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Supporting the Menopausal Transition

Lifestyle and Non-Pharmacological Approaches

Menopause defines the natural transition that results from the cessation of normal menstrual cycles; an inevitable process in the life of a woman as she ages. However, while this transition is natural, it is also associated with physiological changes that lead many women to seek symptom relief. In addition, the risk for certain chronic diseases of aging (e.g., cardiovascular disease, osteoporosis, cognitive decline) increase in women as they pass menopause. Thus, menopause is often viewed as a medical syndrome- complete with diagnosis, epidemiology, and a wide-range of therapeutic options. This review will briefly discuss the physiological and clinical aspects of the menopausal transition, along with its common symptoms and risks. We will particularly highlight emerging concepts for understanding how functional metabolic reserves can affect the menopausal transition. Finally, in keeping with the theme of our monograph series, the balance of this monograph will weigh the evidence for non-pharmacological therapeutic approaches reported to help women through this natural process.

The Fundamentals of Menopause Physiology

Somewhere between the ages of 45 and 55, most women experience a change in their normal menstrual cycle that eventually results in a complete cessation of menstruation. These transitional years, often referred to as the perimenopausal or climacteric years, lead to a number of physiological and psychological changes that, for many women, negatively affect their quality of life. Globally, there are over one billion women who are postmenopausal; and in the US, over one million women reach menopause each year.[1] However, while the menopausal transition is experienced by women around world, the unique combination of diet, lifestyle (particularly stress), cultural attitudes and longevity give it particularly clinical significance in the Western world.[2,3] Furthermore, since menopause is accompanied by increased incidence of bone fractures, heart disease, depression, fatigue, a reduction in mental acuity, increased sexual difficulties and various cancers, it is often concluded that the transition itself must be an unnatural state, or even a diseased state.

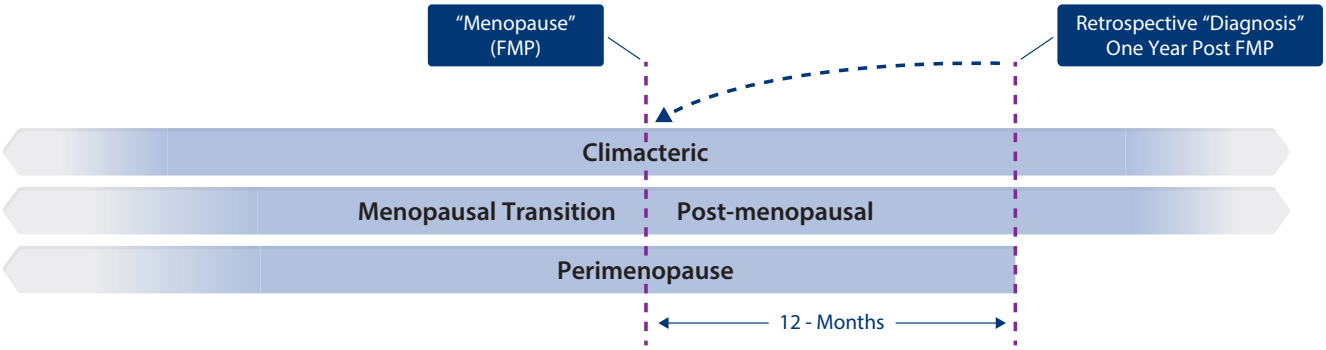

Figure 1: The Overlapping Definitions of Menopause. The nomenclature of menopause is confusing, since different terms and definitions are used by different medical disciplines and the public. Menopause is defined as the final menstrual period (FMP), but only after 12-months of no menses. Therefore, the definition of postmenopausal can begin (retrospectively) at the FMP or 12 months later. Likewise, perimenopause can be defined as the beginning of noticeable changes to the menstrual cycle (usually 1-2 years before the FMP), and ends once menopause is "diagnosed." The term climacteric is a broad term that defines the whole transition- though it is not as common outside the scientific literature. Figure modified from: Ambikairajah A, Walsh E, Cherbuin N. A review of menopause nomenclature. *Reprod Health.* 2022 Jan 31;19(1):29.

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At the same time, there are movements and organizations (even a popular musical) that emphasize the positive aspects of menopause, and the wisdom and influence of postmenopausal women on their families and greater culture. Therefore, it is important for the clinician to understand the delicate physiological and emotional changes that take place during the menopausal transition, so they can empower women to navigate this important time of life and to leverage, where appropriate, therapies to mitigate symptoms and risks that accompany this transition.

The cascade of hormonal signals that orchestrates the menstrual cycle is an exquisitely controlled process that involves primary inputs from the hypothalamus, pituitary, and gonadal tissues; and includes intricate positive and negative feedback loops.[4] While the initiating signals of this cycle start in the brain with gonadotropin releasing hormone (GnRH, from the hypothalamus) and follicle stimulating hormone and luteinizing hormone (FSH/LH, from the pituitary), the dominant signals driving the physiology of the menstrual cycle are the steroid hormones produced in the ovaries by the growing follicles; namely estrogen and progesterone. Since these two hormones are also involved in other physiological processes (in non-uterine tissues), their fluctuations and great diminution during perimenopause and menopause results in a wide-range of functional changes in women that will likely affect her well past menopause.

At birth, each woman is endowed with 1-2 million primordial follicles. This pool of follicles decreases to about 300,000 by the time of menarche (puberty). During each menstrual cycle, FSH-signaling recruits several hundred to several thousand follicles. Of these, only one (occasionally, several) mature to the point of ovulation while all the others die by atresia. This process results in approximately 400 ovulatory cycles within a women's lifetime and constitutes what is normally referred to as the premenopausal or reproductive years. The number of follicles left in the ovary reserve seems to be critical to the regulation of the menstrual cycle. At about 38 years of age, when approximately 25,000 follicles remain, the rate at which follicles are recruited increases nearly two-fold, resulting in a rapid decrease in the ovary reserve. At that point, follicle stimulating hormone (FSH) levels in these women increases during each cycle, signaling the beginning of a loss in the feedback mechanisms. Research suggests that the progressive rise in FSH is related to the decreased ovarian production of molecules called inhibins, which function to inhibit pituitary production of FSH.[5] Few women notice any dramatic changes at this time since estradiol (E2) and progesterone levels are affected little by these changes (although fecundity is significantly reduced at this age). However, for most women, the climacteric years begin with some noticeable changes to their menstrual cycle, usually within a year or two of their final menstrual cycle.

By age 51, the median age for the final menstrual period, the ovary reserve is about 1000 follicles. If symptoms hadn't started previous to this point, this is typically when the signs and symptoms of menopause begin to occur, as it corresponds with a significant drop in estrogen production. It is significant to note that while a woman may stop menstruating at this time, endogenous cycling and ovulation may still occur for months and even years. This can be an important distinction because therapeutic decisions may differ for women with ongoing endogenous amenorrheic cycles (presumed to be postmenopausal). The official definition of natural menopause is deemed to have occurred (retrospectively) only after 12 consecutive months of amenorrhea, for which no other

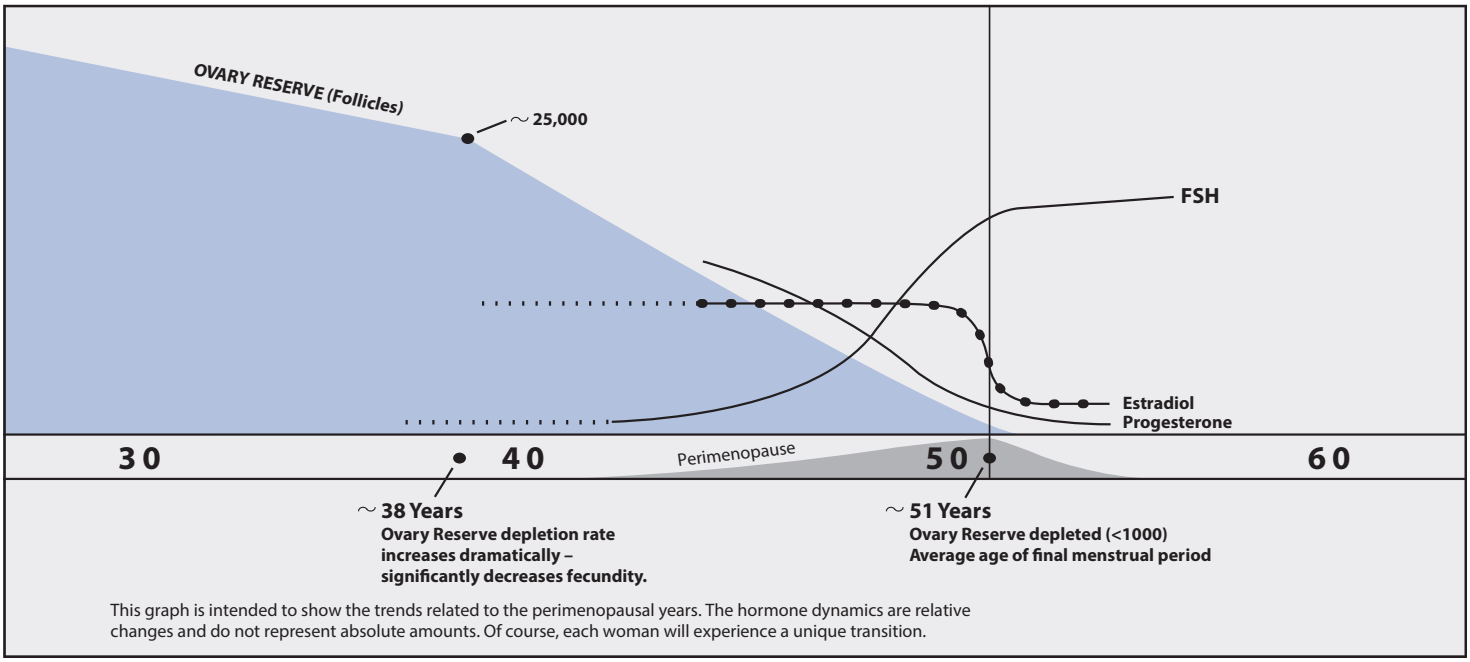

Figure 2: The Hormonal Dynamics of Menopause See text for more further explanation.

obvious pathological or physiological causes could be determined.[6] We should note that another peptide produced by growing follicles, known as anti-Müllerian hormone (AMH), is strongly associated with functional ovarian reserves in the years just prior to menopause.[7] Although the clinical utility is often debated, serum AMH levels have been used to predict the timing of menopause.[8,9] AMH levels, in younger women, have also been used to diagnose premature ovarian insufficiency (POI, when AMH is low) and polycystic ovarian syndrome (PCOS, when AMH is high).[10]

The Symptoms and Risks of Menopause

The dramatic change in hormone signaling that occurs throughout the climacteric affects the function of many cells, tissues and physiological pathways; and along with the processes associated with aging, these changes contribute to a number of symptoms and risks unique to the care of peri- and postmenopausal women. In fact, 80-90% of women report noticeable symptoms (e.g., vasomotor, genitourinary, sexual, cognitive, etc.) during menopause and approximately a third of women report that menopause-related symptoms severely affect their daily quality of life.[11] However, while vasomotor symptoms may be the telltale signs of menopause, they are rarely life threatening and usually fade once a woman is past the climacteric years. Still, the permanent change in hormone levels has been implicated as a factor in the increased risk of several serious life-threatening diseases such as osteoporosis, heart disease, and cancers of the breast and endometrium. In the case of both symptoms and risk factors, aging plays a confounding factor. This is particularly true in the case of increased risk of cardiovascular disease, depression, and decreases in cognitive ability and libido; all of which affect men of similar ages. Since menopausal symptoms are varied, a number of scales or indices have been created to measure the severity of menopausal symptoms for clinical research. The Blatt-Kupperman index (i.e., Kupperman Index/KI) has been in use for more than six decades, though its limited focus on vasomotor symptoms has reduced its use by some researchers who prefer the menopause rating scale (MRS).[12,13] These, and a variety of quality-of-life scales, are commonly used to determine the efficacy of therapies being tested for their ability to prevent or treat menopausal symptoms.[14,15]

Vasomotor symptoms (VMS)

Of the many signs and symptoms related to menopause, hot flashes (or flushes) are probably the most universally experienced- and nearly synonymous with what are called vasomotor symptoms (VMS).[16] When surveyed, 80% of American menopausal women say they experience hot flash episodes for an average of 4-5 years, though some experience hot flashes for more than 10 years after menopause.[17] The experience is a sensation of heat, sweating, flushing and chills lasting from 1 to 5 minutes. For many, anxiety and palpitations can also be experienced during these hot flash episodes. The proximal cause for hot flashes appears to be an over-compensation to a slight increase in core body temperature which triggers a dramatic increase in peripheral blood flow resulting in a rapid rise in skin temperature (0.5° C, as a mechanism for cooling body temperature). The physiological processes linking hot flashes with the climacteric years are not fully understood, nor is the exact relationship between how lowered estrogen triggers the onset or frequency of vasomotor symptoms. Recent evidence suggests the important role of the temperature regulating centers of the hypothalamus, especially the hypothalamic kisspeptin, neurokinin B and dynorphin (KND) signaling system.[18] In fact, in 2023 FDA approved a neurokinin 3 (NK3) receptor antagonist (fezolinetant) for the treatment of moderate to severe vasomotor symptoms, or hot flashes, caused by menopause.[19,20]

The combination of hot flashes, estrogen-related altered circadian rhythms, and increased frequency of depression frequently results in reduced sleep quality in many women.[21] While it is difficult to assess how much each factor contributes to decreasing sleep quality, this can be a major factor in reducing the quality of life during the menopausal transition. Often, insomnia (primarily waking after sleep onset) will be the primary reason for seeking medical attention. While hormone replacement therapy (HRT) is associated with the reduction in many VMS (especially hot flashes), HRT is not generally effective in improving menopause-related insomnia when unrelated to VMS.[22]

Genitourinary Symptoms

Another common set of symptoms related to the climacteric, now often collectively termed genitourinary syndrome of menopause, results from physiological changes in the genitourinary tissues-vagina, vulva, bladder, and urethra.[23] Genitourinary syndrome of menopause (GSM) encompasses genital symptoms of dryness, burning, and irritation; urinary symptoms and conditions of dysuria, urgency, and recurrent urinary tract infections (UTIs); and sexual symptoms of pain and dryness.[24] While the etiology of GSM is mostly linked to decreased estrogen signaling, aging and changes to the vaginal microbiota are also important factors in most cases.[25,26] Though symptoms associated with GSM are highly prevalent (nearly 80% of postmenopausal women in some cohorts), these symptoms often remain undiagnosed and untreated.[27] Unlike VMS, which often diminish with time after menopause, GSM symptoms often remain or get worse with time. Decreased lubrication and thinning of the vaginal tissues increases the risk for infections, irritations and the chance for mechanical injury during intercourse. These factors, along with menopausal drops in estrogen, progesterone, and testosterone can lead to a dramatic change in sexual function and desire.[28] Various hormone replacement regimens are often recommended to relieve GSM, as are the use of over-the-counter vaginal moisturizer or lubricant products.[29,30,31]

Osteoporosis

Osteoporosis is a metabolic bone disease that results in deterioration of the micro-architecture of the bone, resulting in lower bone mass and increased risk of fractures. These fractures (mostly of the spine, hip or forearm) dramatically increase the rate of mortality and need for long-term care. Interestingly, while bone mineral density (BMD) and risk for osteoporosis are strongly associated with age and menopause status, BMD is more closely tied to the years since the

final menstrual period than chronological age, thus lifetime fracture risk is higher in women with early (or surgical) menopause.[32]

While estrogen plays an important role in maintaining bone mass in women by suppressing bone remodeling and maintaining a balance between osteoblast and osteoclast activities, BMD typically begins to decline in women after they reach peak bone mass (~35 years of age), well before estrogen decline begins in perimenopause. However, this decline in BMD accelerates once estrogen production begins to noticeably decline during perimenopause. As the bone metabolic activities shift toward osteoclast (resorption) and away from osteoblast (bone building) activities, bone density and strength decreases. Though not without controversy, hormone replacement therapy (HRT) has been successfully used for osteoporosis (prevention and treatment) in women who are candidates for HRT, though bone loss resumes when HRT is stopped.[33]

One of the most critical factors in the prevention of osteoporosis is reaching a protective peak bone mass prior to menopause, a biological process that is influenced by the first three decades of life.[34] This protective peak bone mass acts as a metabolic reserve which buffers against the eventual bone density loss that comes during menopause. Unfortunately, many women do not achieve this protective buffer- often due to poor lifestyle and diet; though genetics and environmental factors play a role as well.[35,36] Unlike VMS and GSM, the symptoms of which are difficult to predict prior to perimenopause, bone mineral density and osteoporosis prevention is something that should be discussed with young women well before they reach peak bone mass and during the decades prior to menopause. There are many options available to help prevent the loss of BMD and reduce the risk of postmenopausal fractures. We have reviewed many of these options including non-pharmacological (vitamin and mineral supplementation, phytoestrogens, etc.) and lifestyle (diet, weight-bearing exercises, stress management etc.) prevention and treatment strategies elsewhere.[37]

Cardiovascular Disease (CVD)

Epidemiological reports confirm that postmenopausal women are at a greater risk for cardiovascular disease than premenopausal women; though there is much controversy about what drives this relationship (beyond age). Notably, many of the risk factors for CVD are higher in postmenopausal women (e.g., visceral adiposity, atherogenic dyslipidemia, impaired glucose tolerance, metabolic fatty liver disease and hypertension), compared to premenopausal women.[38] The association between hormone levels in women (particularly estrogen) and cardiovascular risk is not clear; and the controversial history of estrogen-replacement and cardiovascular risk has resulted in much debate as to how to manage this risk in women through their menopausal transition (see discussion of HRT and CVD on pages 6-7).[39,40,41] For the most part, the assessment of cardiovascular and cardiometabolic risk in postmenopausal women is similar to risk assessment in most other individuals (men or women), and is beyond the scope of this monograph. However, there are lifestyle factors and non-pharmacological therapies that can greatly improve cardiovascular health and reduce the incidence of CVD, many of which can be used as adjunct therapies in menopausal women. In some cases, these same lifestyle risks and therapies are associated with improvements in other menopausal symptoms.

Brain Structure and Function Changes

It is well documented that Alzheimer's disease effects women at a rate that is nearly double that of men.[42,43] While this has often been dismissed as a function of age (i.e., women living longer than men), studies now suggest other factors may be at play. In fact, many other menopause-related phenomena (related to reduced estrogen-signaling) may be influenced by changes in altered metabolism in the brain; including thermoregulation, circadian synchrony, cognition and mood.[44] Recent studies have even shown that, using magnetic resonance imaging (MRI), critical areas of the brain of postmenopausal women have reduced volume compared to premenopausal women.[45] These metabolic and structural changes also create an increased vulnerability to beta-amyloid accumulation, especially in women with APOE-4 genotypes.[46] Other researchers have shown that functional connectivity within the brain of postmenopausal women is directly associated with their serum estradiol levels.[47]

Since this area of research is relatively new, there are many unanswered questions; especially related to ways to mitigate the effects of menopause on brain structure and function. The question of how estrogen-signaling increases or decreases these changes (either lifetime exposure or replacement therapies), is still being worked out; and may differ by a variety of menopausal phenotypes.[48] Nonetheless, clinicians should be aware of this growing area of research as they evaluate all the ways in which menopause influences a woman's physiology.

Lifestyle Factors Influencing Menopausal Symptoms

There are many factors that play a role in the age of onset or the severity of the symptoms associated with the menopause. In many women, the timing of menopause will often mirror the timing of their mother's menopause.[49] Studies have also shown that women who experience moderate to severe symptoms related to premenstrual syndrome/disorders (PMS/PMD) have an increased prevalence of experiencing moderate to severe vasomotor symptoms during their menopause.[50] These associations may be due to a consistent pattern of hormone regulation throughout a woman's life (perhaps both from genetics and lifestyle factors) or may be a function of increased scrutiny and awareness of these symptoms. However, other lifestyle and environmental factors are also known to influence menopausal symptoms. In general, lifestyle inputs that are generally considered to be healthy (i.e., those shown to reduce the risks of most chronic conditions such as CVD, diabetes, cancer, etc.) are often linked to lower VMS and menopause-related risks. Here we discuss a few common lifestyle and environmental inputs that may help guide the clinician in prioritizing preventative or treatment strategies for women through their menopausal transition.

It should come as no surprise, that individuals that maintain a **healthy dietary pattern** generally have fewer symptoms during the menopausal transition that those who do not.[51,52,53] Prudent dietary patterns such as the Mediterranean diet (MedDiet) are associated with less frequent VMS (i.e., low adherence to MedDiet associated with higher VMS), and are also associated with lower risks for cardiometabolic disease, cognitive decline and most other diseases of aging; thus they are generally the recommended starting point for all dietary prevention and interventions strategies during the climacteric years.[54,55,56] However, modifications of this prudent dietary pattern to meet the specific needs or preferences of the individual (e.g., vegan/vegetarian, avoidance of allergens, etc.) in order to create a personalized dietary plan is recommended. Though small, some clinical trials have shown that plant-based diets and/or lacto-ovo-vegetarian diets may be associated with fewer VMS, compared to control omnivorous diets.[57,58,59] The use of specific foods (e.g., soy) or supplemental nutrients (e.g., vitamins, minerals, fatty acids, botanicals) will be discussed below.

The association between **physical activity** and menopause is complex and often confusing, especially as an intervention intended to reduce menopausal symptoms. With few exceptions, physical activity that reduces prolonged **sedentary behavior**, increases muscle mass and reduces obesity is recommended for everyone at any age; and is generally associated with benefits in a variety of menopausal symptoms and risks.[60,61,62] Walking programs have been particularly popular as a means of increasing weekly physical activity and creating social networks; both of which are influential in the improvement of menopausal symptoms.[63] Additionally, **exercise programs** of various types have been shown to help reduce VMS and improve measures of anxiety, depression and stress, and reduce metabolic risk factors in menopausal women.[64,65] These include low impact stretching-type activities, to more intense resistance training programs.[66,67]

As one would expect, many studies investigating the relationship between lifestyle and menopause (both observational and interventional) often focus on weight or fat mass and their associated risks for cardiometabolic disorders such as obesity, type 2 diabetes and cardiovascular events; in addition to their influence on other menopausal symptoms.[68] In general, **obesity** (using various metrics) and **increased visceral adiposity** are associated with increased incidence and severity of VMS.[69,70,71] Interestingly, one study showed that persistent VMS precedes additional weight gain, suggesting that obesity and VMS may create a feed-forward loop much as stress can drive eating habits that increase obesity.[72] Conversely, interventional **weight loss** is often associated with improved VMS, though the benefits of weight loss extend to most other symptoms and risks in menopausal women even with no change in VMS.[73,74]

The relationship between obesity, adipose biology and steroid hormone metabolism is quite complex and beyond the scope of this monograph.[75] However, clinicians should be aware of the bi-directional relationship between estradiol and adipose metabolism. Altered estrogen production can trigger changes in the location and function of adipose tissue on the one hand; while insulin-resistant adipocytes can influence the formation of estrogens from their precursor steroids or alter estrogen receptor expression within stored fat tissues, on the other.[76,77] Estrogens are now also recognized as having an epigenetic effect on adipocyte metabolism, which suggests that estrogen signaling over a woman's lifetime may influence how menopause affects obesity or related fat-storage issues.[78]

Complicating matters further in this complex relationship between estrogen, adipocyte biology, obesity and menopause is a person's exposure to metabolic and **endocrine disrupting environmental toxins**. Evidence now suggests that these chemicals (e.g., dioxins, polychlorinated biphenyls, bisphenol A, phthalates, parabens, lead, cadmium, etc.) are associated with altering menopausal onset and symptom severity, along with the well-known dysregulation of adipose biology and increases in cardiometabolic risk.[79,80,81] While it is difficult to reverse the effects of early-life exposure to these chemicals, clinicians should consider ways to help patients discover and avoid endocrine-disrupting chemicals in their current food, water, personal care products, and living/working spaces; and become educated on ways to reduce toxic burden in stored adipocytes.

Finally, **psychosocial stress** and other signals that contribute to **acute or chronic HPA axis dysfunction** can contribute to increased symptoms during menopause, especially since they are associated with anxiety, depression and sleep disturbances.[82,83] However, defining which specific patterns of hypothalamus-pituitary-adrenal (HPA) axis dysfunction contribute to which specific patterns of menopausal symptoms and risks; and subsequently, what specific therapies can alleviate both, is simply too complicated for most research models to decipher. It is known, for instance, that adrenal steroids in the delta-5 pathway (i.e., dehydroepiandrosterone--DHEA, its sulfate form DHEA-S, androstenedione, and androstenediol or Adiol) actually increase during the late perimenopausal and early menopausal years and, because these hormones can be converted to estrogens, may function as a buffer for estrogen decline during the menopausal transition.[84,85] Also, the adrenal hormone most commonly associated with stress, cortisol, plays a powerful role in the metabolic processes that affect obesity, adipose biology, estrogen metabolism and hypothalamic and pituitary signaling; all of which influences the complex relationship between the HPA axis (normal and stress-induced) and the menopausal transition.[86] Clinicians should be aware that a women's current stress levels, as well as early-life stress, can impact the level of HPA axis involvement on the menopausal transition.[87] In addition, since the HPA axis is one of the key controllers of circadian function and metabolism, understanding the drivers (i.e., stressors) that trigger HPA axis dysfunction is a critical part of chronic disease management in all patients. For a comprehensive discussion of this topic, see our textbook on this topic (*The Role of Stress and the HPA Axis in Chronic Disease Management, 2nd Edition-2020, Point Institute*).

Hormone Replacement During Menopause: History and Controversy.

The perimenopausal fluctuations in estrogen and progesterone, followed by their postmenopausal decline, are considered to be the primary drivers of the symptoms and risks associated with menopause. Naturally, the notion that replacing these hormones to re-establish "appropriate" levels may somehow result in the improvement of these symptoms and risks was long held by many (even before estrogen or progesterone were isolated and purified).[I,II] Though some ancient practices have been described, it was not until the 1890s that glandular therapy, in the form of ground bovine ovarian tissue, was made commercially available to menopausal women (Ovariin, by Merck & Company).[III] Later, in the 1930s, a product made from concentrating the urine of pregnant woman became available (Emmenin, by Ayerst); products which were soon replaced by those derived from pregnant mare urine. In 1942, the US Food and Drug Administration (FDA) had approved one of these products, marketed by Wyeth-Ayerst, called Premarin.[IV] Unlike the "bio-identical" conjugated hormones in the products derived from pregnant women, Premarin contained a number of different estrogenic molecules known collectively as conjugated equine estrogens (CEE). Primarily composed of estrone-conjugates, CEE also contains equilin, equilenin, and estradiol-conjugates; along with at least a dozen other estrogenic compounds.[V,VI]

While Premarin emerged as the most widely used pharmaceutical hormone replacement product, there were many other commercially-available products that included bio-identical estrogens, synthetic estrogens, and estrogen-like compounds (e.g., DES-diethylstilbesterol). By 1947, there were some 53 formulations designed to treat menopause (oral, transdermal, patches, etc.) listed in the Physician's Desk Reference, sold by 23 different companies.[IV] However, until 1962, FDA only required that drugs be proven safe in order to be approved; they were not required to demonstrate efficacy. By 1972, Premarin and several other products had been deemed effective for the treatment of menopausal symptoms and their use continued to increase, especially with the help of the popular book *Feminine Forever*- written by Robert Wilson and published in 1966.[VII] This momentum was then substantially slowed by the reports of increased risk for endometrial cancer connected with estrogen-only HRT (i.e., unopposed estrogen) in the mid-1970s.[VIII] By the 1980s, it was discovered that the use of progesterone with estrogen could eliminate nearly all the increased risk that was associated using estrogen-only HRT (for women with a uterus) and routine use of HRT continued to grow.[IX,X]

All of this, in more ways than one, seems like ancient history in light of the publications leading up to, and culminating with, the Women's Health Initiative (WHI). By the mid-1980s, HRT was widely considered to be effective for vasomotor symptoms and for preventing osteoporosis, but its role in preventing heart disease (a major risk factor in postmenopausal women) was still being debated. In 1985, two large observational studies were published which showed nearly opposite results; the Framingham Heart Study (reporting an almost doubling of CVD risk over 8 years of estrogen use), and the Nurse's Health Study (reporting half the risk in women using estrogen compared to those who never used estrogens).[XI,XII] Other cohort studies in the 1980s and 90s, like the Nurse's Health Study, also showed substantial risk-reductions associated with estrogen use; leading to an industry request for FDA to approve HRT for the indication of CVD risk reduction in postmenopausal women.[XIII] Though the advisory committee approved this request, FDA never acted on this request for approval. Nonetheless, the American College of Physicians released a position statement in 1992 recommending that all postmenopausal women be offered HRT to help prevent heart disease.[XIV]

Then, during the 1990s, some of the first prospective trials were conducted to fully investigate the influence of HRT on cardiovascular risk in peri- and postmenopausal women. One of the first was a trial sponsored by Wyeth called the Heart and Estrogen/progestin Replacement Study (HERS) in which Prempro (0.625 mg CEE with 2.5 mg of medroxyprogesterone acetate; or placebo) was given to 2,763 postmenopausal women with coronary disease.[XV] After four years of therapy, they saw no statistical CHD risk reduction in the HRT group, though risk for increase CHD events was higher in the HRT group during the first year, as were the incidence of thromboembolic events and gallbladder disease throughout the study. A few years later, in 2002, the Prempro arm of the multi-center Women's Health Initiative (WHI) was halted because the early results showed women who took this combination hormone therapy had increased risk of coronary heart disease, stroke, pulmonary embolism, and breast cancer.[XVI,XVII] The news of these results sent shockwaves around the medical world, and the sales of Wyeth's Prempro and Premarin dropped dramatically (decreasing 66% and 33%, respectively) soon after the news of the trial results were made public.[XVIII] Two years later, the estrogen-only arm of the WHI (in women without a uterus) was also stopped early when a statistical increase in the risk for strokes emerged compared to placebo.[XIX]

The results of the WHI have spawned many different interpretations, re-assessments, follow-ups and conclusions; many of which are influenced by a person's general view of the need for pharmaceutical intervention for menopause, the goals, design and participants of the WHI study, or the nature of the compounds used in the WHI. Summarizing this complex debate, which is still ongoing, is beyond the scope of this monograph; but we do want to discuss one particular issue that may be important to those interested in "natural supplementation." The WHI used Premarin and Prempro, two products that contain hormones that are not "bio-identical" when compared to those that are produced naturally in women (as mentioned above). Therefore, many clinicians consider bio-identical hormone replacement therapies (BHRT) using compounded micronized oral products, transdermal creams, patches or pellets to be inherently more efficacious, safer and with fewer side-effects. Unfortunately, with few exceptions, these claims have never been tested in well-designed placebo-controlled clinical trials; and while estradiol and progesterone products are used by many different clinicians, compounded oral products (often containing combinations of estradiol, estriol, and estrone) have often been the focus of negative recommendations from various professional societies. [XX,XXI,XXII] As with any subject this nuanced, we strongly recommend that clinicians fully understand the risks and benefits of the hormone therapies they recommend or prescribe, including any tests used to decide formulations and dosing of these therapies.

A final point should be made when discussing natural or bio-identical hormones used to make therapeutic products. With the exception of the early products derived from the urine of pregnant women, these bio-identical hormones are actually synthesize using precursor molecules; typically derived from wild yam or soy. Using the "Marker Degradation" reactions discovered by Russell Marker in the 1930's, diosgenin from Mexican wild yams can be used to produce progesterone (and then used to synthesize other steroid hormones as well).[XIII] These precursor botanicals (i.e., wild yam) do not contain progesterone, nor are their precursor molecules converted to progesterone/estrogens/androgens after ingestion in humans. We discuss the phytoestrogenic potential of polyphenols derived from soy and other botanicals on page 9.

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Microbiomes and Menopause

The past several decades has witnessed a revolution in our understanding of how the various microbiomes that reside within and upon the human host affect almost every aspect of human physiology. It should come as no surprise, then, that various characteristics that define a healthy or unhealthy microbiome are associated with a variety of menopausal outcomes. While most of our knowledge is based upon these associations within the gastrointestinal and vaginal microbiomes, research has also linked changed in oral and skin microbiomes with menopausal outcomes.[88,89] As seen in many other systems studied, there is a multidimensional relationship between menopause physiology and these microbiomes, such that it is often difficult to determine a cause-effect relationship; especially since both phenomena are affected by the aging, diet, lifestyle, and many other shared metabolic pathways. For instance, metabolic activities derived from gastrointestinal microbes are critical for the final removal of endogenous estrogens, and as discussed below, are vital for the bioactivation of most phytoestrogens.[90]

One particular area of research has focused on the association between various characteristics of the vaginal microbiota and genitourinary symptoms during menopause; a link that is thought to be related to the abundance of certain *Lactobacilli* species and their ability to help maintain a lower vaginal pH.[91,92] The supplementation of various probiotics (oral, or sometimes by vaginal suppository) has been partially successful in reducing some of the GMS experienced in post-menopausal women, though less effective at reducing VMS.[93] Clinicians should always be mindful of the status of the various microbiomes in all women, but particular investigation of the gastrointestinal and vaginal microbiomes is warranted. in women experiencing GMS or who are at risk for other metabolic disorders tied closely to GI dysbiosis. While recommendations for specific prebiotics or probiotics is premature based on the limited published data, it seems likely that microbiome modulation through diet, probiotics, prebiotics and the reduction of factors that contribute to dysbiosis (e.g., antibiotic use, proton pump inhibitors, overuse of laxatives, etc.) will result in favorable outcomes for many women during and after menopause.

Non-Pharmacological Therapies for Menopause

While the risks associated with aging (generally) and dramatic hormone changes (specifically) in menopausal women may be cause for considering pharmacological therapy, many women going through this transition prefer to use non-pharmacological therapies to reduce the symptoms commonly associated with menopause. Here, we summarize the evidence for commonly used non-pharmacological agents; mostly oral therapies that are classified as dietary supplements in the United States (or similarly regulated in other countries); focusing mainly upon their affects upon VMS and GSM.

Supplemental Vitamins and Minerals

Compared to other factors that influence nutrient status such as diet quality, digestion and absorption efficiency, bowel transit time, metabolic needs, nutrient transport efficiency, and the use of drugs that impede nutrient absorption, menopause itself is only a minor factor in directing the need for vitamin and mineral supplementation. Nonetheless, there are a few nutrients that are associated with vasomotor symptoms during menopause which clinicians should be aware of as they make their assessments and recommendations. Foremost amongst these is the hormone-like nutrient, **vitamin D**. As one would expect, menopausal women frequently present with insufficient vitamin D status, and low vitamin D status has been reported to increase VMS, GSM, osteoporosis, and cardiometabolic events in postmenopausal women.[94-98] In keeping with our overall position, we recommend a serum 25(OH)D target goal of 30 ng/mL (75 nmol/L) for all patients and suggest that serum 25(OH)D levels between 40-70 ng/mL (100-175 nmol/L) may be needed to optimize various vitamin D-related physiological processes that prevent chronic health conditions; a level that is likely to require regular supplementation of vitamin D3 (3,000-5,000 IU/day may be needed to sustain target vitamin D status). Nonetheless, intervention trials using vitamin D supplementation with menopausal symptoms as the primary endpoint are limited, so specific recommendations for this outcome cannot be made. Most other vitamins and minerals (i.e., status or supplementation) linked with benefits during menopause are typically associated with other non-VMS risk factors such as osteoporosis (e.g., calcium, vitamin K, magnesium, etc.) or cardiovascular health (e.g., folate, magnesium, vitamin B6 etc.); though mixed results have been published using vitamin E supplementation for some vasomotor symptoms.[99] We recommend that clinicians evaluate each patient's nutrient status and vulnerabilities in relation to the overall health goals, and make dietary and nutrient supplementation recommendations accordingly.

Fatty Acids

Fatty acids represent a wide-range of hydrocarbon molecules which are used for a variety of metabolic and signaling functions in the body. While some fatty acids can be synthesized by humans, many important fatty acids must be consumed in the diet (i.e., essential fatty acids) or are mainly provided by the diet (e.g., oleic acid, eicosapentaenoic acid/EPA and docosahexaenoic acid/DHA). In the past few decades, researchers have investigated the intake and status of most fatty acids in relation to a wide-range of health and disease conditions, including various menopause-related outcomes. Omega-3 fatty acids (e.g., linolenic acid, EPA, DHA, etc.) are known to have many therapeutic benefits and may benefit menopausal women by reducing cardiometabolic risk, cognitive decline, depression and osteoporosis.[100,101,102] However, results from

studies using omega-3 fatty acid supplementation for the reduction of VMS in menopausal women have been equivocal.[103] Nonetheless, we recommend that clinicians help menopausal women to achieve an omega-3 index (i.e., %EPA + DHA in RBC membranes) of 8% through diet and supplementation to maximize their overall risk reduction, irrespective of their VMS severity.[104,105]

The other fatty acid that is often noted for its effect on female menstrual cycle or menopause-related difficulties is gamma-linolenic acid (GLA, an omega-6 isomer [18:1:n6] of the omega-3 alpha-linolenic acid). Historically, GLA is most commonly delivered by consuming the seed oil of Evening primrose (*Oenothera biennis*) which contains 8-14% GLA or Borage (*Borago officinalis*) which contains 15-22 % GLA; though black current (*Ribes nigrum*) seed oil is also used and contains ~15% GLA. However, while these GLA-containing oils have been popular in Western herbal traditions (especially evening primrose oil), the limited published research related to their ability to mitigate menopausal symptoms does not allow us to make a recommendation for this indication.[106,107]

Phytonutrients and Botanicals for Menopausal Symptoms

The most common category of non-pharmacological therapy for menopausal symptoms (i.e., VMS and GSM) are plant-derived compounds consumed as foods, botanical (herbal) preparations or concentrated phytonutrients. Many of these remedies have been used for many centuries as part of an indigenous herbal tradition (e.g., traditional Chinese medicine, Ayurveda, Western herbalism, etc.); though comparatively few have been investigated using recent validated scientific measures for evaluating their efficacy in menopausal women (i.e., using guideline definitions and outcomes measures). However, while many herbal preparations which are viewed as having great efficacy within their traditional medicinal setting show limited statistically significant benefits when evaluated by modern diagnostic and clinical trial methods, this should not be construed as a lack of efficacy within their original model of use. Nonetheless, we focus below on those botanicals and phytonutrients that are commonly used and researched for their ability to alleviate menopausal symptoms- mostly outside of their indigenous use, if such exists. We first start with a class of compounds that are found in a variety of different plants, some of which are further detailed in their own section below.

Dietary Phytoestrogens

Phytoestrogens are plant-derived molecules that are able to activate or inhibit processes in which estrogen plays a role.[108] Several different mechanisms may be involved, such as weak but direct binding to estrogen receptor molecules (the stricter definition of a phytoestrogen), binding or inhibiting secondary binding molecules like sex hormone binding globulin (SHBG), or effects on hypothalamus or pituitary signals that alter estrogenic secretion. Very often, phytoestrogens have structures that are remarkably similar to the endogenous estradiol molecule which led some to make the comparison (therapeutically and mechanistically) to selective estrogen receptor modulators (SERMs).[109]

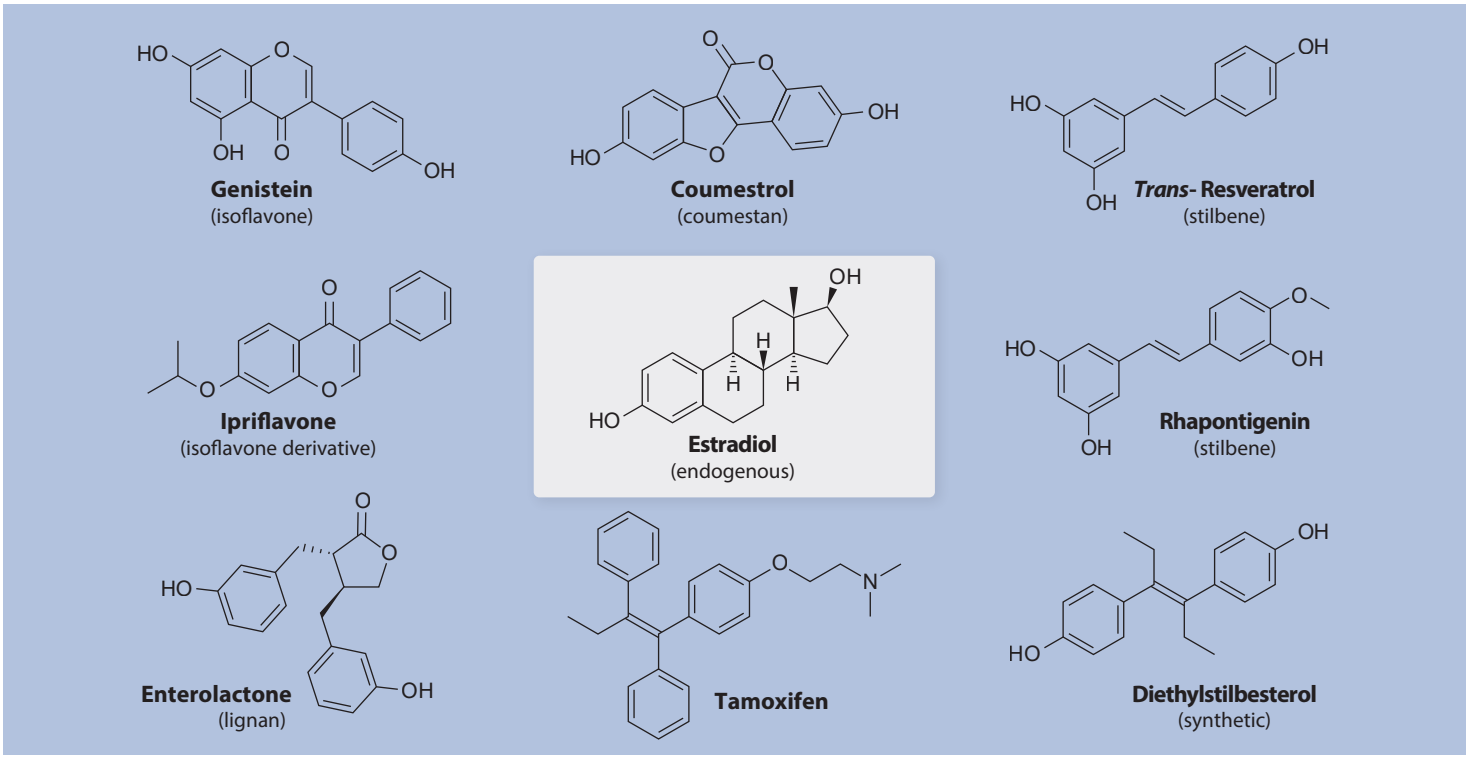

Figure 3: Molecular Structures of Select Phytoestrogens. Displayed here are the molecular structures of common phytoestrogens and several synthetic analogs or SERMs. The endogenous estradiol (E2) is shown for comparison.

There are three main classes of phytoestrogens: isoflavones, coumestans, and lignans. Plants that contain high amounts of phytoestrogens include soy (*Glycine max*), red clover (*Trifolium pratense*, high in biochanin A), alfalfa (*Medicago sativa*) and flaxseeds (*Linum usitatissimum*, the highest source of dietary lignans), though many other botanicals produce phytoestrogenic compounds. Figure 3 shows representative molecules in each class as well as derivative molecules used therapeutically. The most researched and widely available phytoestrogens are those found in the soybean. Soybeans contain 1-2 mg of isoflavones per gram of soy protein, approximately 60% of which is genistein, 30% daidzein, and 10% other isoflavones. Epidemiological and interventional studies suggest that the intake of soy and isolated soy isoflavones (as supplements) can positively influence menopause related symptoms and risks.[110] In the late 1990s, the Menopause and Osteoporosis Center in Italy conducted an experiment in which they divided 104 postmenopausal women into two groups: one to receive 60 grams of isolated soy protein (containing 76 mg isoflavones) or 60 grams of casein (no isoflavones) each day for 12 weeks.[111] Each patient was assessed at week 4, 8 and 12 by diary entries of menopausal symptoms according to the Kupperman index. The soy group showed a significant reduction in hot flash frequencies when compared to baseline and placebo (casein). A similar study was performed using soy isoflavone extracts standardized to contain genistein and daidzein (50 mg of a 1:1 mixture per day) a few years later. They found a significant decrease in both the number and severity of hot flash episodes over the 12-week study period.[112] In the past two decades, a vast amount of research has been conducted to understand the role that soy (and soy isoflavones) plays in affecting the biological changes and risks triggered by menopause. However, when systematic reviews are conducted to synthesize the many studies that have attempted to understand the association between soy isoflavones and menopause-related outcomes (VMS, GMS, cancer risk, CVD risk, osteoporosis risk, etc.), their results are difficult to convert into specific soy-based recommendations (of types, doses, duration of use, and expected outcomes).[113]

This conundrum is likely due to many phenomena, including the widely different research approaches taken to understand the soy-menopause relationship. However, a major factor is this relationship is one that is fundamentally linked to the metabolism of almost all polyphenolic compounds in the diet. Once ingested, phytoestrogens are metabolized in the gastrointestinal tract to other polyphenolic compounds, a process that is dependent on a person's gut microbiota.[114] In fact, research shows that the ability to convert certain polyphenols into their bioactive metabolite is dependent on the abundance of certain species of bacteria in a person's microbiome; which has been dubbed their polyphenol-microbiome metabotype.[115,116] Importantly for our discussion here, soy isoflavones (i.e., genistein, and daidzein) are metabolized to equol, the putative bioactive estrogenic compound, only in individuals with an abundance of certain bacteria in their GI tract; often referred to as equol-producers (see Figure 4).[117] And even though a person's equol-producer metabotype is not the only factor in determining their overall benefit when consuming dietary soy or isolated soy isoflavones, this factor has only recently become a criteria for inclusion/exclusion/analysis of such clinical studies to allow us to consider this factor. Interestingly, oral equol supplementation has been shown to improve VMS symptoms in many, though not all, non-equol producing menopausal women.[118]

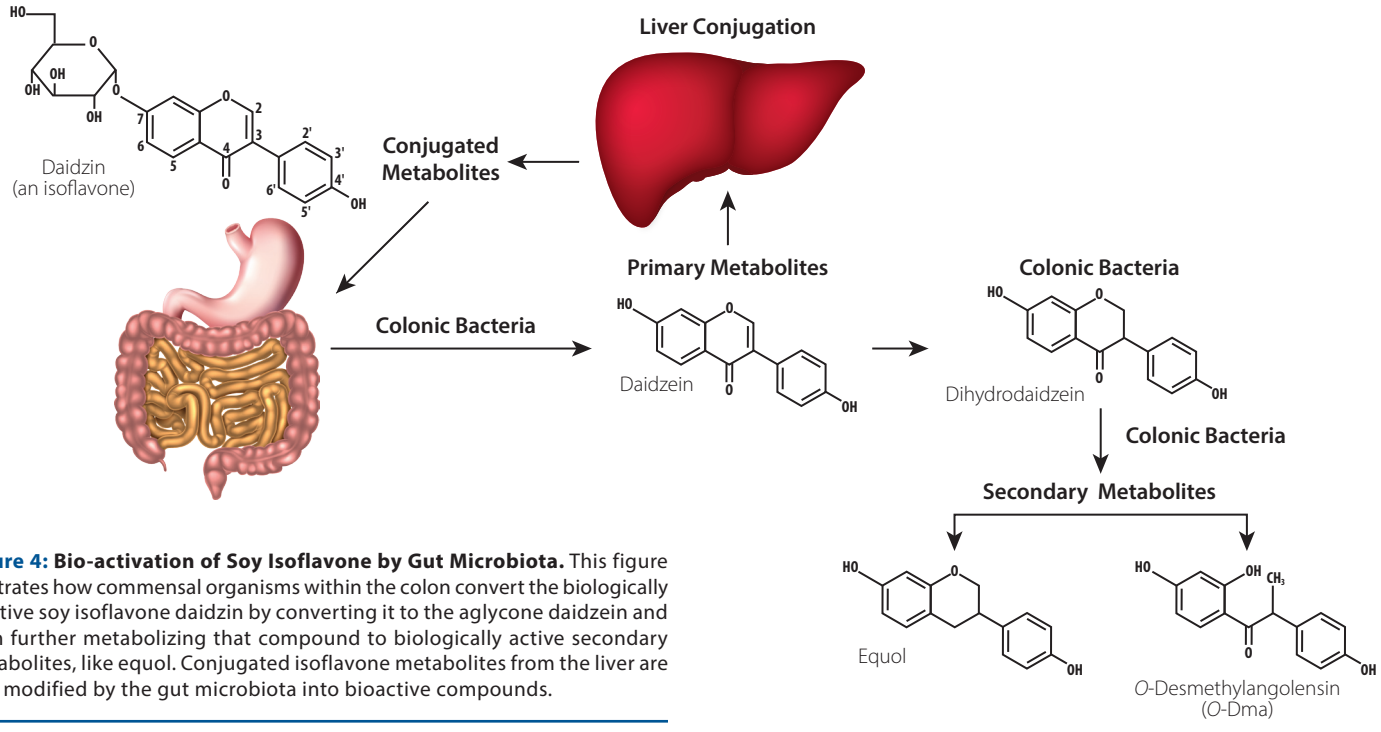

Figure 4: Bio-activation of Soy Isoflavone by Gut Microbiota. This figure illustrates how commensal organisms within the colon convert the biologically inactive soy isoflavone daidzin by converting it to the aglycone daidzein and then further metabolizing that compound to biologically active secondary metabolites, like equol. Conjugated isoflavone metabolites from the liver are also modified by the gut microbiota into bioactive compounds.

Perhaps just as important for clinicians is the question of whether specific therapies can alter or change the metabotype such that an equol non-producer can become an equol-producer, and thus alter their potential benefit from soy isoflavone intake. Equally significant is the potential role that other factors that affect gut microbiome stability (GI infections, antibiotic overuse, proton pump inhibitor use, gastrointestinal hyperpermeability, etc.) have in influencing the conversion of plant polyphenols into their effective bioactive metabolites. Finally, it is important to understand that epidemiological studies that link long-term soy intake with reduced risk (e.g., breast cancer), may not translate to interventional use of soy supplementation during menopause for risk reduction. For instance, epidemiological and animal-model studies suggests that soy's breast cancer prevention stems from early (pre-pubertal) exposure to isoflavones that affects the proliferative potential of these tissues in later years.[119] Most all of these issues apply to isoflavones found in red clover as well, preparations of which have had mixed benefits when studied for their ability to ameliorate VMS and other symptoms and risks associated with menopause.[120]

Dong Quai

Danggui (Chinese Angelica root; Dong quai; *Angelica sinensis*), is a widely used remedy in Asia for a variety of female conditions, and has become popular as an herbal remedy in Europe and the United States.[121] Traditionally, dong quai is thought to have a balancing or tonic effect on the female hormonal system, as well as a beneficial effect on the cardiovascular system. The roots contain a number of volatile oils and coumarins, many of which have been shown to have biological activity. The coumarin, ligustilide, is often used as a standardizing component when dong quai is made into powdered extracts, though there is debate about whether it should be viewed as the primary active component or simply a marker of extract strength.[122] However, dong quai is most often combined with other ingredients when used traditionally (e.g., in Traditional Chinese medicine/TCM); including its common combination with the root preparations of *Astragalus membranaceus* (this combination is known as Danggui Buxue Tang).[123]

Not surprisingly then, the evaluation of dong quai preparations (especially as monotherapies) outside their TCM framework, has been disappointing. [124] For instance, one early report that evaluated dong quai's ability to reduce hot flashes and improve vaginal and endometrial indices over a 24-week period failed to show any statistical improvements in these measures.[125] The failure of dong quai in this study could have stemmed from a number of issues. Primarily, the diagnostic paradigms between TCM and Western medicine are sufficiently different to make such a single preparation of dong quai at these doses (a powdered aqueous extract equivalent to 4.5 grams of root/day) difficult to assess these findings. Therefore, since there is a lack of sufficient evidence to guide the use of dong quai preparations outside their traditional use (i.e., TCM), it is difficult to make specific recommendations on the types, doses and expectation of the various formulas in which it is contained for menopausal protocols. Nonetheless, dong quai preparations should be considered safe and have a long history of positive reports (though anecdotal) by clinicians familiar with its use- or in formulation with other botanicals.

Black Cohosh

Black Cohosh (*Actaea racemosa*, aka: *Cimicifuga racemosa*) is a plant native to eastern North America; the root and rhizome portion of which had been used by Native Americans who dubbed it "squaw root", long before its introduction to settlers and Western herbalist. The pharmacological and clinical research of the past several decades has made black cohosh (BC) preparations one of the most widely used natural alternative to hormone replacement therapy in the Western world.[126] Though it had ranked in the top 10 of herbs sold in the US in 2018, it still remained in the top 20 in 2021 (when immune-specific ingredients surged during the Covid pandemic).[127,128] BC and its extracts have been recognized in many Western pharmacopoeias- specifically as a therapy for menopausal symptoms, including the American herbal Pharmacopoeia 2002, British Herbal Compendium 1992, British Herbal Pharmacopoeia 1996, British Pharmaceutical Codex 1934, Complete German Commission E monographs (where it is "approved for PMS, dysmenorrhea or menopausal (climacteric) neurovegetative (vasomotor etc.) ailments") and others.[126] In Canada, root preparations of BC are recognized as an active ingredient of registered natural health products intended for oral use with therapeutic uses such as pain associated with menstruation, relief of premenstrual symptoms, and relief of symptoms associated with menopause.[129]

The phytochemistry of black cohosh root is quite complex, including the presence of triterpene glycosides, a wide-range of phenolic acid, flavonoids, and alkaloids amongst over 130 chemical constituents identified.[130] Much of the research focus (and often presumed primary bioactive ingredients) has been given to a group of triterpene glycosides, namely actein, cimicifugosides and the often standardized component, 27-deoxyacteine.[131,132] While these compounds had been deemed estrogenic by some (i.e., binding to estrogen receptors), there are conflicting views as to the exact mechanism(s) that accounts for BC extract bioactivities (especially since most products are isopropanolic extracts containing dozens of BC phytochemicals).[133] Much of the historic debate rested on the presence or absence of the isoflavone formononetin; and whether its presence was caused by contamination of the extract or a result of differing extraction procedures or even sub-species differences.[134] Today, researchers believe that BC constituents likely signal non-estrogen receptors in the hypothalamus which account for much of its effects on VMS in menopausal women.[135]

Black Cohosh extracts have been sold as commercial preparations since the 1950s in Germany and have been studied for their therapeutic benefits in menopausal women for many decades, though mostly in German publications. In the early 1980s, the effectiveness of a black cohosh extract (standardized liquid) was studied using 629 patients with menopausal complaints.[136] After only 4 weeks of treatment, a clear improvement was documented by 80% of the women and after 6-8 weeks 50% reported a complete disappearance of symptoms. While this study lacked a placebo control group, these observations, along with no reported dropouts due to side effects, mirrored the anecdotal reports by hundreds of doctors in Germany for many years prior to this study. BC extracts were also compared with the common HRT therapy conjugated equine estrogens in randomized clinical trials.[137] In

one such trial, the first group was given a preparation of black cohosh extract (delivering 4 mg of 27-deoxyacteine) per day, the second group received 0.625 mg conjugated estrogens and group three received placebo. Results were scored using the Kupperman index, Hamilton Anxiety scale (HAMA), and indices on vaginal epithelial maturation. The results showed that the black cohosh group improved in all categories, when compared to placebo and even in relation to the estrogen group (recall that no progesterone was added). Again, in 2003, a BC extract preparation (CR BNO 1055- 40 mg/day) was compared to 0.6 mg of conjugated estrogens (CE) and placebo in 62 postmenopausal women over 3 months.[138] Their analysis showed that this preparation and dose of BC extract was equipotent as CE in reducing menopausal symptoms and measures of bone metabolism, with no increase in endothelium thickness (unlike the CE therapy).

Since these early studies, many more have followed with differing designs, CR preparations and outcomes measures. A recent review and meta-analysis of these reports has summarized the bulk of the published data concluding that "*Compared to placebo, isopropanolic Cimicifuga racemosa extracts (iCR) was significantly superior for treating neurovegetative and psychological menopausal symptoms, with a standardized mean difference of -0.694 in favor of iCR (p < 0.0001). Effect sizes were larger when higher dosages of iCR as monotherapy or in combination with St. John's wort (Hypericum perforatum [HP]) were given (-1.020 and -0.999, respectively), suggesting a dose-dependency.… Efficacy of iCR was comparable to low-dose transdermal estradiol or tibolone. Yet, due to its better tolerability, iCR had a significantly better benefit-risk profile than tibolone*".[139]

Understanding the proper dosing for black cohosh is confusing, since many clinical trials use different doses, or describe the used ingredient in different ways. The early publications seem to have used daily amounts of extract yielding 8 mg of triterpenes (usually measured as 27-deoxyacteine), sometimes described as 4 mg in divided doses; though often both are described as being "equivalent" to 20 or 40 mg of the herbal drug. Available products are described in numerous different ways, depending on whether the product is a non-extract powder, an extract ration (i.e., 5:1, etc.), a standardized extract, or based on the amount of triterpene glycosides alone. In general, a quality extract containing 2-4 mg of triterpenes daily is recommended. The safety of black cohosh and its herbal preparations have been confirmed in numerous studies, but this herb should not be confused with Blue Cohosh (*Caulophyllum thalictroides*), an herb that if used improperly, has potential toxic effects for women, and has no efficacy related to menopause.[140]

Rheum rhaponticum (Siberian rhubarb)

Rhapontic (or Siberian) rhubarb (*Rheum rhaponticum*) is one of nearly 60 different species in the *Rheum* genus, and has been used for culinary and medicinal purposes for many centuries in the various regions it grows naturally (mostly Central Asia, Russia, and parts of Europe).[141] Within the medicinal traditions of these regions, the roots of *R. rhaponticum* (and similar species) were used for a wide-range of ailments, much like a tonic, related to GI health, cardiovascular, liver, spleen, lungs, female reproductive disorders, and numerous topical applications.[141] However, after careful examination of the phytochemistry of *R. rhaponticum*, a wide-range of stilbenoids were identified, many of which were thought to have estrogenic or SERM potential (mostly rhapontigenin, resveratrol, pterostilbene and piceatannol derivatives- see Figure 3).[142,143]

The estrogenic potential and safety of *R. rhaponticum* root extracts began to be investigated in animal and human studies, primarily using an extract dubbed ERr731®, since the early 2000s.[144,145] The standardized extract ERr731® is a dried aqueous extract (~16 to 26:1), which contains rhaponticins, and their aglycones rhapontigenins; where the anthraquinone glycosides (i.e., emodin or rhein) have effectively been removed along with their laxative potential. An initial efficacy and safety study was published in 2006 using ERr731® (one capsule daily providing 4 mg of the extract) or placebo in 109 women with climacteric complaints.[146] This randomized trial lasted 12 weeks and the primary outcome was the change in Menopause Rating Scale II (MRS II) and other secondary measures of menopause-related quality of life. After the 12 weeks, the MRS II total score (including each component symptom) significant decreased in the women taking ERr731® compared to the placebo group ($P < 0.0001$). No between-group differences were noted for gynecological findings such as endometrial biopsies, bleeding, weight, blood pressure, pulse, and laboratory safety parameters between the treatment groups. A follow-up study allowed these same women to continue taking the ERr731® for an additional 48 or 96 weeks to test the long-term safety and efficacy of this extract.[147] Not only did they see further diminution of menopausal symptoms in subjects that continued taking the extract, but women who had previously been on placebo reached similar benefits after 18 weeks of ERr731® supplementation (compared to the previous 12-week randomized trial results). This same research group, using an identical clinical trial design, confirmed similar efficacy and safety outcomes of this extract in 112 perimenopausal women, defined as a break in cycle regularity during the previous 12 months or last menstruation at least 3 but no longer than 12 months prior.[148]

Compared to nearly all other botanical-based products used for menopause, *R. rhaponticum* has the advantage that nearly all the modern research has been performed using a single product at the same dose; allowing for a clear recommendation based on the commercial products available. In addition, the maker of the ERr731® have published post-market safety data collected from 1993 to 2014 (~150 million doses) in Europe and North America where it has gained the most popularity, recording just more than 200 adverse events (mostly GI upset and hypersensitivity reactions).[149] However, the most recent publication was an open-label study performed in 129 perimenopausal women living in India.[150] Similar to previous trials, they consumed one capsule containing 4 mg of the ERr731® extract daily for 12 weeks and saw a 67% drop (from baseline, $P < 0.001$) in the mean MRS II total score, with no adverse event.

Overall, these data show that *R. rhaponticum*, and especially the ERr731® extract, is both safe and effective for reducing VMS in perimenopausal and postmenopausal women; though we are

unaware of trials that compare it to HRT or other therapies. Benefits for anxiety, depression and well-being in this same population have also been reported for ERr731®.[151]

Other Botanicals

A survey of the published literature over the past few decades reveals the investigation of dozens of different botanicals and phytochemicals for their potential to relieve menopausal symptoms, including numerous recent reviews that summarize these publications.[152,153,154] These include nearly every herb that is popularly consumed, even if it has no history of traditional use for menopausal complaints. Those that have some positive clinical (or animal-model) results are usually those containing a putative phytoestrogenic compound, are known for their historic use in women's hormonal regulation, are considered adaptogenic, or are known for their ability to affect mood, anxiety or depression. Most of them are represented by one (or only a few) clinical studies, or are combined with other ingredients- both of which limit the ability to make specific recommendations. Here we list a few of the more commonly available botanicals that have published data, this list is by no means exhaustive.

Chaste Tree *(Vitex agnus castus)* extracts (from the ripened berries of the chaste tree) is most often used in premenopausal women experiencing irregular menstrual complaints.[155] One of the mechanisms proposed for vitex is an increase in LH secretion, which has a progesterone favoring effect. In the early stages of perimenopause, when cycle irregularities and slow persistent bleeding are associated with an estrogen dominant luteal phase, chaste berry extracts may be helpful in reducing symptoms of perimenopausal irregularity, but it has not been reliably used for VMS or other symptoms of menopause.

Resveratrol is a naturally occurring stilbene compound abundant in grapes and other plant foods, produced by these plants under stress to protect them from environmental or pathogenic attack. The trans configuration is the naturally occurring isomer, and is nearly identical to the synthetic estrogen diethylstilbesterol (see Figure 3). This unique structure has estrogenic, antiestrogenic, antioxidant (free radical scavenging) cardioprotective and anticancer activities.[156] The ability for resveratrol to act as a potential estrogenic agent, while at the same time protecting against cardiovascular risk factors, inhibiting various cancers and increasing antioxidant protection is a potent combination, especially for the combined risk factors associated with menopause.[157,158] Trans-resveratrol can be extracted from grapes or is also commercially available from rhizome extracts of *Polygonum cuspidatum*, a plant used in traditional Chinese medicine under the name huzhang (tiger cane).

Botanical adaptogens, also called tonics in some traditions, are herbs or herbal extracts that have a balancing effect on various body systems; often permitting the organism to withstand stressful conditions and increase overall resilience to immune or metabolic stress.[159,160] Several well-known adaptogens have been reported to have beneficial effects related to menopausal symptoms including **ashwagandha**, ***Panax ginseng***, ***Schisandra***, and **licorice**.[161,162,163] We should note that in the case of ginseng, there are many published studies evaluating its potential benefits with mixed results.[164] While there are many reasons for these findings, recent studies suggest there are numerous gut microbiome metabotypes in humans that affect their ability to utilize and metabolize the primary polyphenols in ginseng (i.e., ginsenosides); a likely confounder to many of the studies in menopausal women.[165] Botanicals known for their anxiolytic, antidepressive, or benefit for sleep have also been evaluated in clinical trials with reported beneficial effects. Some of these include various preparations of **valerian**, **hops**, **St. John's wort**, **saffron**, and **German chamomile**.[166-173] Others that are more common from their use as food include **chlorogenic acid** (from coffee beans), **fennel**, **fenugreek, maca,** and **common sage** (*Salvia officinalis*).[174-178]

Summary

The perceptions about how to view menopause (culturally, medically) vary widely. Some view it as a natural transition which requires navigating though unpleasant hormonal changes, while others view it as a pathophysiological condition requiring significant, and often pharmaceutical, intervention. Thankfully, there are many options for women to choose from, allowing them to prioritize the relief of unpleasant symptoms such as hot flashes, while reducing their risks for osteoporosis, cardiovascular disease, cancer and other chronic diseases of aging. Since the halting of the WHI trials (see sidebar on page 6), a debate continues to rage about the use of hormone replacement therapy- including the type of estrogens, the dose, delivery method, length of treatment and which women will be benefited or harmed. While it is clear that HRT, when prescribed by a competently trained clinician, can result in positive benefits; it is also clear that many women choose, for a variety of reasons, to avoid HRT altogether. Likewise, they may choose to avoid the growing number of pharmaceuticals that are, or will be, approved for vasomotor and other symptoms associated with menopause.

Fortunately, there are numerous lifestyle and non-pharmacological options which have been investigated for their ability to relieve menopausal symptoms and promote health during the climacteric years; many of which show great promise as we have shown. We should note however, with the exception of surgical menopause, the complex changes during the menopause transition are combined with numerous other challenges of the aging process itself. Thus, understanding that a patient's risks for osteoporosis, heart disease, cancer and dementia may be more tied to their past history of diet, stress, GI dysbiosis and exposure to environmental toxins than it is to the change in hormone production is an important reminder. Understanding how to help a woman prioritize and build her metabolic reserves as a means of resilience against chronic disease, while directing her toward therapies that significantly reduce those symptoms that significantly alter her quality of life through menopause, is achievable for today's clinician.

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