

Complementary Therapies for Menopause

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- Complete the questions at the end of the course.
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Faculty Disclosure

Contributing faculty, Chelsey McIntyre, PharmD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This introductory course is designed for psychologists whose patients are taking or are interested in using complementary therapies to manage symptoms of menopause.

Accreditations & Approvals



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Course Objective

The purpose of this course is to help psychologists in all practice settings increase their understanding of nutrients, lifestyle changes, complementary modalities, and herbal products that are often used during menopause.

Learning Objectives

Upon completion of this course, you should be able to:

1. List the most common health concerns associated with menopause.
2. Discuss the risks and benefits of certain vitamins and minerals in menopause.
3. Review the evidence for lifestyle changes and complementary modalities during menopause.
4. Describe the proposed and actual effects of phytoestrogens for menopause-related symptoms.
5. Explain the safety concerns associated with the use of herbs during menopause.




EVIDENCE-BASED
PRACTICE
RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

MENOPAUSE AND PERIMENOPAUSE

Natural menopause typically occurs between 40 and 58 years of age, with an average age of 51 years. Considering that the average life expectancy for a woman in the United States is 81.4 years, the average woman can expect to spend many years postmenopause. There are currently about 50 million postmenopausal adults in the United States [1].

Prior to entering menopause, a person must go through perimenopause (also called climacteric or the menopausal transition). This marks the transition between fertility and menopause when menses becomes less frequent. This process, which is often defined by the presence of various symptoms, may last for years. Menopause occurs when the menstrual cycle ceases for 12 consecutive months.



The National Institute for Health and Care Excellence recommends giving information to menopausal women and their family members or carers (as appropriate) that includes an explanation of the stages of menopause; common symptoms and diagnosis; lifestyle changes and interventions that could help general health and well-being; benefits and risks of treatments for menopausal symptoms; and long-term health implications of menopause.

(<https://www.nice.org.uk/guidance/ng23>. Last accessed January 23, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

COMMON SYMPTOMS

Symptoms of perimenopause can persist for weeks, months, or years, and symptom severity varies greatly. An early sign of perimenopause is irregular or prolonged menstrual bleeding that can become severe. As estrogen levels decline, vasomotor symptoms, including hot flashes and night sweats (hot flashes with drenching sweats), can also occur. These symptoms can interfere with sleep, which in turn can cause exhaustion, irritability, and altered mood. Up to 85% of people experience hot flashes with widely varying intensity and frequency [1].

Many people will also experience non-vasomotor symptoms, including:

- Anxiety
- Depression
- Difficulty with concentration and/or memory
- Headaches
- Incontinence
- Insomnia
- Irritability and mood swings
- Joint pain
- Loss of libido
- Tiredness
- Vaginal dryness

Long-Term Effects of Menopause

Menopause is associated with a number of other long-term changes in the body, including bone loss, weight redistribution, and muscle loss.

Bone Loss

The reduction in estrogen levels that occurs with menopause accelerates age-related bone loss. It is estimated that, on average, a person loses up to 10% of bone mass in the first five years after menopause [1].

Weight Redistribution

The hormonal changes that occur during menopause can change the way that weight distributes in the body. Those who are postmenopausal may be more likely to gain weight around the abdomen than around the hips and thighs.

Muscle Loss

The loss of muscle tissue that occurs with age can reduce overall metabolism, which can contribute to the accumulation of fat and weight gain. Age-related muscle loss occurs in all adults and is not necessarily tied to menopause. However, menopause may worsen the apparent effects of age-related muscle loss.

CONVENTIONAL TREATMENT

For many years, hormone replacement therapy (HRT) was a commonly accepted treatment during perimenopause and postmenopause. However, in 2000, the results from the Women's Health Initiative (WHI) study and the Heart and Estrogen/Progestin Replacement Study (HERS II) changed this approach. These studies found an association between the use of oral conjugated estrogen plus medroxyprogesterone and increased risk of myocardial infarction, stroke, venous thromboembolism, breast cancer, and gallbladder disease [2].

Since these initial findings were released, further studies, meta-analyses, and subgroup analyses have suggested that these risks may be limited to patients older than 60 years of age and may also be minimized with the use of alternate routes of administration, lower doses, and limited duration of use [2].

Although HRT still has a place in the management of menopausal symptoms, awareness of the risks associated with this option have limited the widespread and long-term use of systemic hormones. This has led many patients and healthcare professionals to consider alternative or complementary options.

BIOIDENTICAL HRT

Some patients may ask about compounded bioidentical HRT as a “natural alternative” to traditional HRT. However, this is a misconception. The term bioidentical simply indicates that the hormone has the same chemical and molecular structure as the endogenous hormone. Many of the prescription hormones that are approved by the U.S. Food and Drug Administration (FDA) for the management of vasomotor symptoms in menopause are also bioidentical. And although some of the hormones used in compounded products may be derived from natural sources, these natural hormones must still be converted to the active form in a laboratory [22].

In most cases, the dosing of compounded bioidentical HRT is based on unvalidated hormone testing, often using serum, salivary, or urine samples. The use of these tests to guide HRT dosing has not been validated in clinical research and is generally considered unreliable due to natural inter- and intra-individual variations in hormone levels [22]. Additionally, due to a lack of oversight, these compounded products carry a risk of under- or overdosing, lack of sterility, and the presence of impurities.

LIFESTYLE MODIFICATION

Menopause marks a significant change in the way that the body functions. Although each person responds differently to these changes, some general guidance on lifestyle modifications can significantly improve both short-term and long-term health.

NUTRITION

Nutrition can have an important impact on some of the long-term changes that occur after menopause. Ensuring adequate intake of certain nutrients can help reduce the risk of osteoporosis that comes with the rapid bone loss associated with menopause.

Calcium and Vitamin D

Although calcium and vitamin D have distinctive effects, they are often discussed in combination in relation to bone health, and for good reason. While calcium is the nutrient that directly builds and maintains bone, vitamin D is crucial to the appropriate absorption of calcium from the intestine. Thus, adequate vitamin D intake is an important component of adequate calcium intake [3; 4].

Due to age-related bone loss, the recommended dietary allowance (RDA) for both calcium and vitamin D increases with age (*Table 1*). And due to hormonal changes associated with menopause, the recommended intake for calcium increases faster for women than for men.

RECOMMENDED DIETARY ALLOWANCES OF CALCIUM AND VITAMIN D BY AGE AND SEX	
Population	Recommended Daily Dietary Allowance
Vitamin D	
Persons 1 to 70 years of age	600 IU (15 mcg)
Persons 71 years of age or older	800 IU (20 mcg)
Calcium	
Women 19 to 50 years of age	1,000 mg
Women 51 years of age and older	1,200 mg
Men 19 to 69 years of age	1,000 mg
Men 70 years of age and older	1,200 mg
Source: [3; 4] Table 1	

Whenever possible, these RDAs should be met by obtaining nutrients from the diet. In fact, due to a lack of strongly supportive evidence, guidelines do not recommend the routine use of calcium and vitamin D supplements during menopause [4].

For the prevention of fractures in community-dwelling adults, the U.S. Preventive Services Task Force (USPSTF) concludes that there is insufficient evidence to assess the balance of benefits and harms when calcium and vitamin D are supplemented in doses of at least 1,000 mg daily and 400 IU daily, respectively. The USPSTF also recommends against daily supplementation with lower doses of calcium and/or vitamin D [5].

The Bone Health and Osteoporosis Foundation (BHOFF) 2022 guidelines recommend a diet with adequate total calcium intake based on the RDA, incorporating calcium supplements if intake is insufficient. These guidelines also recommend maintenance of serum vitamin D sufficiency (a 25-hydroxyvitamin D level of 30–50 ng/mL), with the use of supplemental vitamin D as needed to achieve sufficient vitamin D levels [6].

The USPSTF guideline recommendation is based mostly on the results of the WHI study. This large study in postmenopausal women 50 to 79 years of age showed that although taking calcium 1,000 mg

plus vitamin D 400 IU daily for seven years modestly improves bone mineral density (BMD), it does not significantly reduce fracture risk. It is possible that this lack of effect may have been due to low adherence to the treatment regimen. In those who were at least 80% adherent, supplementation reduced the risk of hip fracture by about 29% [3; 5].

Clinical research on the use of calcium and vitamin D supplements specifically for the prevention of fractures is mixed and inconclusive. Although some research suggests that supplementation may modestly reduce the risk of fractures, the benefits appear to be greatest in those with existing osteoporosis, as well as the elderly and those who are no longer community dwelling [3; 4].

Additionally, some experts have expressed concerns regarding the risks of calcium supplementation.

Safety Concerns with Calcium Supplementation

There has been some concern that calcium supplementation may increase the risk of cardiovascular disease (CVD) in postmenopausal adults. Although meta-analyses of high-quality clinical research have not confirmed an association between calcium supplementation and CVD in the general population, a meta-analysis of research in postmenopausal adults did find that taking calcium for two to seven years, often in amounts over the RDA, increases the risk of CVD and coronary heart disease by 1.1–1.2 times when compared with control. However, many of these studies have been criticized for excluding patients who were also taking vitamin D, and other clinical research has not confirmed this finding [3].

There is also some concern that calcium supplementation increases the risk of urinary tract stones. The WHI study suggests that for every 273 patients receiving calcium supplementation over seven years, one additional patient will be diagnosed with a urinary tract stone. However, this finding has not been corroborated in other large clinical trials evaluating the long-term health effects of calcium supplementation [3].

Until more is known, remind patients not to take calcium supplements in doses exceeding their age-based RDA, and ensure that all patients have adequate intake of vitamin D.

Based on the available evidence and guideline recommendations, most postmenopausal adults should focus on obtaining calcium and vitamin D from the diet. However, for patients who are unable to obtain adequate intake from the diet, healthcare professionals should be well-versed on the use of supplements [3; 4].

Calcium Supplements

There are many different calcium supplements available on the market. Some of these supplements provide calcium alone, whereas others combine calcium with vitamin D. Although the body needs vitamin D to adequately absorb calcium, it is not necessary for vitamin D to be taken at the same time [3].

Calcium supplements are available in various salt forms, some of which provide greater amounts of elemental calcium. For example, calcium carbonate contains 400 mg of elemental calcium per gram, whereas calcium citrate contains 211 mg of elemental calcium per gram. The RDA for calcium is based on elemental calcium [3].

There may also be questions regarding the absorption of different calcium salts. For example, some early research suggested that calcium citrate may be better absorbed than calcium carbonate. However, a follow-up study using a highly sensitive tracer method found no significant difference in the absorption of calcium from either calcium citrate or calcium carbonate. Additionally, calcium from milk seems to be absorbed similarly to the calcium from supplements [3].

Calcium Absorption

The active transport system for calcium in the small intestine is easily saturated. Thus, calcium supplements are typically divided into two doses daily to increase absorption. It is also usually recommended to take it with food in doses providing no more than 500 mg elemental calcium [3].

In order to ensure appropriate calcium intake, educate patients on the difference between elemental calcium and calcium salt content. Also, encourage them to take calcium supplements with food in divided doses.

Vitamin D

Vitamin D supplements are available in two forms—D3 (cholecalciferol) and D2 (ergocalciferol). Although the RDA assumes that these forms are equivalent, some evidence suggests that vitamin D2 is less than one-third as potent as vitamin D3. Therefore, many experts now specifically recommend vitamin D3 [4].

For most patients, daily supplementation of 400–1,000 IU (10–25 mcg) is adequate to meet daily requirements. In fact, the BHOE recommends daily intake of 800–1,000 IU (20–25 mcg) for adults older than 50 years of age [4; 6].

Except in patients with confirmed vitamin D deficiency, caution against the regular use of very high doses. Over the long-term, regular use of high doses, such as those above the tolerable upper intake level of 4,000 IU (100 mcg) daily, can increase the risk of serious adverse effects such as hypercalcemia, kidney stones, and azotemia. Toxicity typically occurs when blood levels exceed 150 ng/mL [4].

Magnesium

Magnesium, which is crucial to the structural integrity of bone tissue, is another important nutrient for bone health. Magnesium deficiency can increase the formation and activity of osteoclasts, which resorb bone. Increased bone resorption causes release of magnesium and calcium from the bone, which can increase magnesium levels in times of deficiency [7].

No large prospective studies have been conducted to evaluate the benefits of magnesium supplementation for the prevention of osteoporosis. However, it is important for patients to ensure adequate intake of magnesium from the diet.

The daily RDA for magnesium is 320 mg for those 31 years of age and older. Many foods are rich in magnesium (e.g., whole grains, dark-green, leafy vegetables) and will allow most patients to attain this RDA [7].

Some patients may be at increased risk for magnesium deficiency due to the use of certain medications, including certain antibiotics, diuretics, some antineoplastic drugs, calcineurin inhibitors, and proton pump inhibitors (PPIs). Healthcare professionals should be aware of the medications most likely to increase this risk and counsel patients accordingly.

There is also interest in the use of magnesium supplements for the management of menopausal symptoms such as hot flashes. However, a large, high-quality study shows that taking magnesium oxide 800–1,200 mg daily for eight weeks does not reduce hot flashes when compared with placebo [7].

Proton Pump Inhibitors (PPIs)

Taking a PPI long-term, especially for longer than one year, has been linked to an increased risk of hypomagnesemia in observational research. Higher doses are associated with a two-fold increase in the odds of hypomagnesemia when compared with lower doses.

The American College of Gastroenterology (ACG) does not provide a recommendation related to monitoring magnesium levels in patients taking PPIs. However, other experts, including the FDA, recommend that serum magnesium levels should be checked at baseline and annually thereafter in patients who are likely to take a PPI long-term. In up to 25% of patients who develop hypomagnesemia, the PPI will need to be discontinued permanently to return magnesium levels to normal. In some patients, it is possible to continue the PPI and take a magnesium supplement concurrently to maintain magnesium levels [7].

Diuretics

Loop diuretics and, to a lesser extent, thiazide diuretics interfere with magnesium reabsorption in the kidneys, increasing urinary losses and reducing serum magnesium levels. Potassium-sparing diuretics, however, are also magnesium-sparing, and can therefore counteract the magnesium losses seen with loop diuretics and thiazides. Although the overall risk for magnesium deficiency with diuretics is low, patients taking multiple medications that can lower magnesium levels may be at increased risk [7].

Protein

Due to concerns regarding age-related muscle loss, adequate protein intake is also important after menopause. The RDA for protein in all adults 18 years of age and older is 0.8 grams/kg. However, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) actually recommends a higher protein intake for women older than 50 years of age. This recommendation calls for 1–1.2 grams/kg. This comes out to about 20–25 grams of protein per meal [8].

As with other nutrients, patients should be counseled to obtain adequate protein intake from a well-rounded diet whenever possible. Although protein supplements may be appropriate for some patients, most patients are able to obtain adequate protein by making healthy changes to their diet.

EXERCISE

Increased physical activity and exercise can be key to combatting the increased weight gain that is seen after menopause. In addition, it can help to reverse age-related muscle loss (sarcopenia) and even slow bone loss.

The Centers for Disease Control and Prevention (CDC) recommends that all adults older than 65 years of age [9]:

- Obtain at least 150 minutes of moderate-intensity activity per week, such as brisk walking. Alternatively, this can be replaced with 75 minutes of vigorous-intensity activity, such as hiking, jogging, or running.
- Participate in muscle-strengthening exercises at least two days per week.
- Participate in activities that improve balance at least three days per week.

Muscle-strengthening exercises can include a wide range of options and are not solely limited to weightlifting. Patients can also consider the use of resistance bands; exercises that use their own body weight for resistance, such as push-ups, sit-ups, and certain forms of yoga and Pilates; and even heavy gardening.

Balance exercises are more specific and involve activities such as walking backwards, standing on one leg, or using a wobble board.

If a patient has had only limited physical activity and is interested in initiating a new exercise program, encourage them to seek guidance from a physical therapist. To avoid injury, patients should also be evaluated before initiating a new exercise program involving compressive or contractile stressors (such as running or weightlifting) [9].

CAUTIONS

Some of the lifestyle changes that can be most beneficial during menopause may require patients to break some long-standing habits. These recommendations should be customized to each individual patient, as needed.

Smoking

Smoking is known to be detrimental to overall health and is also detrimental to bone health. Smoking cessation should be encouraged, when relevant, for all postmenopausal adults.

Alcohol

Moderate alcohol intake, which is defined as 0.5 to 2 alcoholic beverages per day, does not seem to have detrimental effects on BMD. However, alcohol intake in amounts greater than two drinks per day can be detrimental to bone health.

There is conflicting evidence on other possible long-term effects from regular alcohol use. While some research indicates that moderate alcohol intake may have health benefits, other research suggests that it may increase the risk for certain conditions. In general, encourage patients to limit alcohol intake. Some experts recommend reducing intake to no more than 0.5 to 1 drink per day.

There have been reports of increased severity of hot flashes with alcohol use. This association has not been evaluated in prospective research, but patients may consider reducing alcohol consumption and monitoring symptoms to determine whether this improves quality of life.

Caffeine

Caffeine increases the excretion of calcium in the urine. At excessive doses, this might affect bone health. According to evidence reviews conducted in the United States and Canada, healthy adults with adequate calcium intake are not at increased risk for decreased BMD, osteoporosis, or fractures as long as daily caffeine intake is limited to 400 mg (about four cups of coffee) [10].

It should be noted that about 8% of people may have a specific genetic variant of the vitamin D receptor (VDR)—the CC genotype. This genotype increases the risk for bone loss with caffeine use. Testing for this variant is not standard practice, although it is included in some vitamin D deficiency and nephrology gene panels and is also offered as a single gene test through some laboratories. If a patient is known to be carrying the CC genotype, caffeine intake should be reduced to 200–300 mg daily and calcium intake may need to be increased [10].

Some people have reported increased severity of hot flashes with caffeine use. This association has not been evaluated in prospective research, but patients may consider reducing caffeine consumption and monitoring symptoms to determine whether this improves quality of life.

Spicy Foods

Some patients may find that spicy foods trigger or worsen hot flashes. If patients are struggling with persistent and/or severe hot flashes, suggest trialing the elimination of spicy foods from the diet.

COMPLEMENTARY MODALITIES

In addition to lifestyle changes, some patients may also benefit from various complementary therapy modalities. These include options such as acupuncture, mindfulness, meditation, and yoga.

ACUPOINT THERAPIES

Acupoint therapies, which utilize concepts based in traditional Chinese medicine, have grown in popularity over recent years. These include acupuncture, acupressure, moxibustion, and acustimulation.

Although there is general interest in the use of these therapies for the management of menopause-associated hot flashes, only acupuncture has been studied for this purpose, and the research thus far is inconclusive. While some research suggests that acupuncture may reduce hot flash severity, other studies have not supported this finding. Also, a large clinical study evaluating the use of electroacupuncture, administered in 24 separate treatment sessions over eight weeks, found no benefit for symptoms of menopause, although patients did experience a modest improvement in quality of life [11].

For now, let patients know that the evidence supporting the use of acupoint modalities is unclear. However, there is no reason to expect safety concerns as long as the therapy is administered by a licensed practitioner using appropriate technique.

MINDFULNESS

Mindfulness, a practice derived from Buddhist theory, has also become popular for general well-being and the management of various symptoms. Mindfulness involves a purposeful attention and awareness of present thoughts, emotions, and sensations without evaluation or judgment of what is occurring.

Mindfulness-based stress reduction (MBSR) is a well-studied and standardized mindfulness practice. It usually includes eight weekly 2.5-hour sessions, as well as daily home recordings of mindfulness exercises and a half-day retreat after the sixth class. It includes three main components [12]:

- Didactic material that explains the concept of mindfulness
- Practicing mindfulness exercises during group sessions and at home
- Discussing and sharing MBSR experiences with a group

Clinical research in various populations has shown that mindfulness or MBSR is beneficial for anxiety, insomnia, and stress. Although it has not been evaluated specifically for these uses in perimenopausal or postmenopausal adults, it would be reasonable to consider this as a safe treatment option [12].

Anxiety

In general, mindfulness seems to modestly reduce anxiety, although benefits appear to be short-term. It is unclear how mindfulness or MBSR compares with other nonpharmacologic options.

Meta-analyses, small clinical studies, and observational research in patients with various forms of anxiety, or without diagnosed anxiety, show that practicing MBSR or modified MBSR improves anxiety severity when compared with baseline or no intervention. However, most research shows that MBSR does not continue to reduce the severity of anxiety immediately after or 3 to 12 months after treatment when compared with cognitive-behavioral therapy (CBT) or psychotherapy education [12].

Insomnia

Most research suggests that mindfulness improves sleep quality, although it might not be beneficial for other measures of insomnia and may not be more beneficial than other nonpharmacologic modalities.

A meta-analysis in patients with insomnia shows that mindfulness meditation improves total wake time and sleep quality, but not sleep onset latency, total sleep time, or sleep efficiency, when compared with control. Another meta-analysis of randomized controlled trials in adults with insomnia shows that practicing MBSR or modified MBSR for six to eight weeks improves sleep quality when compared with receiving education or CBT. A secondary analysis of a clinical trial in generally healthy adults also shows that practicing MBSR for eight weeks improves sleep scores when compared with no intervention, but not when compared with exercise [12].

Stress

Research suggests that mindfulness may reduce stress in patients with various medical conditions, although it is unclear if it is beneficial for general stress.

Some clinical studies in patients being treated for cancer show that MBSR and other mindfulness-based therapies reduce stress and stress-related symptoms such as depression and quality of life. A small clinical study in patients with solid organ transplants shows that completing an MBSR program improves anxiety, depression, and sleep quality for up to one year when compared with a peer-led health education program. Similarly, a small clinical trial in women with infertility shows that an eight-week mindfulness-based program reduces stress when compared to baseline [12].

Research on the use of mindfulness specifically for the management of menopausal symptoms is limited. One small clinical study shows that practicing MBSR reduces menopause-related stress, sleep disturbance, and symptom severity when compared with a control group that was placed on a wait list. In the MBSR group, those that practiced at home more frequently had greater reductions in symptom severity. However, there was no improvement in pain or physical function [12].

Another small study shows that eight weekly sessions of MBSR modestly improves quality of life after menopause for up to three months after treatment when compared with control. Improvements were noted in psychosocial, physical, and sexual domains [12].

YOGA

The practice of mindfulness should not be confused with yoga, which may sometimes incorporate components of MBSR. Yoga is a key aspect of Ayurvedic medicine, a traditional system of medicine that originated in India. Yoga uses several exercises involving controlled breathing, meditation, and body posturing. Many different styles of yoga exist that use a variety of techniques at a range of intensities. However, Western yoga practice most often focuses on physical yoga poses specifically [13].

Effects in Menopause

Clinical research has found that yoga is beneficial for reducing feelings of perimenopause-related anxiety and depression. Yoga also seems to be beneficial for alleviating menopause-related hot flashes, sleep disturbances, and psychological, somatic, and urogenital symptoms when compared with no intervention. These beneficial effects appear comparable to those seen with other forms of exercise [13].

It is important to note that yoga is also recognized as a form of both muscle-strengthening and balancing exercises, which are recommended for all older adults. Considering that yoga has also shown benefit for the improvement of many menopause-related symptoms, it should be considered as a complementary treatment modality for those in perimenopause and post-menopause.

Safety

Yoga is generally considered safe, with temporary musculoskeletal pain as the most common adverse effect. However, for adults with limited prior exercise, mobility concerns, or other serious health issues, encourage a consultation with a trained practitioner prior to participation in yoga [13].

HERBAL THERAPIES

Some patients may also inquire about the use of herbal therapies for menopause. While a number of herbal therapies are touted online, only a small number of these options have been adequately evaluated in clinical research.

PHYTOESTROGENS

Most of the herbal therapies promoted for symptoms of menopause are classified as phytoestrogens, or “plant estrogens.” The three main kinds of phytoestrogens are isoflavones, lignans, and coumestans. Of these, isoflavones are the most potent and also the most common.

Phytoestrogens are not structurally related to estrogen. Instead, they contain a phenolic ring that allows for binding to estrogen receptors. These chemicals are 100 to 10,000 times weaker than endogenous estrogen, and, depending on the tissue type and location in the body, phytoestrogens can act as estrogens or antiestrogens. This is similar to selective estrogen receptor modulators (SERMs) [14].

The estrogenic activity of phytoestrogens also appears to vary with the level of endogenous estrogen. In premenopausal adults with normal endogenous estrogen levels, isoflavones found in soy exhibit an antiestrogen effect, since they can displace endogenous estrogen from receptors. In postmenopausal adults with low endogenous estrogen levels, soy isoflavones are more likely to act as weak estrogens.

However, not all plants that contain phytoestrogens have clinically relevant estrogenic activity. The following section will review the evidence for the most well-studied and commonly used options.

Soy (*Glycine max*)

Vasomotor Symptoms

A large body of evidence suggests that consuming soy can decrease the frequency and severity of hot flashes. Improvement seems to be greater in those with a higher frequency of hot flashes at baseline.

The daily doses used in these studies include soy protein 15–60 grams, providing 34–100 mg isoflavones, as well as extracts providing 35–200 mg isoflavones. Higher isoflavone doses of 100–200 mg and higher frequency of dosing intervals seem to have greater benefit. Similarly, the amount of genistein found in these products may influence outcomes, with higher doses associated with more consistent benefits [14].

Soy has also been compared to conventional HRT, with most research indicating that soy isoflavones may have a similar or modestly reduced effect, and a slower onset of action, when compared with HRT. There is some speculation that the benefits of soy isoflavones for this purpose may partly depend on the conversion of daidzein to equol, which will be discussed in further detail later in this course.

Urogenital Symptoms

Three small clinical trials show that taking supplemental soy providing 50–118 mg of isoflavones daily for 12 weeks reduces urogenital symptoms when compared with a control group. However, this benefit may not occur in patients consuming soy as part of the diet. A small clinical study in perimenopausal patients shows that a soy-rich diet does not relieve urogenital symptoms, including vaginal dryness, vulvar itching, and urinary incontinence, when compared with a soy-free diet [14].

A vaginal gel containing soy extract has also been evaluated. One small clinical study suggests that applying one gram of soy extract 4% vaginal gel daily for 12 weeks reduces vaginal dryness and pain during sexual intercourse and improves vaginal epithelial thickness when compared with placebo [14].

Bone Health

Most clinical research suggests that soy protein or soy extract containing 75–90 mg of isoflavones can increase BMD, or attenuate BMD loss, in peri- and postmenopausal adults when compared with control. Also, an observational study in postmenopausal Asian adults has found that consuming higher dietary soy protein is associated with a lower risk of developing fractures when compared with lower amounts [14].

However, not all research has shown a benefit of soy protein on BMD in postmenopausal adults. These conflicting findings may be due to differences in formulations, concomitant treatments, or patient populations. Additionally, these effects may be modulated by the conversion of daidzein to equol.

Safety

Soy is well tolerated when consumed as part of the diet or as a supplement. The most commonly reported adverse effects are bloating, constipation, diarrhea, and nausea. In postmenopausal adults, specifically, soy isoflavone supplements have also been shown to increase the rate of insomnia.

As with other phytoestrogens, there have been many concerns raised over the years regarding the association between soy intake and the risk for long-term health issues. However, most research in postmenopausal adults indicates that these concerns are not likely to be clinically relevant [14].

Population research has found that soy, as part of the diet or as a supplement, is protective against breast cancer. This research has consistently found that a high-soy diet in Asian and Asian-American women is associated with a reduced risk of breast cancer. However, the amount of soy consumed in a Western diet, even among those who consume the highest amounts of soy, was not found to have a preventative effect [14].

Despite some early research suggesting that soy supplements might stimulate the growth of breast tissue, there does not seem to be a concern for increased risk of breast cancer with the use of soy, even in those with a history of breast cancer. One clinical study shows that taking a tablet containing 50 mg soy isoflavones daily for 12 months does not alter mammographic or breast MRI tissue density in those at high risk of breast cancer, those with non-endocrine-treated breast cancer, or those previously treated for breast cancer and without recurrence [14].

Population and clinical research suggest that soy foods do not have a proliferative effect on endometrial cells. In fact, increased dietary intake of soy and other phytoestrogens is associated with reduced endometrial cancer risk.

Soy supplements also do not seem to increase risk for endometrial cancer. Taking high doses of soy isoflavones, such as 150 mg daily for five years, might increase the risk of simple endometrial hyperplasia. However, there is no evidence that soy isoflavones increase the risk of atypical hyperplasia, which is a greater risk factor for the development of endometrial cancer [14].

There is some evidence that soy intake can inhibit thyroid hormone synthesis and increase the secretion of thyroid-stimulating hormone (TSH) in postmenopausal adults. However, this risk seems to be limited to those with low iodine levels. In postmenopausal patients with normal levels of iodine, taking a soy extract for six months did not affect thyroid hormone levels [14].

Interactions

Soy may potentiate the effects of antidiabetes or antihypertensive medications, potentially increasing the risk of hypoglycemia or hypotension. There is also some concern that soy isoflavones, including genistein and daidzein, might antagonize the anti-tumor effects of tamoxifen. Although research on this topic is conflicting, advise patients requiring treatment with tamoxifen to avoid the use of soy supplements [14].

Summary

It is important to remember that soy is also a good source of dietary protein and has been shown to improve muscle strength in older adults who are also participating in exercise. It does not seem to provide any additional benefit over other sources of protein, such as whey, beef, or dairy, for this purpose. However, soy protein as a source of soy isoflavones may offer various benefits for many postmenopausal patients [14].

Equol

Equol is an isoflavone that is produced when daidzein, a soy isoflavone, undergoes biotransformation. This is catalyzed by specific intestinal bacteria, including *Asaccharobacter celatus* and *Slackia isoflanoni-convertans*. The conversion of soy to equol is thought to be approximately 8–15 mg of equol for every 6–11 grams of soy consumed daily [15].

Equol is chemically classified as a nonsteroidal estrogen. The S-enantiomer of this chemical (S-equol) is the only form produced by humans. It has demonstrated an affinity for the beta estrogen receptor that is approximately 20% that of estrogen. Beta estrogen receptors are found in the heart, vasculature, bone, and bladder, but not the uterus [15].

Not all humans host the bacteria necessary to convert daidzein to equol, and thus, not all humans are considered “equol producers.” Approximately 40% to 60% of Japanese, Korean, and Chinese adults, as well as vegetarians from Western countries, are capable of producing equol. Conversely, only about 20% to 30% of Western, non-vegetarian adults produce equol. It is not entirely clear what drives these differences, although some researchers have hypothesized that the types of soy foods consumed by each of these groups may play a role [15].

There is speculation that some of the variable benefits of soy seen in clinical trials are related to the equol-producing status of study participants. However, this has not been definitively confirmed in clinical research.

Effects in Menopause

Multiple clinical studies show that taking S-equol 10–30 mg daily modestly reduces symptoms of menopause, including hot flashes, and improves mood when compared with placebo. Most of this research has been conducted in Japan; however, one clinical trial has evaluated equol in North Americans. In this study, taking S-equol 10 mg, 20 mg, or 40 mg daily for two months resulted in similar reductions in hot flash frequency as a soy isoflavone tablet containing 24 mg daidzein, 22 mg genistein, and 2 mg glycitein. The lack of a placebo group limits the validity of these findings [15].

There is also interest in using equol for various other purposes during menopause, including for improving BMD and reducing facial wrinkles. However, the available research is exploratory, and findings are inconclusive.

Safety

Equol is generally well tolerated. As with soy, research does not suggest that taking equol increases the risk for breast or endometrial cancer. However, laboratory research suggests that equol may inhibit the binding of estradiol to serum proteins, which could theoretically increase the concentration of free, bioactive estrogen and increase the adverse effects of estrogen replacement therapy [15].

Black Cohosh (*Actaea racemosa*)

Black cohosh, an herb that is native to eastern North America, appears to have estrogen-like effects, although these effects are exerted via an unknown mechanism. Laboratory research suggests that black cohosh extracts do not bind to estrogen receptors or upregulate estrogen-dependent genes. However, it might have SERM-like activity, exerting estrogenic effects in some tissues and antiestrogenic effects in others. Clinically, black cohosh does not appear to affect levels of hormones such as estradiol, luteinizing hormone (LH), or follicle-stimulating hormone (FSH) [16].

Effects in Menopause

Research on the use of black cohosh for vasomotor symptoms of menopause has primarily evaluated a specific branded product (Remifemin). When taken in doses of 40–127 mg daily for up to 12 weeks, this product reduces symptoms of menopause and hot flash frequency when compared with placebo. It also seems to be comparable to certain forms of HRT, including low-dose transdermal estradiol 25 mcg every week, conjugated equine estrogens 0.625 mg daily, or tibolone 2.5 mg daily [16]. (Tibolone is a synthetic steroid with estrogenic properties that is approved for use in Europe.)

However, research evaluating other proprietary black cohosh extracts has been less consistent. One extract (Klimadynon/Menofem) taken as 40 mg daily for 60 to 90 days does not reduce menopausal symptoms when compared with control groups. However, another extract (Remixin) taken as 40 mg daily for six months modestly reduces hot flashes and night sweats when compared with fluoxetine 20 mg daily. Studies of non-branded black cohosh extracts have been mostly negative, suggesting a lack of benefit on vasomotor symptoms [16].

Although there is speculation that the benefits seen with Remifemin may be due to bias introduced by industry funding, it is also possible that conflicting findings may be related to cultivation and processing methods. Remifemin is standardized across batches to triterpene glycosides, whereas the contents of other products are not clearly defined. Additionally,

some non-standardized black cohosh products have been found to contain other species of *Actaea*, which may have different effects [16].

There is also interest in the use of black cohosh for a variety of other purposes during menopause, such as anxiety, bone health, cognitive function, and cardiovascular risk. However, clinical research to date has shown no benefit for these uses.

Safety

Black cohosh seems to be generally well tolerated, with limited adverse effects reported in clinical studies. However, there are some specific safety concerns that may be relevant for certain patients.

In studies with Remifemin, some patients reported vaginal bleeding or breast tenderness; however, the frequency of these events seems to be less than that of tibolone [16].

There has been some concern about the risk of endometrial hyperplasia with black cohosh. Most clinical research in postmenopausal adults has found that taking black cohosh for up to 12 weeks does not increase endometrial thickening or the presence of superficial cells. However, the long-term effects of black cohosh remain unclear.

There is some concern that black cohosh might cause hepatotoxicity or hepatitis. These effects have not been seen in clinical studies, but multiple case reports have suggested a correlation. Many of these cases are poorly documented, and it is unclear whether black cohosh was contaminated or whether it was the probable cause for liver issues. Regardless, the U.S. Pharmacopeia (USP) recommends labeling on black cohosh products regarding potential liver toxicity. Until more is known, consider monitoring liver function during black cohosh use [16].

Interactions

There is conflicting information regarding the effect of black cohosh on cytochrome P450 (CYP) 2D6 metabolism. Some clinical research suggests that black cohosh might modestly inhibit CYP2D6. However, a clinical study evaluating Remifemin shows that taking 40 mg twice daily does not inhibit

CYP2D6 metabolism in healthy volunteers. Until more is known, use black cohosh with caution in patients taking drugs metabolized by CYP2D6 [16].

Summary

Black cohosh may have modest benefits for some postmenopausal adults. However, only certain extracts seem to exert these benefits, and individual risk factors should be evaluated prior to use.

Chasteberry (*Vitex agnus-castus*)

Chasteberry is a deciduous shrub that is native to the Mediterranean and Central Asia. The plant has a long history of use for menstrual and menopausal conditions, as well as for reducing sexual desire. This contributed to its nickname as the “chaste tree.”

Laboratory research suggests that chasteberry has activity at beta estrogen receptors. It is also thought to exert indirect effects on various neurotransmitters, including dopamine [17].

Effects in Menopause

One large clinical study shows that taking a chasteberry extract 15 mg twice daily for eight weeks improves some menopausal symptoms, including anxiety and vasomotor dysfunction, by 76% and 88%, respectively, when compared with baseline. However, there was no effect on depression or sexual dysfunction. Due to the lack of a comparator group, the clinical relevance of these findings is unclear [17].

Safety

Chasteberry is generally well tolerated, although it has been reported to cause diarrhea, fatigue, headache, insomnia, nausea, skin irritation, stomach pain, and vomiting [17].

Summary

The available evidence does not support the use of chasteberry for the management of menopausal symptoms.

Flaxseed (*Linum usitatissimum*)

Flaxseed, a common dietary source of fiber and omega-3 fatty acids, is also a rich source of lignan phytoestrogens.

Effects in Menopause

Most small studies evaluating flaxseed powder have identified modest benefit for reducing symptoms, but only when compared with baseline. The improvement identified in these studies is similar to that seen with placebo. Additionally, high-quality research on the use of flaxseed-containing food products has yielded negative findings, suggesting no benefit of these products for improving vasomotor symptoms. Similarly, research on the use of flaxseed, either as powder or extract, has shown no benefit on BMD [18].

Summary

Flaxseed can be utilized as a valuable source of fiber and omega-3 fatty acids in the diet. However, the evidence does not support its use for the management of menopausal symptoms [18].

Kudzu (*Pueraria montana* var. *lobata*)

Kudzu is a climbing vine that is native to Asia but is now considered an invasive weed in the United States. It contains isoflavones, which have demonstrated estrogenic and antiestrogenic activity in laboratory research, similar to SERMs [19].

Effects in Menopause

Clinical research on the use of kudzu during or after menopause is limited. Small clinical studies in perimenopausal patients shows that taking kudzu 25 mg, 50 mg, or 100 mg daily for six months improves vasomotor symptoms when compared with baseline, and that taking 50 mg daily reduces vasomotor symptoms similarly to conjugated equine estrogen 0.625 mg, with or without medroxyprogesterone acetate 2.5 mg daily. However, taking kudzu does not seem to significantly improve sex hormone levels and may worsen lipid levels [19].

In postmenopausal adults, small clinical studies suggest that taking kudzu orally might improve flexible thinking and attention, although it does not appear to improve vaginal dryness or pH.

Research on a vaginal gel containing kudzu has yielded conflicting results. Although one study suggests that applying 0.5 grams of a gel containing kudzu 6% to the vagina for 11 weeks improves vaginal symptoms similarly to conjugated estrogen cream, another clinical study shows that applying a 5% gel does not improve symptoms when compared with a placebo gel [19].

Safety

Kudzu is generally well tolerated; most reported adverse effects occur at the same rate as placebo. However, there have been several case reports of elevated liver transaminases after the use of kudzu.

The isoflavones in kudzu are reported to have antiplatelet activity, which may be a concern for patients on anticoagulant or antiplatelet therapy. There is also some concern that kudzu might inhibit organic anion transporters (OATs), which are responsible for the excretion of various drugs [19].

Summary

Due to the limited research and inconsistent benefits identified to date, clinicians should not recommend kudzu for the relief of menopausal symptoms.

Ginseng

Many plants have been referred to as ginseng; *Panax ginseng* is the species most commonly associated with this name. The root of this plant has a long history of use in traditional Chinese medicine.

Although the hormonal effects of *Panax ginseng* remain controversial, some laboratory and clinical research has indicated the presence of some estrogen-like activity. Additionally, *Panax ginseng* may affect levels of dehydroepiandrosterone (DHEA) and testosterone [20].

Panax ginseng has been evaluated for various purposes in postmenopausal adults; however, the available research is limited and conflicting.

Vasomotor Symptoms

One study shows that taking *Panax ginseng* 1 gram three times daily for 12 weeks reduces hot flashes and other symptoms when compared with placebo.

Another study shows that taking an extract of Korean red ginseng, a specific form of *Panax ginseng*, 500 mg four times daily for two months modestly improves fatigue severity scores when compared with placebo. However, one study shows that taking a lower dose of 200 mg daily orally for four months does not improve symptoms when compared with placebo [20].

Genitourinary Symptoms

A small clinical trial in postmenopausal adults with genitourinary syndrome shows that taking *Panax ginseng* 500 mg twice daily for four weeks does not affect vaginal maturation index or pH but may improve vaginal itching and burning when compared with placebo. One study also shows that taking Korean red ginseng 3 grams daily for two months modestly improves sexual arousal and satisfaction when compared with placebo [20].

Safety

The most common adverse effect reported with *Panax ginseng* is insomnia. In postmenopausal adults, specifically, it has also been reported to cause vaginal bleeding. *Panax ginseng* has also been associated with prolongation of the QT interval when used short-term; its effects when used long-term are unclear [20].

There is some evidence that *Panax ginseng* can modestly inhibit the CYP2D6 enzyme, although the clinical significance of this effect is unclear. *Panax ginseng* may also modify the function of the CYP3A4 enzyme [20].

Some reports suggest that it can inhibit CYP3A4 activity, while other research suggests it may induce activity. Until more is known, use *Panax ginseng* with caution in patients taking CYP2D6 or CYP3A4 substrates.

There is also some concern that *Panax ginseng* may decrease platelet aggregation or alter the metabolism of warfarin. However, the available research is conflicting and clinical relevance is unclear [20].

Summary

Panax ginseng may offer modest benefits for some patients with vasomotor or genitourinary symptoms. However, it should be used with caution in patients with certain medical conditions or those taking certain medications.

Wild Yam (*Dioscorea* species)

Wild yams contain diosgenin, which has been used historically to synthesize corticosteroids and sex hormones. Some wild yam products are actually promoted as natural DHEA, which is a precursor for human sex hormones. However, DHEA can only be synthesized from diosgenin in a laboratory. This transformation does not occur in the human body. Thus, wild yam should not be recommended as a treatment for menopause [21].

Other Phytoestrogens

There is interest in using a number of other plants as potential phytoestrogens. However, many have shown weak or absent estrogenic effects in clinical and laboratory research. These plants include dong quai (*Angelica sinensis*), red clover (*Trifolium pratense*), hops (*Humulus lupulus*), and common sage (*Salvia officinalis*).

OTHER HERBAL MEDICATIONS

St. John's Wort (*Hypericum perforatum*)

St. John's wort is a plant native to Europe with yellow, star-shaped flowers. It is relatively well-known for its modest antidepressant effects, as well as its ability to cause significant drug-drug interactions by inducing CYP enzymes [23].

St. John's wort has been shown to modulate the effects of serotonin, dopamine, and norepinephrine, and inhibit the reuptake of these chemicals. These effects are thought to be beneficial in menopause.

Effects in Menopause

Most clinical research shows that taking St. John's wort can reduce symptoms of perimenopause. A meta-analysis of small clinical trials shows that taking St. John's wort up to 900 mg daily for up to 16

weeks, alone or in combination with other herbs, reduces the frequency and severity of hot flashes when compared with placebo. Some research also suggests that St. John's wort might improve quality of life and psychological symptoms when compared with placebo [23].

Safety

St. John's wort is generally well tolerated but may cause diarrhea, dizziness, dry mouth, mild gastrointestinal discomfort, fatigue, headache, insomnia, and sedation.

This plant is a potent inducer of CYP3A4 and a moderate inducer of CYPs 1A2, 2B6, 2C19, and 2C9, as well as P-glycoprotein. Thus, St. John's wort interacts with many drugs available on the market and should be used with caution in most patients [23].

Other Miscellaneous Herbs

There has been interest in using many other plants and extracts for the management of menopause-related symptoms. The proposed mechanism of action for each of these supplements varies. However, most have either not been adequately evaluated in clinical research or have not shown promise in clinical studies. Examples include evening primrose oil (*Oenothera biennis*), saffron (*Crocus sativus*), valerian (*Valeriana officinalis*), ashwagandha (*Withania somnifera*), and black seed (*Nigella sativa*).

CONCLUSION

Menopause introduces a number of short- and long-term health effects, which patients may be interested in managing via nonpharmacologic methods. Many menopause-related health effects may be mitigated by a variety of lifestyle modifications, including exercise and dietary changes, with a focus on increasing the intake of beneficial substances and decreasing the intake of detrimental substances. These lifestyle modifications should be recommended for most adults in perimenopause and postmenopause.

Some complementary modalities, such as mindfulness and yoga, can also offer short- and long-term benefits. Additionally, certain herbal therapies, such as soy, can be considered as complementary treatment options for many patients. However, some herbal therapies that are commonly discussed for menopause should be used with caution and individualized to patient needs and risk factors.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.



For postmenopausal women seeking relief of vasomotor symptoms of menopause with over-the-counter or complementary medicine therapies, the Endocrine Society suggests counseling regarding the lack of consistent evidence for benefit for botanicals, black cohosh, omega-3-fatty acids, red clover, vitamin E, and mind/body alternatives including anxiety control, acupuncture, paced breathing, and hypnosis. (<https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines/treatment-of-menopause>. Last accessed January 23, 2023.)

Level of Evidence: 2 | ⊕⊕⊕ (Suggestion based on low-quality evidence)

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