletal pelvic pain syndromes and may include trigger point release, Thiele massage, scar tissue release, and desensitization techniques [94–97].

Home biofeedback units used with vaginal or rectal sensors or surface EMG sensors, some of which may connect to phone apps, provide visual and audio feedback to improve muscle performance, the mind-to-muscle coordination for voluntary "downtraining" and relaxing high-tone PFM, or "uptraining" and strengthening weak PFM [82–85]. Biofeedback provides neuromuscular re-education to reinforce and restore normal muscle coordination and function.

11.6.4 Behavioral Modifications

Lifestyle and behavioral modifications to improve lower urinary tract symptoms are aimed at patient education on healthy bladder habits, establishing normal voiding intervals, elimination of bladder irritants from the diet, management of fluid intake, weight control, constipation management, and smoking cessation [98]. These recommended behavioral interventions have strong support internationally and have been published by the International Consultation on Incontinence, the American College of Obstetricians and Gynecologists, the Society of Obstetricians and Gynaecologists of Canada, the United Kingdom's National Institute for Health and Excellence, Indian Journal of Urology and more [98–102].

11.6.4.1 Dietary Management

Bladder irritants, such as acidic foods, carbonated beverages, alcohol, and caffeine and artificial sweeteners, may irritate the inner lining of the bladder with an increase in urine acidity and bladder spasms. This ultimately results in urinary urgency, frequency, and increased bladder spasms [103]. Excessive fluid intake may contribute to OAB and incontinence by overworking the detrusor muscle. Alternatively restricted water intake may lead to dehydration and concentration of urine in the bladder. This in turn acts as a bladder irritant. By minimizing dietary irritants and adequate hydration (six to eight glasses per 24-h period for most active adults) can be a simple first step in mitigating some lower urinary tract symptoms [98, 103].

11.6.4.2 Cardiovascular Exercise

Cardiovascular (CV) exercise is essential to all physical therapy prescriptions and PFPT is no exception. The American Heart Association recommends a minimum of 20 min daily CV aerobic exercise for women [104, 105]. PHPTs remind patients that this recommendation applies not only to cardiac muscle and circulation but also for pelvic organs, PFM tissue health, and circulation. The moment we shift from sit to stand, our PFM becomes activated. The more active our daily lives, the more our PFM is engaged and potentially strengthened. In addition, CV exercise is vital to combat weight gain often experienced with menopause (see Chap. 12). PHPTs may guide menopausal women in progressive CV exercise programs and weight management programs such as high intensity interval training, low impact, and core strengthening regimen with the maxim: "move it AND lose it" [106, 107].

11.6.4.3 Bladder Management

Timed voiding and urge suppression techniques are bladder retraining techniques to help break the cycle of urgency and frequency by using consistent incremental voiding schedules. Obeying every signal of urinary urge or "just in case" (JIC) voiding reinforces detrusor overactivity. Women are taught instead to stand or sit still, practice diaphragmatic breathing techniques, distract themselves with a task or hobby, and contract the PFM with a rhythmic squeeze and lift for several minutes. These

strategies can affect the reciprocal inhibition of the bladder via the activation of the PFM contractions and thus relax the detrusor and suppress urinary urge. Once the wave of urgency passes, they may walk calmly to the bathroom. Retraining the brain to ignore the signals from the detrusor muscle can be beneficial in improving bladder capacity [98, 103].

11.6.4.4 Bowel Management

Constipation is defined as difficult or a rare passage of stool (less than 3 times per week) and is typically associated with passing hard stools, straining, or incomplete bowel emptying. The prevalence of constipation has been widely noted as a risk factor for incontinence and OAB [108, 109]. In a large cross-sectional study in China by Zhang et al. [110], 4684 women were surveyed, and the authors concluded that constipation was a strong predictor of moderate to severe OAB [111]. The mechanism of the impact that straining behavior, or valsalva maneuver, has on the pelvic floor relates to the structural changes seen particularly at the rectum, anus, and perineum. Increased intraabdominal pressure in combination with forceful straining may cause pelvic organ and perineal descent which may damage the nerves to the external anal sphincter and the puborectalis muscles and can cause POP [110]. With the denervation of these muscles, PFM weakness, tissue damage, and pain symptoms may result. Constipation management strategies include increasing dietary fiber intake, engaging in regular exercise, obeying fecal urge without delay, PFM relaxation and lengthening techniques, practicing abdominal massage, and improving toileting mechanics (leaning pelvis forward, relaxing mindfully, practicing diaphragmatic breathing, using low vocalizations, pelvic rocking, and placing feet on a low footstool or a "squatty potty") [112, 113].

11.6.4.5 Weight Management and Smoking Cessation

Obesity and a body mass index >30 kg/m^2 are risk factors for OAB, stress incontinence, and POP. Every extra 10 lb above may create up to 100 lb of force below [114]. Studies have shown that moderate weight loss of 5–10% can improve incontinence [115]. The chemicals in cigarette smoke can be considered a bladder irritant, increasing the chances of painful bladder symptoms. Smoking cessation is seen as being critical in reducing chronic coughing and the subsequent pressure on the pelvic floor muscles [116]. Research also shows that smoking strongly correlates with urge urinary incontinence in women. The association between the risk factors and lower uterine tract symptoms relate to anatomic, physiologic, and pressure changes created in the continence mechanism. One study examined the urodynamic factors in smokers and found the maximal intravesical peak pressure generated by a cough to be higher in smokers compared with nonsmokers [117].

11.6.5 External Support for Pelvic Organ Prolapse

Mechanical aids for SUI and POP can provide additional support when combined with PFMT. A vaginal pessary may support the weight of the bladder, urethra,

vagina, and uterus while reducing the strain on suspensory ligaments and fascia of those organs. Vaginal inserts such as the Poise Impressa® may be used during stress activities such as running to also reduce incontinence and improve vaginal hygiene. Belly binders or elastic abdominal supportive underwear may contribute to external bracing to assist abdominal and PFM support.

11.6.6 Hypoactive Sexual Desire Disorder (HSDD) Treatment

Cognitive and motivational treatment for HSDD includes sensate focus, cognitive behavioral therapy (CBT), and mindfulness. Overall, there is a lack of clinical trials determining efficacy of psychotherapeutic treatment options for HSDD. The most supportive evidence is for mindfulness-based cognitive behavioral therapy. Neurochemical and endocrine options for HSDD include a serotonin receptor modulator and dopamine antagonist flibanserin, a subcutaneously administered melanocortin agonist bremelanotide, a sex steroid testosterone, and bupropion and buspirone, both norepinephrine and dopamine agonists [11]. Clinical trials support the use of off-label testosterone therapy in doses that achieve approximate premenopausal serum testosterone levels in menopausal women with HSDD in terms of efficacy and short-term safety profile [11]. Double-blinded, placebo-controlled clinical trials in menopausal women, including surgically induced menopause, show improvements in sexual desire, the number and quality of sexual events, and decrease in sexual distress compared to placebo [118–120]. The Global Consensus Position Statement on the use of testosterone therapy in women does not support the use of pellets, injectables, or formulations that result in supraphysiologic levels, as there is no long-term safety data [75]. Currently topical testosterone is approved in Australia for use in all women, and flibanserin and bremelanotide are approved by the US Food and Drug Administration (FDA) to treat premenopausal women with generalized acquired HSDD.

11.6.7 Vaginal Renewal™ Program

The Vaginal Renewal (VR) program from "A Woman's Touch" and https://sexualityresources.com/ is a method to treat vaginal dryness and atrophy by improving lubrication and circulation of the vulvar, perineal, and vaginal tissues through manual or mechanical stimulation of the clitoris and vagina [121]. VR may be recommended in PHPT as a strengthening program for vaginal atrophy and a weak PFM, while improving sexual function and tolerance with the goal of return to pain-free, pleasurable sexual intercourse. It essentially involves clitoral stimulation manually or with a vibrator to evoke an orgasm or multiple orgasms, and thereby increase blood circulation, muscle activity, flushing of lymph and waste products while stimulating pleasure and restoring pelvic organ and PFM health, with or without a sexual partner [https://sexualityresources.com/]. Women who described improved sexual function demonstrated the greatest increases in pelvic floor muscle strength and endurance [122].

11.6.8 "OtherCourse"

"OtherCourse" is a practice which provides an alternative to sexual intimacy when pain prevents vaginal intercourse [121]. As the brain is our largest sexual organ, and all experiences and senses are mapped in the brain, painful sex may be addressed initially by exploring other options or sharing intimacy, sensuality, and sexuality without vaginal penetration. Imagination, verbiage and dialogue, guided imagery, and visualization are techniques which may help retrain the brain by changing the neural input to the brain and change brain-mapping of pain [123].

11.6.9 Energy-Based Treatments

Energy-based therapy, such as fractionated CO_2 laser, has been marketed to healthcare providers and patients for the treatment of vulvovaginal atrophy; however, there has not been sufficient evidence to determine if this modality is safe or effective. In the United States, these devices have not been approved by the United States FDA for the indication of GSM due to lack of long-term placebo-controlled randomized trials on this treatment modality. Several small studies examining the fractionated CO_2 laser and a radiofrequency device indicate improvement in vaginal atrophy, incontinence, dyspareunia, sexual function, and pelvic floor laxity [124–126]. In July 2018, the FDA issued a safety warning about the risks of energy-based devices (including laser and radiofrequency devices), for the treatment of symptoms related to the menopause transition and sexual function, as well as vaginal rejuvenation and cosmesis. The risks of energy-based therapies include vaginal burns, scarring, pain with intercourse, and chronic pain [127]. The International Urogynecological Association (IUGA) released a committee opinion stating that there is insufficient evidence to determine long-term efficacy and safety for energy-based devices in the treatment of GSM. Recently, a randomized trial comparing vaginal laser therapy to vaginal estrogen in women with GSM showed similar improvement in genitourinary symptoms and sexual function at 6 months [128]. There are additional ongoing clinical trials examining the safety and efficacy of these treatments. These results are needed before this treatment modality can be a recommended therapy.

11.7 Interventional Therapies

Various interventional therapies can be utilized to treat UI and other bladder symptoms seen with GSM. Posterior tibial nerve stimulation (PTNS), OnabotulinumtoxinA injections, and sacral nerve stimulation (SNS) are all treatment options that may be considered in addition to pelvic floor training and behavioral modifications.

Posterior tibial nerve stimulation (PTNS) is a treatment regimen administered in a clinic setting to treat UUI, OAB, urinary urgency, frequency, overactive bladder, nocturia (waking up at night to pass urine). PTNS involves stimulating the posterior tibial nerve which shares the same nerve root as the nerve supply of the bladder and rectum. Twelve sessions are typically prescribed on a weekly basis, and utilized on an as needed basis. PTNS has been found to be safe and effective in 37–100% of patients with OAB and in 41–100% of patients with nonobstructive urinary retention [129]. Women may also be educated on how to self-administer transcutaneous tibial nerve stimulation (TTNS) using a small home device.

Injection of OnabotulinumtoxinA (Botox®) into the detrusor muscle is another established option for the treatment of UUI and OAB. According to the *International Journal of Urology*, OnabotulinumtoxinA injections have been found to be effective in decreasing UI, urinary frequency, and urgency with only mild adverse effects (mostly urinary tract infections and urinary retention) [130].

Sacral nerve stimulation is a more invasive procedure to address UUI and OAB symptoms and works by directly stimulating the sacral nerves which control bladder and bowel function. It involves inserting an implant under the skin in the upper buttock, and it requires long-term follow-up.

Injection of bulking agents is a minimally invasive procedure offered to women with SUI. It involves the transurethral or periurethral injection of a synthetic material (e.g., autologous fat, collagen, or carbon beads) to help keep the urethra closed in order to reduce urinary leakage. Improvement rates can range from 18% to 40%, with repeated injections required to maintain effectiveness [131].

11.8 Surgery

Multiple procedures and pelvic surgeries exist for women experiencing SUI and POP. A specialized surgeon (obstetrician-gynecologists and urogynecologists) can assist in making the decision on what type of surgery is most appropriate. Typically, the decision is made when conservative measures such as pelvic floor exercises are exhausted, and it can be based on various factors including age, previous surgical history, severity of condition, and general health and lifestyle. For SUI, surgical options are typically slings and urethropexy. Sling procedures include pubovaginal slings and midurethral slings (i.e., retropubic sling, single incision sling [mini-sling], tension-free vaginal tape, and transobturator sling). Urethropexy options include needle urethropexy and retropubic urethropexy [131]. In general, there are two types of prolapse surgery: reconstructive and vaginal closure surgery. The goal of reconstructive surgery is to restore organs to their original position while maintaining sexual function. These procedures can be done vaginally (e.g., sacrospinous or uterosacral ligament suspensions) or abdominally (e.g. sacrocolpopexy), or by utilizing laparoscopic or robotic approaches.

Sexual intercourse is not possible after obliterative surgery as it narrows or closes off the vagina to provide support for prolapsed organs.

11.9 Conclusion

Vulvovaginal and urinary symptoms are very common during the menopausal transition and often worsen with time after menopause. Many women do not feel comfortable disclosing symptoms of GSM or are unaware that treatment options exist. Treatment improves not only vulvovaginal health and sexual function but also urinary health. There are nonhormonal and local hormonal treatments for GSM that have been shown to be safe and effective. Pelvic floor physical therapy, lifestyle changes, and behavioral modifications are also considered first-line treatments for many of the symptoms seen with GSM. With increased education and awareness, healthcare providers can support patients in maintaining desired intimacy with partners and improve quality of life measures related to genitourinary health.

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Nutrition and Weight Management in Midlife

12

Maya Feller

12.1 Introduction

The menopause transition is a natural event and part of the aging process for women. It comprises the stages of perimenopause, menopause, and postmenopause. Perimenopause occurs when menstrual periods vary by more than 7 days at least twice within a 12-month span. Variations and alterations in menstrual flow can begin 7–10 years prior to a woman's final menstrual period (FMP) [1]. With climacteric shifts, many, but not all, women begin to report symptoms such as hot flashes, sleep disruptions, mood changes, and vaginal dryness. Menopause is said to have occurred when a woman has experienced 12 consecutive months without a menstrual period (see Chap. 1). Some women experience early or premature menopause due to hysterectomy, oophorectomy, damage to the ovaries, chemotherapy, or some other unknown factors (see Chap. 7). Postmenopause refers to the 24–36 months after the FMP, when symptoms typically subside for most women, and to the remaining lifespan.

This chapter will examine sociocultural experiences of the menopause transition, the relationship between patterns of eating and alterations in body composition, the impact of senescence (biological aging) versus menopause stage on health outcomes, as well as the incidence and development of noncommunicable conditions.

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12.2 Sociocultural Factors and Symptom Reporting

How a woman views the menopause transition and the adverse symptoms she reports have been linked, at least in part, to the views her culture holds of aging in general and the menopause transition specifically. Watling et al. [2] examined culture from three lenses and came to the conclusion that "culture resists a simple definition." As we move across the globe and through regions, social norms vary widely. Other culturally related practices and customs, such as eating patterns and culture around dieting, lifestyle, medication use, substance use, beauty standards, weight bias, as well as biological factors, influence how individuals experience the stages of menopause.

In a literature review exploring the relationship between culture and the menopause transition, Melby suggested the existence of a complex interplay between biological and sociocultural factors in the reporting of menopausal symptoms [3]. A series of papers relying on data from the Study of Women's Health Across the Nation (SWAN), a multisite, multiethnic longitudinal, epidemiologic study in the United States that examined the physical, biological, psychological, and social changes women face during their middle years, supported the idea of a cultural relationship in the experience and the reporting of symptoms [4, 5] (see Chap. 1).

When discussing issues of culture, it is important to establish a common vocabulary to guard against misunderstandings. For the purpose of this chapter, the definition of culture contained within the W.K. Kellogg Foundation's Racial Equity Resource Guide will be used. The Foundation defines culture as "a social system of meaning and custom that is developed by a group of people to assure its adaptation and survival. These groups are distinguished by a set of unspoken rules that shape values, beliefs, habits, patterns of thinking, behaviors and styles of communication" [6]. Note that culture is not linked to a geographic location, nationality, or an ethnicity. We all live within and move between different cultural circles, particularly regarding matters of health. Therefore, it is unwise to assume cultural attitudes of an individual solely based on their country of origin, where they reside, race/ethnicity, or other demographic or social factors.

Several large projects have been developed with a goal to better understand the complexities of local healthcare experiences and evaluate strategies communities can employ in the pursuit of improving the health and well-being of their citizens. The Robert Wood Johnson Foundation's *Sentinel Communities Project* aims to study 30 US cities, counties, regions, and states selected to reflect the diverse populations in terms of geography, demographics, and approaches to improving health [7, 8]. Likewise, the Foundation's *American Health Values Survey* seeks to better understand attitudes toward health across the United States by developing distinct groups to study based on shared beliefs and values—or culture. Supported by the World Health Organization, The European Observatory on Health Systems and Policies reviewed health systems across European countries specifically to evaluate policies that impacted health programs and country-specific outcomes (Health Systems Reviews).

Cultural humility, a term first defined in 1988 by Melaine Tervalon and Jann Murray-Garcia, is defined as a process of "self-reflection and discovery in order to build honest and trustworthy relationships" [9]. Cultural norms, beliefs, and attitudes toward health alter in relation to geographic region. Working from a lens of cultural humility better allows the provider to fully understand how a woman views and experiences the menopause transition (see Chap. 3).

12.2.1 Social Determinants of Health and Their Impact on Menopausal Experience

Social determinants of health play a role in both how the menopause transition is experienced by women around the world and strategies to mitigate negative health outcomes related to aging and menopause. Social determinants of health are generally recognized as conditions in the environment where people live, work, study, and play that can impact their health outcomes. These variables include, but are not limited to, those factors listed in Table 12.1.

Social determinants of health, health disparities, and health inequities directly influence and impact health outcomes, disease rates, and illness, including those associated with menopause stage and aging in women. Health inequities are defined as "avoidable, unfair differences in health status seen within and between populations." The World Health Organization's Global Commission on Social Determinants of Health identifies inequities in the conditions in which people are born, live, work, and age, which are driven by inequities in power, money, and resources, and have been present for centuries [10]. In Latin American and the Caribbean, cycles of poverty and disadvantage have resulted in poorer health outcomes [11]. In the United States, social determinants of health have disproportionately disadvantaged communities of color, particularly Black and brown communities, as well as recent immigrants and refugees.

The Centers for Disease Control and Prevention (CDC) Health Disparities and Inequalities Report consistently points to Black and other communities of color as disproportionately experiencing health inequity in all areas compared to their white counterparts. Due to systemic racism in the United States, Black and brown people are more likely to live in lower income neighborhoods with fewer social services, less access to healthy foods, and a higher exposure to environmental contaminants. People of color report deep distrust of organized medicine based on the effects of

Table 12.1 Social determinants of health

• Socioeconomic status
• Employment
• Education
• Access to safe and affordable housing
• Access to healthcare and adequate health insurance
• Access to plentiful, affordable, and nutritious food

unethical medical research conducted on Black and brown people as well as residual, unconscious stereotypes about their bodies and lifestyles [12]. These factors have a large impact on health and nutrition-related outcomes as well as access to consistent affordable quality healthcare.

It is important to openly acknowledge that structural racism and income disparities are major drivers of health outcomes of marginalized people everywhere. In addition to striving to correct those inequities and their impacts on the healthcare and services provided to communities of color and lower income populations, the health community must also commit to working to heal distrust.

Similarly, it is important that we stop blaming racially and economically disadvantaged peoples for poor health outcomes and instead become partners in advancing optimal health, working together to address the social determinants that negatively impact their health.

12.3 Health Impacts of Aging vs. Menopause Transition

Teasing out cause and effect regarding menopause-related symptoms is complicated by the fact that many of the troubling symptoms that occur during the menopausal transition are also related to aging. There is a complex interplay of factors including current health status, lifestyle, cellular senescence, and hormonal changes that impact symptoms. These symptoms include anxious feelings, sleep disruption, and vasomotor symptoms (see Chap. 1). Understanding the contributions of hormonal changes and other factors has important implications for research, clinical care, and public policy.

During the menopause transition, women ultimately experience a decline in estrogen and progesterone production. The hormonal shifts that accompany the menopause transition set the stage for senescence and have the potential to accelerate the process of noncommunicable disorders and diseases [13, 14]. The impact of physical, physiological, and neuroendocrine changes that occur during this life stage not only result in increases in blood pressure, visceral adiposity, proinflammatory cytokines, and oxidative stress. Reductions in glucose tolerance and heart rate variability, atherogenic changes in lipid and coagulation profiles, and impaired endothelial function may exacerbate the effects of insulin resistance which in turn contribute to the increased risk of atherosclerosis and cardiovascular disease [15] (see Chap. 5).

When women reach the postmenopause stage, the risk for conditions such as osteoporosis, cardiovascular disease, urinary incontinence, and weight gain increases [16]. Women who are at an increased risk of developing metabolic syndrome, diabetes, cardiovascular disease, and obesity often experience disorders of glucose metabolism during the menopausal transition.

Many studies conducted around the world attempt to explain the reasons behind the metabolic changes. Many of the physiological changes have not been found to be directly related to hormone level changes, but rather appear to be mostly related to aging and lifestyle factors.

Although not necessarily caused by menopause [17], there is a potential relationship between the menopause transition and changes in body composition: increased abdominal adiposity and concurrent decrease in lean body mass. The changes in body composition and the metabolic changes associated with transition from the premenopausal to the postmenopausal state are related to an increase in metabolic syndrome [18].

Epidemiologically, the prevalence of metabolic syndrome also increases with age. A sedentary lifestyle with increased industrialization and urbanization in countries such as India, for example, is leading to an increase in obesity and metabolic syndrome similar to what has occurred in high-resource countries, such as the United States. One study found that an increase in waist circumference, which is related to insulin resistance and cardiovascular disease, was more common in South Asian Indian women than White women [19].

12.4 Energy Balance and Weight Management in the Menopause Transition

The World Health Organization highlighted a key fact, noting that, "most of the world's population live in countries where overweight and obesity kills more people than underweight" [20]. Obesity is defined as a body mass index (BMI) of 30 kg/m^2 or greater. Worldwide rates of obesity have steadily increased since the 1970s and have impacted both higher income populations as well as disadvantaged and marginalized groups. Sub-Saharan Africa and Asia are the only regions that are not burdened with high rates of overweight and obesity in comparison to other regions of the globe. Although rates of obesity continue to trend upwards worldwide, obesity alone is not the problem. A woman can have a diagnosis of obesity and be metabolically healthy without the presence of cardiometabolic diseases [21]. Alternatively, there is sufficient data that suggests obesity is often associated with an increased risk of developing metabolic dysfunction, namely cardiovascular disease, endocrine disorders including insulin resistance and diabetes, disorders of lipid metabolism, and musculoskeletal disorders [22].

12.4.1 Metabolic Alterations in the Menopause Transition

Decrease in the sex hormone estradiol seen during the menopause transition impacts the metabolism of dietary fatty acids namely their clearance and storage. Additionally, there is a relationship between postprandial elevations in insulin and triglyceride storage in postmenopausal women and the subsequent potential for weight gain [23]. Prior to the menopause transition, subcutaneous adipose tissue (SAT) is involved in the buffering of postprandial triglyceride spikes. The combination of aging and the menopause transition impairs the ability to convert fatty acids to SATs. This leads to greater accumulation of triglycerides, circulating glucose

Table 12.2 Diagnostic criteria for Met-S among women

• Waist circumference greater than 35″
• Pre-hypertension (blood pressure >130/85 mm/Hg)
• Elevated triglycerides (>150 mg/dL)
• Elevated blood glucose levels (>100 mg/dL)
• Decreased HDL cholesterol (<50 mg/dL)

post meals, circulating insulin, and adipocytes [23]. These alterations in metabolism have the potential to impact energy balance and weight gain.

Increased weight prior to and during perimenopause can further exacerbate metabolic alterations that have a negative impact on health as well as disease development and progression. Body composition changes, specifically an increase in adipocytes and decrease in lean body mass, common in women of menopausal age, can further precipitate the development of metabolic disease. Also, commonly referred to as metabolic syndrome (Met-S), this clustering of interrelated conditions supports the risk and progression of diabetes, stroke, and heart disease [24] (Table 12.2).

12.4.2 Energy Balance

Maintaining energy balance is a crucial focus to blunt the negative health impacts attributable to an increase in weight due to aging and a shift in body composition experienced by many women during the menopause transition. With aging there are reduced requirements for energy intake [25]. Striking the proper balance between energy intake and energy expenditure through intentional physical activity and a balanced pattern of nourishment is integral to modifying health outcomes. Individuals should be encouraged to choose a majority of nutrient-rich whole and minimally processed foods that follow their foodways in place of energy dense and processed options. In general, foods that are energy dense generally contain a higher number of calories per serving. Whole foods that are nutrient dense contain a higher level of vitamins, minerals, and other nutrients of significance with little or no added sugars or fats. A sugar-sweetened yogurt provides more energy and additives in comparison to plain yogurt, and fruit jam provides more energy and fewer nutrients in comparison to fresh fruit that is rich in antioxidants and fiber. Foods in their whole and minimally processed form all have a higher proportion of fiber, phytonutrients, vitamins, and minerals with limited added sugars, fats, and salts in comparison to the energy-dense, nutrient-poor counterpart.

What follows are the current guidelines from the Nutrition Care Manual on weight management, including recommended nutrition interventions [26]. While there are numerous interventions that can address energy balance, weight management, and metabolic disease, it is important to consider them in the patient's context. Factors stemming from socioeconomic conditions, cultural or religious traditions, personal dietary restrictions due to preference or health issues, and

availability of accessible resources must be considered. Traditional, western-centric ideals of body shape and size do not translate across every population, demographic, and gender identity. It is important to tailor the nutrition intervention to the individual while taking their lived experience into consideration.

To promote sustainable changes and ensure the individual is well-equipped to move forward autonomously, engaging in medical nutrition therapy from a lens of cultural humility, lasting a minimum of 6 months is recommended [26]. Medical nutrition therapy (MNT) is an evidence-based medical approach to treating certain chronic conditions through the use of an individually tailored nutrition plan implemented by a registered dietitian. To be effective, it must prioritize the individual's nutrition-related diagnosis with a realistic and achievable intervention. Weight reduction may be one of the end goals; however, there are often accompanying conditions and social health determinants that are obstacles and can be barriers to change. Recommendations are to individualize weight loss when deemed medically necessary and wanted by the patient. Focusing on weight alone should never be the goal, rather a holistic approach focused on improving metabolic parameters.

Intake of a well-rounded pattern of eating is characterized by a regular and consistent intake of consumption of fruits, vegetables, beans, legumes, and unrefined starches in their whole and minimally processed form, with a concurrent reduction of saturated fats derived from animal sources. Opting instead for mono- and poly-unsaturated plant-based fats and high intake of anti-inflammatory, bioactive compounds, such as polyphenols and omega-3 fatty acids is supportive of optimal health [27] (Table 12.3).

Encouraging culturally appropriate food choices that promote reduced energy intake and facilitate cardioprotective eating patterns will support healthy, sustainable weight loss while aiding in decreasing risk of associated diseases.

12.4.3 Glucose Metabolism

The global burden of diabetes impacts more than 422 million adults, and in 2012, having a diagnosis of diabetes resulted in 1.5 million deaths worldwide with an additional 2.2 million deaths reported in adults with blood sugar levels outside of recommended ranges [29]. Worldwide, there has been a 5% increase in early death from diabetes between 2000 and 2016 [29]. During the menopausal transition, women are at increased risk of developing diabetes (see Chap. 5).

Glucose metabolism is an essential biochemical process that enables delivery of nutrients and energy throughout the body. There is an age-related decrease in glucose tolerance with an increased risk of abnormal glucose metabolism. This is in part due to the decrease in lean body mass and an increase in free fat mass including visceral adiposity, resulting in insulin resistance [30].

Menopausal decrease in both estrogen and progesterone contributes to the challenges of blood glucose management expressed by impaired insulin secretion as well as decreased insulin sensitivity. Estrogens are involved in glucose metabolism,

Table 12.3 Selected food sources of polyphenols and omega-3 fatty acids

Selected food sources of polyphenols [28]
• Black berries 100 g serving contains ~8–27 mg per serving
• Blueberries 100 g serving contains ~25–500 mg per serving
• Black grape 200 g serving contains ~50–1500 mg per serving
• Kiwis 100 g serving contains ~60–100 mg per serving
• Cherries 200 g serving contains ~36–230 mg per serving
• Yellow onion 100 g serving contains ~35–120 mg per serving
• Eggplant 200 g serving contains ~1500 mg per serving
Selected food sources of omega-3 fatty acids (NIH Tip Sheet Omega-3 Fatty Acids)
• Fatty and cold-water fish: sardines, mackerel, herring, anchovies, trout, haddock
• Beans: black beans, pinto beans, navy beans, mung beans
• Nuts: almonds, walnuts, cashews, pistachios, Brazil nuts, macadamia nuts
• Seeds: flax seeds, chia seeds, sesame seeds, sunflower seeds, pumpkin seeds
• Sea vegetables

specifically within the beta cells of the pancreas [31]. As estrogen activity decreases, glucose metabolism is impaired.

Insulin is an endocrine peptide hormone which binds to plasma membrane receptors in target cells, creating an anabolic response to nutrient and glucose availability. With the assistance of insulin, glucose is taken up by cells where it is metabolized into energy or stored as glycogen for future needs. Defective insulin production, insulin inaction, or a combination of the two can cause hyperglycemia and is associated with impaired glucose metabolism [24].

Insulin resistance is determined when there is sufficient insulin production by the pancreas, but an inadequate utilization and response to insulin by cells. The full cause of insulin resistance remains unknown. There is a diverse set of bioactive factors which are capable of impairing insulin sensitivity. Increased abdominal adiposity and physical inactivity are primary factors involved in the development of the condition [32].

Continuous overnutrition paired with insulin resistance contributes to a cycle of hyperinsulinemia, glucose and lipid toxicity that culminates in an eventual pancreatic Beta cell failure, leading to type 2 diabetes [33].

Genetic and environmental factors, including obesity, physical inactivity, age, and high intake of refined grains, added sugars, and synthetic fats are also regularly associated with increased risk of developing type 2 diabetes. Some of these defects in insulin action are reversible by modifying factors related to nutrition and lifestyle.

Individuals presenting with altered glucose metabolism and higher weights during each stage of menopause are at an increased risk for the development of diabetes and CVD [34]. Regular intentional physical activity has been shown to be positively associated with improved glucose and insulin metabolism by decreasing plasma glucose and insulin, while increasing glucose uptake and insulin sensitivity [34].

12.4.3.1 Body Composition and Glucose Metabolism

Many women of menopausal age tend to gain weight, particularly increased body fat around the midsection, which increases the risk of insulin resistance. Insulin resistance often presents with no symptoms so a woman may not realize there has been an alteration with their glucose metabolism until receiving a diagnosis. For these reasons, it is especially important to be aware of the interplay between body composition changes during the peri- and postmenopausal years and counsel patients on the supportive role of nutrition and the importance of intentional regular physical activity.

While carbohydrates in the diet provide fuel in the form of glucose, excess or rapidly changing serum glucose levels contribute to the development of chronic health conditions such as type 2 diabetes, insulin resistance, and metabolic syndrome. Carbohydrate type and digestibility influence postprandial plasma glucose concentrations and the inflammatory response. Regular and consistent excessive intake of foods with a high glycemic index such as liquid carbohydrates found in juice drinks and sugar sweetened beverages, added sugars, or refined starches are associated with an increased risk of significant variability in blood glucose and the increased risk of developing a disorder of glucose metabolism.

Elevated glucose caused mitochondrial damage and dysfunction in muscle cell culture experiments. This effect may lead to impaired tissue energy metabolism and substrate utilization, contributing to the development of oxidative stress, inflammation, and insulin resistance. These effects of hyperglycemia may enhance muscle protein catabolism, leading to reduced lean body mass. Hyperglycemia paired with the decrease of estradiol during menopause may exacerbate the reduction in lean body mass [35].

12.4.3.2 Microbiome and Glucose Metabolism

The role of the gut microbiota in reducing oxidative stress and inflammation should be promoted as a key point of education in the menopausal transition. The gut is an integral part of the immune system, involved in endocrine function and cell signaling. An unfavorable microbiome, as seen in decreased diversity among gut bacteria, may contribute to the onset of metabolic dysfunction by triggering pro-inflammatory responses. Alternatively, a favorable microbiome where there is a plethora of diverse colonic bacteria may offer protection against metabolic diseases. A pattern of eating featuring nondigestible plant fibers positively influences colonic fermentation resulting in the production of short chain fatty acids and increased diversification of gut bacteria which may have a protective role against many diseases [36].

12.5 Carbohydrate Literacy

A balanced eating pattern instead of a strict generalized diet, along with increasing carbohydrate literacy, is recommended to reduce the risk of the progression from impaired glucose tolerance, or prediabetes, to type 2 diabetes. Encouraging mindfulness around carbohydrate consumption is key while educating women on the

importance of higher fiber slower release carbohydrates in place of refined grains will support the body's glucose response. Examples of slower release carbohydrates and low glycemic index carbohydrates are beans, nuts, seeds, whole grains, and non-starchy vegetables. Increasing the protein–carbohydrate ratio can decrease glycemic variability and lessen the risk of developing impaired glucose metabolism. For example, consuming a piece of fruit with a source of protein will slow the absorption of glucose into the bloodstream and reduce rapid increases in blood sugars.

This approach encourages the individual to have agency and choice in the foods they consume while accommodating cultural dietary preferences, as well as allowing flexibility with their daily intake. Examples of well-known eating patterns that support glucose metabolism include Mediterranean patterns of eating as well as eating patterns centered around plant-based approaches. The Mediterranean includes 22 countries with diverse ethnic and cultural cuisines. The basis of these modes of eating are centered around an abundance of vegetables, fruits, beans, nuts, seeds, seafood, and minimal amounts of lean proteins. Added sugars, synthetic fats, and salts are consumed at a minimum.

12.6 Nutrient Recommendations

As a baseline, macronutrient distribution derived from the dietary reference intakes (DRI) should be tailored to the individual's needs and current health status. Macronutrient ranges may include: 10–35% of total daily energy intake from protein (1–1.5 g/kg body weight), 20–35% from fat, and 45–65% from carbohydrate [26, 37]. Clinical judgement should be used when determining a patient's protein needs as older women generally benefit from protein intakes on the higher end of the range. Fiber plays a key role in maintaining blood glucose levels and promoting satiety. The USDA Dietary Guidelines recommends 14 g of fiber per 1000 kcal or 20–35 g/day [26]. Increasing fiber intake above the recommendations can be done with proper medical guidance by a registered dietitian nutritionist or qualified care provider.

Food-based dietary guidelines for the European Union, Iceland, Switzerland, Norway, and the United Kingdom recommend a varied pattern of eating that includes grains, beans, nuts, seeds, vegetables, fruits, dairy products, and animal proteins with country-specific recommendations on added sugars, salts, and fats [38].

Focusing on constructing a plate rich in phytonutrients, with an abundance of non-starchy vegetables at each meal, is of utmost importance. Encourage animal proteins as the complement rather than the main component of the meal. Beans and other high fiber plant-based foods such as leafy greens and cruciferous vegetables are supportive of euglycemia. Even modest increases in plant foods have been clinically and statistically significant with regard to improved blood sugar management [39]. Modifications to the pattern of eating, with an emphasis on the proportion, portion, and types of carbohydrate, are critical to improve utilization of blood glucose in the body.

12.7 Fluid Recommendations

When blood sugar levels remain elevated, the kidneys compensate by increasing urination as a mechanism for clearing excess sugars. Adequate hydration aids metabolic processes, including moving glucose out of circulation. When determining adequate fluid intake, consideration should be paid to current health status, daily physical movement, and geographic location/weather. The standard recommendation can be determined using the mL/kg of body weight.

Although plant-based foods contribute to overall hydration, water should be the first beverage of choice when considering hydration. Unsweetened herbal teas can also be enjoyed and are contributors to daily hydration. Educating patients on appropriate sources of hydration should be a part of the discussion as well as assessing the current beverages the patient consumes throughout the day.

12.8 Eating Patterns and Menopause Symptoms

Research has been conducted on various dietary eating patterns in relation to positive health outcomes as well as on the impact on reported levels of adverse symptoms associated with the menopause transition, including vasomotor symptoms, irritability, and mood swings. Higher fiber patterns of eating that included a regular intake of whole and minimally processed fruits, vegetables, including both starchy and non-starchy, beans, nuts, seeds, and unrefined grains as seen in traditional and vegetarian diets resulted in a clinically significant reduction in menopausal symptoms, specifically vasomotor symptoms [40, 41]. A 10% weight loss over 1 year, following the above dietary recommendations, significantly reduced vasomotor symptoms [42] (Table 12.4).

12.9 Mindful Weight Management

When weight loss is desired, individuals showing impaired glucose metabolism should aim for a targeted loss of 7% of body weight and increase moderate intensity physical activity to at least 150 min/week, as they are able [26]. Medical nutrition therapy to decrease total body weight should aim for no more than 1- to 2-pound deficit per week in the beginning of therapy with an end goal of a 7–10% decrease in total body weight [24]. This can be achieved over time by modifying intake along with daily intentional physical activity. Among individuals who are overweight or obese with a desire to lose weight, a deficit of between 250 and 500 kcal/day is recommended to encourage healthy weight loss and decrease the risk of disease progression [43]. Healthy weight loss through physical activity not only supports long-term weight management, it also supports a reduction in glycemic variability and reduces the risk of cardiovascular disease [26].

As an alternative to energy restriction, focusing on the proportions of food as well as the frequency with which they are consumed can support a mindfulness

Table 12.4 Patient centerd nutrition considerations different dietary patterns on the menopause experience of individual patients

• Begin with a culturally appropriate individualized assessment of eating patterns. Avoid generalizing patterns of eating based solely on ethnicity and/or race, as there is tremendous variation in dietary consumption patterns within ethnicities and global regions
• Meet clients/patients where they are in terms of eating plans, suggesting adjustments that are culturally sensitive and that allow them to continue to celebrate traditions
• Refrain from demonizing specific foods—particularly those of cultural significance—but instead approach them with suggestions on how to prepare traditional foods differently to keep flavor but make it healthier when warranted
• Include a discussion of when it is appropriate to consume the favorite or special dish without modification
• Avoid judgement, work from a perspective of cultural humility and maintain sensitivity to ensure the patient is receptive to suggestions and is not put off or made to feel blamed for their health outcomes; work in partnership to achieve better health outcomes
• Consider dietary patterns of individuals consumed across the life cycle (premenopausal, perimenopausal, and postmenopausal) as there might be impactful differences at different stages
• Factor differences in regional/cultural cooking methods of similar foods, such as steaming, frying, grilling of meats and the use of different spices/herbs and/or use of sweeteners and sodium in food preparation when suggesting healthier swaps

around food consumption. Encouraging patients to think about the whole and minimally processed foods that can be added to their regular routine while reducing their overall intake of sugar-sweetened beverages, refined grains, and processed foods allows them to lean into long-term thinking and modifications around food.

12.10 Implementing Recommendations in Glucose Metabolism

Dietary and lifestyle changes can have a substantial effect on overall health, metabolism, and treatment of associated complications among individuals with impaired glucose metabolism. In addition to carbohydrate literacy, individualized medical nutrition therapy is necessary to fit the plan to the individual's needs and achieve treatment goals. Moving away from a one-size-fits-all nutrition prescription is the first part of individualizing the prescription. When counseling an individual about their current nutrition patterns and the need for individualized modifications, it is advisable to focus on the addition of "better-for-you" foods, instead of eliminating "bad" foods or adhering to an overly restrictive diet. For example, in the case where someone is consistently consuming a processed Western pattern of eating that is abundant in refined grains, fried animal proteins, added sugars, salts, and fats, rather than suggesting the elimination of the entire meal, present healthier replacement options and allow the patient to be involved in the choices. Think about ways the patient can increase the proportion of plants on their plate while reducing fried options or meals with higher amounts of added sugars, salts, and fats. While the plate is taking on a different, healthier nutrient profile, it still resembles what is

Table 12.5 Recommendation suggestions

• The majority of the plate is fruits and vegetables
• Lean animal proteins are prioritized in place of higher fat cuts
• Seafood is consumed weekly
• Sea vegetables are a part of the pattern of eating
• Utilizing local produce markets when possible to source fresh fruits and vegetables
• Including whole and ancient grains and starchy vegetables
• Including legumes regularly
• Increasing phytonutrients from fresh and dried herbs and spices
• Limiting heavily processed foods and fast foods
• Limiting sugar-sweetened beverages and juices
• Mindful interactions with alcoholic beverages according to current recommendations
• Hydrating with water

familiar. This plate transformation can be applied in several ways to a variety of cuisines and preparations. Consider suggesting these easy to follow, adaptable recommendations (Table 12.5):

12.11 Lipid Metabolism

Lipid profiles are one of the clinical markers used to determine risk for developing heart disease and stroke. Worldwide, approximately 3.9 million deaths were associated with nonoptimal levels of lipids [44].

Lipid metabolism disorders are another dietary-related condition that can sometimes emerge during the time of the menopause transition particularly in women with a predisposition to having elevated lipids secondary to nutrition, lifestyle, or genetics. While lipid metabolism tends to change with age, menopausal decreased levels of estrogens and increased levels of circulating androgens may exacerbate disorders of lipid metabolism. Ovarian estrogens lead to accumulation of peripheral fat in the gluteal and femoral subcutaneous regions. At the same time, androgens can lead to increased visceral abdominal fat [45]. These hormonal and metabolic changes and the concurrent increase in abdominal adiposity have the potential to alter insulin, total cholesterol, LDL-C, HDL-C, and the total cholesterol-to-HDL ratio, leading to a 50% risk of developing metabolic syndrome [46].

12.11.1 Implementing Recommendations for Heart Health

Elevated lipids that are modifiable with dietary changes are often tied to the pro-inflammatory Standard American Diet or Western style eating patterns heavy in refined grains, synthetic fats, and added sugars. The combination of pro-inflammatory eating patterns and hormonal shifts during the menopause transition results in elevated lipid levels and an increased risk of cardiovascular disease. Ko notes that low-energy eating patterns are recommended for postmenopausal women to prevent

Table 12.6 Dietary patterns that support healthy lipid metabolism

• A total reduction in refined grains
• Reducing daily intake of added sugars to no more than 5% of total energy intake
• Increasing the intake of fiber-rich foods from legumes, sea vegetables, non-starchy and starchy vegetables, as well as fruits
• Considering a significant reduction in higher fat and processed animal proteins
• Limiting daily intake of saturated fats to less than 10% of total energy intake
• Avoiding synthetic, *trans* fats and interesterified fats

metabolic alterations, citing a cross-sectional study involving 4984 Korean women who reported a diet high in "sea fish, seaweeds, dairy products, cereals, fresh vegetables and fruits and low in consumption of fast foods, animal-rich foods, added sugars and fried foods." This pattern of eating appeared to have a protective effect against dysregulated lipid metabolism [47].

The increased risk for metabolic disorders that derive from the altered lipids during the menopause stages can lead to an increased risk for cardiovascular disease, particularly postmenopause. As such, women who have reached menopause should be counseled to consume a healthy pattern of eating, high in phytonutrients and antioxidants including fruits, vegetables, and whole grains and low in animal-rich fats, added sugars, and refined carbohydrates. As women move through the life cycle, energy intake needs also decrease after menopause, so women should be encouraged to transition to a nutrient dense, lower energy eating pattern (Table 12.6).

Consistent nutrition modifications over 3 months have the potential to result in significant decreases in non-HDL cholesterol [48]. The link between the menopause transition and lipid metabolism disorders needs to be better understood to address the growing challenges of overweight and obesity and the associated chronic conditions.

12.12 Hypertension

Hypertension is a global public health burden with 1.13 billion people worldwide living with hypertension. When left untreated or not well managed, elevated blood pressure can bring on cardiovascular disease and neurological dysfunction. The majority of people living with hypertension are not managing the condition, contributing to high rates of death worldwide [49].

Hypertension is a common yet modifiable condition of chronically elevated blood pressure. Generally asymptomatic, it can silently contribute to atherosclerosis while increasing risk of cardiovascular disease, renal disease, neurological changes, and increased cerebral microinfarcts [50]. Hormonal changes occurring during the menopause transition, specifically the decline in estrogen, are closely related to the increase in blood pressure, along with weight gain and diabetes [50, 51] (see Chap. 5).

Epidemiological studies have shown that premenopausal women have a reduced rate of cardiovascular disease compared to their same-aged male counterparts

([52]). Postmenopause, however, the incidence and severity of cardiovascular disease in women increases. The lower incidence observed in women prior to the menopause transition and during the reproductive years suggests a cardioprotective effect in women partially attributable to estrogen. As most coronary heart disease events occur in women older than 63 years, the importance of adequate nutrition and lifestyle patterns becomes more apparent [51].

Implementing early, premenopausal nutrition and lifestyle pattern interventions is the best approach to combating the development and progression of cardiovascular disease postmenopause. A well-rounded pattern of eating that encourages heart health includes fruits and vegetables, whole grains, legumes, nuts and seeds, lean proteins, both plant and animal as well as fermented dairy foods while limiting the intake of overly processed foods, red meat and processed meats, alcohol, and added sugars including sugar-sweetened beverages [26]. Additionally, adequate fiber intake should be encouraged, along with regular physical activity to encourage a healthy weight or safe and healthy weight loss if indicated.

Eating for optimal health throughout the lifecycle is integral to reducing the risk of many diseases and improving health outcomes. A cardioprotective pattern of eating should be tailored to the needs of the individual following it, taking into consideration stated cultural beliefs and values, as well as social determinant of health that may make adhering to the plan more of a challenge. Working from the perspective of what can be added to support cardiovascular health should be a central part of the nutrition prescription (Table 12.7).

12.13 Implementing Recommendations for Heart Health and Blood Pressure

When working with an individual to make modifications toward a more cardioprotective pattern of eating, small, measurable changes are better than a drastic or restrictive overhaul to ensure the modification is achievable and sustainable. Medical nutrition therapy interventions for hypertension in conjunction with patient

Table 12.7 Primary focal points

- Decreasing sodium intake to 1500 mg/day
- Limiting dietary sources of saturated fat, *trans* fat, and interesterified fats
- Consuming
  - Increasing amount of fruits consumed daily (2–3 servings)
  - Increasing the amount of vegetables consumed daily (5+ servings)
  - Including whole and ancient grains in the pattern of eating
- Opting for lean protein sources
  - Seafood
  - Poultry
  - Lean cuts of meat
  - Legumes/nuts/seeds

education on reading a nutrition facts label on packaged goods have demonstrated positive results in lowering blood pressure [50].

Nutrition facts labels are valuable tools for consumers as they name the ingredients in the packaged goods as well as provide measurable details on products' content of macronutrients, sugars, and salts. Utilizing these tools better allows patients to make choices that are supportive of their individual health. Regulations on nutrition information displayed on a nutrition facts label are country dependent. In the European Union, labels are mandated to list energy, fats, sugars, protein, and sodium. In the United States, the Food and Drug Administration (FDA) regulates the nutrition facts label which must list serving size, calories, fats, cholesterol, sodium, carbohydrate, protein, vitamin D, calcium, iron, and potassium. Some countries in Latin America and the Caribbean have adopted laws enabling the placement of warnings on packaged foods with high amounts of added sugars, salts, and fats [53].

One adjustment most individuals can control regardless of socioeconomic or cultural factors is reducing sodium intake. Lowering sodium intake, ideally below 2000 mg/day, has been linked to decreasing hypertension [43]. Avoidance of cured foods, processed foods, and added salt when cooking can be suggested. Given the prevalence of salty foods in the typical Western daily diet, the process of weaning can be difficult and typically takes 6–8 weeks to slowly adjust taste preferences toward less salty foods. Restricting sodium in the pattern of eating is associated with a 17% decrease in incidence of hypertension and a reduction in blood pressure across all demographics, especially older adults [54].

Primary strategies to also include in the medical nutrition therapy plan are increased physical activity, weight loss when indicated, smoking cessation, and limited alcohol intake as part of a strategy to reduce risk of hypertension and cardiovascular disease (Table 12.8).

With implementation of these strategies, it is possible to reduce or reverse certain risk factors associated with hypertension as they relate to the menopausal stages. Adopting the necessary nutrition and lifestyle changes as part of everyday life promotes heart longevity and overall health, while lowering the risk of comorbidity.

Table 12.8 Modifications and recommendations *for blood pressure management*

Modification	Recommendation *for blood pressure management*
Weight management	• Weight loss as indicated; 4 kg decrease in weight correlates with a 4.5 mmHg decrease in blood pressure [55]
Decreased sodium intake	• Maximum of 2000 mg/day • Restriction of sodium to 1500–2000 mg/day shows greater reduction in blood pressure [54]
Low-sodium patterns of eating	• DASH (The Dietary Approaches to Stop Hypertension) Diet includes eating patterns rich in fruits, vegetables, lean protein, low-fat dairy, and limited saturated and total fat
Physical activity	• 30–45 min of moderate to vigorous physical movement at least 5 days/week
Alcohol and smoking	• Reduced alcohol intake to 1 alcoholic beverage per day • Smoking cessation

12.14 Bone Health

Bone health begins in the early years of a woman's life, during puberty, when there is a high rate of bone mass accumulation. Adolescence is the time when calcium can be retained in amounts significant enough to support peak bone mass. This sets the stage for bone health later in life.

An eating pattern that promotes healthy, strong bones throughout a woman's life cycle is essential in reducing the risk of developing osteoporosis and other osteo-related medical conditions. Bone health is often dismissed or disregarded relative to health imperatives, particularly in the reproductive years, given the length of time it takes for complications to manifest. Osteogenesis, or bone formation, is complete around the age of 18 years in women. Bone strength peaks between the ages of 25 and 30 years with a noticeable decline around age 40 years [56].

Loss of bone mass begins after 30 years of age when the rate of bone formation declines and bone resorption increases. Before entering menopause, bone continuously undergoes balanced remodeling, resorption, and deposition of calcium to new bone; however, after menopause, bone breakdown exceeds formation leading to bone loss and weakness [57]. This decline is inevitable and is accelerated by the decrease in estrogen levels during the menopause transition. While hormonal interventions can mitigate age and menopause-related side effects, including osteoporosis, they are contraindicated in those with preexisting cardiovascular-related conditions and may increase risk of blood clots, stroke, and heart attack in specific populations [56] (see Chaps. 6 and 13).

Bones are primarily composed of calcium and collagen and include other minerals such as phosphorus and magnesium [58]. The body builds bone with calcium obtained through the diet and is constantly replenishing bone calcium. If calcium intake is low or inadequate, however, the body may begin to leach nutrients from bone reserves and may utilize osteo-derived calcium for necessary functions and needs in the body.

Bone formation, along with osteoblast and osteoclast activity, is largely influenced/supported by magnesium. In association with parathyroid hormone and vitamin D_3—the active form of vitamin D—magnesium plays a significant role in supporting bone mineral density and overall bone homeostasis (see Chap. 13). Women with osteoporosis tend to present with lower serum magnesium levels compared to those with osteopenia and those who do not have osteoporosis or osteopenia, indicating that magnesium deficiency could be a risk factor for osteoporosis [59]. Patterns of eating that provide recommended levels of magnesium enhance bone health, but further research is needed to elucidate the role of magnesium in the prevention and management of osteoporosis [59]. Magnesium is easy to supplement, generally with a multivitamin, but is also found in foods like spinach, nuts, whole-meal bread, and some cold water fatty fish (e.g., salmon, mackerel, halibut). Although controversial, studies have found that patterns of eating that are rich in fruits and vegetables have the potential to reduce the acid load in the body and support positive calcium balance while reducing osteoclast and osteoblast activity [60].

Vitamin D deficiency is widespread worldwide and becomes more prevalent among the population with age [56, 61]. Adequate vitamin D and calcium intake are essential for optimal bone health and mitigation of age-related deficiency. With progression through the lifecycle and menopausal years, individuals are less able to synthesize vitamin D from sun exposure. Changes in vitamin D and calcium metabolism increase the risk for insufficient vitamin D and secondary hyperparathyroidism which further compounds bone loss [56]. Individuals at increased risk, including women in the menopause transition, should be aware of their vitamin D status and adjust oral intake and safe sun exposure accordingly to ensure adequate amounts.

12.14.1 Implementing Recommendations for Bone Health

There are some foods with small amounts of vitamin D that, as part of a well-balanced pattern of eating, may mitigate reduced sun exposure. A few examples of such foods include liver, egg yolks, fortified foods (e.g., orange juice, milk, soymilk, and other fortified milk substitutes, some fat spreads, and most fortified breakfast cereals), and cold-water fatty fish (e.g., salmon and trout and to a lesser extent tuna, sardines, herring, mackerel, and halibut). Vitamin D supplementation may be indicated in the case of an overt deficiency.

As the most abundant mineral in the body, calcium supports nerve transmission, muscle function, vascular signaling, and hormonal responses. It is one of the only minerals that does not shift serum levels with inadequate dietary intake as it is found in abundance within bone tissue, supporting tightly regulated levels [57]. Foods that are rich in calcium include dairy products (e.g., milk and cheese, or alternatively soy drinks with added calcium), green leafy vegetables (e.g., kale, chard, okra, spinach), foods made with made fortified flour (e.g., breads, cereals, pasta), and fish where the bones are eaten (e.g., sardines, anchovies).

12.15 Lean Body Mass

After the age of 30 years, lean body mass begins to decline. Lean body mass refers to the composition of the body that is non-fat mass, including muscle, tendons, bones, and internal organs. The loss of lean body mass, called sarcopenia, is common among all aging people [62]. Sarcopenia can have a significant impact on quality of life, and this loss can, in turn, decrease metabolism, cardiovascular capacity, and overall strength [58] (see Chap. 13).

Women experience significant decreases in lean body mass between perimenopause and early menopause. Dual-energy X-ray absorptiometry (DXA) and computed tomography (CT) imaging studies show the reductions between 0.5% and 1.5% [63].

As has been discussed throughout this chapter, there are adverse health risks associated with increased adiposity and shifts in body composition, namely the changes in distribution of body fat favoring the abdominal region in women of

menopausal age. These include disorders of glucose metabolism, such as insulin resistance, impaired glucose tolerance and type 2 diabetes; disorders of lipid metabolism; and hypertension. Also associated with postmenopause is a decrease in bone density and strength leading to osteoporosis and other osteo-related conditions. All of this underscores how essential it is for women to engage in activities to preserve lean body mass and related strength prior to menopause and throughout their lifecycle.

Regular physical activity and adequate daily protein intake can aid in the preservation of lean body mass and decrease the risk of chronic disease development [64]. Consistent daily physical activity, specifically walking 6000 steps or more, decreases the risk of cardiovascular disease and diabetes among middle-aged women, independent of menopause status [65]. This suggests that physical activity prior to the menopausal transition can decrease the risk of metabolic abnormalities and cardiovascular-related diseases [58]. Weight-bearing exercises are recommended along with endurance exercise, stretching, and balance work to support lean body mass. In conjunction, when complemented with optimal protein intake of more than 2 g/kg total body weight, menopausal women tend to have increased lean body mass and sustained metabolic control [65]. Women with osteoporosis should consult a qualified provider to determine the types of intentional physical activity that are the most beneficial for preserving lean body mass.

12.16 Physical Activity

Physical movement is another primary component of a comprehensive intervention that supports metabolic health and weight management. Geography, home environment, ability and mobility, accessibility, and affordability all play a role in the type of exercise plan recommended. Goals should be realistic, achievable, and sustainable. Recommendations should consider an individual's ability and any mobility challenges they may have. Other factors to consider when designing an exercise or physical activity plan include access to a safe neighborhood space for exercise, financial resources to purchase equipment such as light weights or fitness bands or to join a fitness center, and time constraints due to family and work obligations.

Discuss any potential barriers that might prevent the regular engagement in physical activity and brainstorm potential solutions. Suggesting strategies such as taking the stairs whenever possible, finding creative ways to walk daily or engage in other safe exercises, holding dance parties with friends and loved ones, or using household items for weightlifting are possible ideas to include.

Body movement can take on a variety of forms focusing on flexibility, aerobic conditioning, strength training, and restorative moments. It is important to remember that with increased physical activity, estimated macro and micronutrient needs may increase depending on the individual. A discussion on adequate hydration should also be a part of the nutrition plan to support physical activity.

12.17 Conclusion: Menopause Is a Natural Transition, Not a Disease

While we have spent much of this chapter discussing nutrition, the effects of aging, and the menopause transition on potential adverse health outcomes, it is essential to emphasize that menopause is not a disease. Each woman experiences menopause differently influenced by genetics, diet, lifestyle, cultural expectations and attitudes, and duration and severity of symptoms. Many women report no physical changes during the perimenopausal years other than irregular menstrual periods. Some women experience some or all of the symptoms commonly associated with menopause, such as hot flashes, sleep disturbances, weight gain, increased anxiety or mood changes, vaginal dryness, or memory problems. Many of these issues are unrelated to hormone changes, and many, such as hot flashes and memory disturbances, usually resolve postmenopause. Heading into the menopausal years, understanding the importance of nutrition along with healthy dietary and lifestyle habits is essential for overall optimal health and might even make the menopause transition an easier one.

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Musculoskeletal Health in Menopause

13

Kathleen A. Geier and A. J. Benham

13.1 Bone Physiology

13.1.1 Introduction

To best understand the metabolic skeletal alterations associated with menopause, particularly osteoporosis, clinicians need to understand bone physiology. Bone is not a static mass of hard material, despite the skeleton's appearance when seen outside the body. Bone is constantly turning over and being remodeled in a regular, predictable sequence and time frame in the healthy person (see Fig. 13.1). This process creates a steady metabolic state and a constant mass and composition of the skeleton. Alterations in this equilibrium lead to metabolic bone disorders such as osteoporosis.

Several factors may alter normal bone equilibrium. The most influential elements in maintaining bone strength and hardness are calcium, vitamin D, magnesium, phosphate, parathyroid hormone, and estrogen. The maintenance of healthy bone relies on the appropriate function of several important metabolic processes influenced by these factors.

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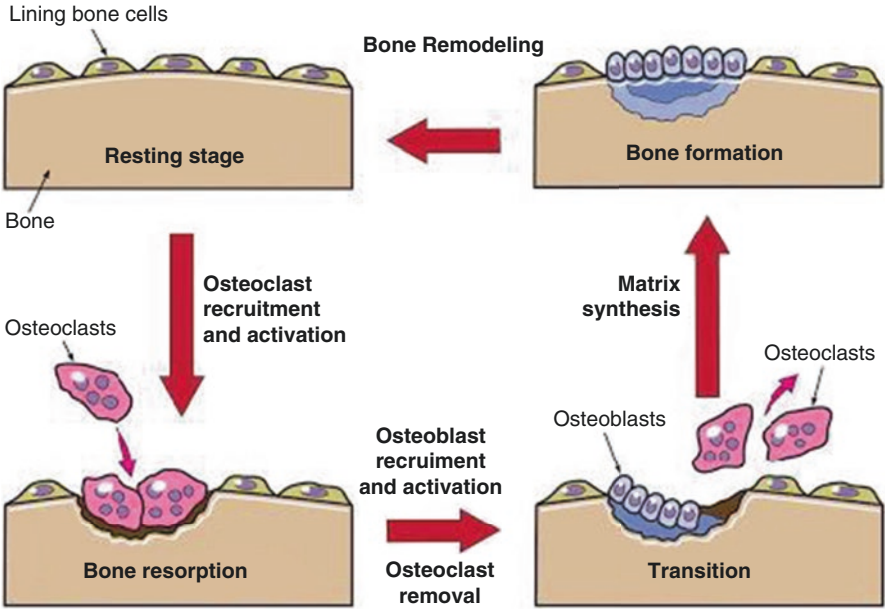

Fig. 13.1 Normal bone remodeling. (Reprinted with permission by Rolera LLC, http://www.clicker.com/clipart-426111.html)

13.1.2 Calcium

Calcium, an essential mineral present in all body tissue, participates in many physiological processes, including the formation of bones and teeth, blood coagulation, neuromuscular excitability, cardiac rhythmicity maintenance, and lactation. Ninety-nine percent of the body's total calcium is stored in the organic matrix of bones, providing the skeleton's strength and hardness, and is readily mobilized to meet the body's physiological needs. Intricate homeostatic feedback systems maintain serum calcium at its normal level of 8.5–10.5 mg/dL.

Calcium is not produced by the body; it must be supplied by diet and/or supplements. Many foods, including dairy, plant foods, and bony fish, are high in calcium content. Some food and dairy products may also be fortified with calcium and vitamin D. Even people who eat healthy, balanced diets may not be ingesting and absorbing enough calcium. This is particularly true for those who follow vegan diets, have lactose intolerance, or consume large amounts of sodium or protein, which increase calcium excretion. Other factors that can interfere with adequate calcium intake and absorption are long-term corticosteroid treatment and gastrointestinal conditions.

Corticosteroids affect calcium and bone metabolism in several direct and indirect ways. The direct effects of long-term corticosteroid use lead to (1) increased rates of bone breakdown (resorption) at the cellular level; (2) decreased rates of bone formation, also at the cellular level; (3) decreased calcium absorption by the

Table 13.1 Recommended daily calcium requirements [1]

Age	Male	Female	Pregnant	Lactating
0–6 months[a]	200 mg	200 mg		
7–12 months[a]	260 mg	260 mg		
1–3 years	700 mg	700 mg		
4–8 years	1000 mg	1000 mg		
9–13 years	1300 mg	1300 mg		
14–18 years	1300 mg	1300 mg	1300 mg	1300 mg
19–50 years	1000 mg	1000 mg	1000 mg	1000 mg
51–70 years	1000 mg	1200 mg		
71+ years	1200 mg	1200 mg		

[a]*AI* adequate intake

intestines; and (4) increased calcium excretion by the kidneys. Due to their effects on calcium, long-term corticosteroids may also indirectly trigger the parathyroid glands to increase parathyroid hormone (PTH) secretion leading to further bone destruction.

In the presence of certain gastrointestinal conditions, such as inflammatory bowel disease or celiac disease, adequate calcium often cannot be absorbed. In clinical situations where inadequate calcium is provided to meet the body's physiological needs—regardless of etiology—calcium supplements may help meet the recommended daily requirements (see Table 13.1 for recommended daily calcium requirements).

Many different preparations and doses of supplemental calcium are available over-the-counter (OTC). Clinicians making specific recommendations for individual patients must consider several factors. Supplement expense and tablet size may make them prohibitive for patients on limited incomes and difficult for people with swallowing challenges. Calcium supplements come in pill, liquid, and chewable forms, which allow the clinician to choose the most appropriate supplement for a particular patient's needs.

The two main forms of calcium found in supplements are *citrate* and *carbonate*. Calcium carbonate is inexpensive, commonly available, and best absorbed when taken with food due to its dependence on stomach acid for absorption. When making supplemental calcium recommendations to patients consider the following:

- The amount of elemental calcium contained in the recommended product, that is, the actual amount of calcium in the supplement. Calcium carbonate supplements provide more elemental calcium per pill than calcium citrate supplements, increasing the number of calcium citrate tablets needed to achieve the daily recommended calcium intake.
- The amount of calcium taken at one time. Calcium is best absorbed when taken in divided doses of 500–600 mg, several times per day.
- Whether or not the supplemental calcium should be taken with food. Except for calcium citrate supplements, most calcium products are best absorbed when taken with food.

Table 13.2 Comparison of calcium supplements

Supplement	Amount of elemental calcium
Calcium carbonate	40%
Calcium citrate	21%
Calcium lactate	13%
Calcium gluconate	9%

https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/calcium-supplements/art-20047097 [4]

- Potential side effects. Some products, most commonly calcium carbonate supplements, are more likely to cause gastrointestinal issues such as gas and constipation. These side effects can sometimes be alleviated by using divided doses or by taking supplements with meals.
- Possible interactions between recommended calcium supplements and any other prescription or OTC medications the patient may be taking.

Calcium citrate is well absorbed, also referred to as more bioavailable, with or without food. It is useful for patients with absorption disorders or those who experience gastrointestinal side effects with calcium carbonate [2]. Some fortified juices contain calcium citrate malate, a well-absorbed form of calcium [3]. Many calcium supplements are combined with vitamin D, an added convenience for patients who require vitamin D supplementation. The types and varieties of available calcium supplements and their elemental calcium content are listed in Table 13.2.

13.1.3 Magnesium and Phosphorus

Magnesium and phosphorus are also important elements in bone metabolism. Approximately 60% of the body's magnesium is found in bone. An essential enzyme, magnesium makes up 0.5–1% of bone. Neuromuscular activity, membrane stability, calcium metabolism, calcium channel activity, and ion transport rely on normal magnesium levels. Low magnesium levels inhibit crystal formation by bone cells, thereby contributing directly to osteoporosis. Indirectly, low magnesium levels contribute to osteoporosis by influencing the secretion and the activity of parathyroid hormone (PTH). Low magnesium levels also promote low-grade inflammation [5] (see Fig. 13.2).

Magnesium is obtained from healthy dietary intake and is easily found in cereal grains, nuts, meat, fish, fruits, and legumes. Research has revealed inadequate magnesium dietary intake in North America and Europe, most likely associated with dietary habits involving processed foods and low micronutrient intake.

Phosphorus is a mineral that combines with other substances to form organic and inorganic phosphate compounds. The importance of phosphorus in bone metabolism is best seen in the organic matrix of bone, which is comprised mostly of phosphorus and calcium. In the kidneys, these two elements operate in opposition to

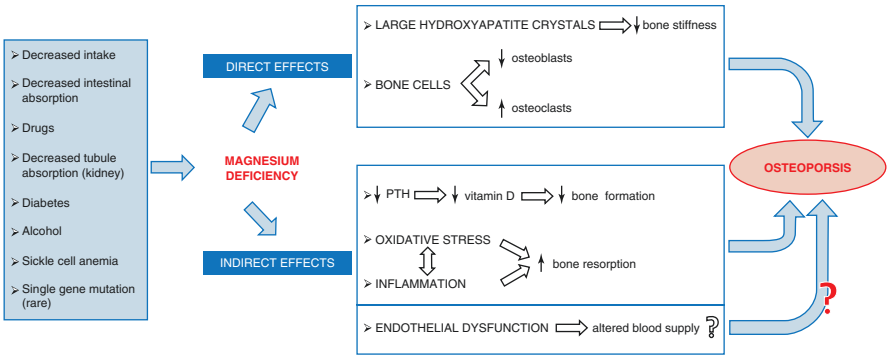

Fig. 13.2 Present knowledge about the mechanisms involved in linking magnesium deficiency and osteoporosis. (Castiglioni et al. [5], Reprinted from Nutrients 2013, 5(8), 3022–3033; https://doi.org/10.3390/nu5083022 with permission [Open Access])

each other. When phosphorus is lost or depleted for any reason, calcium is reabsorbed by the kidneys.

Phosphate is one of the most abundant minerals in the body, and its serum levels are regulated by a complex set of processes that occur in the intestine, skeleton, and kidneys. Primary sources of dietary phosphate include milk, other dairy products, and meats.

Phosphate is easily absorbed by the intestines, except in the presence of excessive calcium. Phosphate will bind with excessive calcium to form calcium phosphate, which, in the absence of vitamin D, is poorly absorbed by the intestines and excreted in feces.

13.1.4 Vitamin D

Vitamin D, more appropriately described as a steroid hormone, is an important component in bone health and an essential factor in calcium and phosphorus metabolism. The precursor to vitamin D is inactive and present on the skin. With adequate exposure to ultraviolet rays of the sun, it is converted in the liver and kidney to the active form (1,25-dihydroxycholecalciferol), which promotes calcium absorption in the intestinal epithelium. The active form of vitamin D has two effects on the bone at a cellular level: (1) it facilitates osteoid (the unmineralized, organic portion of bone matrix) mineralization and (2) it supports PTH in its mobilization of calcium from bone in the presence of hypocalcemia. Well documented for its role in bone health, adequate levels of vitamin D may also help protect us from depression, diabetes, heart disease, and some types of cancer [6].

Checking blood levels of vitamin D became a common clinical practice in the United States following the 2010 Institute of Medicine (IOM) identification of a vitamin D level of 20 ng/mL or higher as adequate for good bone health [7]. Levels

of vitamin D below 20 ng/mL were considered deficient, and treatment was recommended.

This recommendation has since changed, and the notion of vitamin D deficiency is now somewhat controversial, with concerns that clinicians may continue to overscreen and treat patients who are not deficient. Current literature supports screening high-risk individuals only [8–10]. As perimenopausal women often fit this category, they should have their vitamin D levels checked. A study published in 2015 followed more than 2000 perimenopausal women for nearly 10 years and found that vitamin D levels under 20 ng/mL were associated with a slightly increased risk of nontraumatic fractures [11]. Based on this finding, recommendations were given to provide vitamin D supplementation to perimenopausal women with levels under 20 ng/mL. There is speculation that gradual muscle mass and function loss with aging may also be related to decreased vitamin D levels following menopause [11].

Others at risk for true vitamin D deficiency include people who have had gastric bypass surgery, people with anorexia nervosa, those who suffer from malabsorption syndromes such as celiac sprue, and those who have dark skin or wear total skin covering and are not absorbing sunlight. All people falling into one or more of these categories should be screened for vitamin D deficiency and treated if their levels are under 20 ng/mL. Individuals with osteopenia and osteoporosis should also be screened and appropriately treated if found to be vitamin D deficient. Note that many foods are high in vitamin D, including some fish, egg yolks, and fortified cereals and dairy products. Supplemental vitamin D can be provided when adequate intake is not achieved through dietary sources.

Skin tends to lose its ability to generate vitamin D as we age. Those unable to get sun exposure, for example, individuals who live in institutional settings such as nursing homes and those who spend very little time outdoors, can benefit from supplemental vitamin D. An additional concern is that many people use sunscreen to prevent skin cancer from the ultraviolet sun rays, and sunscreen with an SPF of 8 can decrease vitamin D production by 95%.

The National Osteoporosis Foundation (NOF) recommends the following dosage for supplemental vitamin D for adults (although some people will require more): under age 50 years, 400–800 IU/day; ages 51–70 years, 1000 IU/day; age 70 years and above, 800 IU/day. The safe upper limit of oral vitamin D supplementation, according to NOF, is 4000 IU/day [12].

13.1.5 Parathyroid Hormone

Parathyroid hormone is a critical factor in serum calcium regulation due to its direct action on the bone and, in the kidneys, its indirect effect on the gastrointestinal system. The intricate feedback mechanism that regulates serum calcium levels is based on the sensitive parathyroid glands' secretion of PTH in response to low serum calcium [13].

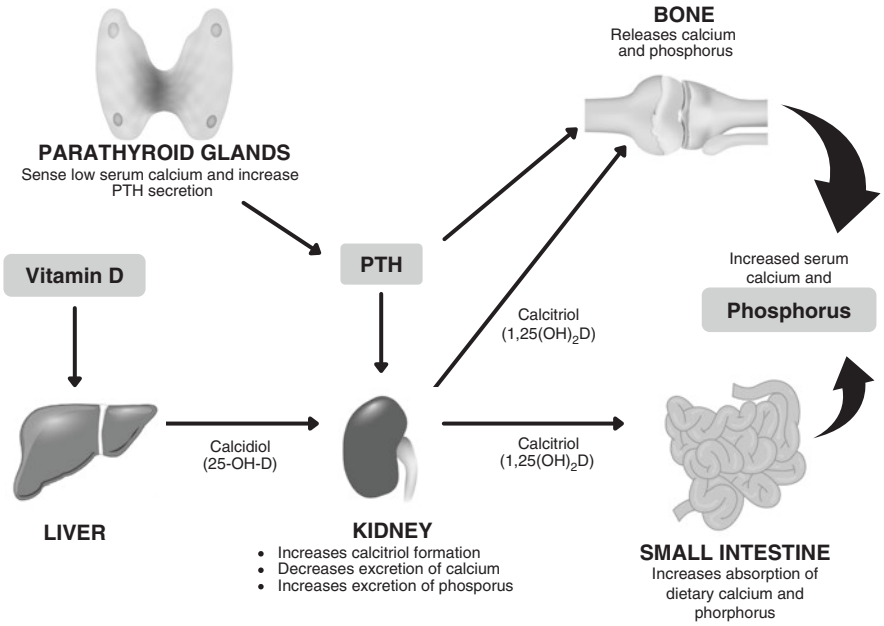

Fig. 13.3 The effects of parathyroid hormone on calcium metabolism

In the presence of hypocalcemia, the parathyroid glands increase PTH secretion, which leads to increased activation of vitamin D in the kidneys, increased renal reabsorption of calcium, and increased excretion of phosphate. On a cellular level in bones, increased PTH levels lead to increased destruction or dissolution of bone mineral crystals via biochemical activity (bone resorption) of calcium. The net result of this metabolic feedback system is increased serum calcium, often at the expense of the skeleton (see Fig. 13.3).

When hypercalcemia is present, all of the hormonal regulatory actions described for hypocalcemia occur in the opposite direction. Figure 13.4 depicts the hormonal regulations of calcium balance.

13.1.6 Calcitonin

Calcitonin effects are opposite to those of PTH in calcium regulation and bone metabolism. Calcitonin is a hormone secreted by the thyroid gland in response to elevated serum calcium levels. It lowers serum calcium concentration in the following three ways:

1. Inhibiting the formation of new osteoclasts
2. Inhibiting osteoclastic bone resorption
3. Increasing osteoblastic activity

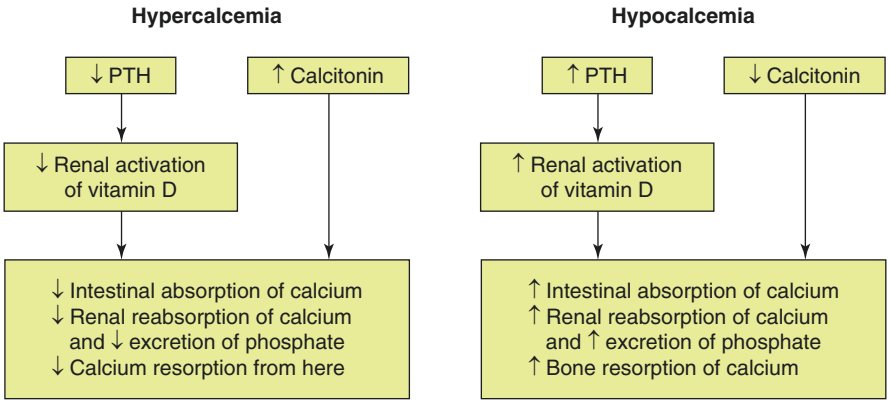

Fig. 13.4 Hormonal regulation of calcium balance: the effects of PTH and calcitonin on calcium regulation

The effects of calcitonin and PTH on calcium regulation are summarized in Fig. 13.4.

13.1.7 Estrogen

Estrogen is a bone mass regulator that, when present, prevents bone loss in women. In women, estrogen is the major hormonal regulator of bone metabolism. Produced primarily by the ovary, estrogen protects bones by (1) promoting intestinal absorption of calcium, (2) promoting renal reabsorption of calcium, and (3) suppressing osteoclastic activity and increasing osteoblastic activity. The cessation of ovarian function surrounding menopause leads to a rapid bone loss, with the maximum rate of loss occurring during the first 5 years following menses cessation.

Hypoestrogenic postmenopause bone loss and osteoporosis are primarily due to increased bone resorption by osteoclasts. Research focus on these cellular estrogen effects has led to new approaches for the prevention and treatment of osteoporosis.

13.2 Osteoporosis

13.2.1 Epidemiology and Physiology

Osteoporosis is preventable and treatable. Defined as a skeletal condition where low bone mass and structural deterioration of bone tissue lead to weakened and fragile bones that are more likely to fracture, osteoporosis is the most common chronic metabolic bone disorder in the world. With increasing prevalence due to the aging population and increased life expectancy, osteoporosis is a common disease worldwide [14] and thought to affect more than 200 million people [15]. A classic statistic

revealed by the 2008 Women's Health Initiative Observational Study, and frequently quoted in literature, is that the number of women who will experience a fracture in 1 year exceeds the combined number of women who will experience incident breast cancer, myocardial infarction, and stroke [16].

13.2.1.1 Incidence and Burden of Osteoporosis Fractures

Worldwide, one in three women over the age of 50 years will experience an osteoporotic fracture in their lifetime [17]. In the United States and Europe, the prevalence is even higher, estimated to range from 40% to 50% [18]. Hip fractures worldwide in 1990 were estimated to be 1.66 million, a number that is projected to increase to 6.26 million in 2050 [19]. Women accounted for 1.19 million of the 1990 estimated hip fractures, with 90% occurring over the age of 50 years, and the majority resulting from falls from standing height [20]. More than other fracture types, there is also a higher significant mortality rate associated with hip fractures, estimated at approximately 3% of women over 50 years who are hospitalized following hip fracture [14]. Only 40% of hip fracture patients regain their pre-fracture level of independence [21].

There are geographic, ethnic, and socioeconomic status variations in fracture incidence as well [22]. Scandinavian countries have the highest incidence of vertebral fractures, whereas an 11-fold variation in hip fracture incidence has been documented within Europe [23]. In their classic study, Iffors et al. reported the profound European variance in hip fracture incidence was not further explained by activity levels, smoking, alcohol consumption, obesity, or migration status [23].

There are likely multiple reasons for worldwide fracture incidence variation, including bone mineral density variations between ethnic groups [22]. In addition, lower vitamin D levels associated with less sun exposure may also be responsible for the higher fracture incidences seen in countries in more northern latitudes [24].

The cost of osteoporosis-induced fractures and associated care in the United States is estimated to exceed $25 billion by 2025 Lewiecki et al. [25]. This figure is projected to rise even further by 2040, to a projected $95 billion, unless strategies are put in place to curtail the rising number of fractures [26].

13.2.1.2 Physiology of Osteoporosis and Menopause

Peak bone mass is defined as the maximum amount of bone a person has during their life. Strongly influenced by genetics, 95% of adult bone mass usually occurs in women by age 20 years and is lower in women than in men. Higher peak bone mass at the time of skeletal maturity can be an important determinant in osteoporotic fracture risk [27].

Post peak, the rate of bone loss varies from one individual to another, associated with several factors including genetics, calcium intake, and physical activity. There is an approximately 5-year period following menopause when bone loss accelerates due to estrogen deficiency. During this rapid bone loss period, 4–8% trabecular bone loss can occur [28]. The typical rate of bone loss then slows to 1–1.5% per year. Rapid bone loss continues in some women and can lead to as much as a 30–40% overall bone mass loss by age 70 years [29]. The most common

Table 13.3 Factors in addition to menopause that can contribute to low bone mineral density and osteoporosis. National Osteoporosis Foundation [30]

Long-term use of certain medications, particularly corticosteroids and thyroid medications
Cushing syndrome
Kidney failure
Diseases of the thyroid or adrenal glands
Not getting enough calcium, vitamin D, vitamin A, vitamin K, and magnesium
Anorexia nervosa
Alcohol use disorder
Rheumatoid arthritis

osteoporosis fracture sites are the hip, spine, and wrist due to the increased amount of cancellous (or trabecular) bone at these locations. Cancellous, or soft bone, is more metabolically active than cortical or hard bone.

The Women's Health Initiative identified osteoporosis as one of the most common causes of death, disability, and impaired life quality in postmenopausal women. In addition to age and menopause, other factors can contribute to low bone mineral density and osteoporosis. These are listed in Table 13.3.

13.2.2 Screening, Diagnosis, and Management: Osteoporosis vs. Fracture Risk

Because bone mass is considered an accurate determinant of fracture risk, its measurement is supported in clinical practice for diagnosis and for monitoring patients undergoing treatment [31]. Bone mineral density (BMD) is defined as the quantity of bone per unit of volume or per unit of area.

A shift in risk assessment occurred following WHO's 1993 recommendations, with the realization that bone density, although an important determinant for fracture risk, is not the only significant measurement to consider. The change in semantics, from "osteoporosis risk" to "fracture risk," evolved as clinical trials concluded that osteoporosis can be prevented and treated. Treatment algorithms and clinical guidelines have been developed and published, with strategies to assess fracture risk and treat osteoporosis based on absolute fracture risk, not simply on BMD measured by dual energy absorptiometry (DXA) scores.

Combining bone density measurements with other validated fracture risk factors provides a more accurate assessment of a patient's fracture risk than will bone density alone. However, "osteoporosis risk factors" are still considered independently of "fracture risks" by most healthcare providers because this is the information that guides initial assessment, intervention, and education in the postmenopausal woman. The common osteoporosis risk factors are listed in Table 13.4. Among the modifiable fracture risks are many lifestyle factors on which healthcare providers can focus their initial care.

Table 13.4 Osteoporosis risk factors [12]

Non-modifiable risk factors
Age >50 years
Female
Menopause
Family history of osteoporosis
Low body weight/being small and thin
History of broken bones or height loss
Modifiable risk factors
Insufficient intake of calcium and vitamin D
Insufficient dietary fruits and vegetables
Excess dietary protein, sodium, and caffeine
Inactive lifestyle
Smoking
Excess alcohol intake
Weight loss

Women are at a higher risk for osteoporotic or fragility fractures than men. Low body weight and frame and low estrogen levels can increase risk. Incidence of fragility fractures can vary with age, gender, and ethnicity.

13.2.2.1 Fracture Risk Assessment

When evaluating a patient's fracture risk, clinical risk factors must be considered along with the results of any diagnostic imaging studies. The most commonly used and clinical gold standard BMD test is dual energy absorptiometry (DXA), and the most commonly measured sites for assessing osteoporosis risk with DXA are the proximal femur, including the femoral neck, and the lumbar spine from L1 to L4 [31]. Peripheral machines can measure at other sites like the forearm, heel, or finger using X-ray or ultrasound but are not advised for osteoporosis diagnosis because they can be falsely elevated.

Since 1993, as an outcome of a consensus meeting of the World Health Organization (WHO), the diagnosis of osteoporosis in postmenopausal women has been based on DXA [32]. Screening guidelines vary among professional organizations and can be confusing for healthcare providers in clinical practice. The following is a summary of current recommendations:

- The US Preventive Services Task Force (USPSTF) recommends BMD screening in all women 65 years of age and older. Their recommendations also include screening younger women whose fracture risk is the same, or greater than, that of a 65-year-old white woman who has no additional risk factors [33].
- The National Osteoporosis Foundation (NOF) of the United States recommends bone mineral density (BMD) testing in all women 65 years and older [21]. NOF also recommends BMD testing 1–2 years after initiating therapy to reduce fracture risk and every 2 years thereafter.

- The American College of Obstetricians and Gynecologists recommends BMD screening starting at age 65 years, and no more than every 2 years thereafter [34]. Similar to other professional organizations, ACOG recommends selective screening in women younger than 65 years of age if they are postmenopausal and have other risk factors for osteoporosis.
- The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) [35] agree with bone mineral density testing for all women 65 years and older. Younger postmenopausal women over age 50 years, with increased risk for bone loss and fracture based on fracture risk analysis should have BMD screening. Fracture risks should first be evaluated using a clinical fracture risk assessment algorithm without bone mineral density testing in postmenopausal women. Bone mineral density testing is not recommended in premenopausal women by either group unless there is significant fracture history or there are specific risk factors for bone loss, such as long-term steroid use.
- The International Society for Clinical Densitometry (ISCD) recommends BMD screening in all women 65 years and older, postmenopausal women aged 50–70 years when risk factors are present or who have fragility fractures, and women with conditions or who are taking medications associated with low bone mass or bone loss [36].

Additional bone density scanning recommendations and guidelines can be found on the International Society for Clinical Densitometry website at https://iscd.org, including recommendations for DXA in transgender and gender nonconforming individuals. There is a significant worldwide variability in the access to and quality of DXA services. In a global survey of fracture management services, ISCD and the International Osteoporosis Foundation (IOF) concluded that one fourth of the facilities surveyed reported inadequate training, accreditation, education, quality assurance, and reporting procedures [37].

Dual Energy X-ray Absorptiometry (DEXA or DXA) is currently considered the clinical gold standard for bone mineral density scanning and is reported in T-scores and *Z*-scores. A T-score is the measurement value indicating in standard deviations the comparison of the patient's bone density to that of a healthy 30-year old. One standard deviation equals 10–12% difference in bone mass. For example, if a patient's T-score equals "0," their bone mass is equal to the peak bone mass of a mean 30-year-old. A score below 0 indicates bone mass less than that of a mean 30-year old (see Table 13.8).

Z-scores are comparisons of a patient's bone density with that of an average person of the same age and gender. *Z*-scores are helpful for identifying secondary osteoporosis causes due to medical conditions or medications and are always used for premenopausal women. A low *Z*-score, particularly greater than 2 standard deviations below 0, is interpreted as a warning sign. *Z*-scores should not be used alone as diagnostic indicators, particularly in postmenopausal women.

Osteoporosis was defined by the WHO in 1994 as follows: (1) T-score 25% lower than the average 30-year old; (2) 2.5 standard deviations below the mean; or (3)

Table 13.5 World Health Organization (WHO) osteoporosis definition based on DEXA [39]

Normal BMD = T-score between −1 and +1 SD
Low BMD (osteopenia) = T-score between −1.1 and −2.4 SD
Osteoporosis = T-score of −2.5 SD or lower
Severe osteoporosis = T-score of −2.5 SD and fracture(s)

SD standard deviation

T-score lower than 2.5 [38]. A low T-score from a DXA scan alone does not qualify as a comprehensive fracture risk assessment.

Used along with other assessment tools, DXA is still considered a useful clinical test to measure bone mineral density, and central scanning of the spine and the hip is the preferred method for diagnosing osteoporosis. Table 13.5 defines bone mineral density diagnosis based on DXA scores as categorized by the WHO.

Cost of services must be a part of any discussion involving bone density scanning. In the United States, the insurance reimbursement landscape tends to change regularly, but a bone density scan is covered every 2 years by Medicare for estrogen-deficient (menopausal) women at clinical risk for osteoporosis or for patients on treatment. There has been a decrease in DXA testing in the United States since 2008, partly due to reimbursement issues [25]. More specific United States financial reimbursement information can be found on Medicare's website at https://www.medicare.gov/coverage/bone-mass-measurements

The FRAX Tool DXA alone has been identified as an unreliable fracture risk guide [40, 41]. Additional fracture risk assessment algorithms like the FRAX and other tools have been developed, which, when used in conjunction with DEXA scanning, provide more accurate assessments of a postmenopausal woman's fracture risk [42]. Tools vary in validity and reliability. Fracture risk assessment tools are based on individual patient models that combine clinical risk factors and bone mineral density. Most fracture risk prediction algorithms include demographics, personal and family history, physical characteristics, health status, and medication use. The algorithms result in an estimated fracture probability based on multiple risks.

One of the most commonly used fracture prediction algorithms is the Fracture Risk Assessment Tool (FRAX) [43]. Developed in the United Kingdom, FRAX has been validated in population-based cohort studies around the world and has been incorporated into several national osteoporosis assessment and treatment guidelines. The FRAX tool is relatively simple to use. There are paper versions as well as computer-adapted models that provide 10-year fracture probabilities.

There are some limitations to the FRAX tool. Falling is not included in the risk factors, nor are rates of bone loss and bone turnover. Medications other than glucocorticoids are not considered, and family history of fractures only includes parental hip fracture. Also, the bone mineral density input in FRAX is limited to the hip. The FRAX tool is limited to ages 40–90 years and does not apply to premenopausal women. It remains adequate for use with the untreated patient who has not begun

any pharmaceutical intervention in the past 12 months for already-diagnosed osteoporosis.

Patients are considered at high risk if they have been diagnosed with osteoporosis. Further, patients are considered at very high risk if they have had a recent fracture (within the past 12 months); fracture while on approved osteoporosis therapy; have multiple fractures; or fracture while on drugs causing skeletal harm, such as long-term glucocorticoids. Also falling into the very high-risk category are patients with very low T-scores (less than −3.0), patients with high fall risks or a history of injurious falls, and those with a very high fracture probability by FRAX (fracture risk assessment tool) or other validated fracture risk algorithms. High fracture probability is defined by FRAX as a major osteoporosis fracture over 30% or a hip fracture risk above 4.5% [44].

13.2.2.2 Prevention and Management Guidelines

Osteoporosis is underdiagnosed and undertreated, and the prevention of fragility fractures deserves more clinical focus. Too often, the first indication that a postmenopausal woman has low bone mineral density is the occurrence of a fragility fracture, a fracture that results from a fall from a standing height or less or that presents in the absence of trauma. Weight-bearing exercise, adequate calcium and vitamin D intake, fall prevention, smoking cessation, and avoidance of excessive alcohol intake are the primary lifestyle topics on which healthcare providers can focus in helping women prevent the occurrence of these and other types of fractures.

Clinical practice guidelines are available to guide the clinician's prevention and treatment strategies. The American College of Physicians (ACP) 2016 revision of its original 2008 guideline includes recommendations on the treatment of low bone density and osteoporosis to prevent fractures [45]. It is endorsed by the American Academy of Family Physicians and includes pharmacological treatments as well as nonprescription medications, such as calcium and vitamin D recommendations. Table 13.6 presents a summary of the ACP guidelines.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published their 2020 Postmenopausal Osteoporosis Treatment Guidelines, which are summarized by the algorithm in Fig. 13.5 [35]. Both sets of guidelines are currently used in clinical practice in the United States, and they have similarities. Both sets are based on current literature reviews and evidence-based science, and each addresses the importance of identifying and managing osteoporosis and fracture risk in postmenopausal women.

There are some differences between the ACP and AACE/ACE guidelines. Reassessment guidelines for women on pharmacologic therapy vary. ACP recommends against bone density monitoring during the 5-year pharmacologic treatment period for osteoporosis in women. AACE/ACE suggests a more individualized

approach to DEXA scanning frequency, AACE/ACE recommends DEXA scanning every 1–2 years after the initiation of therapy and until findings are stable. Their rationale for this is twofold: (1) it is important to identify individuals who do not respond to therapy so a change can be made before the occurrence of a fracture, and (2) nonresponding women often have previously undetected disorders that contribute to bone loss, or they may have absorption problems or adherence issues.

Table 13.6 American College of Physicians Summary Guideline on the Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women. Qaseem A, Forciea MA, McLean RM, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med. 2017 Jun 6;166(11):818–839 Reprinted from Annals of Internal Medicine. 166(11):818–838, with permission from The American College of Physicians

Disease/condition	Low BMD or osteoporosis
Target audience	All clinicians
Target patient population	Adults with low BMD or osteoporosis
Interventions evaluated	Bisphosphonates: alendronate, residronate, ibandronate, zoledronic acid; denosumab; teriparatide; selective estrogen receptor modulators (raloxifene, bazedoxifene); estrogen; calcium; vitamin D
Outcomes evaluated	Reduction in fracture (total, vertebral, nonvertebral, spine, hip, wrist, other) adverse events
Benefits of treatment	Bisphosphonates, denosumab, teriparatide, raloxifene: reduction in vertebral fractures Alendronate, risedronate, zoledronic acid, denosumab, teriparatide: reduction in nonvertebral fracture Alendronate, risedronate, zoledronic acid, denosumab: reduction in hip fracture
Harms of treatment	Bisphosphonates in general: mild upper GI symptoms, atypical subtrochanteric fracture, osteonecrosis of the jaw Raloxifene: cardiovascular (serious), thromboembolic events, pulmonary embolism, cerebrovascular death, hot flashes Ibandronate: myalgias, cramps and limb pain Zoledronic acid: atrial fibrillation, arthritis and arthralgias, headaches, hypocalcemia, uveitis or ocular events possibly or probably related to the study drug, influenza-like symptoms Denosumab: mild upper-GI symptoms, rash/eczema Teriparatide: upper GI symptoms, renal, headaches, hypercalcemia, hypercalciuria

(continued)

Table 13.6 (continued)

Disease/condition	Low BMD or osteoporosis
Recommendations	Recommendation 1: ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women with known osteoporosis. (Grade: strong recommendation; high-quality evidence) Recommendation 2: ACP recommends that clinicians treat osteoporotic women with pharmacologic treatment for 5 years. (Grade: weak recommendation; low-quality evidence) Recommendation 3: ACP recommends that clinicians offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence) Recommendation 4: ACP recommends against bone density monitoring during the 5-year pharmacologic treatment period for osteoporosis in women. (Grade: weak recommendation; low-quality evidence) Recommendation 5: ACP recommends against using menopausal estrogen therapy or estrogen plus progestogen therapy or raloxifene for treatment of osteoporosis in women. (Grade: strong recommendation; moderate quality-evidence) Recommendation 6: ACP recommends that clinicians should make the decision whether to treat osteopenic women 65 years of age or older who are at high risk for fracture based on a discussion of patient preferences, fracture risk profile, and benefits, harms, and costs of medications. (Grade: weak recommendation, low-quality evidence)
Inconclusive areas of evidence	Comparative effectiveness trials evaluating pharmacologic treatments for low bone density or osteoporosis are lacking. In addition, though FRAX scores are widely used, there is a lack of evidence linking FRAX scores to treatment efficacy
High value care	The current evidence does not support frequent monitoring of women with normal BMD for osteoporosis, because data showed that most women with normal DEXA scores did not progress to osteoporosis within 15 years. Data also does not support monitoring BMD during the initial 5 years of treatment in patients taking pharmacologic agents to treat osteoporosis. Clinicians should select generic drugs to treat osteoporotic patients when possible
Clinical considerations	Comparative effectiveness of the different treatments is unknown. Treatment duration is unknown, although high-risk patients may benefit from longer treatments

There are a few other significant differences between the two sets of guidelines that are specific to pharmacological treatments. The Selective Estrogen Receptor Modulator (SERM), raloxifene, prevents and treats osteoporosis by copying estrogen's bone protective effects. It also decreases invasive breast cancer risks by blocking the effects of estrogen on breast tissue. In the ACP guidelines, raloxifene is not recommended for use in postmenopausal osteoporosis prevention or treatment. AACE/ACE guidelines recognize that raloxifene is not effective in reducing hip fracture but continue to list it as an appropriate initial therapy in some women who

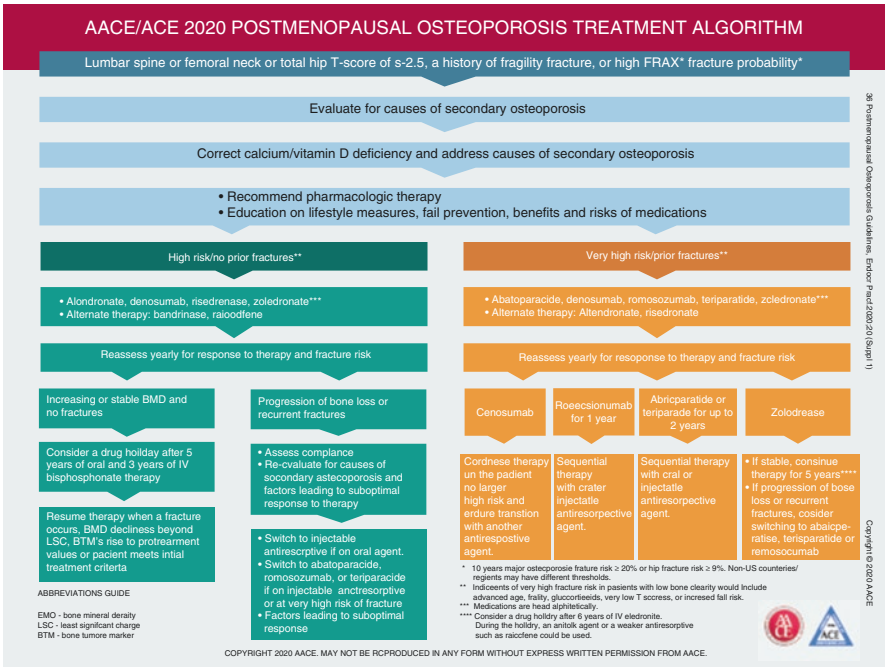

Fig. 13.5 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) 2020 Postmenopausal Osteoporosis Treatment Algorithm (Camacho, Petak, Binkley, et al. 2020, p. 36). (Reprinted with permission from American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis: 2020 Update. Endocrine Practice 26 (Suppl 1) May 2020: p. 1–46)

only need spine-specific pharmacologic therapy, especially when other antiresorptive drugs are either not tolerated or contradicted. The added benefit of reducing breast cancer may be desirable in some women who have a high spine fracture risk but are not at risk for hip or nonvertebral fractures.

ACP recommends that clinicians treat osteoporotic women with pharmacologic therapy for 5 years, whereas AACE/ACE recommends a more individualized approach that could possibly be more or less than 5 years [35, 45]. Drug holidays, that is, stopping therapy for a while after a designated period of treatment (usually 5 years) are not recommended for patients on denosumab because the vertebral fracture protection can be lost within 3–18 months of stopping the drug. Guidelines on drug holidays should be individualized according to AACE/ACE.

In summary, both sets of guidelines address osteoporosis treatment and management, but they have distinct disparities in three areas: (1) the frequency of bone mineral density monitoring, (2) treatment with anabolic agents, and (3) the duration of therapy with antiresorptive agents.

There are other comprehensive, reliable, and useful clinical guidelines available worldwide for the prevention and treatment of osteoporosis, each with variations

Table 13.7 Clinical approach to managing osteoporosis in postmenopausal women and men age 50 and older: A universal approach

General principles	Medical management criteria	Nonmedical management	Follow-up
A detailed patient history to identify risk factors for osteoporosis-related fractures and falls	Vertebral fracture (clinical or asymptomatic) or hip fracture	Modify risk factors related to falling	Patients not requiring medical therapy at the time of initial evaluation should be clinically re-evaluated with change in medical condition
Physical examination and diagnostic studies to identify osteoporosis and its secondary causes	Hip DEXA (femoral or total hip) or lumbar spine T-score ≤−2.5	Referrals for physical and/or occupational therapy (e.g., walking aids, assistive devices)	Patients using pharmacotherapy should have laboratory and DEXA re-evaluation at 2 years, or more frequently when medically appropriate
Modifications of lifestyle, diet/supplements, and other clinical risk factors for fracture	Low bone mass (osteopenia) plus WHO 10-year probability of hip fracture ≥3% or any major osteoporosis-related fracture of ≥20%	Weight-bearing, muscle-strengthening exercise, and balance training	Repeat vertebral imaging with documented height loss, new back pain, postural change, or suspicious finding on chest X-ray and in patients being considered for temporary cessation of drug therapy
Estimate 10-year probability of hip and major osteoporotic fracture using FRAX. Perform vertebral imaging when appropriate	Patient preference may indicate treatment for people with 10-year fracture probabilities above or below these levels		Regularly, and at least annually, assess compliance and persistence with therapeutic regimen
Decisions on who and how to treat based on guidelines, all available clinical information, and clinical judgement			

Adapted from Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R. Clinician's guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation. Osteopors Int. 2014;25(10):2359–81

specific to an individual country's pharmacologic use patterns and availability of specific treatments. Based on Cosman et al.'s [21] Universal Recommendations (see Table 13.7), there are more similarities than differences in prevention and treatment recommendations. Some osteoporosis clinical guidelines, treatment recommendations, and algorithms are also available in electronic format for mobile devices.

Table 13.8 Bone-enhancing foods and nutrients

Magnesium. Avocado, banana, cantaloupe, honeydew, lima beans, low-fat milk, nectarine, orange juice, potato, spinach		
Potassium. Whole grains, nuts, spinach, oatmeal, potato, peanut butter		
Vitamin D. The body makes vitamin D after exposure to sunlight. It is also found in fatty fish, fortified cereals, and milk		
Vitamin K. Leafy greens, cauliflower		
Calcium		
≥100 mg/serving	***100–300 mg/serving***	***>300 mg/serving***
Soy/rice milk, broccoli, turnip greens	Spaghetti/lasagna, fortified cereals, cottage cheese, baked beans, nonfat milk, canned salmon, fortified orange juice, tofu, soybeans	Cheddar cheese, sardines, oatmeal, milk, yogurt, fortified plant milk

Integrative and Behavioral Interventions

For patients who already have osteoporosis or for those with risks, intervention as early as possible may help increase bone mass, prevent further bone loss, and prevent fractures. Calcium does not prevent or cure osteoporosis. However, adequate calcium intake is an essential component of any prevention or treatment program. Lifestyle choices are also important, including eating a diet rich in fruits and vegetables and engaging in weight-bearing exercises to enhance bone strength.

Nutrition

A diet rich in bone-building foods and nutrients may help prevent bone loss. Important bone-enhancing foods and nutrients are listed in Table 13.8 with a summary of calcium-rich foods organized from low to high calcium content. There are many accessible sources of nutrient rich foods tailored to specific regional diets (see Chap. 12).

Certain vitamins and minerals, in addition to calcium, are important for bone health. Phosphorus, magnesium, boron, manganese, copper, zinc, folate, and vitamins B12, B6, C, and K are all needed by the body. It is important to advise patients at risk for osteoporosis or those who already have it to moderate their intake of sodium, alcohol, and caffeine as well.

Exercise

Delaying osteoporosis onset, improving balance, and promoting muscular fitness are all evidence-based benefits of exercise [45, 46]. Exercise is considered the primary nonpharmacological treatment for osteoporosis prevention, as well as for the prevention of fall-related fractures [47]. Progressive resistance exercise training (RET), in particular, helps increase muscle mass, endurance, and strength, which also increases the mass and strength of bones. Beneficial bone stress stimulates osteoblasts.

Weight-bearing aerobic exercise has the same bone effect, specifically for the lower extremities, and has demonstrated improved bone mineral density in the hips.

Table 13.9 Exercise recommendations. *Reprinted with permission from National Osteoporosis Foundation. (2015) Healthcare Professionals Toolkit (available online from NOF at www.nof.org) EXERCISES Reprinted from "Exercise for Strong Bones" published online by the National Osteoporosis Foundation at nof.org*

Exercise recommendations	
Weight-bearing exercises	30 min on most days of the week. A 30-min session or multiple sessions spread out throughout the day
Muscle-strengthening exercises	2–3 days/week. Can be done all at once or in multiple short sessions, full body or one body part per day (e.g., arms one day, legs the next, and trunk the next)
Balance, posture, and functional exercises	Every day or as often as needed. Focus on area of most need: if a patient has fallen, balance exercises should be emphasized. If patient's spine is bent, focus should be on posture exercises. If patient has trouble climbing stairs or getting up from the couch, he/she should do more functional exercises. These exercises can be performed at one time

In their comprehensive systematic review and meta-analysis of types of exercise on bone mineral density in postmenopausal women, Kemmler et al. provide compelling evidence supporting the positive exercise benefits in osteoporosis prevention [48]. Kemmler's research reveals that both resistance exercises and weight-bearing exercises, either alone or in combination, positively affect bone mineral density in the lumbar spine, femoral neck, and total hip in postmenopausal women.

The exact exercise prescription for osteoporosis prevention and the prevention of fractures is not readily found in the literature. General exercise guidelines are published by several well-respected organizations. Devoted specifically to osteoporosis detection, prevention, and treatment, the NOF provides helpful information for the clinician in primary care practice who cares for patients at risk for fractures [49]. Specific exercise guidelines are included in the NOF *Healthcare Professionals Toolkit* (available online at www.nof.org) (Table 13.9). The inclusion of body mechanics, safety, and activity types make this reference especially useful for clinicians.

Soy Isoflavones

Similar to the way selective estrogen receptor modulators (SERMs) work, some plant-derived estrogen-like substances exhibit beneficial effects on bones. Soy isoflavones, classified as phytoestrogens, are in this category. Phytoestrogens are bioactive molecules existing as nutritional components of many commonly ingested food products that exhibit binding to estrogen receptors and induce an estrogenic/antiestrogenic response in target tissues, such as bone [50]. Foods that contain phytoestrogens are listed in Table 13.10, with soy products having the highest phytoestrogen content.

Research involving phytoestrogens began in the 1950s when it was realized that some plant-derived substances caused estrogenic effects. Fertility problems occurred in sheep grazing on pastures growing red clover. It was discovered that the clover contained high amounts of isoflavones [51]. In human research and initially observed in epidemiological studies, women who frequently ingested soy foods showed

Table 13.10 Foods high in phytoestrogens based on Bacciottini et al. [51]

Nuts and seeds	Fruits	Vegetables
• Flax seeds (ground) • Sunflower seeds • Sesame seeds • Almonds • Walnuts	• Apples • Pomegranates • Strawberries • Cranberries • Grapes	• Yams • Lentils • Alfalfa sprouts • Mung beans • Sprouts • Carrots
Soy products	**Herbs**	**Liquids**
• Soybeans • Tofu • Tempeh • Miso soup • Miso paste	• Red clover • Licorice root • Hops	• Coffee • Bourbon • Beer • Red wine • Olive oil • Jasmine oil
Grains		
• Oats • Barley • Wheat germ		

lower osteoporosis risks [50]. Not all foods have been investigated or demonstrated efficacy in estrogen effects including osteoporosis.

Clinical trials support the effectiveness of phytoestrogens in osteoporosis prevention. In their systematic review of the effects of soy isoflavones on bone mineral density, Akhlaghi et al reviewed 52 randomized controlled trials and concluded that soy isoflavones prevent bone loss in subjects of any weight status, ethnicity, treatment duration, and dose [52].

Similar support for phytoestrogen's use in osteoporosis prevention was reported by Tit et al. [53] in their parallel study comparing phytoestrogens with menopause hormone therapy (MHT) [53]. Subjects were not randomized but were given the choice of study group based on the selection method, taking into consideration their willingness to take soy isoflavones or MHT. Also included in the selection for each group were the patient's background, diagnosis, risks, assessment, and benefits of the planned treatment. The reported advantages of a study model using this type of selection method, rather than a randomized assignment to groups, include patient choice and safety. Before hormone therapy can be initiated, according to clinical treatment guidelines and therapeutic protocols, a woman must be informed by the healthcare provider that hormonal therapy is associated with potential risks.

The three study groups in the Tit et al. clinical trial were: (1) treatment with MHT (1 mg estradiol and 0.5 mg norethisterone acetate PO daily); (2) treatment with 40 mg PO soy isoflavone (genistein and daidzein) phytoestrogens daily; and (3) a control group. Treatment response was determined by urinary measurement of biochemical markers of bone resorption (deoxypyridinoline) and by bone mineral density measurements at 6 months and 12 months, respectively. Tit et al. concluded that both therapies, the hormone and phytoestrogens, exhibited beneficial effects on bone metabolism over placebo, causing a significant decrease in bone resorption

process with a stronger effect in women without additional risk factors for osteoporosis and in MHT than phytoestrogens [53].

Pharmacologic Treatments

Bisphosphonates

Bisphosphonates alendronate, risedronate, and zoledronic acid are first-line treatments for the prevention of osteoporotic fractures in postmenopausal women who meet the FRAX risk factor criteria for treatment. The biologic agent denosumab is also used in first-tier treatment for osteoporosis.

First used in 1969, the widespread use of bisphosphonates in osteoporosis therapy occurred after 1993 when the WHO established the diagnosis of osteoporosis by the DXA technique [38]. Alendronate, risedronate, ibandronate, and zoledronic acid are the bisphosphonates currently approved for the treatment of osteoporosis. The anti-fracture efficacy of these drugs has been established by large population studies. Of the four approved bisphosphonates, zoledronate is the only one developed exclusively for use as an intravenous (IV) formulation; it can be prescribed when IV therapy is indicated.

The selection of pharmaceutical treatment for a specific patient is based on several factors. Once a diagnosis of osteoporosis is established, it is important to consider the body location of the lowest BMD (hip, vertebral, nonvertebral) and therefore at the highest risk for fracture. Some medications performed better in clinical trials in the hip than the spine and vice versa (Table 13.11). It is also imperative to know if the patient has any esophageal or upper gastrointestinal issues because most oral bisphosphonates can be associated with severe esophagitis. Adherence must be considered and may be improved with less frequently administered therapy, such as weekly, monthly, every 3 months, or even annually.

Safety of Bisphosphonates in Osteoporosis Treatment

Bisphosphonates (BPs) are considered very safe for osteoporosis prevention and treatment, but some patient safety concerns must be considered by the prescribing clinician. In addition to the potential gastrointestinal issues, there is a rare risk of atypical femur fracture (AFF) and/or osteonecrosis of the jaw (ONJ) with long-term use [55]. The documented incidence of these two potential complications is 0.004% in patients with osteoporosis up to 6.7% in patients receiving chemotherapy [54].

Atypical femoral fracture associated with long-term BP use (2–100 per 100,000 women) reportedly increases with the duration of therapy, adding support to the recommended BP drug holiday of 2–3 years in women with low fracture risk after 3–5 years of BP treatment [54, 56].

Antiresorptive-associated ONJ, the second rare adverse effect of BP therapy, is reportedly associated with higher drug potency, higher cumulative dose, parenteral route of administration, and concomitant cancer therapy rather than duration of use [54]. Conflicting evidence exists in the literature regarding duration of BPs and the potential for ONJ. The American Society for Bone and Mineral Research (ASBMR) states that the evidence supporting higher risk with longer use is of poor quality

Table 13.11 Osteoporosis prevention and treatment medications

Bone effect/class	Medication	Dose	Vertebral fracture risk[a]	Hip fracture risk[a]	Nonvertebral fracture risk[a]	Notes
First-line treatments						
Antiresorptive/ bisphosphonate	Alendronate [Fosamax®, Binosto®]	Prevention: 5 mg/day PO or 35 mg/week PO Treatment: 10 mg/day PO or 70 mg/week PO	40–64% Most studies used 10 mg/day dose	21–55% Most studies used 10 mg/day dose	11–49% Most studies used 10 mg/day dose	Contraindications: Abnormalities of the esophagus; hypocalcemia Major adverse effects: GI/esophageal irritation; AFF; ONJ (0.3%, up to 4.3% in special populations) Patient must be able to stand or sit upright for at least 30 min
Antiresorptive/ bisphosphonate	Risidronate [Actonel®, Atelvia®]	Prevention/ treatment (immediate release): 5 mg/day or 35 mg/week or 150 mg/month Treatment (delayed release): 35 mg/week	46–69%	36–40%	19–60%	Contraindications: Abnormalities of the esophagus; hypocalcemia Major adverse effects: GI/esophageal irritation; AFF; ONJ (0.3% up to 4.3% in special populations) Patient must be able to stand or sit upright for at least 30 min

(continued)

Table 13.11 (continued)

Bone effect/class	Medication	Dose	Vertebral fracture risk[a]	Hip fracture risk[a]	Nonvertebral fracture risk[a]	Notes
Antiresorptive/ bisphosphonate	Zoledronic acid [Reclast®]	Prevention: 5 mg IV infusion every 2 years Treatment: 5 mg IV infusion/year	66–77%	44%	27–28%	Contraindications: Hypocalcemia Major adverse effects: AFF (subtrochanteric fracture 2–100 per 100,000 women); ONJ (0.03% up to 4.3% in special populations) Patients must be appropriately hydrated prior to treatment
Antiresorptive/ RANKL inhibitor	Denosumab [Prolia®]	Treatment: 60 mg subQ as single dose once q 6 months	60%	41%	20%	Contraindications: Hypocalcemia; pregnancy
Alternate treatments						
Anabolic/recombinant human parathyroid hormone	Teriparatide [Forteo®]	Treatment: 20 mcg subQ once/day for up to 2 years	64–69%	No difference	35–40%	Major adverse effects: Orthostatic hypotension; may exacerbate urolithiasis; osteosarcoma: use limited to 2 years. Must follow with another agent Initial administration should occur when patient is sitting or lying down. Requires refrigeration

Antiresorptive/ bisphosphonate	Ibandronate [Boniva®]	Prevention: 150 mg/month PO Treatment: 150 mg/month PO or 3 mg IV quarterly	51%	No difference (data for fracture not separated in studies)	No difference	Contraindications: Abnormalities of the esophagus; hypocalcemia Major adverse effects: GI/esophageal irritation; AFF; ONJ (0.03% up to 4.3% in special populations) Patients must be able to stand or sit upright for at least 30 min
Antiresorptive/ estrogen agonist/ antagonist	Raloxifene [Evista®] [b]	Treatment: 60 mg/day	34–44%	No difference	No difference	Contraindications: History of or current venous thromboembolic disease (discontinue at least 72 h prior to, and during, prolonged immobilization); pregnancy or breastfeeding Increased risk of fatal stroke in postmenopausal women with documented CHD or increased risk for major coronary reactions Approved for risk reduction for invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women with high risk for invasive breast cancer

(continued)

Table 13.11 (continued)

Bone effect/class	Medication	Dose	Vertebral fracture risk[a]	Hip fracture risk[a]	Nonvertebral fracture risk[a]	Notes
Last-line treatments						
Antiresorptive/ tissue-selective estrogen complex or third generation selective estrogen receptor modulator	Bazedoxifene 20 mg with conjugated estrogens 0.45 mg [Duavee®][b]	Prevention only: 1 tab per day	No data	No data	No data	Contraindications: Undiagnosed AUB; active, past history of, or increased risk of, venous or arterial thromboembolic disease; estrogen-dependent tumors; hepatic impairment or disease; pregnancy or breastfeeding; history of angioedema; anaphylaxis to any of the components
Antiresorptive/ calcitonin	Calcitonin (subQ or IM injection [Miacalcin®]; intranasal formulations are available only as generics)	Treatment: Intranasal 200 units (1 spray) in one nostril once daily IM or subQ 100 units/day	Decreases (studies included intranasal formulation only)	No difference	No difference	Major adverse effects with nasal spray: Rhinitis; epistaxis; allergic rhinitis. Possible increase risk malignancy however causal relationship not established Calcitonin should be used for treatment of osteoporosis in women ≥5 years postmenopause who are unable to take other treatments

AFF atypical femur fracture, *ONJ* osteonecrosis of the jaw, *CHD* coronary heart disease, *AUB* abnormal uterine bleeding

Table based on Aggarwal and Masuda [54]. Osteoporosis pharmacologic treatment: postmenopausal women. (2021). In Epocrates Essentials for Apple iOS (Version 21.5.1) [Mobile application software]. Retrieved from http://www.epocrates.com/mobile/iPhone/essentials

[a]Fractures are relative risk reduction. Percentages are pooled from trials with drug vs. placebo in research involving postmenopausal women and should not be used to directly compare medications

[b]The American College of Physicians recommends against the use of menopausal estrogen therapy or menopausal estrogen plus progesterone therapy or raloxifene for the treatment of osteoporosis in women [45]

[57]. In a systematic review of clinical trials evaluating the risk of rare serious adverse effects of long-term use of bisphosphonates for the treatment of osteoporosis, Lu et al. [55] concluded that bisphosphonates significantly increased the risk of AFF and ONJ and prolonged union time [55].

Finding reliable clinical treatment guidelines regarding the duration of use of BPs can also be challenging. In a comprehensive report on duration of BP treatment for osteoporosis patients, the Canadian Agency for Drugs and Technologies in Health (CADTH) reviewed internationally available clinical evidence and evidence-based guidelines for treatment durations and courses of BPs for osteoporosis [58]. The authors identified six evidence-based guidelines that included recommendations regarding the length of treatment with bisphosphonates for osteoporosis, including possible correlations between length of therapy and incidence of adverse events [58]. None of the evidence-based guidelines reviewed in the CADTH report offered clear direction on duration of a treatment, and no specific correlations between length of therapy and ONJ or AFF were reported [59]. Duration of treatment varied widely among the six sets of guidelines, from 3 to 5 years to an indeterminate period of time. Most of the reviewed guidelines recommend regular patient monitoring and treatment individualization based on clinical response to BP therapy. Drug holidays are recommended similarly, based on patient assessment and treatment response [58].

Specific guidelines are available to the clinician regarding how to protect the patient on BPs who undergoes dental procedures. According to The American Association of Maxillofacial Surgeons (AAOMS), precautions should be taken in all patients on BP therapy who undergo dental surgery. AAOMS recommends the discontinuation of oral BPs for 2 months prior to and 3 months following elective invasive dental surgery (or until osseous healing has occurred), in patients who have been taking oral BPs for 4 years or more [56].

Evaluating each patient carefully for risks and benefits of bisphosphonate therapy is essential. In general, the benefits of vertebral fracture reduction significantly outweigh the risks of AFF or ONJ [57]. It is important to consider the strength of evidence for possible causal relationships of side effects and to carefully evaluate the risk/benefit profile of a selected drug and its impact on an individual's specific physical, mental, and socioeconomic status. Most experts recommend initiation of bisphosphonate therapy in appropriately screened patients with careful monitoring of therapy duration. Bisphosphonates should not be given to people with severe renal impairment (creatinine clearance below 30–35 mL/min) due to their potential nephrotoxicity [60]. Bisphosphonates are eliminated almost exclusively by the kidney where they can potentially accumulate in the renally compromised patient.

Estrogen

The use of hormonal products to address estrogen deficiency in postmenopausal women inhibits bone resorption, thereby slowing the loss of bone. This physiological and biochemical estrogen effect will work whether MHT is initiated in the first years following menopause onset or later in age [61]. Before the development of bisphosphonate treatments for menopausal osteoporosis, MHT was accepted as an

effective treatment. MHT is no longer recommended as a first-line treatment because of its associated risks of venous thrombotic disease, breast cancer, coronary artery disease, and stroke [62] (see Chap. 6).

13.3 Sarcopenia

Sarcopenia is a relatively new term that is used to indicate age-related loss of skeletal muscle mass and function. The word comes from two Greek words, *sarco* and *penia*, and literally means skeletal muscle deficiency. Now recognized as an independent disease, sarcopenia has its own International Classification Diseases-10 code (ICD-10-CM: M62.84) and is characterized by low muscle mass in combination with low muscle strength or low physical performance [63, 64].

Although frequently presumed to be part of normal aging, the decline in estrogen following menopause contributes to skeletal muscle mass loss in women. The gradual decline in muscle mass initiated earlier in life accelerates after age 50 years [65]. The age-related decline of growth hormone and testosterone are also associated with sarcopenia, which accounts for risk in men. Several operational definitions of sarcopenia have been published, all with established diagnostic criteria requiring muscle mass measurement [66–68].

13.3.1 Epidemiology

Sarcopenia contributes to risks of physical frailty, functional impairment, poor health-related quality of life, and premature death in the woman in the life stage of postmenopause [67]. Sarcopenia-related risk for physical disability is independent of age, ethnicity, obesity, socioeconomic status, morbidity, and health behaviors. The varied definitions of sarcopenia creates challenges in reporting accurate incidence. In their systematic literature review, Shaw et al. emphasized the need for a consensual definition that incorporates the commonly used descriptive characteristics of muscle mass, strength, and function [69].

The reported incidence and related burden of cost due to sarcopenia also vary widely. Cruz-Jentoft, Landi, Schneider, et al. reported sarcopenia incidence rates between 1% and 29% in community-dwelling populations and 14–33% in residents requiring long-term care [70]. According to Abellan Van Kan [71], the prevalence of sarcopenia ranges from 13% in individuals 60–70 years old and as high as 50% in those over 80 years of age. Direct medical costs attributable to sarcopenia in the United States in 2000 were estimated to range from $11.8 to $26.2 billion [72]. With population growth and rising healthcare costs since these statistics were reported, the burden of this condition will increase.

13.3.2 Physiology

Sarcopenia is characterized by atrophy of muscle fibers and accumulation of fat within the muscle. Pathophysiology also involves insulin resistance. According to the classic research of Ferrucci et al., after the age of 50 years, skeletal muscle mass is lost at a usual rate of 1–2% per year [73]. Estrogen deficiency contributes to this skeletal muscle mass loss.

Signs and symptoms of sarcopenia include difficulty climbing up and down stairs, difficulty rising from a chair, and loss of balance. Patients with severe sarcopenia typically have difficulty walking on uneven surfaces. These symptoms, along with recurrent falls, weight loss, presence of diabetes mellitus, or a slow gait speed, can all indicate the presence of sarcopenia. Early diagnosis can help prevent long-term complications and help clinicians manage sarcopenia better [74].

13.3.3 Screening, Diagnosis, and Management

Two consensus conferences addressed sarcopenia and have published screening, diagnostic, and treatment clinical guidelines [67, 75]. Assessment techniques do not need to include the use of expensive, inconvenient diagnostic imaging such as magnetic resonance imaging (MRI), computed tomography (CT), or dual-energy X-ray absorptiometry (DEXA). Measuring muscle mass, muscle strength, and muscle function can readily be completed using simple and inexpensive screening tools.

Several diagnostic tools are available for the clinical assessment of skeletal muscle mass loss that facilitate early detection in clinical practice. Analogous to using the FRAX tool for osteoporosis screening, sarcopenia can be clinically evaluated using the SARC-F questionnaire [76]. Developed as a rapid diagnostic tool, the SARC-F questionnaire has five functional status components: strength, assistance with walking, rising from a chair, climbing stairs, and falls.

13.3.3.1 Treatment

Aerobic and resistance exercises, along with appropriate nutrition that includes supplemental vitamin D, comprise the primary early treatment strategies for sarcopenia. Adequate protein, usually recommended at 0.8 g/kg/day, and sufficient daily caloric intake help nourish depleted muscle mass [77] (see Chap. 12). When combined with aerobic exercises, muscle protein synthesis and muscle quality are improved and intramuscular fat is reduced. Adding resistance exercises to the treatment plan helps improve muscle mass and strength. Based on a Cochrane review of 121 randomized controlled trials, the most beneficial exercise for the treatment of sarcopenia involves a progressive resistance therapy program of 2–3 times per week [78].

Estrogen remains a controversial treatment for sarcopenia, despite the known correlation between postmenopausal estrogen depletion and the subsequent loss of muscle mass. Similar to the prescriptions of menopausal hormone therapy (MHT) for postmenopausal osteoporosis, preexisting cardiovascular disease and the risk for

increased breast cancer must be considered before treating sarcopenia with estrogen (see Chap. 6). Treatment of sarcopenia therefore remains focused on resistance exercise and nutrition.

13.4 Arthralgia and Myalgia

13.4.1 Epidemiology and Physiology

Similar to the word *sarcopenia*, the term *arthralgia* also originates from two Greek words: *arthro* (joint) and *algos* (pain). While sarcopenia refers only to muscles, the term arthralgia refers only to joints and is accurately used to refer to pain in the joints not caused by inflammatory diseases, such as arthritis [79]. Despite its literal definition and classification, clinicians often use the term arthralgia in reference to any joint pain as a catch-all word for many possible underlying joint conditions. Causes of arthralgia can range from soft tissue injury (ligaments, tendons, or bursae) around joints to inflammation, infection, or allergic responses. Arthralgia might also be indicative of cancer or chronic joint disease, such as osteoarthritis. Menopause can also be an underlying cause of arthralgia.

The term *myalgia* means muscle pain. Overuse, injury, and strain or sprain are the most common causes of myalgia. The differential etiologies also include infection or idiopathic response to some medications or vaccinations. Dehydration or extensive physical exercise can cause muscle pain that rarely, but sometimes, leads to the serious condition of rhabdomyolysis. The connection between the menopause transition and myalgia, as with arthralgia, is believed to be due to diminished estrogen levels [80]. Joint and muscle pain and stiffness that were not present before menopause transition are therefore frequently attributed to declining hormone levels. However, many epidemiological studies do not differentiate musculoskeletal pain from arthritis, so assessing the burden of arthralgia/myalgia is difficult in this population.

An example of this challenge is found in a study by Lu et al. [81]. Although not specifically called "myalgia" and "arthralgia," musculoskeletal pain (MSP) was identified by Lu et al. as one of the most severe conditions experienced by perimenopausal women with an estimated overall prevalence of 71% [81]. Their systematic review and meta-analysis included 16 studies, published between 1997 and 2020 in 12 countries, and their conclusions support a high musculoskeletal pain prevalence among perimenopausal women. Musculoskeletal pain emerged in this study as a significant physical and psychological health burden. Clinicians report that menopausal women in many geographic areas complain more of arthralgia/myalgia than they do of vasomotor symptoms during menopause [82]. Musculoskeletal pain is reported by more than half of women with an approximate doubling in incidence over premenopause in the life stage of the menopause transition and with the most frequent presentation occurring between 45 and 55 years of age [83].

Reports vary, but pain has been documented as the predominant symptom in 21% of menopausal women [83]. Often pain is not the primary symptom in the presentation of menopausal arthralgia/myalgia, but it is a component of the broader, common menopausal signs and symptoms. Fatigue, sleep disturbance, increased body mass index (BMI), stress, anxiety, and mood alterations may also be present (see Chap. 1). Musculoskeletal pain, or the woman's ability to manage it, may be accentuated by the multiple menopausal symptoms. Conversely, the menopausal symptoms may be compounded by the presence of arthralgia/myalgia, making pain management challenging for patients and clinicians.

Despite anecdotal clinical evidence and some supportive research data, and although the association appears strong for a causal link between estrogen deficiency and musculoskeletal pain, the physiological link between musculoskeletal pain and the life stage of menopausal transition remains somewhat ambiguous. There are estrogen receptors throughout the body that protect and help maintain many normal physiological functions [79]. The decline in estrogen associated with menopause can theoretically exacerbate muscle and joint pain that is associated with aging, such as the normal wear and tear of joints and the inflammatory processes that occur with age. However, musculoskeletal pain is common throughout life, so what appears to be direct causal evidence of reduced estrogen may not really exist. More research is needed to validate the extent to which estrogen deficiency causes increased incidence of arthralgia/myalgia in the menopause transition. Since hormone decline is only one possible cause of myalgia and arthralgia, the clinician needs to explore other etiologies of muscle and joint pain when the menopausal woman presents for evaluation.

13.4.2 Screening, Diagnosis, and Management

The diagnosis of arthralgia/myalgia is traditionally made by history-taking and physical examination. A comprehensive history and musculoskeletal physical examination needs to be completed by the evaluating clinician in order to rule out underlying joint and/or muscle and soft tissues diagnoses besides arthralgia/myalgia before considering treatment options (Table 13.12).

For example, knee osteoarthritis is a common cause of knee pain in menopausal women, and rotator cuff tendinopathy often leads to shoulder pain in this age group. A thorough pain assessment and careful, hands-on physical examination of the painful body area are imperative in the differential diagnosis of menopausal musculoskeletal pain.

Diagnostic clues are often found in the patient's history. A family history of psoriasis or other inflammatory arthritis would alert the clinician to a possible inflammatory arthritic condition, whereas a history of joint injury may point to posttraumatic degenerative arthritis. History of menopause and associated symptoms must be elicited, as well as any history of symptoms suggesting secondary causes of arthralgia and myalgia, including thyroid disease or vitamin D deficiency (see Table 13.13).

Table 13.12 Causes of musculoskeletal pain in the perimenopause (adapted from [79])

Joint-based pain (arthralgia)
• Primary/idiopathic arthralgia (menopausal-associated arthralgia)
• Arthralgia due to secondary causes (see Table 13.13)
• Arthritis (osteoarthritis, inflammatory arthritis, e.g., rheumatoid arthritis, psoriatic arthritis, gout, pseudogout)
Myalgia
• Endocrine (vitamin D, deficiency, thyroid, Cushing's)
• Menopausal
• Polymyalgia rheumatica
• Drug induced (statins, fibrates)
Entheseal/tendon/bursitis pain
• Injury
• Asymmetric gait/overload (obesity/biomechanical factors such as flat feet)
• Drug-induced (quinolones)
Bone pain
• Metabolic (Paget's disease)
• Neoplasia (myeloma, metastatic disease)
• Infection (brucellosis, tuberculosis)
• Fracture (trauma, osteoporotic fracture)
Fibromyalgia
• Associated with: Fatigue, sleep disturbance, anxiety or depression, catastrophizing, other pain syndromes, e.g., migraine, IBS, atypical chest pain

The clinical management of menopause-associated arthralgia/myalgia is dependent on the differential diagnosis (Table 13.12). If arthritis is the cause of joint pain, the type of arthritis must be identified as treatment options vary widely. With rheumatoid arthritis, quick referral to rheumatology is essential for early treatment, whereas early osteoarthritis can often be managed in the primary care setting. If no secondary cause for diagnosed menopausal musculoskeletal pain is diagnosed, treatment can be initiated with pain control as the goal.

13.4.2.1 Treatment: The Role of Exercise

Research supports the theory that increasing physical activity or enhancing physical fitness may help prevent or attenuate menopause-related arthralgia and myalgia including in the postmenopausal stage of life [84–87]. In contrast, some studies do not validate these clear associations between exercise and other menopause symptoms such as vasomotor symptoms [88].

With the primary goal of analyzing the association of moderate to vigorous physical activity (MVPA), and a secondary goal of assessing the association of different components of physical fitness with menopause symptomatology, including arthralgia/myalgia, *The Flamenco Project* was initiated in Granada, Spain [80]. Although results of the *Flamenco Project* did not reveal a strong association between moderate to vigorous physical activity and a diminished occurrence of arthralgia/myalgia during menopause, several positive correlations were revealed between better physical fitness and decreased arthralgia/myalgia in menopause. For example, a weak

Table 13.13 Causes of arthralgia in menopausal women (adapted from [79])

Cause	Features
Primary/idiopathic (perimenopausal)	Timing (and presence) of other hypoestrogenic symptoms (in the absence of identifiable secondary causes)
Secondary causes	
Endocrine	
• Hypothyroidism	Fatigue; weight gain; hyporeflexia; proximal myopathy
• Hyperparathyroidism (primary or secondary)	Abdominal pains; high serum calcium
• Vitamin D deficiency	Fatigue; shortness of breath
Drug-related	
• Statins and other lipid-lowering agents • Aromatase inhibitors • Selective estrogen receptor modulators (SERMS) • Bisphosphonates (particularly intravenous) • Thiazide diuretics	Relevant temporal history Response, if appropriate, to drug holiday/cessation (aromatase inhibitors should not be stopped without oncology guidance)
Metabolic	
• Liver disease • Renal disease	Appropriate history or abnormality on blood testing
Rheumatic	
• Connective tissue disease (lupus[a], scleroderma, Sjogrens[a]) • Sarcoidosis[a] • Vasculitis • Hyperuricemia • Hypermobility	Rashes, oral ulcers, other clinical features of the disease Other blood test abnormalities, e.g., ANA or ANCA positivity, raised serum ACE, raised serum urate Evidence of hypermobility on examination
Infection	
• Parvovirus[a] • Hepatitis B[a]/C[a]/HIV[a] • Ross river virus[a] • Brucelllosis[a] • Whipple's disease[a] • Lyme disease[a]	Relevant rash, viral symptoms Relevant travel or other risk history History of insect bite
Malignancy	
• Disseminated bony malignancy • Paraneoplastic syndrome	Red flags, e.g., weight loss, bone pain, fever Other clinical features of malignancy

[a]May be associated with arthralgia or a frank arthritis

but statistically significant correlation was found between both increased lower-body muscle strength and upper-body flexibility with decreased arthralgia/myalgia. In addition, cardiorespiratory fitness, a known outcome of exercise, was associated with less arthralgia/myalgia in the study population. More research is needed to

validate the extent to which increased physical activity and enhanced physical fitness can positively influence menopausal symptoms.

13.4.2.2 General Treatment

Although little evidence-based research exists for integrative management of menopause-associated arthralgia/myalgia, there are valid and reliable sources for comprehensive general treatment options for musculoskeletal (MSK) pain. The authors of a systematic review of 11 MSK clinical practice guidelines identified improved care quality as an urgent need for musculoskeletal pain conditions, as well as a priority for clinicians, healthcare services, researchers, and policy makers [89]. Lin et al. contend that musculoskeletal pain manifests similar features in different body areas, and it should be possible to identify consistent recommendations for assessment and management.

The 11 clinical guidelines reviewed by these authors were all designed to provide best-practice recommendations for high-quality MSK care for the most common pain sites encountered by clinicians in emergency and primary care. These pain sites include spine (cervical, thoracic, and lumbar), hip/knee, and shoulder. From the 11 sets of clinical practice guidelines, a summary of recommendations for the management of MSK pain conditions evolved (Table 13.14).

13.4.2.3 Summary

Musculoskeletal pain, more common in women than men, increases during and after menopause. Not all joint pain is arthritis, and not all musculoskeletal pain is arthralgia/myalgia.

Table 13.14 Consistent recommendations across musculoskeletal (MSK) pain conditions (adapted from [89])

1. Care should be patient-centered. This includes care that responds to the individual context of the patient, employs effective communication, and uses shared decision-making processes	
2. Screen patients to identify those with a higher likelihood of serious pathology/red flag conditions	
3. Assess psychosocial factors	
4. Radiological imaging is discouraged unless:	(a) Serious pathology is suspected (b) There has been unsatisfactory response to conservative care or unexplained progression of signs and symptoms (c) It is likely to change management
5. Undertake a physical examination, which could include neurological screening tests, assessment of mobility and/or muscle strength	
6. Patient progress should be evaluated including the use of outcome measures	
7. Provide patients with education/information about their condition and management options	
8. Provide management addressing physical activity and/or exercise	
9. Apply manual therapy only as an adjunct to other evidence-based treatments	
10. Unless specifically indicated (e.g., red flag condition), offer evidence-informed nonsurgical care prior to surgery	
11. Facilitate continuation or resumption of work	

Careful screening of each woman presenting with MSK pain will guide the clinician's differential diagnostic steps that lead to appropriate shared decision-making healthcare management.

13.5 Conclusion

Musculoskeletal health during menopause deserves more attention in clinical practice. The goal of this chapter was to review the physiology of musculoskeletal changes during the life transition of menopause and to provide evidence-based clinical guidelines to aid the clinician in the prevention, diagnosis, and management of commonly encountered musculoskeletal conditions: osteoporosis, sarcopenia, myalgia, and arthralgia. Comprehensive, multidisciplinary approaches to prevention and treatment were provided for each condition.

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Breast Health

14

Michelle Frankland and Trish Brown

14.1 Introduction: Incidence of Breast Cancer

Breast cancer is the most common non-cutaneous, malignant disease among women worldwide, accounting for 24% of new cancer cases in 2018. Approximately 645,000 premenopausal and 1.4 million postmenopausal breast cancer cases were diagnosed worldwide in 2018 [1]. Globally, breast cancer cases will increase to over 2 million new cases/year by 2030 [2]. Nearly half of this burden is observed in high-resource countries, many of which have established screening programs. There is a 11–13% chance a woman will be diagnosed with breast cancer in her lifetime. Breast cancer is a heterogenous disease with many associated risk factors, including environment, reproductive history, genetics, and trends in western-based lifestyle. Breast cancer originates in the ducts (85%), lobules (15%), or the epithelium. When the cancer is limited to the duct or lobule, it is classified as in situ disease. Once it invades the surrounding tissues, it is referred to as invasive disease.

14.2 Racial/Ethnic Disparities in Breast Cancer Diagnosis, Treatment, and Survival

14.2.1 Race/Ethnicity and Breast Cancer Survival

Worldwide, breast cancer survival rates vary greatly, with approximately 80% survival in North America, Japan, and Sweden to about 60% in middle resource

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countries and below 40% in low-resource countries. The incidence and outcome of breast cancer also differ within regions. Despite the incidence of breast cancer being lower in African American women, the mortality rate of breast cancer is significantly higher compared to white women [3]. Documented breast cancer mortality rates in the United States are relatively low for the following: Asian/Pacific Islander, 11.3/100,000; American Indian/Alaska Native, 14.1/100,000; and Hispanic women, 14.4/100,000 [4]. Contributing factors include socioeconomic status, differential access to health care/screening, and disease-related molecular mechanistic differences. In New Zealand, almost 30% of all new cancer cases and 14% of all cancer deaths in 2012 were breast cancer. Despite global improved survival rates, net survival in New Zealand is inferior to some other high-resource nations, including Australia. Poorest outcomes are experienced by Maori (indigenous people constituting 14% of New Zealand women) and Pacific women (immigrants or descendants from immigrants from the Pacific Islands, constituting 7% of New Zealand women) [5]. Compared with their New Zealand European counterparts, Maori and Pacific women were more likely to be diagnosed with advanced breast cancer that was less likely to be diagnosed through screening. It is believed that the barriers in screening access/coverage equates to later diagnosis and therefore poorer survival outcomes.

14.2.2 Race/Ethnicity, Genetics, and Breast Cancer

The lifetime risk of developing breast cancer is not significantly different between women of different races/ethnicities [6, 7]. The Million Women Study in the UK looked at breast cancer incident by race/ethnicity, including 5877 South Asian women, 4919 Black women, and 1,038,144 white women in England, and found breast cancer incidence to be similar among ethnicities when adjusted for known risk factors [8].

The prevalence of *BRCA* variants is not significantly different, either [7]. In a small study of 182 African American women diagnosed with invasive breast cancer that looked at the presence *BRCA* and additional genes associated with inherited breast cancer, it was found that 12% of women had an inherited form of breast cancer, and, in addition to *BRCA*, pathogenic variants were found in *ATM*, *RAD50*, *CDH1*, *MSH6*, *MUTYH*, *NF1*, and *BRIP1* genes [9]. Similar findings are found in studies of other ethnicities such as Arabic [10] and Korean [11]. Despite these similarities in inherited cancer genes, there are real-world observable differences between racial/ethnic groups in breast cancer incidence by age and survival. Scientists now better understand the role that predisposition genes and other environmental factors can play in developing acquired cancer. However, the vast majority of studies on genetics and environmental factors have been conducted in European populations. In an analysis of available data on genetic predisposition genes through January of 2019 [12], it was noted that 78% of individuals analyzed were of European ancestry, followed by 10% Asian, 2% African, and 1% Hispanic, with the remainder made up of multiple other ethnicities. Some have assumed that

findings in European populations can be generalized to other racial/ethnic groups, but a comprehensive analysis by Wojcik et al. [13] demonstrated there can be significant differences in predisposition genes and their effects between ethnic groups. For example, a small study conducted by Wang et al. [14] looked at predisposition genetic data for breast cancer in 3686 women of African ancestry and found that prior risk stratification studies created using European and Asian women were not comparable or useful for women of African ancestry.

Why disparities exist in incidence and survival between ethnic groups is not fully understood, but as research is starting to focus on this question, some important observations and themes emerge.

14.2.3 Race/Ethnicity and Incidence by Age

While lifetime risks seem comparable between race/ethnic groups over time, ranging between 9% and 15%, there can be significant differences in risk and incidence between race/ethnic groups by age. While white women tend to be at a higher lifetime risk overall, data from the US shows that Black women are more likely to develop breast cancer at a younger age [4, 15] (see Fig. 14.1).

14.2.4 Race/Ethnicity and Stage of Cancer at Diagnosis and Mortality

In the US, non-white women are more likely to be diagnosed at more advanced stages of cancer [4, 15, 16] (Fig. 14.2).

This has a downstream impact on morbidity and mortality. In a study of over 930,000 women in 18 breast cancer registries spanning from 1975 to 2009, a

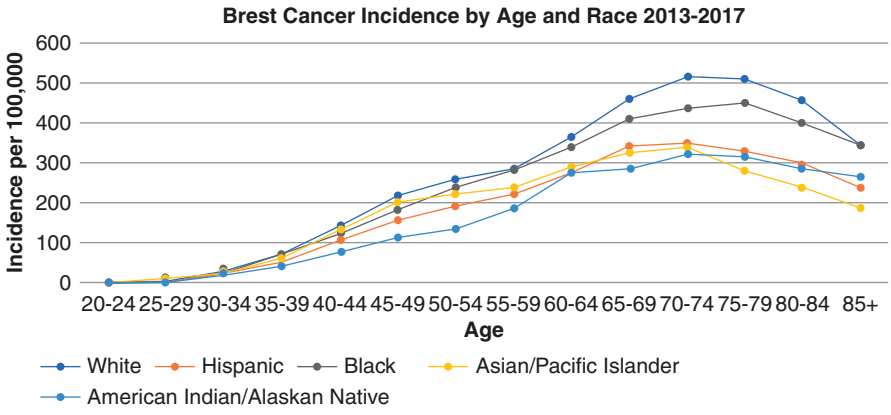


Fig. 14.1 Breast cancer incidence in the United States by age and race 2013–2017. (Based on data from [4])

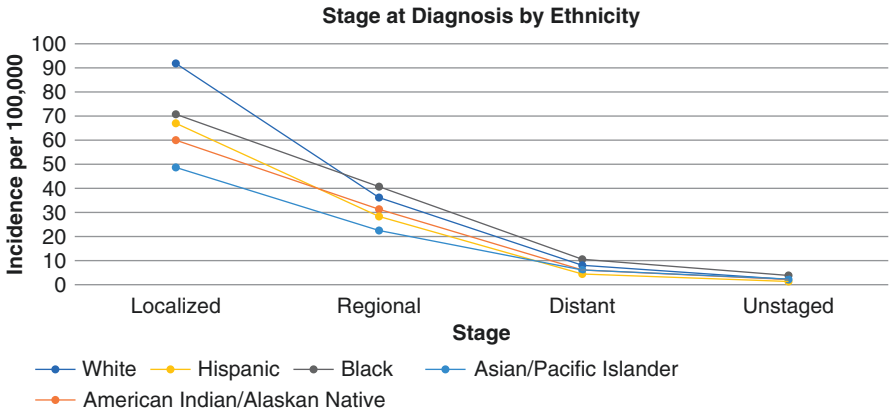


Fig. 14.2 Stage at diagnosis by ethnicity in the United States. (Based on data from [4])

disparate survival rate between white women and all other races/ethnicities was observed, even taking into consideration improvements in screening, therapies, and access to care. The largest discrepancy was noted in Black women throughout all the time periods, with the 5-year survivability of Black women lagging by 20 years behind white women in the 2005–2009 data [16]. Black women are 42% more likely to die from breast cancer than white women [15].

14.2.5 Race/Ethnicity and Biological Differences in Tumors

Black women tend to be diagnosed with more aggressive cancers, and are more than twice as likely to be diagnosed with a HER2-negative, estrogen receptor (ER) negative, progesterone receptor (PR) negative tumor, also known as a triple-negative tumor, than white women [15]. The reasons behind this go beyond biology into social and cultural issues, namely reproduction and breastfeeding. Pregnancy helps reduce the risk of having breast cancer. It appears, however, that pregnancy is protective from hormone-positive breast cancer, but possibly the inverse is true in hormone receptor-negative breast cancer. In a study from 1995 to 2009 comparing 457 cases of ER+/PR+ to 318 cases of ER−/PR− breast cancer nested in a cohort of 59,000 women in the Black Women's Health Study, it was found that women who had three or more pregnancies and had not breastfed were more likely to have a more aggressive ER−/PR− breast cancer. When compared to white counterparts, white women were more likely to have fewer pregnancies and more likely to have breastfed [17]. In the Hispanic population, a study from 1995 to 2007 of 6000 women from four population registries in the US and Mexico found no association with the number of pregnancies and hormone-positive or -negative breast cancer, but did find an association with hormone-positive breast cancer with an older age at first birth, and a strong association with breastfeeding being protective against hormone-negative breast cancer. Breast feeding also reduced the risk of hormone-positive breast cancer associated with an older age at first birth [18].

14.3 Barriers to Breast Cancer Screening, Diagnosis, and Care

There are many socioeconomic barriers that impact access to and participation in breast screening and the preventative endocrine therapies. Barriers include lower income, lower educational status, lack of health insurance, unemployment, access to screening, and cultural/personal concerns about breast cancer, as well as clinical barriers. Although most high- and middle-resource countries have funded screening programs, geographic access to screening limits participation. A meta-analysis of 28 studies showed that the proportion of women who had ever had a mammogram was higher in urban populations than in the rural population in Australia, Canada, and the United States, but there were contrasting findings in Northern Ireland and the Republic of Korea [19]. Fear of cost is consistently cited as an additional barrier; fear of cost not only includes cost of screening imaging but of potential costs associated with a diagnosis and subsequent treatment of breast cancer [20].

Some studies cite lower educational status or lack of knowledge of breast cancer as a barrier to screening; however, many studies from diverse cultural areas such as Nigeria, Turkey, and Chinese immigrants in the USA indicate that more knowledge about breast cancer does not necessarily lead to increased screening rates. Some cultures perceive breast cancer screening as a risky behavior due to the associated social and personal consequences of a breast cancer diagnosis. There is a strong sense of fatalism associated with a cancer diagnosis of any kind. Studies from Israel, Kenya, Mexico, and the United States have all found that fatalism can be considered a barrier to screening. Screening could be perceived as worthwhile if breast cancer can be seen as a curable disease when detected early but if cancer is only viewed as a fatal diagnosis, screening can be perceived as having no value [21]. African American/Black, Asian/Pacific Islander, and Hispanic women living in the USA reported lack of information regarding need for screening/benefit versus risk, as well as lack of information regarding logistics of scheduling, obtaining, and insurance coverage of screening [22]. In a review of knowledge of breast cancer screening in Latin America and the Caribbean by Doede et al. [23], source of knowledge impacted attitude toward screening. Women with close relationships, family or friends, who had a breast cancer diagnosis had improved attitude toward breast cancer screening. Women who report physicians and other healthcare providers as an important knowledge source and who discussed mammography with their healthcare provider were more likely to adhere to screening guidelines. Mamdouh et al. [24] looked at barriers to screening in Egyptian women and found 81.8% of women studied would not seek care until they were ill, 77% were unwilling to have a mammogram until it was recommended by a doctor, 71.4% blamed the lack of privacy as a barrier, 69.2% felt medical check-ups were not worthwhile, and 64.6% blamed cost of services as a barrier. Outside of improving logistical access to screening, mailed information that is concise, telephone calls, and scheduled appointments improve participation [25]. Further studies to evaluate ways to improve access and participation in breast cancer screening are needed. In addition, education and opportunities for participation in screening need to emphasize a woman's right to

informed decision-making. Informed decision-making should include knowledge, attitudes, and test choices, as well as at least two different measurement tools assessing the informed decision-making process [26].

14.3.1 Clinical Barriers to Screening

There are clinical implications associated with breast cancer screening. Clinical implications include false-positive as well as false-negative imaging results, increase in call backs/biopsies, increased radiation exposure, and overtreatment. Discussion regarding risks of overdiagnosis and overtreatment of breast cancer continues. In some populations, the estimated prevalence of breast cancer overdiagnosis was as high as 54% [27]. Early screening and improved imaging has led to increased detection of very small, early stage breast cancers, and stage 0 DCIS (Ductal Carcinoma In Situ) breast cancers. Despite concerns of overdiagnosis and overtreatment, implementing appropriate screening in high-risk individuals and initiating treatment of early stage cancers can avoid many of the adverse outcomes associated with more aggressive treatments in later stages of disease.

The high sensitivity of breast MRI leads to more breast biopsies. A large observational cohort study of six Breast Cancer Surveillance Consortium Registries found episodes of breast biopsy in women with a personal history of breast cancer were 6.3% with MRI versus 2.2% with mammography. In women without a personal history of breast cancer, episodes were even higher with MRI 10.5% versus 1.6% with mammography; however, the cancer yield was lower [28]. There are also a small percentage of breast cancers that are nonpalpable and mammographically occult, resulting in a delay to diagnosis and treatment.

A common concern is radiation exposure. Radiation minimization is an ongoing goal in radiology. Mammography exposes the patient to a very small amount of radiation, approximately equivalent to the average woman's environmental exposure over a 7-week period. A systematic review conducted by the US Preventive Services Task Force found no direct studies of radiation exposure from mammography; however, two modeling studies have estimated deaths caused by radiation-induced cancer. One modeling study estimated death caused by mammography radiation-induced cancer was 2 per 100,000 in women 50–59 years of age screened biennially. Another modeling study estimated 125 cases of radiation induced breast cancer and 16 cases of radiation-induced breast cancer deaths in 100,000 women aged 40–74 years, screened annually, compared to 968 cases of cancer deaths prevented by early detection through screening [29].

14.3.2 Socioeconomic Barriers to Screening and Care

Socioeconomic issues go beyond race/ethnicity. In studies that separate the two, it was found that the differences based on race/ethnicity alone were reduced when socioeconomic issues were included [15]. Regardless, issues of the socioeconomic

concerns of poverty, access to care, healthcare system distrust, and social injustice cannot be easily separated from race/ethnicity.

14.3.2.1 Poverty

Low-income women have lower rates of breast cancer screening, higher probability of a late stage diagnosis, lack of access to care, and overall a higher mortality rate, regardless of race/ethnicity. However, race/ethnicity cannot be neatly excised as white individuals are less likely to live in poverty than other racial/ethnic groups (Fig. 14.3).

Women living in poverty are less likely to have access to a primary care physician. Geographic barriers exist as well, as poverty is often found in geographical areas where health care is not easily accessible. Healthcare providers in these areas are less likely to be specialists or board certified and are less likely to be able to keep up with continuing education on cancer screening and prevention. Poverty also forces women to prioritize various health issues for themselves and their families. Women in poverty are more likely to work hourly jobs, and have multiple jobs; missing work for preventive care is not a high priority. This holds true for other disease risks in women, such as cardiovascular disease, hypertension, diabetes, or respiratory diseases. The possibility of a comorbidity competing with breast cancer screening, seeking a diagnosis, and treatment is high. In regions reliant on third-party payers for health care, health insurance is often not available or is minimal. Prevention and risk reduction strategies may not be available to women living in poverty. Good nutrition, exercise, a healthy weight are less attainable for those living in poverty. Access to nutritious food is difficult, and the diet is more likely to be high fat with limited fruits and vegetables. Women in poverty are less likely to

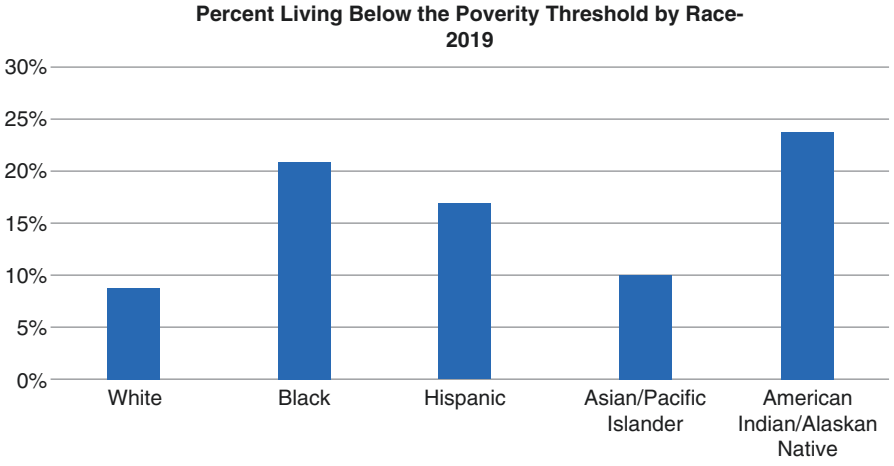


Fig. 14.3 Percent living below the poverty threshold in the United States by race/ethnicity 2019. (Based on data from 2021 Kaiser Family Foundation report for 2019. At this time, the US Census Bureau's poverty threshold for a family with two adults and one child was an annual income of $20,578)

engage in regular physical exercise, in part because there may be safety-related barriers. For example, a high percentage of Black Americans live in neighborhoods without safe open spaces, sidewalks, or parks [15, 30]. This issue goes beyond poverty into racially based health inequities.

14.3.2.2 Social Injustice

Social injustice includes discrimination and prejudice that result in unfair treatment based on race and ethnicity and may be linked to the incidence of breast cancer as well as unequal delivery of breast cancer-related services. In a prospective analysis of the Black Women's Health study, Taylor et al. [31] found a weak association among a cohort of 593 women with breast cancer living in the USA. These participants completed a one-time questionnaire in 1997 about discriminatory experiences related to their work, housing, and police interactions. Women who had reported frequent discriminatory experiences had a slightly higher chance of developing breast cancer compared to those who reported infrequent discrimination. The association was strongest among women under age 50 years, and those who reported multiple sources of discrimination. Black women are more likely than white women to cite lack of a physician recommendation as a reason why they did not participate in breast cancer screening programs [30]. Multiple studies have demonstrated that Black women have significantly longer wait times between abnormal mammograms and breast cancer treatment initiation. Gorin et al. [32] found that among women aged 65 years and older, Black women in the USA were more likely to wait more than 60 days between an abnormal mammogram and biopsy, and more than 30 days after diagnosis for treatment to start.

Some studies have examined racial attitudes of healthcare providers. A statement in 2003 by the Institute of Medicine [33] noted that while most clinicians endorse egalitarian and non-racist attitudes, there is strong evidence that clinician implicit bias, stereotyping, prejudice, and clinical uncertainty play a role in disparity of care. A telephone interview to identify any issues of explicit or implicit bias was conducted with 134 providers and 2908 of their patients stratified by ethnicity/race. The providers filled out a questionnaire that examined explicit racial biases and took Implicit Association Tests (IATs) measuring implicit bias against Blacks and Latinos. Very little explicit provider bias was found, but almost two-thirds of the clinicians had implicit bias against Blacks (43% moderate to strong) and Latinos (51% moderate to strong). Black patients rated those with high implicit bias lower in patient-centered care than did a comparable group of white patients. Latinos overall gave clinicians lower ratings than other groups that were independent of the clinicians implicit bias [34].

14.3.2.3 Healthcare System Distrust

Healthcare system distrust (HCSD) is an important phenomenon that has been demonstrated to impact breast cancer outcomes. While trust includes belief in the competence of a healthcare system, it also includes concepts such as patient control, cooperation, compliance, vulnerability, competence, and value. Distrust includes the premise that individuals or entities within a potentially trusted system may

actively act in a way that is not in the patient's best interest and includes historical trauma, lack of trust in Western Medicine, and cultural insensitivity. In a review of the literature including 20 studies, Morgane et al. (2020) found that distrust was higher across certain themes by race/ethnicity. They also noted that Black women were a primary focus of the research, and no studies addressed Pacific Islanders or Arabs. Notably, few studies of HCSD included white women. While white women overall have the highest rates of breast cancer-related care and are considered the comparator group, there are white sub-groups such as impoverished or under-insured white women that should not be overlooked. The findings across the various studies included:

- Breast cancer screening
  - Adherence to mammography recommendations required trust in the system
  - Interviewed Blacks and Latinas mistrust the healthcare system due to historical trauma, oppression, and cultural insensitivity
  - Interviewed American Indian women mistrust Western Medicine
  - Interviewed Hmong women also identified mistrust in Western Medicine, but did not identify medical mistrust as a barrier to breast cancer screening
- Genetic testing
  - Blacks and Latinas have reduced trust for genetic counseling and perceive that any advantages they might get from genetic testing could be outweighed from potential abuses of the genetic information. There was no significant difference in mistrust of genetic testing between women in this group who complied with mammography screening recommendations and those who did not.
  - In Korean women who mistrusted genetic testing, there was a correlation between the mistrust and decreased mammography screening in the past 2 years.
- Treatment
  - Black women reported an increased perception of emotional problems, physical problems, sexual issues, and resource problems than other groups.
  - Black, Latina, and white women who did not receive breast cancer treatment reported a high mistrust in the healthcare system.
  - Those with high distrust felt that there was a discordance in treatment offered to them compared to other patients.
  - Black women reported they distrusted the need for chemotherapy and reported a lower quality of life and reported less communication occurred regarding radiation ratings. This was correlated in one study with increased cancer stage at diagnosis. The association of HCSD with their level of knowledge about their cancer showed mixed results.

The overall conclusion is that the concepts of mistrust are complex and vary between racial/ethnic groups. More studies are needed to fully appreciate the ways in which ethnicity and culture lead to HCSD internationally.

14.3.3 Barriers to Use of Chemoprevention

Extensive research has demonstrated the benefit of endocrine therapy as chemoprevention in women at high risk of breast cancer, yet adoption has been poor. The National Health Interview Survey (NHIS) of the United States found the use of tamoxifen among women with a personal history of breast cancer was 0.2% in 2000 and decreased to 0.08% by 2005. In addition, raloxifene use decreased after FDA approval in the breast cancer chemoprevention setting [35]. Barriers to use included insufficient knowledge and information about risk-reduction strategies, understanding how to use risk assessment tools, and misconceptions about the risks associated with endocrine therapy. A Canadian study of high-risk women demonstrated a 62–67% self-reported likelihood of taking endocrine therapy within the next 5 years with the respondents requiring strong evidence of not only efficacy but that side effects would be tolerable [36].

Side effects of blood clot and endometrial cancer are most feared with the selective estrogen receptor modulators (SERMs) and of strokes and loss of bone density with the aromatase inhibitors (AIs). Additional side effect concerns with chemoprevention are hot flashes, other menopausal symptoms, and urogenital symptoms. Some women are reluctant to give up menopausal hormone therapy for preventative therapy. The strongest barriers for providers are lack of knowledge in how to use high-risk assessment tools, personal experience with breast cancer, and side effect profile. A study of 350 primary care physicians found they were more likely to prescribe medication for chemoprevention if it was easy to determine who was eligible, their colleagues were prescribing chemoprevention medications, they understood the benefits versus risks, and patients asked about the medication [37]. Lack of time for patient counseling and reimbursement for time spent was also cited as a barrier to provider prescribing. Kaplan et al. [38] surveyed 882 physicians who reported lack of time (40.3%), concerns regarding reimbursement for time (13%) and insufficient information regarding risk reduction options (19.1%) as most significant barriers. In Australia, a survey of women and healthcare providers supported similar findings, the strongest barriers for women were side effects (31%) and inadequate information (23%), the predominant family physician barriers were insufficient knowledge (45%) and in breast surgeons, medication side effects (40%) [39]. Overwhelmingly, the research validated the need for strategies and programs to educate women about breast cancer and their personal risk, as well as develop more easily accessible and accurate risk assessment tools and decision aids that convey the benefits of chemoprevention for healthcare providers.

14.4 Breast Health Screening

14.4.1 History of Breast Health Screening

Breast cancer screening aims to reduce rates of breast cancer morbidity and mortality. Screening for breast cancer continues to evolve. Breast self-exam, clinical breast exam, and mammography have been the gold standard for decades. Breast self-exam, as a screening tool, has not been shown to be effective in reducing breast

cancer mortality but has led to an increase in breast biopsies [40]. Many organization guidelines have also removed clinical breast exam from their screening recommendations, including the Canadian Task Force on Preventive Health Care, the US Preventive Services Task Force, the American Cancer Society, the UK National Health Services, and the World Health Organization. In contrast, the US National Comprehensive Cancer Network, the American College of Obstetricians and Gynecologists and the Memorial Sloan Kettering Cancer Center still include clinical breast exam [41].

A European study examined 500,000 women across nine countries and found a 41% reduction in cancer deaths within 10 years of cancer diagnosis among women who underwent mammography screening. In addition, they found the incidence of advanced breast cancer at diagnosis dropped by 25%, substantiating the benefit of screening mammography [42]. Data from the UK Age Trial at 23-year follow-up confirms results reported at 17-year follow-up. Women who accepted an invitation to yearly mammograms between age 40 and 49 years saw a reduction in breast cancer mortality of 25% in the first 10 years. The effect of screening mammography was tempered thereafter, with little or no effect on breast cancer deaths occurring 10 or more years after randomization. However, at 23 year follow-up the absolute benefit continued with approximately one death prevented per 1000 women screened [42]. Guidelines for initiation of screening mammography vary by country. The World Health Organization recommends cancer screening with mammography begin at age 50 years. The American College of Radiology, Society of Breast Imaging, and the American Society of Breast Surgeons recommend women of average risk of breast cancer begin having annual screening mammograms at 40 years of age. Currently mammography is the only breast imaging proven to reduce breast cancer mortality.

14.4.2 Modalities: Mammography, Ultrasound, Breast MRI

14.4.2.1 Mammography: Two Dimensional Versus Three Dimensional

Mammography uses X-ray imaging to evaluate changes in breast tissue. Compression of the breast during the exam minimizes motion and creates a flat plane, both reducing the amount of radiation required to pass through the tissue and improving the image quality. Mammography sensitivity is 70–90%, with variability based on breast density. In denser breasts, sensitivity is as low as 30–48%, whereas in women with fatty breasts, it is as high as 80–98% [43]. Fatty tissue will appear translucent while fibrous tissue, glandular tissue, calcifications, or a tumor appear whiter against the gray background. Characteristics of a suspicious area include size, shape, degree of contrast compared to surrounding tissue, and appearance of margins. Calcifications and microcalcifications are often benign, but changes in grouping or clustering of calcifications can indicate a need for biopsy. Computer-Assisted Detection (CAD) provides a second review of the mammogram image following the radiologist's reading. The computer software detects and marks subtle findings for further review. Evidence is equivocal on whether or not CAD helps detect more breast cancers [44].

Two-dimensional (2D) mammography takes images from the front and side of the breast to create a single image. Digital breast tomosynthesis takes images from several angles of the breast to create a three-dimensional (3D) image. Tomosynthesis has been shown to improve cancer detection rates with improved detection of small cancers and to reduce false-positive screening recalls [45]. Tomosynthesis is done in conjunction with a 2D mammogram, increasing radiation exposure. Ongoing studies seek to determine if specific populations of women benefit from tomosynthesis more than others. Limitations of mammography include, lack of availability in low resource areas, efficacy in evaluating dense breasts, use of ionizing radiation, portability, and cost.

14.4.2.2 Ultrasound

Breast ultrasound uses high-frequency sound waves and does not involve ionizing radiation. Cancers usually appear darker than the lighter gray fat or white fibrous breast tissue. Other suspicious findings on ultrasound include masses that are taller than wide (a non-parallel orientation), hypoechoic areas, irregular borders, and spiculation, as well as loss of the fatty hilum and increased size of lymph nodes in the axilla. On mammography, dense breast tissue and breast cancer both appear white, possibly obscuring a tumor. However, on ultrasound, dense tissue is echogenic, whereas breast cancer is hypoechoic. Ultrasound leverages these differences in tissue characteristics and can help improve cancer detection in women with dense breast tissue [46].

Indication for screening ultrasound requires accurately defining breast density by mammography, ultrasound, or magnetic resonance imaging (MRI) using the breast-imaging reporting and data system (BIRAD). A limitation to an increased use of screening ultrasound is operator-dependent accuracy, requiring skilled radiologists. In addition, ultrasound cannot detect breast calcifications, so screening mammography is still necessary. Further studies are required to substantiate the benefit of screening ultrasound as an adjunct to mammography in women with higher breast tissue density.

14.4.2.3 Magnetic Resonance Imaging (MRI)

Breast MRI uses magnets and radio wave pulses to manipulate the natural magnetic properties of the breasts and surrounding tissues to produce images. Breast MRI is conducted with and without gadolinium contrast to evaluate anatomy and blood flow patterns. Radiologists look for irregular or spiculated borders or rim-enhancement on the periphery. Gadolinium contrast allows evaluation of the kinetics of signal intensity and wash-out period of a lesion. In a malignant lesion, the signal intensity is rapid, followed by the wash-out in the following few minutes. A benign lesion tends to exhibit a progressive, slow rise in signal intensity and no wash-out of contrast. Radiologists classify contrast-enhanced lesions based on morphology and kinetics to assign a BIRAD score. Breast MRI sensitivity in high-risk women has been found to be superior to mammography but generally specificity is lower, leading to an increase in breast biopsies [47]. Current indications for screening breast MRI are defined by a patient's risk of breast cancer. Limitations of breast

MRI include body habitus, inability to shallow breath/breath hold, and potential inability to lie prone with arms overhead, as well as access to technology and cost.

Utilizing multiple imaging modalities has an evolving role in breast cancer screening. A large study conducted by the American College of Radiology Imaging enrolled 2700 women with dense breasts and increased risk of breast cancer across 20 sites in the USA, Canada, and Argentina. The study examined the role of the addition of screening breast ultrasound to mammography, as well as the benefit of screening MRI in a subset of women who had undergone three negative screening mammograms and ultrasound exams. Addition of ultrasound resulted in an additional 4.3 cancers detected per 1000 screened. After three rounds of negative screening with mammography and ultrasound, screening breast MRI found an additional 14.7 cancers per 1000 screened, a yield four times greater than adding ultrasound to mammography screening. Despite limitations, the authors concluded that, with further validation, screening ultrasound could be a potential alternative to mammography, especially in countries lacking structured screening programs. In countries with screening mammography, there is potential role for ultrasound, particularly in women with dense breasts who do not meet high-risk criteria for screening MRI or high-risk women who cannot tolerate breast MRI [48].

14.5 Breast Density

14.5.1 Breast Imaging Reporting and Data System (BIRAD)

The breast imaging reporting and data system (BIRAD) is a reporting schema used for imaging of the breast: mammography, ultrasound, and breast MRI. The BIRAD reporting system was developed in the United States. The fifth edition is available in six language translations and is widely utilized throughout the United States and Europe [49, 50]. The standard reporting includes breast composition, important findings and comparison to previous studies. The score indicates recommendations for follow-up, ranging from routine mammography 1 year later to requirements for additional imaging, to biopsy. In the United States, the Mammography Quality Standards Act requires breast imaging to have a BIRAD score (Table 14.1).

14.5.2 Breast Density on Mammography

Breast density is often determined by mammogram. The higher the ratio of fibroglandular tissue to fatty breast tissue, the higher the breast density. Breast density can change over time, generally becoming less dense or more fatty with age. Numerous studies indicated a two- to sixfold increased risk of breast cancer in a woman with extremely dense breasts compared to a woman with fatty breasts [51, 52]. One study suggested that dense breast tissue is associated with a pro-inflammatory microenvironment, which increased the risk of development of breast cancer [53]. Del Carmen et al. [54] compared breast density among white,

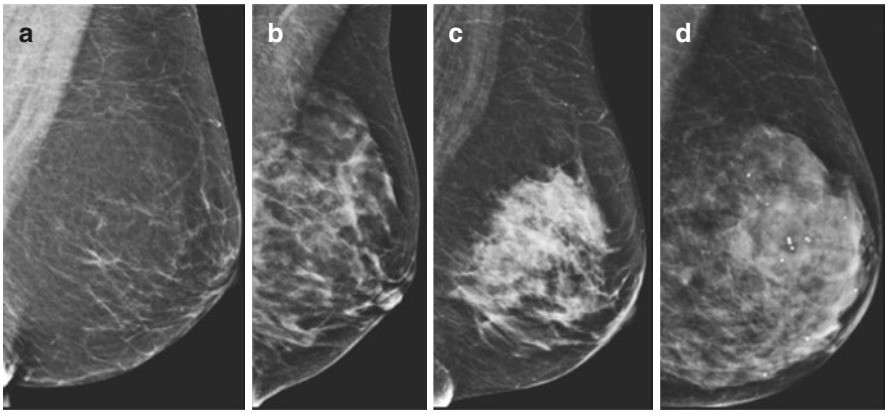
Table 14.1 Breast Imaging Reporting and Data System (BIRAD) assessment categories and management recommendations. Adapted from the American College of Radiology—https://www.acr.org/-/media/ACR/Files/RADS/BI-RADS/Mammography-Reporting.pdf

	Category	Management	Likelihood of cancer
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	N/A
1	Negative	Routine screening	Essentially 0%
2	Benign	Routine screening	Essentially 0%
3	Probably benign	Short interval follow-up (6 months)	>0% but ≤2%
4	Suspicious	Tissue diagnosis	(a) Low suspicion for malignancy (>2% to ≤10%) (b) Moderate suspicion for malignancy (>10% to ≤50%) (c) High suspicion for malignancy (>50% to <95%)
5	Highly suggestive of malignancy	Tissue diagnosis	≥95%
6	Biopsy-proven cancer	Surgical excision when clinically appropriate	N/A

African American, and Asian women, then correlated breast density and race with age, body mass index (BMI), and breast cup size. They found inherent mammographic breast density differences among racial/ethnic groups do not explain known breast cancer development risk difference across race/ethnicity. Moore et al. [55] sought to address the question of determinants of mammographic breast density and found BMI, regardless of race/ethnicity, was the greatest explanation of breast density. Figure 14.4 shows variations in breast density as seen on mammography. A summary of breast cancer screening guidelines for women of average risk is found in (Table 14.2).

14.6 Defining the Woman of High Risk for Breast Cancer

Identification of the woman of high risk is important in determining screen regimens, indicating the need for further testing such as genetic testing and implementation of prevention endocrine therapy. Numerous factors contribute to defining a patient as high risk for developing breast cancer: breast density, genetic mutations, family history (in the setting of negative genetics), nonmalignant breast lesions (lobular carcinoma in situ, atypical ductal hyperplasia, and lobular hyperplasia), and history of chest wall radiation when less than 30 years of age. Different factors convey varying risks, with risk as low as 9–10% as in the setting of atypical ductal hyperplasia or lobular hyperplasia and higher than 60% in women with a BRCA mutation. With advances in breast cancer screening and prevention of breast cancer, healthcare providers play a crucial role in understanding which women are at higher risk, how to assess their risk, and how to approach a shared decision-making discussion regarding screening and prevention. Many risk-assessment tools are available.



A. Almost entirely fatty – 10% of women	B. Scattered areas of fibroglandular density – 40% of women	C. Heterogeneously dense – 40% of women	D. Extremely dense – 10% of women

Fig. 14.4 Mammographic images depicting beast density with percentage of women with varying density. (**a**) Almost entirely fatty—10% of women. (**b**) Scattered areas of fibroglandular density—40% of women. (**c**) Heterogeneously dense—40% of women. (**d**) Extremely dense—10% of women. (Based on [56]. Image used with permission of The Mayo Foundation for Medical Education and Research)

Obtaining a patient's personal and family history is the first step in determining which tool is most appropriate in assessing each woman's personal risk.

14.6.1 Family History

A family medical history should be obtained and updated regularly as new information may change the risk profile. The National Comprehensive Cancer Network (NCCN) maintains a list of family and medical history criteria that are key to understanding both acquired and inherited risk [6]. Discussing a patient's family and medical history must be approached with an understanding that it includes an evaluation of the patient's desires, needs, and concerns about a personal cancer risk, and an appreciation that many people have family dynamics that may prevent knowing a complete history. Even in the absence of a family history, a risk evaluation can still be completed.

A complete family medical history for a cancer risk evaluation includes:

- Identifying all first-, second-, and third-degree relatives on both sides of the family by building a pedigree.
- Identify family members (including the patient) who had cancer, type of cancer, age of onset, and contralateral cancer, if applicable. It is a common mistake for patients to focus only on reporting breast cancer when doing a breast cancer risk

Table 14.2 Summary of breast cancer screening guidelines for women of average risk. Adapted and sourced from CDC (Center for Disease Control)

Guideline	Women 40–49 years	Women 50–74 years	Women 75 years or older	Women with dense breasts
WHO (World Health Organization)	In well-resourced settings, consider implementing mammography screening programs, in the context of rigorous research, once an organized, population-based screening program for women 50–69 years is well established. In limited resource settings, WHO recommends against implementation of population-based screening	Well-resourced settings: 50–69 years: screening mammography once every 2 years, with shared decision-making. 70–75 years: implement a screening mammography program conducted in the context of rigorous research. Limited resource settings with weak health systems: 50–69 years: clinical breast exam seems promising and could be implemented when necessary. 70–75 years: recommend against screening programs	No recommendation	No recommendation

International Agency for Research on Cancer	Limited evidence that screening with mammography reduces breast cancer mortality in women 40–49 years	Sufficient evidence that screening mammography reduces breast cancer mortality to an extent that its benefits substantially outweigh the risk of radiation-induced cancer from mammography. Inadequate evidence that clinical breast exam reduces breast cancer mortality. Sufficient evidence that clinical breast examination shifts the stage distribution of tumors detected toward a lower stage	Not addressed	Inadequate evidence that ultrasonography as an adjunct to mammography reduces breast cancer mortality. Limited evidence that ultrasonography as an adjunct to mammography increases the breast cancer detection rate. Sufficient evidence that ultrasonography as an adjunct to mammography increases the proportion of false-positive screening outcomes
US Preventive Services Task Force	Decision to start screening with mammography in women prior to age 50 years should be individualized. Women who place a higher value on potential benefit than harm may choose to begin screening once every 2 years between age 40 and 49 years	Screening with mammography once every 2 years is recommended. Insufficient evidence to assess the additional benefits and harms of clinical breast exam	Insufficient evidence to assess the balance of benefits and harms of screening mammography in women 75 years or older	Insufficient evidence to assess the balance of benefits and harms of adjunctive screening for breast cancer using breast ultrasound, MRI, digital breast tomosynthesis, or other methods on an otherwise negative screening mammogram

(continued)

Table 14.2 (continued)

Guideline	Women 40–49 years	Women 50–74 years	Women 75 years or older	Women with dense breasts
American Cancer Society	40–44 years: should have the choice to start mammographic breast cancer screening once a year. Consider the risks of screening as well as the potential benefits. 45–49 years: screen annually with mammography	50–54 years: screen with mammography annually. 55 years and older: screening mammography once every 2 years with the opportunity to continue annual screening. Among average risk women, clinical breast exam is not recommended	Continue with screening mammography as long as overall health is good with a life expectancy of 10 years or more	Insufficient evidence to recommend for or against yearly MRI screening
American College of Obstetrician and Gynecologists	After counseling, if an individual desires screening, mammography may be offered once a year or once every 2 years. Clinical breast exam may be offered once a year	Screening mammography annually to biannually. Clinical breast exams may be offered annually. Recommendations should be made/offered in the context of shared decision-making that recognizes the uncertainty of additional benefits and harms of clinical breast exam beyond screening mammography	Decision to stop screening should be based on a shared decision-making process that includes a discussion of the woman's health status and longevity	Other than screening with mammography, the organization does not recommend routine use of alternative or additional tests
American College of Radiology	Yearly screening with mammography	Yearly screening with mammography	The age to stop screening with mammography should be based on each woman's health status rather than an age-based determination	Contrast-enhanced breast MRI In addition to mammography. After weighing benefits and risks, ultrasound can be considered for those who cannot undergo MRI

assessment. Other cancers can be related to breast cancer, and all family cancers should be reported. Having close relatives with cancer, particularly if the age of onset is younger than age 50 years, is associated with an increased risk of developing cancer.

- Ask if any affected family members had genetic testing related to their cancer, and obtain the results of the testing. If unknown, encourage the individual to try to obtain the information.
- It is standard, prior to genetic testing, to ask if pathology reports are available on affected family members to confirm the diagnosis. Patients often do not have this information or do not want to ask for it, but confirmation is important. It is the author's experience that comments such as "I heard my uncle had liver cancer" may actually be alcohol-related cirrhosis that families wanted to keep private.
- Ask the patient's biological ethnicity, as narrowly as possible, if known. Some populations, most notably Ashkenazi Jewish, have a higher chance of carrying a BRCA mutation than other populations, and guidelines specifically note that having a grandparent that identifies as Ashkenazi Jewish is enough to merit considering BRCA testing. Beyond this recommendation, however, the role of race/ethnicity when considering genetic testing is controversial as the overall prevalence of BRCA and other mutations in at-risk women is very similar, ranging from 9% to 15%, regardless of race/ethnicity [6, 7].

14.6.2 Personal Medical History

There are other factors that individually, or in combination with mode rate or low penetrance breast cancer genes, contribute to the overall breast cancer risk (see Table 14.3) [57]. Review past test results and medical history and discuss the following risk factors with the patient [58]:

- **Age**. The risk of breast cancer increases with age.
- **Age of first period**. Women with menarche before the age of 12 years may have an increased risk.
- **Age of menopause**. Final menstrual period after age 55 years may be associated with an increased risk.

Table 14.3 Relative risk of postmenopausal breast cancer by race/ethnicity, weight, and breast density. Adapted from Bissell MCS, Kerlikowske K, Sprague BL, et al. Breast Cancer Population Attributable Risk Proportions Associated with Body Mass Index and Breast Density by Race/Ethnicity and Menopausal Status. Cancer Epidemiol Biomarkers Prev. 2020;29(10):2048–2056

Risk factor	White	Black	Asian	Hispanic
BMI 25–29 kg/m^2	1.26	1.25	1.45	1.13
BMI 30–34.9 kg/m^2	1.41	1.76	2.21	1.37
BMI ≥35 kg/m^2	1.43	0.76	2.21	1.37
Heterogeneously dense breasts	1.39	1.58	1.26	1.36
Extremely dense breasts	1.62	1.69	1.49	2.06

- **Breast density on mammogram**. Women with dense breasts are more likely to develop breast cancer, and cancer may be harder to detect on imaging. Postmenopausal women with heterogeneously dense or extremely dense breasts have the highest relative risk.
- **Weight**. Being overweight or obese, particularly postmenopausal, is associated with an increased risk.
- **Past history of cancer**. Some cancers are associated with an increased risk of developing breast cancer, or having a recurring or bilateral breast cancer.
- **History of benign breast disease (BDD)**. Having atypical hyperplasia or other breast tissue changes may increase risk.
- **History of taking diethylstilbestrol (DES)**. DES was given to some pregnant women between 1940 and 1970 to prevent miscarriage and is associated with an increased risk of breast cancer.
- **History of taking hormones**. Oral menopause hormone therapy (MHT) and oral contraceptives may increase risk varying with baseline risk, type of hormone therapy, duration, and time since last use. In menopausal women, the highest risk is for those currently taking an estrogen plus a progestogen [59]. The relative risks by duration of use from typical age of menopause (mean age of 51 years) for current users are:
  - <1 year = 1.2
  - 1–4 years = 1.6
  - 5–9 years = 1.97
  - 10–14 years = 2.26
  - ≥15 years = 2.51
  - The Endocrine Society Clinical Practice Guideline addresses MHT by baseline risk determined by the National Cancer Institute and recommends a cautious approach for intermediate-risk women and to avoid MHT in high-risk women. To put the relative risks determined by the CGHFBC into the context of this baseline risk, Santen et al. [60] re-analyzed the data and developed the following risk information in Table 14.4 that could be used in counseling and determining screening and management plans.

Table 14.4 Calculated risk of breast cancer and menopausal hormone therapy; estrogen + progestogen by duration and baseline risk adapted from Santen RJ, Heitjan DF, Gompel A, Lumsden MA, Pinkerton JV, Davis SR, Stuenkel CA. Underlying Breast Cancer Risk and Menopausal Hormone Therapy. J Clin Endocrinol Metab. 2020 Jun 1;105(6):dgaa073

	Calculated attributable risk by baseline risk category[a]		
Duration of current MHT use	Low (%)	Intermediate (%)	High (%)
1–4 years	1.17	2.3	4.7
5–9 years	4.4	8.9	17.7
10–14 years	8.4	16.9	34
15+ years	11.3	22.5	45

[a]Baseline risk of low, intermediate, and high risk of developing breast cancer as determined by the NCI assessment, considered as underlying risks of 1.5%, 3.0%, and 6.0% at 5 years, respectively

These data predominately represent women taking an oral estrogen with a synthetic progestin. Risk may vary with progestogen formulation (see Chap. 6). While short-term MHT in *BRCA* carriers has not been associated with an increased risk of postmenopausal breast cancer, NCCN recommends that caution be used when considering this management approach as the current studies are nonrandomized and limited [6].

- **Pregnancy history**. Never being pregnant, or having a first pregnancy after 30 years, can raise risk.
- **Breastfeeding history**. Not breastfeeding can contribute to risk.
- **Exercise**. Sedentary women have a higher risk
- **Alcohol**. Alcohol intake can increase the risk of breast cancer. In a global meta-analysis examining the association of alcohol and breast cancer risk [61], alcohol was attributed as the cause in 8.6% of cases and 7.3% of related deaths. Most of these cases were in a younger population, with only 38.7% of the alcohol-attributed cases and 49.8% of the alcohol-attributed deaths occurring in women over 60 years. The highest alcohol-attributable breast cancer cases occurred in Northern and Western Europe, followed by North America. The lowest levels were found in South Central Asia. Even light drinkers, described as consuming <21 g/day (less than 2 drinks per day) of alcohol, were found to have a higher risk of breast cancer. Multiple studies found that the relative risk in light drinkers ranged from 1.1 to 1.2, whereas in moderate and heavy drinkers (2 or more drinks per day), the relative risks range from 1.3 to 1.46.

There are a few commercial tests on the market that attempt to combine low penetrance breast cancer gene test results with personal medical history to create a personal risk score, called a polygenic risk score. None have been validated through clinical trials and are generally not recommended for clinical use.

14.7 Risk Assessment Tools

The personal and family history helps determine which risk assessment tool is most suitable. This approach is intended to be used as a breast cancer risk assessment in women without a personal history of breast cancer, without ductal carcinoma in situ, lobular carcinoma in situ, or atypical ductal hyperplasia and who have not undergone high-dose chest wall radiation between the ages of 10 and 30 years, or who have a known high-risk genetic mutation [62]. One of the most commonly used tools was developed in the United States, the Breast Cancer Risk Assessment Tool (BCRAT) also known as the Gail Model (GM). It has been adapted for different ethnic populations within the United States, including white American, Asian, Pacific Islander, and African American populations; however, its applicability to different ethnic populations outside of the United States has yet to be established [63]. Studies have shown the BCRAT to underestimate breast cancer risk in Hispanic women by approximately 18%. A newer tool, The National Cancer Institute's (NCI)

Hispanic Risk Model (HRM) is used to predict US-born and foreign-born Hispanic women's breast cancer risk [64]. In Australia, the Peter MacCallum Cancer Centre has a web-based application, iPrevent, designed for individuals or clinicians to use to assess breast cancer risk and then provide individualized screening and prevention recommendations (https://www.petermac.org/iprevent/information-clinicians).

14.7.1 National Cancer Institute Gail Model (https://bcrisktool.cancer.gov)

As addressed above, the Gail Model has been validated in several populations in the United States but has poor individual discrimination. This model was used in studies on chemoprevention establishing the estimates of risk versus benefit of these medications; therefore, it can be used within the context of decision-making regarding chemoprevention [62].

14.7.2 Breast Cancer Surveillance Consortium Model (BCSC) (https://tools.bcsc-scc.org/BC5yearrisk/calculator.htm)

The BCSC builds on the Gail model and includes information regarding key risk factors, including breast biopsy results and breast density. Tice et al. [65] evaluated the accuracy of the BCSC in a cohort of 252,997 racially/ethnically diverse women in the Chicago area. They concluded that it underestimated the incidence of breast cancer in younger women with lower breast density and therefore could be particularly useful in women with dense breast tissue [65].

14.7.3 Tyrer-Cuzick Version 8 (http://www.ems-trials.org/riskevaluator/)

The Tyrer-Cuzick, also called the IBIS model, was developed in the United Kingdom. Tyrer-Cuzick allows for input of a more comprehensive family history, hormonal factors, weight, height, and history of atypia as well as breast density. Brentnall et al. [66] evaluated the accuracy of Tyrer-Cuzick in long-term breast cancer risk assessment over a timeframe of 19 years and found the risk assessment tool may be beneficial in high-risk clinics using a combined risk assessment that accounts for more than familial risk associated with genetic factors. Tyrer-Cuzick is the model of choice for radiologists when evaluating eligibility for screening breast MRI as it is the only model that includes comprehensive family history and can generate a lifetime risk, both of which are criteria for screening breast MRI [62] (see Table 14.5) which suggests approach to assessing an individual's risk of breast cancer. Table 14.6 guides clinical screening based on risk assessment results.

Table 14.5 Stepwise approach to assessing an individual's risk of breast cancer. *USPSTF* United States Preventative Task Force, *NCCN* National Comprehensive Cancer Network, *NCI* National Cancer Institute, *BIRAD* Breast Imaging Reporting and Data System, *BCSC* Breast Cancer Surveillance Consortium, *IBIS* International Breast Cancer Intervention Study, [62], with permission, © *2020 Mayo Foundation for Medical Education and Research*

First step	Second step	Third step	Fourth step
Assess Family History, suggest using USPSTF or NCCN.	Assess Personal History	Choose a Risk Assessment Tool	Interpret Risk Assessment as average, moderate, or high to guide screening and potentially chemoprevention medication
• USPSTF (2019): ask about personal and family history of BRCA-related cancers (breast, ovarian, tubal, or peritoneal) and ancestry. If history present, use a brief familial risk assessment tool such as 7-Question Family Screening.	– Demographics: age, ethnicity	– NCI Gail Model: can be used in the context of chemoprevention, otherwise routine use is not recommended.	
• NCCN (2019): ask about all cancers diagnosed in first- or second-degree relatives, including type of cancer and age of diagnosis.	– Hormonal risk factors: age of menarche/ menopause, age at first live birth/ nulliparity, exogenous hormone use, obesity	– BCSC tool: can be used for most patients except those with a significant family history, then use Tyrer-Cuzick	
• If family history screen is positive using either tool, refer to genetic counseling. • If family history screen is negative proceed to step 2	– Radiographic Breast Density: BIRAD category C or D – Other: proceed to high-risk protocol if patient has a previous breast biopsy consistent with atypical ductal hyperplasia or lobular carcinoma in situ, or history of chest radiation between ages of 10 and 30 years	– IBIS/Tyrer-Cuzick: should be used if family history of breast cancer diagnosed <50 years of age, second-degree relatives with cancers, male breast cancers or ovarian cancer	

Table 14.6 Breast cancer risk assessment and recommended imaging. Used with permission, *© 2020 Mayo Foundation for Medical Education and Research*, [62]

Risk category	Management
Women of average risk	
<15% lifetime risk Tyrer-Cuzick or <1.66% 5-year BCSC	Offer routine mammography per average risk screening guidelines
Women of intermediate risk	
15–20% lifetime risk based on Tyrer-Cuzick	Emphasis on shared decision-making given lack of high quality data in this group
1.67–2.49% 5-year risk on BCSC	ACOG, ACS, NCCN, and ACR suggest clinician offer screening mammograms starting age 40 years
Women of high risk	
≥20% lifetime with Tyrer-Cuzick or ≥2.5% 5-year risk with BCSC	ACS, NCCN, and ACR all recommend offering annual mammography and annual breast MRI starting 10 years before the age of diagnosis of youngest affected family member but not before the age of 30 years

ACOG American College of Obstetricians and Gynecologists, *ACR* American College of Radiology, *ACS* American Cancer Society, *NCCN* National Comprehensive Cancer Network, *USPSTF* United States Preventive Services Task Force

14.8 Genetics

14.8.1 The Role of Genetics in Breast Health

Genetics is the study of genes, gene function, and gene changes. The deoxyribonucleic acid (DNA) code creates a ribonucleic acid (RNA) template for amino acids. The chain of amino acids becomes a specific protein. Over time, as the result of inherited predispositions or environmental exposures, changes in gene function or the basic DNA code can occur, resulting in missing or poorly functioning protein. This has the potential to impact health [67].

Genes influence breast characteristics such as size and density, and benign breast diseases (BBD) have a heritable component as well (see Table 14.7). Most benign breast conditions do not increase the risk of breast cancer, but 30% of all breast cancers develop in women with a history of BBD [68]. The most attention is focused on how genes influence the risk of developing breast cancer [4].

14.8.2 Cancer Genetics

All cancer results from genetic changes. Most cancers result from acquired genetic mutations rather than inheritance. These somatic mutations occur in the target tissue and occur spontaneously during normal cell growth or because of environmental exposures to carcinogens, such as smoking. Genetic changes in tumor suppressor genes or DNA repair genes that regulate cell growth and stimulate cell death can lead to out of control cell proliferation and cancer. Most of these genetic changes are

Table 14.7 Breast diseases and characteristics with a genetic component

• Benign breast diseases
– Fibroadenomas
– Intraductal papillomas
– Lobular carcinoma in situ (LCIS)
– Phyllodes tumors
– Radial scars
• Breast characteristics
– Breast density
– Fibrocystic breasts
• Breast cancer
– Acquired
– Inherited

recessive, requiring both copies of a gene have accumulated damage over time. This is called the "two-hit hypothesis" [69]. Inherited genetic changes are responsible for 5–10% of all cancers [70] and result from inheriting a germline mutation from one parent. Most inherited cancers require the second copy of the gene inherited from the other parent to accumulate genetic damage for cancer to develop, thus some individuals with inherited gene changes never develop cancer. For example, *BRCA1*-associated Hereditary Breast and Ovarian Cancer syndrome is one of the most well-recognized inherited forms of cancer, but 28–45% of women with a *BRCA1* gene never develop breast cancer [71].

14.8.3 Acquired Breast Cancer

Understanding what genes are most likely to acquire pathogenic variation resulting in breast cancer is important to understanding treatments and prevention strategies. The most relevant acquired gene changes in breast cancer are:

14.8.3.1 *ERBB2* (*HER2*) [72, 73]

- Proteins made by this gene sit on the surface of cells and modulate signal pathways for cell growth. Acquired mutations cause overexpression of *HER2*, resulting in uncontrolled cell growth.
- Estrogen activates *HER2* signaling and is implicated in the overexpression of the aberrant form of *HER2*.
- 15–30% of invasive breast cancer exhibits overexpression of *HER2*. Three to 4% have activating mutations associated with invasive lobular cancers.
- *HER2* overexpression and over-activation are associated with shorter disease-free intervals, a higher risk of recurrence and reduced overall survival.
- *HER2* overexpression analysis is a standard test performed on a biopsy sample when non-metastatic invasive breast cancer is first diagnosed [6, 74].

- *HER2* targeting agents are available for first-line, adjuvant, or second-line treatment for breast cancer and demonstrate improved outcomes. Most of these drugs are available globally; however, treatment is expensive and disparities in access exist.

14.8.3.2 *PI3K/AKT/MTOR* [72, 75]

- The phosphatidylinositol 3-kinase (PI3K) pathway regulates cell processes that oversee growth, proliferation, cell death (apoptosis), and cytoskeletal arrangement.
- Mutations in the *PI3K* alpha-subunit are found in 40% of hormone receptor (HR)-positive breast cancers.
- Testing for the most common aberrations is recommended for women with hormone receptor-positive, *HER2*-negative cancers that are recurrent and unresectable, or stage IV (M1) [6].
- Agents that target this pathway are available for treatment.

14.8.3.3 *FGFR* Gene Family [72]

- Fibroblast growth factor receptors (FGFR) is a family of genes that work together to regulate cell development, growth, proliferation, and survival. This family also includes the epidermal growth factor receptor (*EGFR*) and vascular endothelial growth factor (*VEGF*).
- Pathogenic alterations that result in abnormal *FGFR* signaling are found in 20% of breast cancers. Alterations that result in over-amplification are the most common and are associated with resistance to endocrine therapy, early relapse, and poor survival in HR positive cancers.
- At this time, no FGFR inhibitors are currently approved for clinical use for breast cancer, though several clinical trials are underway and one agent is approved for use in patients with urothelial carcinoma with documented *FGFR3* or *FGFR2* mutations in the USA.

14.8.3.4 *NTRK* [72]

- The neurotrophic tyrosine receptor kinase (*NTRK*) genes are three different genes that code proteins involved in a complex pathway regulating cell development, growth, proliferation, and survival.
- Gene fusions occur when DNA between similar genes combines to form a new hybrid gene and resulting protein that disturbs the normal regulatory function of a biological pathway. *NTRK* fusions are not common in breast cancer generally, but have been found in secretory breast cancers.
- Testing for *NTRK* fusions can be considered on the prior tumor block when individuals have recurrent/stage IV breast cancer and no alternative treatment exists, and must be specially requested [6, 74].
- Treatment options are available for tissue agnostic solid tumors that harbor an *NTRK* fusion

14.8.3.5 *ESR1* [72, 76, 77]

- The estrogen receptor 1 (ESR1) is an important factor with roles in hormone binding, DNA binding, and activation of DNA transcription.
- Pathogenic variants in *ESR1* are not common in primary breast cancers, but are found in 31% of patients with metastatic breast cancer (MBC) after estrogen deprivation due to exposure to aromatase inhibitors (AI). Women who have metastatic breast cancer and receive AIs late in treatment may acquire these pathogenic variants leading to AI therapy resistance.
- Individuals with *ESR1* variants have a worse prognosis when compared to MBC patients who don't have *ESR1* variants.
- There are currently no approved treatments for patients based on their *ESR1* status, but clinical trials are available.

14.8.3.6 *BRCA* [78]

- Breast cancer 1 gene (*BRCA1*) and breast cancer 2 gene (*BRCA2*) are tumor suppressor genes that help modulate DNA repair through a process called homologous recombination repair (HRR). They are most known for their role in inherited cancer, but acquired mutations play a role when those with a single inherited *BRCA* mutation acquire a second pathogenic gene because of age or environmental exposures.
- Individuals with a *BRCA* mutation have been approved for treatment with a poly ADP ribose polymerase (PARP) inhibitor. PARP enzymes are required in DNA repair processes and can overcome some of the issues introduced by the lack of HRR caused by BRCA pathogenic mutations. Therefore, drugs that inhibit the PARP DNA repair processes in cancer tissues where HRR is also compromised can be destructive for the cancer cell.
- Therapies for individuals with a germline *BRCA* mutation are available in most parts of the world.

14.9 Inherited Breast Cancer

There are about 50 hereditary cancer syndromes, and many include breast cancer and/or gynecological cancers as a feature. Inherited gene changes are responsible for about 5–10% of all breast cancers. *BRCA1* and *BRCA2* genes account for about 45% of familial breast cancer and 90% of inherited breast/ovarian cancer [79]. However, a number of other genes are also implicated in inherited breast cancer or in increasing overall cancer risk [70]. Most hereditary breast cancers have an earlier age onset, before menopause, but age of onset does vary. An international study of 10,000 women from 40 US-based and five Latin American clinics found that 5.6% of women aged over 65 years and 14.2% younger than 65 years of age had an inherited form of breast cancer [80]. The observational arm of the Women's Health Initiative (WHI), a long-term health study in the United States reviewed the results from 161,808 postmenopausal women aged 50–79 years at 40 US sites from 1993

through 1998. It was found that 1 in 28 (3.5%) women diagnosed with breast cancer after menopause had a pathogenic variant in a breast cancer-related gene [81].

Genomics knowledge has evolved beyond the early onset high penetrance, autosomal dominant genes *BRCA1* and *BRCA2*. Commercial testing is now available for moderate and low penetrance genes that interact with other genes and the environment to increase breast cancer risk, representing a multi-factorial form of inheritance. The National Comprehensive Cancer Network (NCCN) of the United States maintains an up-to-date list of important genes, related cancer syndromes, and penetrance in their guideline titled *Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic* [6]. Table 14.8 describes some of these important genes. Not all genes are listed here, and knowledge in this space moves quickly, so it is important to regularly check guidelines for updates. Guidelines for the clinical management of women who are positive for one or more of these genes are also found at the NCCN website (https://www.nccn.org/professionals/physician_gls/).

14.9.1 Determining Inherited Breast Cancer Risk

Identifying a patient at a higher risk of breast cancer than the general population relies on obtaining a good family and medical history as previously discussed in family and medical history sections. Various tools are available as well that provide a risk assessment of inherited breast cancer. NCCN has highlighted several [6].

- Pen II (https://pennmodel2.pmacs.upenn.edu/penn2)
  - Developed at the University of Pennsylvania, predicts the risk that a patient has a *BRCA1* or *BRCA2* mutation. It does not calculate out the risk of developing breast cancer.
- Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (https://ccge.medschl.cam.ac.uk/boadicea/)
  - Created by the University of Cambridge Centre for Cancer Genetic Epidemiology, can be used to estimate the risk of breast and ovarian cancer from family history. The tool also estimates the risk of being a *BRCA1* or *BRCA2* carrier.
- CanRisk (https://canrisk.org/)
  - CanRisk is a version of the BOADICEA tool utilizing family history, lifestyle/hormonal risk factors, rare pathogenic variants in moderate and high risk breast/ovarian cancer susceptibility genes, common breast/ovarian cancer genetic susceptibility variants (Polygenic Risk Scores) and mammographic density. It can also be used to calculate the likelihood of carrying mutations in the moderate- to high-risk genes *BRCA1*, *BRCA2*, *PALB2*, *ATM*, and *CHEK2*.
- NICE (https://www.nice.org.uk/guidance/cg164/resources)
  - The NICE Clinical Guideline CG164 Familial breast cancer: classification, care, and managing breast cancer and related risks in people with a family history of breast cancer, contains decision aids, and a downloadable baseline risk assessment tool.

Table 14.8 Familial breast cancer genes and related cancers

Gene name	Related cancers and relative risk of lifetime risk of developing cancer	Other associations
ATM	Breast 15–40% Ovarian <3% Pancreatic 5–10%	Some association with stomach, bladder, and lung cancers. Two mutations cause the autosomal recessive Ataxia Telangectasia, resulting in numerous tumors and movement disorder
BRCA1	Breast >60% Ovarian 39–58% Pancreatic ≤5%	Prostate cancer
BRCA2	Breast >60% Ovarian 13–29% Pancreatic 5–10%	Prostate cancer and melanoma
BRIP1	Ovarian >10%	Breast cancer
CDH1	Breast 41–60%	Hereditary diffuse gastric cancer
CDKN2A	Pancreatic >15%	Melanoma
CHEK2	Breast 15–40%	Colon cancer
MSH2, MLH1, MSH6, PMS2, EPCAM	Breast >15% Ovarian 3% to >10%, gene dependent Pancreatic 5–10% Colon 20–80% Uterine 15–60% Small Bowel 1–6% Urinary Tract 1–18%	Hereditary non-polyposis colon cancer (HNPCC) syndrome, also called Lynch syndrome
NF1	Breast 15–40%	Neurofibromatosis type 1, characterized by nerve sheath tumors
PALB2	Breast 41–60% Ovarian 3–5%	
PTEN	Breast 40–60% Thyroid 28% Endometrial 4–28% Colorectal 9% Renal 34% Melanoma 6%	PTEN hamartoma tumor syndrome, also known as Cowden syndrome, a constellation of thyroid, colon, and endometrial cancers
RAD51C and *RAD51D*	Breast 15–40% Ovarian >10%	

NCCN [6], ATM Gene [82], Lynch Syndrome [83], Tan et al. [84]

14.10 Genetic Counseling and Testing

14.10.1 When to Consider Genetic Testing

Professional society and expert consensus guidelines recommend *BRCA* or multigene panel testing when the pattern of cancer in the family suggests that an inherited form of cancer is present. The various guidelines are not re-created here as they

Table 14.9 Professional societies and expert consensus groups with hereditary cancer guidelines

American Society of Breast Surgeons (ASBrS)
American Society of Clinical Oncology (ASCO)
American College of Obstetricians and Gynecologists (ACOG)
National Society of Genetic Counselors (NSGC)
National Comprehensive Cancer Network (NCCN) Global Harmonized Guidelines [United States, Sub-Saharan Africa, Caribbean, China, Japan, South Korea, Poland, Spain, Brazil, Middle east and north Africa]
Society of Gynecologic Oncology (SGO) [United States]
Endocrine Society [International]
National Institute for Health and Care Excellence (NICE) [United Kingdom]
European Society for Medical Oncology (ESMO)
Cancer Australia
Cancer Care Ontario [Canada]
Canadian Consensus Guidelines
Japanese Breast Cancer Society
Spanish Society for Medical Oncology (SEOM)

change frequently, but a list of primary guideline groups are found in Table 14.9. In general, an inherited form of cancer and genetic testing should be considered in the following situations:

- The patient has a personal history of cancer that was diagnosed younger than age 45 years.
- One or more close blood relatives were diagnosed with cancer younger than age 50 years.
- At least one close blood relative was diagnosed with ovarian cancer, at any age.
- At least one blood relative was diagnosed with a related cancer at any age, and the patient has Ashkenazi Jewish ancestry.
- Two or more close blood relatives were diagnosed with related cancers at any age (see Table 14.8, familial breast cancer genes and related cancers).
- The patient has a limited or unknown biological family history and has a personal cancer diagnosis at any age. A limited family history is defined as fewer than two female first- or second-degree relatives that lived beyond age 45 years.
- The patient has a limited or unknown biological family and indicates a need to further define their breast cancer risk for personal reasons.
- Previous testing was limited to a single gene or did not include genetic rearrangements and the patient is interested in pursuing multi-gene testing.

14.10.2 Pretest Genetic Counseling

When considering initiating genetic testing, multiple factors need to be weighed including test selection, cost and insurance issues, psychosocial issues, and posttest management options.

Genetic testing labs offer a variety of genetic tests that typically include *BRCA1* and *BRCA2*, but will often include other genes that may or may not have strong evidence of being associated with breast cancer [6]. These panels can range from 6 to 100 genes [85]. When considering a large panel, it is important to keep in mind the implications of getting back a result that contains variants of unknown significance (VUS), for which there is no clinical action to be taken, or pathogenic results in a gene without a strong association with breast cancer. Direct to consumer tests, like 23andMe®, may offer versions of inherited breast cancer testing, but may be limited and incomplete [86]. The Food and Drug Administration (FDA) of the United States reports indicate that clinical decisions should not be made from these results.

It is critical to counsel the patient about potential out of pocket costs. In the United States, commercial health insurance companies will typically cover *BRCA1* and *BRCA2* testing when certain clinical criteria are met, but policies vary on coverage for the cost of testing for other genes [85]. Medicare has a National Coverage Determination (NCD) mandate to cover germline *BRCA* testing using an FDA-approved test for women who have breast or ovarian cancer and need a germline test for treatment determination [87]. Women on Medicare who do not meet this criteria may have coverage under local Medicare contractors Local Coverage Determination (LCD) rules [88]. In Europe, most countries cover genetic testing for hereditary breast and ovarian cancer syndromes through their public health programs. The covered gene list may vary between countries [89]. Hereditary cancer testing is available in Latin America, but the public and private healthcare systems cover genetic counseling and testing only in a few select countries such as Brazil and Mexico [90]. In India, no government health funds are available for genetic counseling or testing. Some private insurance may provide coverage, but most women will need to cover the cost out of pocket [91]. This is also true throughout Asia, where genetic testing is covered neither by insurance nor by government funds. Most centralized cancer centers fund these services through grants or philanthropic funds [92].

The psychosocial issues associated with genetic testing for breast cancer risk determination cannot be understated. While some patients may indicate they have no concerns about testing, it is important to provide counsel about unforeseen outcomes [93].

- **Impact on coping with cancer risk**. Patients considering genetic testing may already feel at risk because of their family history or personal experiences, and have coping mechanisms for dealing with that risk. This may include a range of techniques from control to avoidance: being active in cancer support groups, diligent self-breast exams, or choosing to stay away from books, television, or social media stories about cancer. Discussing a test or getting a test may disrupt coping with the breast cancer risk in both positive and negative ways.
- **Concerns about out of pocket costs**.
- **Family and support network issues**. When one person gets a genetic test, other close family members are being tested indirectly. For example, the daughter that gets a pre-symptomatic positive *BRCA* test result could change the likely diagno-

sis of breast cancer for her mother. This may change risk perceptions by other family members who might not welcome the news. Families often act in unanticipated ways, and patients who have undergone testing have reported difficulties in disclosing test results to family members, unexpected communication issues, lack of family support, worry about risks to children, and guilt over negative tests if others are positive. However, some patients report closer family ties and improved communication. Similar issues can exist in an expanded support network as well. The patient finds that the choice they make about testing is unexpectedly supported or criticized by friends or other support people.

Understanding how a positive or negative test result might change clinical management can influence a clinician's decision to recommended and the patient's decision to pursue testing. In some situations, the change in management could be unexpected and dramatic. Several sample scenarios in postmenopausal women who are considering genetic testing are outlined in Table 14.10.

While 1 in 28 (3.5%) of women diagnosed with breast cancer after menopause has a pathogenic variant in a breast cancer-related gene [81], when the testing population is narrowed to only those who meet the guidelines testing criteria, the positive population becomes about 1 in 8 (12.5)% will have a pathogenic variant identified. This change in positivity rate should be included in patient counseling.

14.10.3 Interpreting a Genetic Test

Careful review of test results is necessary to ensure a full understanding of the significance. When receiving results from a new lab, it is worthwhile to contact the lab and make sure your interpretation of the report is correct. It is both the author's experience and has been documented in the literature that confusion from genetic test reports can result in incorrect information being communicated to the patient [97–99].

A positive test result means that the laboratory found a pathogenic change in a gene or protein of interest. It may mean a definitive diagnosis, identify an increased risk for developing disease, or signal the need for additional testing. A negative test result indicates the lab did not find a pathogenic change in the gene or protein of interest. It is important to carefully review a negative genetic test result to ensure that the correct test was done and the expected genes were included.

A test may be returned as uninformative, indeterminate, inconclusive, ambiguous, or variant of unknown significance (VUS). These results occur for a variety of reasons. If the report is not clear, further contact with the laboratory director or genetic counselor is warranted. In general, these results cannot confirm or rule out a diagnosis, or indicate a predisposition to disease. The patient's clinical management cannot be modified based on such results. Often the lab will make recommendations on next steps, such as testing other family members to clarify the significance of the

Table 14.10 Potential scenarios in genetic test results and cancer risk affecting clinical management based on the author's experience

Scenario	Test result	Change in cancer risk	New management recommendations
A 59-year-old woman with breast cancer previously diagnosed at age 36 years requests genetic testing to determine if her children are at high risk	Multi-gene test is negative	None. The patient must continue diligent monitoring as having a prior cancer maintains her higher risk. Her children may have a statistical reduction of risk, but an early onset breast cancer in their first degree relative continues to result in higher risk than the general population	None
A 45-year-old woman presents with left breast invasive ductal carcinoma after a diagnosis of right breast invasive ductal carcinoma and myxofibrosarcoma in her right arm at age 40 years. Her family history reveals multiple family members with cancer, some diagnosed quite young	A mutation in the *TP53* gene is found, and a diagnosis of Li Fraumeni syndrome is made	The cancer risk for multiple primary cancers is >90%	A secondary, bilateral prophylactic mastectomy was offered. In lieu of this, annual breast MRI and mammogram are recommended, annual dermatological exams, annual whole-body MRI, annual brain MRI at the same time or separately, colonoscopies every 2–5 years
A 52-year-old patient presents with new family history information. This patient had breast cancer at age 39 years, and experienced overreactions (OR) in the tumor-surrounding normal tissues post radiotherapy (RT). She reveals that two younger sisters have now been diagnosed with breast cancer, and one also had OR	Two *ATM* pathogenic variants found, a diagnosis of Ataxia Telangectasia is made	Overall risk of developing other cancers is >40%, and includes breast, ovarian, stomach, pancreatic, melanoma, and sarcoma	Ongoing monitoring for other cancers, limited evidence for efficacy of prophylactic prevention measures at this time

(continued)

Table 14.10 (continued)

Scenario	Test result	Change in cancer risk	New management recommendations
A 50-year-old woman is diagnosed with breast cancer. She is Ashkenazi Jewish	A variant of unknown significance (VUS) is found in the *BRCA* gene	None, for now. A VUS is an interesting genetic change but doesn't yet have clinical meaning	This is typically anxiety provoking for the patient, accompanied by uncertainty in how to communicate VUS results with family
A 50-year-old woman seeks BRCA testing because her mother was diagnosed with breast cancer at age 75 years, and her maternal grandmother at age 60 years. She is not Ashkenazi Jewish and has no other family history of cancer	No test is performed. She doesn't meet guideline or insurance criteria, and she doesn't want to pay for the test out of pocket	Increased to a 25% lifetime risk as ascertained through breast cancer risk algorithm that accounted for family and medical history including age of menarche, pregnancies, alcohol use, and weight	Increased surveillance, including annual MRI screening

Management recommendations from [6], [94], [95], [96]

results, or future follow-up to determine if new data has emerged, making a new interpretation of a VUS possible [82, 100].

14.10.4 Posttest Genetic Counseling

NCCN recommends that if you are unfamiliar or uncomfortable with the genetic counseling aspects of genetic testing for inherited cancer, involve an experienced professional such as a genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other professional who has expertise and experience with genetic testing. If you receive results you are unfamiliar with or you have limited experience with novel pathogenic variants, variants of unknown significance, mosaic results, discrepant interpretations of test results, or the patient presents with consumer initiated testing from an unfamiliar lab, consider a referral to the above-mentioned experts.

Elements of posttest genetic counseling require a discussion of the following [6]:

- Test results and impact on cancer risk in the context of family and medical history
- Review of new clinical management options, if applicable
- How to inform family members of the results, including resources for any at risk family members
- How to get at-risk family members referred to specialists in their area for counseling and testing, as appropriate

- Local and national support groups and resources
- For women of reproductive age with a positive result, discuss options for prenatal diagnosis, including pre-implantation genetic diagnosis or assisted reproduction options
- As appropriate, discuss the non-cancer-related diseases and risks that might have been identified and refer to a genetic counselor or other appropriate expert for management

14.11 Chemoprevention in High-Risk Women and Treatment of Hormone Receptor-Positive Early Stage Breast Cancer

14.11.1 Early Stage Hormone Receptor-Positive Breast Cancer

Cancer development strongly parallels normal development in that both are tightly regulated by signaling pathways allowing cells to communicate with each other and their surrounding environment. The complex estrogen (ER) signaling pathway continues to be a focus of research because estrogen receptor-positive breast cancers account for approximately 75% of all breast cancers [101]. Estrogen promotes both normal and cancerous breast epithelial cell growth. The estrogen-activated receptor binds to gene promoters in the nucleus, further activating genes responsible for cell division, inhibition of cell death, new blood vessel formation and protease activity. Endocrine therapy disrupting the ER pathway has shown to be highly effective therapy for both the prevention and treatment of ER-positive breast cancers [102]. The three ways to disrupt or interrupt the estrogen-dependent processes are to interfere with the estrogen receptor binding using selective estrogen receptor modulators (SERM), such as tamoxifen or raloxifene, to reduce or eliminate ER expression using a selective ER down-regulator, fulvestrant, or the most direct way, to decrease or eliminate estrogen availability with ovarian ablation in premenopausal women or with the use of aromatase inhibitors (AIs) in postmenopausal women [103]. The pharmacology and side effect profile of each class of medication is applicable in the setting of chemoprevention as well as treatment of hormone receptor positive breast cancer. It is important to note the international incidence of pre- and postmenopausal triple-negative breast cancer [estrogen and progesterone receptor negative (ER, PR) and human epidermal receptor 2 growth factor negative (HER2)] accounts for 15–20% of breast cancers. Triple-negative breast cancers are more common in premenopausal women and Black women and, due to their molecular phenotype, do not respond to endocrine (hormonal) therapies [104].

14.11.2 Chemoprevention in High-Risk Women

Randomized controlled trials have documented a 38% overall reduction from baseline risk (587 cases versus 852) in breast cancer in high-risk women and a 51% reduction (287 cases versus 543) in estrogen receptor-positive tumors with the use

of oral chemoprevention medications [105]. Most study participants were from North America, Europe, and the United Kingdom. None of the major trials provided outcome data specific to racial or ethnic groups [106]. Long-term follow-up of two major SERM trials demonstrated a consistent 29% annual preventative effect for at least 15 years after completion of treatment, RR years 0–10, 0.74 and RR >10 years, 0.70 [106, 107]. Women with a history of biopsy consistent with atypical ductal hyperplasia or lobular carcinoma in situ, or who have NCI Gail 5-year risk of ≥3% or a Tyrer-Cuzick 10-year risk of ≥5%, are candidates for chemoprevention and should be counseled regarding risk versus benefit of treatment [62].

Selective estrogen receptor modulators (SERMs) are frequently recommended as chemoprevention in high-risk women. SERMs function as tissue-selective estrogen receptor agonists or antagonists in the interaction with estrogen receptors. Estrogen receptors have two subunits, alpha and beta, with roles in the development of the female reproductive system, the maintenance of bone mass, and the protection of the cardiovascular system and central nervous system [108]. Estrogen receptor alpha (ERα) is expressed mainly in sex organs but can also be found in the liver, pituitary, and adrenal glands and hypothalamus. Estrogen receptor beta (ERβ) is not found in reproductive organs, except for the prostate, but is widely distributed throughout the body with expression in skin, bone, brain, lung, urinary bladder, blood vessels, lymphocytes, and fat [109]. Through the interaction of SERMs with either of these subunits, there is a certain level of target-site specificity and tissue specificity [110]. ERα has a well-established role in breast cancer initiation and progression. The role of ERα in ovarian and endometrial cancers is not as well understood and the role of ERβ in all cancers remains unclear [109]. There are two approved SERMs for chemoprevention, tamoxifen and raloxifene.

14.11.2.1 Raloxifene

A meta-analysis of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, the Continuing Outcomes Relevant to Evista (CORE), and the Raloxifene Use for the Heart (RUTH) trial found an overall 56% reduction in invasive breast cancer incidence with raloxifene [111] (see Table 14.11).

14.11.2.2 Tamoxifen

Tamoxifen metabolites bind to estrogen receptors to block activity [122]. It serves as an antagonist to ERα receptors, blocking the signaling pathway to potential breast cancer cells. It has agonistic effects on bone and lipid and partial agonism in the uterus [123]. Tamoxifen is generic and is available worldwide, making it the most commonly prescribed anti-cancer treatment [124]. Studies involving over 50,000 women have produced prevention/risk reduction in the range of 43–49% in three separate settings: patients with a diagnosis of early stage breast cancer (reduction of recurrence and contralateral breast cancer), healthy high-risk women, and patients with DCIS [123]. Key studies supporting tamoxifen's role as chemoprevention include International Breast Cancer Intervention Study (IBIS-I), National Surgical Adjuvant Breast and Bowel Project (NASBP-I), Royal Marsden Hospital Trial, and Italian Tamoxifen Prevention Study [106] (see Table 14.11).

Table 14.11 Summary of studies of chemoprevention of breast cancer. Based on [106, 112–121]

Trial and duration	Population criteria	Cancer risk reduction	Notes
Raloxifene			
MORE Multiple Outcomes of Raloxifene Evaluation Median duration 40 months	Postmenopause with osteoporosis Age 31–80 years; mean 69.9 years 25 countries, mostly North America and Europe	76% RR reduction new diagnoses	
CORE Continuing Outcomes Relevant to Evista Median duration MORE + CORE 7.9 years	Subset of MORE population	50% RR reduction new cancers irrespective of invasiveness	Some additional benefits from prolonged duration of use
RUTH Raloxifene Use for the Heart Median duration 5.6 years	Postmenopause age >55 years; mean 67.5 years 26 countries in five continents	45% RR reduction new invasive cancers	No reduction noninvasive cancers No impact HR− tumors
Tamoxifen			
NASBP-P-1 National Surgical Adjuvant Breast and Bowel Project aka BCPT Breast Cancer Prevention Trial Initial follow-up 4.6 years Long-term follow-up 7 years	Age >60 years or age 35–59 with 5-year predicted risk >1.66% based on modified Gail model or family history North America	49% RR reduction new invasive cancers initial f/u 69% RR reduction ER+ tumors	

(continued)

Table 14.11 (continued)

Trial and duration	Population criteria	Cancer risk reduction	Notes
IBIS-I International Breast Cancer Intervention Study Initial follow-up median 4.2 years Long-term follow-up 8 and 16 years	Ages 45–70 years with twofold RR breast cancer; ages 40–44 years with fourfold RR breast cancer; ages 35–39 years with tenfold RR breast cancer; median age 50.8 years	32% RR reduction new cancer initial f/u Long-term follow-up found benefits similar to 32% RR seen in initial f/u	Initial follow-up RR reduction not affected by age, disease risk, or use MHT Long-term follow-up reduced prevention in women using MHT during 5 years of trial
Royal Marsden Hospital Trial Initial follow-up median 5.8 years Long-term follow-up median 13.2 years	Age 30–70 years; median age 51 years United Kingdom	No RR reduction new cancer initial f/u No RR reduction new cancer overall long-term but 22% RR reduction invasive tumor	Randomized tamoxifen 20 mg/placebo 8 years
Italian Tamoxifen Prevention Study Initial follow-up median 3.8 years Long-term follow-up median 11.2 years	Age 35–70 years with 100% history hysterectomy, ≈50% history oophorectomy Europe and South America	No RR reduction in low-risk women initial and long-term 76% RR reduction in HR+ tumor only in high-risk women long-term	
Aromatase inhibitors			
MAP.3	Postmenopause age ≥35 years with at least one risk factor; median 62.5 years	53% RR reduction all new cancer	Exemestane/placebo
National Cancer Institute of Canada Clinical Trials Group Mammary Prevention.3 Median 35 months	Canada	65% RR reduction invasive cancers	No differences skeletal fractures, cardiovascular events, other cancers, or treatment related deaths

Table 14.11 (continued)

Trial and duration	Population criteria	Cancer risk reduction	Notes
IBIS-II International Breast Cancer Intervention Study II Median 5 years	Postmenopause age 45–60 years with >2-fold RR breast cancer; ages 60–70 years with 1.5-fold RR breast cancer; age 40–44 years with fourfold RR breast cancer	61% RR reduction new cancer RR reduction maintained at 12 years follow-up	Anastrozole/placebo

14.11.2.3 Aromatase Inhibitors

Aromatase inhibitors (AIs) have been used off label as chemoprevention in high-risk postmenopausal women. Unlike the selective antagonist/agonist effect of SERMS, AIs inhibit aromatization, the process of converting androgens into estrogen, without directly interacting with estrogen receptors [125]. Aromatase in highly estrogen-sensitive tissues, like breast tissue, provides local estrogen via autocrine regulation. The aromatase gene promotor is sensitive to increases in inflammatory cytokines in breast tissue. Inflammatory cytokines increase both with age and in the setting of proliferative breast disease and breast cancer [103]. Aromatase inhibitors are not indicated for use in premenopausal women because this population's aromatase production is too high for an effective AI block.

Aromatase inhibitors anastrozole and exemestane have been shown to be effective as chemoprevention in high-risk postmenopausal women. The National Cancer Institute of Canada Clinical Trials Group Mammary Prevention.3 trial (MAP.3) and the International Breast Cancer Intervention Study II (IBIS-II) both found greater than 50% reduction in both invasive and noninvasive breast cancers [107] (see Table 14.11). Studies with aromatase inhibitors for chemoprevention showed reduction in non-invasive breast cancers as well as invasive, whereas the SERMs have only shown benefit in reducing incidence of invasive breast cancers.

14.11.3 Treatment of Early Stage Hormone Receptor-Positive Breast Cancer

Discussion of estrogen receptor-positive breast cancer treatment is intended to provide an overview of therapy in the context of better understanding implications related to the woman in menopause and menopausal symptom management for clinicians in multiple specialties. Discussion is also limited to first-line treatment in estrogen receptor-positive breast cancer. As previously discussed, the majority of diagnosed breast cancers are hormone receptor-positive, with hormone receptor-negative breast cancers accounting internationally for only 15–20% of breast cancers [104]. With a greater understanding of a woman's risk of breast cancer and the

role of breast imaging, as well as refined surgical, radiation, and systemic treatment options, in many high-income countries, breast cancer is being diagnosed at an earlier stage, before extensive lymph node involvement or metastasis. Chemotherapy can be avoided, and breast cancer mortality has decreased. Age-standardized breast cancer mortality dropped 40% between 1980s and 2020 in high-income countries. Breast cancer disparities continue between high- and low/middle-income countries. Five-year survival in high-income countries exceeds 90% but is 66% in India and 40% in South Africa (www.who.int/news-room/fact-sheets/detail/breast-cancer). In March 2021, the World Health Organization (WHO) introduced their collaborative, Global Breast Cancer Initiative, with the goal of reducing global breast cancer mortality by 2.5% yearly until 2040, which would avoid an estimated 2.5 million deaths (https://www.who.int/news/item/08-03-2021-new-global-breast-cancer-initiative-highlights-renewed-commitment-to-improve-survival). Tamoxifen, anastrozole, and leuprolide are on the WHO Model List of Essential Medicines, thereby allowing for treatment of estrogen receptor-positive breast cancer when the medications are available (https://list.essentialmeds.org).

The therapeutic role of chemotherapy is greatest in triple-negative breast cancers and estrogen receptor-positive breast cancers with lymph node involvement or HER 2 positivity [126]. Estrogen receptor-positive breast cancers that do undergo chemotherapy will also be recommended endocrine therapy.

14.11.3.1 Tamoxifen

Tamoxifen has been approved for the treatment of estrogen receptor-positive metastatic breast cancer since the 1970s, with an expanded role in the adjuvant setting in 1985 (see Table 14.12). The NASBP conducted numerous randomized controlled studies evaluating tamoxifen's role in the adjuvant setting. Women with ER-positive, node-negative breast cancer were randomized to 5 years of tamoxifen. Extended follow-up at 10 years in the NASBP-14 trial found disease-free survival of 69% versus 57% in the placebo arm and a modest but significant survival advantage of 80% in the tamoxifen group versus 76% in placebo [127]. Extensive review of 194 randomized clinical trials by the Early Breast Cancer Trialist's Collaborative Groupe (EBCTCG) found 5 years of adjuvant tamoxifen in patients with ER-positive breast cancer reduced breast cancer mortality by 31% and was more effective than 1 or 2 years of tamoxifen therapy [128]. More recently, with ongoing long-term follow-up, the worldwide Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial, showed that continuing tamoxifen for 10 years, versus 5 years, produced further reduction in recurrence and mortality [129]. Tamoxifen 20 mg daily is recommended for the treatment of pre-menopausal ER-positive breast cancer, and may also be used for treatment of post-menopausal ER-positive breast cancer.

14.11.3.2 Aromatase Inhibitors

Aromatase inhibitors have gone through three iterations, with the most current data involving the third generation, anastrozole, letrozole, and exemestane (see Table 14.12). As with tamoxifen, initial studies using AIs in the metastatic

Table 14.12 Summary of adjuvant therapy agents

Indication	Contraindications	Associated effects
Raloxifene 60 mg orally, once daily (package insert, https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022042lbl.pdf)		
Chemoprevention in high-risk postmenopausal women and treatment of osteoporosis (see Chap. 13)	Premenopausal women and women with active or history of venous thrombosis	Serious: risk of venous thrombotic event, death due to stroke in women with documented coronary heart disease or at increased risk for major coronary events Common: hot flashes, leg cramps, peripheral edema, flu-like syndrome, arthralgias, sweating
Tamoxifen 20 mg orally, once daily (package insert https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021807s005lbl.pdf)		
Chemoprevention in high-risk pre- and postmenopausal women, treatment of hormone receptor positive breast cancer	Women requiring concomitant anticoagulation or who has a history of thrombotic event	Serious: uterine malignancies, thrombotic events including stroke, embryo–fetal toxicity, cataracts, changes in liver enzymes Common: hot flashes, fluid retention, vaginal discharge, irregular menses, mood changes, depression, loss of libido
Aromatase inhibitors Anastrazole 1 mg daily (https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020541s024s025lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020541s024s025lbl.pdf) Letrozole 2.5 mg daily (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020726s027lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020726s027lbl.pdf) Exemestane 25 mg daily (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020753s020lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020753s020lbl.pdf) https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020541s024s025lbl.pdf https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020726s027lbl.pdf https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020753s020lbl.pdf		
Treatment of hormone receptor positive breast cancer in postmenopausal women; off-label chemoprevention in high-risk postmenopausal women Possible added benefit of reducing DCIS and ER− tumors	Premenopausal women	Serious: ischemic cardiovascular events, decreased bone density resulting in osteoporotic fractures, increased total cholesterol Common: hot flashes, asthenia, arthritis, arthralgia, hypertension, depression, osteoporosis, back pain, insomnia, peripheral edema, and lymphedema

(continued)

Table 14.12 (continued)

Indication	Contraindications	Associated effects
Leuprolide acetate 7.5 mg IM monthly		
Leuprolide Depot 22.5 mg IM every 3 months		
https://www.oncolink.org/cancer-treatment/oncolink-rx/leuprolide-acetate-lupron-r-lupron-depot-r-eligard-r-prostap-r-viadur-r-for-women		
Use in breast cancer is off-label. Studies have shown benefit in its use for ovarian function suppression, administered during chemotherapy, or in premenopausal women with estrogen receptor-positive breast cancer in combination with oral endocrine therapy	Contraindicated in pregnancy Leuprolide may cause a sudden flare in breast cancer symptoms due to the transient increase in estrogen	Serious: reduced bone mineral density, increased risk of cardiovascular events, increased risk of seizures, and potential liver toxicity Common: vasomotor symptoms, muscle, back or joint pain, depression, injection site irritation, fatigue, vaginal dryness, and changes in libido

setting were followed by the evaluation of application in the adjuvant setting. AI was then compared to megestrol acetate in the second-line setting (after tamoxifen progression) and showed a significant survival advantage, increased time to disease progression and improved overall response rate [130]. Numerous large trials have compared 5 years of an AI daily to tamoxifen daily. The Arimidex, Tamoxifen Alone or in Combination (ATAC) trial compared anastrozole 1 mg daily for 5 years to tamoxifen 20 mg daily for 5 years. At 68 months median follow-up, anastrozole significantly improved disease-free survival, time to recurrence, overall benefit in time to distant recurrences, and rate of contralateral breast cancer development. At long-term follow-up of 10 years, recurrence rates remained significantly lower on anastrozole versus tamoxifen [131]. The Early Breast cancer Trialists' Collaborative Group (EBCTCG) analysis calculated that treatment with tamoxifen for 5 years reduces risk of recurrence by approximately 50% in Years 0–4 and by approximately one third in Years 5–9, with reduction in breast cancer mortality rate by about 30% throughout the first decade and beyond. Aromatase inhibitors reduce recurrence by about two thirds during 5 years of treatment, by approximately one third in Years 5–9 and would reduce breast cancer mortality rate by approximately 40% throughout the first decade and possibly beyond that [132].

Studies have also examined a role for sequential therapy with 2–3 years of tamoxifen followed by an AI with a total 5 years of therapy. The Australian Breast and Colorectal Cancer Study Group (ABCSG) trial 8 enrolled women who had completed 2 years of tamoxifen to one of three arms: 1 mg of anastrozole, 20 mg of tamoxifen, or 30 mg of tamoxifen. Results found 40% decrease in risk for an event in the anastrozole arm [128]. The NSABP B-42 trial evaluated the benefit of an additional 5 years of letrozole after an initial 5 years of tamoxifen or AI. In the extended letrozole group, results found improvement in 7-year cumulative

incidence of breast cancer-free intervals and a trend of 15% reduction in disease-free survival at 7 years which was significant in updated analysis, but showed no improvement in overall survival [133]. The question of superiority of 10 years to 5 years AI use does not have one clear answer. It warrants a conversation and a treatment plan individualized to the patient.

14.11.3.3 Leuprolide

Leuprolide is a synthetic analogue of naturally occurring luteinizing hormone-releasing hormone (LHRH) and is approved in the United States, Europe, and Asia in the treatment of estrogen receptor-positive breast cancer [134] (see Table 14.12). Upon initial administration, leuprolide increases circulating levels of LH and FSH, leading to a transient increase in estrone and estradiol in premenopausal women. However, with ongoing administration, pituitary production of LH and FSH is depleted, generally within 2–4 weeks from initiation, resulting in ovarian suppression [134]. Numerous randomized trials have examined the role of ovarian function suppression with surgical oophorectomy, ovarian ablation with radiation or with LHRH agonists such as leuprolide combined with chemotherapy or endocrine therapy in the treatment of estrogen receptor-positive breast cancer. A Cochrane review of studies in which ovarian function suppression was achieved with LHRH agonists supported the use of LHRH agonists in the adjuvant setting, with increases in overall survival and disease free survival [135].

14.11.4 Additional Clinical Considerations When Prescribing Endocrine Therapy

- Raloxifene is also approved for the treatment of osteoporosis. Tamoxifen acts as an estrogen agonist in bone in postmenopausal women and may improve bone density. In premenopausal women, tamoxifen is believed to have detrimental effects on skeletal health, exhibiting antagonistic effects at the bone in the presence of premenopausal estrogen [136].
- Some antidepressants are strong inhibitors of CYP2D6, including but not limited to paroxetine, fluoxetine, and bupropion. These are most likely to interfere with tamoxifen's effectiveness.
- Tamoxifen exhibits agonistic effects on the endometrium and myometrium. Long-term use causes changes in the endocervix and endometrium, with twofold to threefold increased incidence of endometrial cancer in aged-matched women [137]. Postmenopausal women should be monitored for symptoms of endometrial hyperplasia or cancer (see Chap. 7).
- Aromatase inhibitors confer a two- to fourfold increase incidence of bone loss compared to normal bone loss with menopause, resulting in elevated fracture risk. Seven international and European organizations published a position statement [138], advocating for fracture risk assessment and recommendations regarding exercise and calcium/vitamin D supplementation in all women upon initiating AI treatment (see Chap. 13).

  - With T-score less than −2.0 standard deviations (SD), or T-score less than −1.5 SD with one additional risk factor, or two or more risk factors (without BMD), bone-directed therapy should be recommended for the duration of AI treatment.
  - With T score greater than −1.5 SD and no risk factors, management should be based on BMD loss during the first year and based on local guidelines for postmenopausal osteoporosis.
  - Compliance should be regularly assessed, as well as BMD, after 12–24 months on treatment.
- Summarizing endocrine therapy in estrogen hormone receptor-positive breast cancer:
  - Data on AIs shows more benefit than tamoxifen when used to treat early stage hormone receptor breast cancer.
  - Switching to an AI after 2–3 years of tamoxifen (for a total of 5 years of endocrine therapy) offers more benefits than 5 years of tamoxifen.
  - Five years of AI after taking 5 years of tamoxifen continues to reduce risk of recurrence compared to no treatment after 5 years of tamoxifen.

14.12 Iatrogenic Menopause Post Chemotherapy

Iatrogenic menopause can occur due to anti-cancer treatment. Chemotherapy causes impairment of follicular maturation and can increase rate of oocyte loss at a time when there are fewer remaining primordial follicles (see Chap. 4). The incidence of temporary amenorrhea or premature ovarian insufficiency varies depending on age, pubertal status, existing ovarian reserve and type, and cumulative dose of chemotherapy, with the prevalence of chemotherapy-induced amenorrhea (CIA) ranging from 2% to 82% (Australian Menopause Society). Research across Western countries and Asia found a woman's age to be the most predictive factor of CIA and premature ovarian insufficiency [139]. A review of several studies document women greater than 40 years of age were more likely to experience amenorrhea after adjuvant chemotherapy [139]. Iatrogenic menopause comes with many implications. The perimenopausal woman put into menopause from chemotherapy will have to address menopausal symptoms and quality of life issues sooner than she otherwise would. In addition, women of child-bearing potential will also have to deal with loss of fertility. Medications like leuprolide may be beneficial in protecting fertility while used during chemotherapy; however, the primary outcome for many of the studies was not fertility but resumption of menses and breast cancer outcomes [140]. Providers managing menopausal symptoms in breast cancer survivors will also have to consider contraindications to MHT in estrogen receptor-positive breast cancer. As management of menopausal symptoms has been thoroughly discussed in other chapters, our discussion is specific to contraindications.

14.13 Management of Menopausal Symptoms in Breast Cancer Patients

Management of menopausal symptoms in women with an estrogen receptor-positive breast cancer warrants additional consideration of potential contraindications and a thorough risk versus benefit discussion between the provider and patient. MHT has a well-established role in managing many of the common symptoms of menopause, including vasomotor symptoms, sleep disturbances, and genitourinary symptoms. MHT is also approved for the prevention of osteoporosis [141]. AIs are associated with an increased risk of menopausal symptoms. Hong et al. [142] found a 30.47% incidence of hot flashes, 14.64% incidence of sweating, and 16.52% incidence of insomnia in a meta-analysis of occurrence of menopausal symptoms in breast cancer patients receiving AI therapy. The Hormonal Replacement After Breast Cancer Cancer-Is it Safe? (HABITS) study, in which women with a history of breast cancer were openly randomized to MHT versus best treatment without MHT, initiated in the 1990s, was terminated in 2003 due to an increase in breast cancer events in the MHT arm. Cumulative incidence of breast cancer in the MHT arm at 5 years was 22.2% versus 8.0% in the non-MHT arm [143]. The Stockholm Study, initiated in 1997 and also terminated in 2003, was designed to minimize the dose of progesterone in the MHT arm with the hypothesis of reducing breast cancer recurrence. Women with a breast cancer history (disease free at enrollment) were randomized to MHT versus no MHT (prohibited from taking oral MHT). A long-term follow-up at 10.8 years showed 60 new breast cancer events in the MHT arm versus 48 in the non-MHT arm that was not statistically significant [144].

14.13.1 Vaginal Estrogen and Testosterone

Genitourinary syndrome of menopause, atrophic vaginitis and urogenital symptoms, is a significant issue impacting approximately 70% of postmenopausal breast cancer survivors, compared to 50% of postmenopausal women without breast cancer [122] (see Chap. 11). Studies have shown that the third-generation AIs can inhibit aromatase activity by more than 95%, reducing plasma concentrations of estrogen from a high of 20 pmol/L to a low of 3 pmol/L or less, contributing to the excess of urogenital symptoms in breast cancer patients [122]. Sussman et al. [145] summarized studies measuring serum estradiol in women undergoing treatment with 10 μg estradiol releasing intravaginal tablet, 4 μg estradiol vaginal insert, or intravaginal dehydroepiandrosterone (DHEA). There was minimal elevation in serum estradiol levels, and women experienced significant symptom improvement. A prospective observation cohort study of 45,663 women from the Women's Health Initiative Observational Study (WHI) looked at risk of invasive breast cancer in women with an intact uterus and found no significant difference between those who used vaginal estrogens (cream or tablet) and those who did not [146]. However, the 2020 NAMs Genitourinary Syndrome of Menopause Position Statement concluded that insufficient data exists to confirm the safety of vaginal estrogen, DHEA, or

ospemifene in women with breast cancer [147]. The American College of Obstetricians and Gynecologists' Committee Opinion [148] determined that data does not show an increased risk of cancer recurrence among women currently undergoing breast cancer treatment or those with a personal history of breast cancer who use vaginal estrogen. They stated non-hormonal options should be considered first and that the decision to use vaginal estrogen may be made in coordination with a woman's oncologist [148].

In 2019 The Global Consensus Position statement was issued with regard to testosterone therapy. The section pertinent to women with a history of or current breast cancer noted that this population was excluded from the randomized clinical trials for hypoactive sexual desire disorder (HSDD). Caution is recommended for use in women with hormone sensitive breast cancer [149].

In a small phase I/II trial of postmenopausal women on AIs for breast cancer, the role of vaginal testosterone in the treatment of vaginal atrophy was examined and found to improve vaginal pH and symptoms of dyspareunia and vaginal dryness [150]. Ongoing research in this area would be of benefit, specifically studies looking at the primary endpoint of breast cancer incidence. Glaser et al. [151] examined at the long-term effect of testosterone implants on risk of breast cancer and found that in combination with or without anastrozole there was no increase in incidence of invasive breast cancer. A systemic review found no increased risk of breast cancer in postmenopausal women using transdermal testosterone for hypoactive sexual desire disorder; however, the authors concluded that further research with breast cancer incidence as the primary endpoint is required to substantiate their findings [152].

14.13.2 Summary of Menopausal Symptom Management in the Breast Cancer Patient

Information is from Cancer Australia (https://www.canceraustralia.gov.au/affected-cancer/cancer-types/breast-cancer/management-menopausal-symptoms updated 2020) unless otherwise noted.

- **Vasomotor Symptoms**—Antidepressants, antihypertensives, gabapentin, and oxybutynin are safe to use as prescribed in women taking AIs. In women taking tamoxifen, some antidepressants reduce metabolism into the active agent, decreasing efficacy. Systemic MHT should be avoided. Data supports safety of dietary phytoestrogens but prescription of high-dose phytoestrogens is not recommended [153]. Cognitive behavioral therapy and complementary therapy including acupuncture, relaxation therapy, and yoga with meditation are safe and have varied efficacy (see Chap. 8).
- **Sleep Disturbance**—Sedatives are safe in women with breast cancer. Systemic MHT should be avoided. Cognitive behavioral therapy, complementary therapy including hypnotherapy, relaxation therapy, yoga, acupuncture, and exercise, and isoflavones, excluding prescription doses of phytoestrogens are safe and have varied efficacy (see Chap. 9).

- **Vulvovaginal Symptoms and Sexual function**—Vaginal pH-balanced gel or lubricants are safe. Vaginal estrogen in lowest necessary dose is considered safe. Systemic MHT should be avoided. Transdermal testosterone may be safe, limited data with primary endpoint being incidence of breast cancer. Cognitive behavioral therapy and complementary therapy including hypnotherapy are safe and have varied efficacy (see Chap. 11).
- **Mood**—Antidepressants are safe with same considerations in the woman taking tamoxifen or AI therapy. gabapentin is safe. Cognitive behavioral therapy and complementary therapy including hypnotherapy relaxation therapy are safe and have varied efficacy (see Chap. 10).

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