The Menopause Transition: Optimally Protecting Emotional Health

An Evidence-Based CME Consensus Recommendation from an Expert Panel

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The Menopause Transition: Optimally Protecting Emotional Health
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General Objective

The goal of this publication is to assist primary care clinicians in the assessment of menopausal women for depression and other menopausal symptoms, discuss how these symptoms interact and overlap, and explore possible treatment options.

Learning Objectives

- Recognize that in a clinical setting, women from different ethnic backgrounds will characterize menopause and its associated symptoms differently
- Employ patient-focused, culturally relevant communication techniques when counseling patients regarding menopause and their menopausal symptoms
- Utilize a patient-centered, shared-decision making approach in the evaluation and management of menopausal symptoms, including depression
- Provide objective, up-to-date, evidence-based education regarding possible menopausal symptom treatment options along with an individualized management and follow-up plan

Note From the Steering Committee

The Steering Committee acknowledges that "...the majority of personal experiences with menopause relate to cisgender women (who were born female and identify as female). Transgender men and some people who identify as neither men nor women also experience menopause... [This monograph] refers to "women" in alignment with the available data, which does not routinely identify gender identity. There is a paucity of readily available data on trans and gender-diverse experiences of menopause. Trans and gender-diverse people have unique age-related health needs that clinicians should consider, including referral to specialist services when necessary."

World Health Organization

"Hot flashes" and "hot flushes" are often used interchangeably to refer to the experience of sudden, intense heat, often accompanied by sweating and a reddening of the skin. The choice between "hot flashes" and "hot flushes" largely depends on regional language preferences and local medical conventions. This monograph will use the term 'hot flashes."

Introduction

Each menopausal patient presents with her own life circumstances and experience. Each woman will have her own psychological history, life events, coping skills, family background, relationship history, body image, roles, and social and cultural interpretation of how menopause affects her life. Each woman needs to be given the time to tell her own story.[1]

Amanda A. Deeks, PhD

Menopause is a universal milestone in the life cycle of women and every woman's experience of this phase of life is unique and influenced by a variety of factors. The transition from normal ovarian function to the near-complete loss of estrogen production comes with a range of psychological, endocrinological, and physical changes that occur over years.[2,3] Though some women go through the menopausal transition asymptomatic or with few symptoms, over 85% experience the effects of estrogen fluctuation and eventual deficiency – sweating, hot flashes, insomnia, mood changes, and vaginal dryness. These symptoms can range from mild to moderate discomfort to symptoms that are severe and disabling and are all influenced by psychological, ethnic, and socio-cultural factors.[2,3]

Menopause – the complete cessation of menses for 12 months – usually occurs at about 51 years of age though the age can range between 45 to 55 years.[4] Based on increasing life expectancy, most women will spend up to 40% of their lifespan post-menopausal.[5] Yet many women have limited awareness of the potential implications of this transition and many primary care physicians struggle with how to manage this time in their patients' lives.[6]

Menopausal Transitions

"Menopause is not like a light switch..."

To understand the physiological changes that occur during the menopausal transition, it is useful to define the stages of reproductive aging. The 2001 Stages of Reproductive Aging Workshop (STRAW) designed a staging system to provide guidance

on ovarian aging. This standardization of language and the characteristics of each stage of aging provided consistency across research studies and gave women and their healthcare team guidance regarding contraceptive requirements and fertility.[7] The STRAW criteria were revised in 2011 and became STRAW + 10 to reflect new knowledge regarding the hypothalamic-pituitary-ovarian function changes that take place before and after the final menstrual period.[8] It divided the life of the adult female into three stages - Reproductive, Menopausal Transition, and Post Menopause - to improve understanding of the advances in the science for women and their clinicians.[8]

Clinical Pearl

STRAW and STRAW+10 are primarily research tools. Repeated laboratory testing is not recommended, and contraception should be used until 1 year of absent menses.

The age that a woman enters menopause can be a marker for health.[9,10] Earlier entry into the menopausal transition (typically before the age of 45) is influenced by genetic and environmental factors and how they interact.[11] Genes that affect premature ovarian failure and early menopause and their associated co-morbidities are described here.

Some data suggest that women who enter menopause earlier than the general average age are at greater risk for earlier mortality and more likely to develop chronic conditions such as cardiovascular disease and type 2 diabetes.[9,12,13]

Mishra et al. found women who experienced earlier menarche and nulliparity had a 2-fold increased risk of experiencing menopause at a younger age compared with women who experienced later menarche and had two or more children.[13] Researchers also found a strong association between lead and other heavy metal exposure and a younger age of natural menopause.[12,14,15] Froman et al. noted that a low socioeconomic status in childhood may result in early menarche and low socioeconomic status in adulthood may result in menopause at a younger age.[16]

Entering menopause earlier than the average age is also influenced by smoking. Women who smoke enter menopause earlier than women who do not smoke.[17-21] The International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) looked at 17 observational studies and concluded that former smokers had a 15% higher risk of premature and early menopause while current smokers had double the risk than never smokers, increasing their risk for cardiovascular disease.[20,22]

The menopausal transition is a period of critical physiological changes, both transitory and persistent. Being able to counsel women proactively about the time frame of their menopausal transition and its correlation to long-term health is important. SWAN found that women who were older at the beginning of the menopausal transition spent a shorter amount of time in each stage, later onset of the menopausal transition was also associated with a greater BMI whereas the duration of the transition was not.[21]

Swan also found that African American women tended to have an earlier menopause and longer menopausal transition than White women.[21] However, according to a more recent study that controlled for smoking and C-reactive protein (CRP), which appears to be a predictor of earlier menopause transition in US women, the age at which African American women enter menopause is no different than White women.[23] The researchers concluded that any population differences seen in onset of the menopausal transition is more likely attributable to differences in factors that include smoking, obesity, socioeconomic status, and race-based lived experience.[23]

Symptom Impact

"There are physical symptoms…there are emotional symptoms…we can't focus on one without considering the other."

While the age at which a woman can expect to enter menopause is her early 50's, the perimenopausal transition can vary from months to years and the symptoms that women experience can be extremely variable. The clinical symptoms of menopause can have a major impact on a woman's life and are the main reason for seeking treatment.[24] Depression is more common during this time as is irregular bleeding, vasomotor symptoms, and mood changes. All these symptoms have a negative impact on a woman's quality of life.

Over 80% of women will experience vasomotor symptoms, hot flashes and/or night sweats during the

menopausal transition, with the majority rating them as moderate to severe.[25,26] African American women and Hispanic women have hot flashes for longer periods of time than white or Asian-American women.[27] Lifestyle and sociodemographic factors play a role in the frequency and severity of symptoms with good evidence to support menopausal status, black race, smoking, anxiety or depression prior to menopause, and antiestrogen therapy (GnRH agonists/antagonists; aromatase inhibitors, SERMS) as risk factors for hot flashes.[28]

Smoking and passive smoke exposure are significant determinants of the intensity of vasomotor symptoms.[29,30] Even after adjusting for variables such as race/ethnicity and education level, current smokers are over 60% more likely to report vasomotor symptoms than non-smokers.[25]

Overweight and obesity are also associated with more severe vasomotor symptoms during pre- and perimenopause period.[31] A meta-analysis of menopause and obesity revealed that decreasing lean muscle mass and increasing fat mass begins in the premenopausal period and accelerates during the menopausal transition with a 2-to-4-fold loss in muscle and gain in fat that can lead to overweight and obesity.[32] The menopausal hormonal environment is linked both to an increase in abdominal fat and an increase in total body fat.[33]

Large-scale studies have shown the prevalence of vulvovaginal symptoms - dryness, recurrent urinary tract infections (UTIs), or dyspareunia – which usually occur later in menopause, are present in over 50% of menopausal women[5,34-36] According to the Steering Committee, vulvovaginal symptoms may interfere with work, exercise, make sex painful or impossible, cause personal or relationship distress, impaired self-image, and decreased quality of life.

Assessment of Menopausal Symptoms

Menopause may come with a myriad of symptoms for many women. Not only hot flashes, night sweats, and vaginal dryness, but also depression, palpitations, headaches, difficulty concentrating, insomnia, and lack of energy.[37] For women who want to know which of their symptoms can be attributed to general aging and which to menopause, it is important to know whether and how symptoms occur together.[37]

Depression

Clinical Pearl

There are data that say that it [menopausal transition] is a physical, emotional roller-coaster and that it comes with not only hot flashes, insomnia, and mood fluctuations, but depression as well.

Steering Committee Member

Depression is more common during the menopausal transition than at any other time in a women's life.[38,39] Treatment of menopausal depression is not straightforward as treatment at other times in life due to several factors, including the adverse symptoms and signs associated menopause. The perimenopausal period presents an increased level of vulnerability for women for the development of depressive symptoms and major depressive episodes, even in women with no history of depression.[40,41] With a history of depression, a woman who is going through menopause is 13 times more likely to exhibit depressive symptoms.[42] Night sweats, hot flashes, sexual and sleep disturbances, cognitive changes, and changes in weight/energy all complicate the diagnosis of depression.[43]

Cross-sectional studies have shown 45% to 68% of perimenopausal women reported elevated depressive symptoms compared with 28% to 31% of women who had not yet entered menopause.[44] An analysis of a large cohort of ethnically diverse women found that women in the early perimenopause transition showed a 1.74-fold increased odds of elevated depressive symptoms, however Hispanic women showed a 2.45-fold increased odds[44]

In a longitudinal study of women who were premenopausal and had no previous symptoms, Freeman et al. found that both depression and hot flashes occurred early in the transition to menopause with symptoms of depression more likely to precede hot flashes by 1 ½ years.[45] These symptoms were associated with early changes in Inhibin b and follicle-stimulating hormone (FSH) levels along with the variability of estradiol.[45] In 2016, Gordon et al. presented a model of perimenopausal depression that was based on estradiol fluctuation which increases sensitivity to stress, i.e., stressful life events that occur in close proximity to the transition into menopause may trigger depressive symptoms.[46] In a 2019 pilot study,

Gordon et al. found evidence that estradiol fluctuation in perimenopausal women increases their sensitivity to psychosocial stress as well as their vulnerability to depression.[47] These findings support what previous studies have shown, that while hormonal fluctuations play a role in perimenopausal depression, psychosocial stressors, as well as lower educational levels, being unmarried (either by choice, widowed, or divorced), and going through financial hardships are all major risk factors for depression, and depressive symptoms may be exacerbated during the menopausal period.[46,48-51] The Study of Women's Health Across the Nation (SWAN) also found that the strongest predictor of elevated depressive symptoms in the menopause transition period were very stressful life events.[46]

Clinical Pearl

You can't fit everybody into a little box of major depression… patients will have all the manifestations of depression, but it's brought on by physical symptoms. Hot flashes and night sweats, Irritability, not sleeping, pain with sex…creates a lot of relationship stress. That constellation can lead to the classic signs of depression but…the way to manage it may not be as straightforward as an SSRI…

Steering Committee Member

The Steering Committee suggests that when you have a patient of an appropriate age who may be transiting into menopause, it is important to look beyond the traditional models of the evaluation and management of depression. Changes in hormones, the loss of estrogen, hot flashes, night sweats, and mood changes, all put women at a higher risk for depression.

It is important to look at the constellation of symptoms that the patient is experiencing and temporally relate them to their reported changes in their periods, their menopausal symptoms, and their mood changes. The menopausal transition can exacerbate a pre-exiting underlying depression or reactivate previous major depression and it is important to tease out the difference, as the way the depression is treated can be different. Is the emergence of depressive symptoms related to the onset of menopausal symptoms or do they point to a history of depression or are they caused by life stressors, or a combination of these factors?

It has been shown that hot flashes and insomnia may lead to emotional distress. The stress of aging parents, children leaving home, chronic health problems that exacerbate over time (hypertension, diabetes, thyroid issues), and career pressures, are all additive. Teasing out these details takes work and patients who are going through menopause may not meet the traditional DSM-V criteria of depression. Knowing the difference between the causes of depression can influence how you individualize the management of the condition.

For example, vaginal dryness and dyspareunia are going to affect a couple's sexual relationship and that is going to affect mood. Vulvovaginal symptoms related to genitourinary syndrome of menopause (GSM) can affect both the patient and the partner. The pain that occurs with vaginal penetration contributes to emotional distress, which is exacerbated by a partner who is unhappy with the loss of sexual exchange that occurs from the loss of estrogen. These situations can lead to the classic signs of depression, but the management of it may not be as straightforward as prescribing an SSRI and cognitive behavioral therapy. It is important to understand the etiology of depression because in some cases estrogen therapy is going to be the more appropriate choice as it is not only going to help alleviate their physical symptoms but their emotional ones as well.

Unmasking Depression: Questions to Ask

- Have you lost interest in activities and hobbies you previously enjoyed?
- Do you have overwhelming fatigue
- Do you have a lack of motivation?
- Are you having difficulty making decisions?
- Are you having difficulty absorbing information?
- Are you having trouble concentrating?
- Have you had changes in appetite changes—have you lost your appetite, or are you eating too much?
- Do you have persistent feelings of hopelessness or irritability or sadness?

Sometimes it will be difficult to tease out exactly what is going on with the patient. She may say "I've been in a bad mood for the longest time, since this craziness with my period started…I'm getting hot, and I am totally exhausted because I don't sleep." It can be difficult to figure out if the bad mood is the result of the symptoms of menopause when the patient is not using terminology that would lead you to suspect depression. The patient's labs are fine, there is no anemia, no thyroid issue, nothing that points to a reason for the exhaustion…how do you bring the conversation around to depression and determine if the patient needs anti-depressive treatment?

Asking the right questions is important. Some women in perimenopause/menopause may not recognize that they are depressed, but they will admit they have lost all interest in things they used to enjoy that have occurred in parallel with the hot flashes and night sweats. Clues like this can help in recognizing depression and then explaining it to the patient.

Getting a good history will help to uncover if there is a temporal relationship - either the menopausal symptoms are leading to the patient's depression or depression is exacerbating the menopausal symptoms. Knowing this helps the clinician to better manage outcomes.

There are several validated screening tools to assist clinicians in determining the association and severity of depressive symptoms with other menopausal symptoms. Among these are the Menopause-Specific Quality of Life (MENQOL) questionnaire which assesses a women's menopause-related quality of life.[52] It is important to note that this tool, and other menopause symptoms assessment tools are not designed to screen for MDD. In patients who present with significant depressive symptoms and/or a positive PHQ-2 screen, clinicians should conduct a full PHQ-9 or other validated test to assess for MDD.

Hormone Therapy

The first hormonal therapy to treat the symptoms of menopause was introduced in 1942.[53] In 1960, the feminist movement pushed the use hormonal therapy to relieve symptoms.[54,55] HT, initially approved for the treatment of hot flashes, received approval for the prevention of osteoporosis in 1988.[54] Observational studies suggested that HT could be beneficial in a number of chronic diseases, including cardiovascular disease.[54] This claim prompted the FDA to call for randomized, clinical trials to confirm the benefits of HT on cardiovascular health.[54]

Clinical Pearl

Some patients' symptoms won't be relieved solely by estrogen or other hormonal therapy, as the menopausal symptoms are exacerbating an underlying depression. For moderate to severe vaginal and vulvar symptoms low-dose local vaginal estrogen therapy or, when indicated, systemic estrogen +/-progestin hormone therapy are effective treatments.[52]

The Women's Health Initiative (WHI) which enrolled 16,608 participants, was the largest randomized study at the time.[54] The goal of the study was to evaluate the effect of HT on cardiovascular disease, osteoporosis, and cancer.[54]

In 2002, after a mean follow-up period of 5.2 years, the first results of the study were published.[54] Some arms of the study showed an increase in the incidence of breast cancer and coronary heart disease and a reduction in colorectal cancer and osteoporotic fractures.[56] The investigators at that time concluded that the risk vs benefit profile did not support the use of HT as a viable intervention for chronic disease and recommended that the regimen should not be continued or initiated for the primary prevention of cardiovascular disease.[56] The trial was halted, and the media coverage of the results created a panic among women using HT, as a result the use of HT for menopausal symptoms declined dramatically in the US. The results brought about updated guidelines for the prescribing of HT.[54]

Over the succeeding decades, researchers have continued to debate the results of the WHI and analyze subsets of the data. New studies, the reanalysis of the original data, and a meta-analysis showed that in postmenopausal women within 10 years of menopausal onset and women between 50 to 59 years of age do benefit from HT with a reduction in coronary diseases and all-cause mortality.[54]

In a 2014 study, researchers from a large observational French study of over 78,000 women found that there was no associated increased risk of invasive breast cancer in women taking estrogen and micronized progesterone or dydrogesterone with short-term use of

up to five years.[57] However, HT use over five years was associated with an increased risk of breast cancer but was not statically significant once HT use was stopped.[57]

Chlebowski, et. al. recently reported on the findings from WHI long-term, randomized clinical trials.[58] The study involved over 27,000 women enrolled between 1993 and 1998 and followed through 2017. The researchers found that in the estrogen-only HT arm there was a significant reduction in mortality from breast cancer. Women in the estrogen and progestogen arm of the study had an increased risk of breast cancer, but no significant difference in breast cancer mortality compared with placebo.[58]

HT is not without associated risks (i.e., venous thromboembolism-VTE). It is important for primary care physicians to talk with their patients about whether they may benefit from HT and help dispel the myths surrounding it. The North American Menopause Society (NAMS) has stated that for most symptomatic, healthy women aged 60 or younger or within 10 years of their final period, the benefits of HT outweigh the risks.[59]

A conversation with the patient about HT might go as follows: "The symptoms you have described to me are most likely due to (or are classic for) estrogen deficiency. Supplementing your body with very low doses of estrogen is the best treatment option to provide significant relief to your symptoms. The use of low dose estrogen (combined with progestin/progesterone if patient has a uterus) given your age, proximity to onset of menopause, and lack of risk factors (i.e., VTE, CVD, CVA, Breast cancer) is very safe. We will continue to monitor your symptoms together and discuss annually whether to continue or taper off this hormone therapy."

Words Matter: Menopause and Culture

The role of culture in menopause should not be ignored.[17]

Menopause, besides being an important transition from a biological perspective, is also an important transition from a social perspective.[60] Sociocultural factors, including how menopause and female aging are viewed culturally, familial factors, and gender norms all impact a woman's experience of menopause.[60]

While many peri- and post-menopausal women are unlikely to start a conversation about menopause and what to expect, it may be especially difficult for immigrants or women with language barriers to bring up this topic with their clinician. A systematic literature review reported that immigrant women experience more vasomotor symptoms and poorer mental health than women who are not immigrants and they were dissatisfied with the care they received.[61] A second systematic review found that immigrant women's experience with menopause and self-care were informed by culture.[62] When asked about their dissatisfaction, women listed a lack of information provided by their physician, receiving HT without sufficient education, recommendation of treatment perceived as unnecessary, inadequate treatment option counseling due to time constraints, and an unfriendly manner.[63] This is not unique to immigrant women. Many women, regardless of immigration status, vocalize similar experiences.

Immigration status is a social determinant of health, as are disparities based on gender, ethnicity, race, class, access to education, and pay equity which impact the care of all women during menopause.[63] Studies have found that many women have limited knowledge about menopause and postmenopausal health, with their main source of knowledge being family and friends.[62] Women who immigrated from their country of origin, especially when there is a language barrier, felt that they received little information and support during menopause even when receiving care from physicians of the same cultural background.[63]

Research has found differences regarding women's experience of menopause based on culture and beliefs in the community. Western culture tends to use negative words such as "ovarian failure," suggesting menopause is a condition that requires treatment and not a normal phase of life.[17] Most Western cultures regard menopause as a marker of age progression and a loss of youth and sexual attractiveness, adding to the negative perceptions.[17] Arab culture also views menopause in a negative light. There is a high value placed on fertility, so when an Arab woman begins to lose the ability to be fertile the result is "desperate age" or "the age of despair" while Turkish women describe menopause as "the end of youth."[17,64]

In cultures where menopause is viewed as a positive experience, symptomatology is different. Researchers

found that in cultures that have a more positive outlook on menopause, women had a better attitude toward this phase of their life and had fewer hot flashes.[17] For example, women in rural Ireland saw menopause as part of the normal aging process and not an illness, as a time to take earned rest.[65] Guatemalan and Maya women accepted symptoms with equanimity as menopause brings them more freedom and higher status.[66]

Still, menopause is not often discussed within communities, families, or the healthcare setting. Almost all women experiencing symptoms of menopause may be ashamed or embarrassed to ask for advice and support.[60] In many cultures asking for help or support is uncomfortable or unacceptable and the need to take medication is a sign of weakness.

Primary care clinicians should help patients talk about their symptoms. Asking questions about symptoms validates what the patient is experiencing and will help lead to the real underlying cause of the symptoms.[67] While the patient may not admit to symptoms the first time the questions are asked, the fact that they know their physician felt that it was important to bring up the topic may help the patient to open up on a future visit. The patient may not know that they are experiencing symptoms of menopause or that there are treatment and counseling options available to help alleviate discomfort.[60] Grasping the differences and the similarities between women's attitudes, expectations, and perceptions about menopause will improve the delivery of care that is culturally appropriate and encourage changes in lifestyle that may lead to a decrease in symptoms and improved quality of life.[68]

Recommendations From the Expert Panel

Our patients listen to their neighbors and friends and other people who say, "Don't go on that" or "hormones cause cancer." For patients who would benefit from HT to manage their menopausal symptoms, we need to utilize shared decision making to:

- provide our patients with objective, up-to-date, and evidence-based information about the benefits and risks of HT utilizing terms they can easily understand
- assess their treatment goals, along with their beliefs and fears about HT and other treatment options
- decide together on a mutually agreeable plan for symptom management, along with a clear follow-up plan, including reasons to call/come in asap
- utilize Teach-Back, when possible, to confirm understanding about the plan
- provide clear handouts in patient's preferred language highlighting the management and follow up plan

Talking with the Patient

Educating patients about the menopausal transition before they reach the age of perimenopause, the period of time before menopause occurs, [8] will help ease them into the transition in terms of symptom management and changes in mood. It is important to help your patient understand that the things she is experiencing are very common. One thing that may be helpful is to explain to the patient that they have an imbalance, just like when their blood pressure or blood sugar is unbalanced, and there are medications that can help bring the patient back into balance.

> **Clinical Pearl**
>
> I always thank patients for being comfortable bringing their concerns up to me… I want them to feel validated because too many times in society we make them feel ashamed.
>
> *Steering Committee Member*

Decreased sexual desire is a frequent symptom expressed by menopausal women. This may cause relationship issues, or the woman's partner may think the woman is no longer attracted to them. This lack of desire is very distressing to many women, who just want "things to be like they used to be." Explaining to your patient that this is not uncommon and that there are effective strategies such as HT, to mitigate the symptoms may be enough to reassure both her and her partner. Giving your patient ability to say "I talked to my doctor about this today and she said this is very common in women my age and we're going to work on it" can be reassuring for the couple.

Treatment: Antidepressants…Hormone Therapy…Both…Neither? Recommendations for Clinical Care

For some patients with mood related symptoms (anxiety, irritability, depression), temporally related

menstrual cycle changes, and vasomotor symptoms (hot flashes, night sweats), you may want to initially consider a trial of HT first rather than an antidepressant. This is most reasonable for perimenopausal patients without a prior history of MDD or current suicidal/homicidal ideations (SI/HI), and whose PHQ9 or similar Depression screening tools indicate minimal, mild, or moderate Depression severity (i.e., PHQ9 score <15). It is possible that as their physical symptoms improve, so will their emotional symptoms. In patients whose emotional symptom do not improve on HT, consider underlying depression that is being exacerbated by their hormonal symptoms. Certain selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) have been shown to reduce the frequency and severity of hot flashes in menopausal and post-menopausal women.[44,69]

A 2015 systematic review of 18 randomized controlled trials of consisting of 3,490 perimenopausal and postmenopausal women looked at the effectiveness of SSRIs and SNRIs for the vasomotor symptom treatment.[69] All of the studies assessed vasomotor symptom frequency and average severity. The fastest onset of symptom relief was with the SNRI venlafaxine with a 41% reduction in symptoms in one week and a 26% reduction vs. placebo ($P < .001$). However, there were more frequent adverse effects such as constipation, nausea, and dry mouth. In the SSRI class, paroxetine produced the greatest overall reduction in hot flashes with a 40.6% reduction at 10mg and a 51.7% reduction at 20mgs ($P = .0006$ and $P = .002$, respectively).[69] Other SSRIs which showed efficacy in reducing symptoms were citalopram, escitalopram, and paroxetine.[69]

It is important to note that SNRIs should be used with caution in women with hypertension as it has been associated with increased blood pressure in some patients.[69] SSRIs have been shown to interfere with the metabolism of tamoxifen and therefore should not be used in patients with a history of breast cancer taking tamoxifen.[69]

You may have patients whose symptoms are so severe you may need to treat both their physical symptoms with HT and their emotional symptoms with an SSRI or an SNRI. Asking the right open-ended questions, helping patients feel comfortable asking questions, sometimes having their partner involved, all help tease away what the root of the problem is so it can be treated appropriately. Even if you are not comfortable prescribing medications, you have validated the patient's condition and can direct their care to a provider who does prescribe these medications.

Dealing with Time Constraints

Asking patients about their menopausal symptoms is not opening Pandora's box; you are validating their concerns. Let them know what may be causing their symptoms, acknowledge you want to help them, and that you want to make sure that there is adequate time to address all their concerns. Unless they are experiencing active suicidal/homicidal ideation that necessitates urgent action, you can bring the patient back for a return visit. Suggest continuing the discussion at another appointment within the next several weeks, which can be in-person or via telemedicine. You can have them complete the MENQOL or similar questionnaire before the visit to facilitate the discussion. Clinicians often feel pressured to solve every problem in one visit. We shouldn't. It is okay to tell the patient that you may not be able to address all their issues at once, but you are committed to be with them on the journey until they feel more like their typical self.

Shared Decision Making

Every woman's experience of the menopausal transition is unique, and therefore, strategies for managing this transition need to be individualized.[2] Providing the best care and advice during this time of transition requires a good grasp of the factors that influence what the patient is experiencing. Shared decision making provides an avenue to begin understanding your patient's individual experience and empowering her to participate in her treatment.

> **Clinical Pearl**
>
> Shared decision-making tells the patient that we are taking their fears and beliefs into account and signals that we are in this together and that we're going to be with them throughout this journey.
>
> *Steering Committee Member*

Medications to Treat Menopausal Symptoms

Oral/Transdermal/Intravaginal Systemic Menopausal Hormone Therapy (MHT): Estrogen (E) is the most effective treatment option for relieving menopausal vasomotor symptoms (hot flashes/night sweats). It can also alleviate associated insomnia, irritability, as well as depressive symptoms (especially during the menopausal transition), and vaginal dryness. Women who still have their uterus will also need progestin in addition to estrogen to prevent endometrial hyperplasia. Perimenopausal women desiring menstrual cycle control and/or pregnancy prevention will need contraceptive doses of estrogen and progestin. Systemic Estrogen also helps prevent bone loss but increases the risk of Venous Thromboembolism (VTE). Long-term use of MHT is associated with a small increase in breast cancer risk, but the benefits of estrogen/progestin use under 60yrs of age and within the first 10 years of menopause outweigh these risks.

Common MHT medications

Estrogen-Only Therapy (ET):

- Conjugated equine estrogens (Premarin)
- Estradiol (Estrace)
- Estradiol transdermal system (Vivelle-Dot, Climara)

Combination Estrogen-Progestin Therapy (EPT)

- Conjugated estrogens/ medroxyprogesterone acetate (Prempro)
- Estradiol/norethindrone acetate (Activella)
- Ethinyl estradiol/norethindrone acetate (Femhrt)

Selective Estrogen Receptor Modulators (SERMs):

- Ospemifene (Osphena): Approved for the treatment of dyspareunia due to menopause.

Local Vaginal Estrogen/DHEA or Oral Ospemifene: These are the most effective treatment options for the management of menopausal vaginal dryness and dyspareunia due to estrogen deficiency. Estrogen can be administered directly to the vagina using a vaginal cream, tablet, or ring. DHEA vaginal inserts are converted to estradiol and testosterone in vaginal tissues.

Low-Dose Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) are effective non-hormonal alternatives to alleviate vasomotor symptoms as well as associated depressive symptoms.

Common Antidepressants

SSRIs

- Escitalopram (Lexapro)
- Citalopram (Celexa)
- Paroxetine (Paxil, Brisdelle) *

SNRI

- Venlafaxine (Effexor)
- Desvenlafaxine (Pristiq)
- Duloxetine (Cymbalta)

** Paroxetine (Brisdelle) is the only SSRI FDA-approved for the treatment of menopausal hot flashes. No SNRI is FDA-approved for the treatment of hot flashes. People with breast cancer who are taking tamoxifen should not take paroxetine*

Gabapentin and Pregabalin: FDA-approved for seizures, post-herpetic neuralgia, and restless leg syndrome. However, evidence supports their off-label use as a non-hormonal, but less effective alternative to estrogen for the management of menopausal vasomotor symptoms. Side effects include fatigue and dizziness.

Clonidine: an antihypertensive, available as a patch or a pill, which has been used off-label for relief from menopausal vasomotor symptoms. However, it is rarely used anymore due to common, intolerable side effects including lightheadedness, drowsiness, dry mouth, and constipation.

Neurokinin 3 (NK3) Receptor Antagonist: Fezolinetant is the first FDA-approved (May 2023) oral non-hormonal medication in this class for the treatment of moderate to severe vasomotor symptoms caused by menopause. It works by binding to and blocking the activities of the NK3 receptor, which plays a role in the brain’s regulation of body temperature.

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Have open conversations with your patients and educate them on what to expect during the menopausal transition. They most likely have already collected some information – and misinformation – from friends, family, or the Internet and will arrive at your office with a combination of some amount of knowledge and a host of misperceptions. This is the time to build a relationship with the patient that will lead to effective treatment over the course of the transition and beyond.

The Patient's Perspective

Every woman's experience of menopause is unique, and each woman will have different questions and concerns when they visit you. Following are insights from patients about what they wish they knew before entering menopause.

ML: "I knew about the hot flashes. What I wasn't expecting were the giant mood swings and the depression. It had a major impact on our home life."

TM: "I wish my doctor talked to me about how menopause can affect memory and focus. I was scared I was developing dementia. Had I known this was a symptom, I wouldn't have worried so much."

BP: "I didn't know that menopause was a natural part of life. All of a sudden, I didn't understand what was happening to my body and it was very scary. I wish someone had told me what to expect."

CB: "I wish I knew about the impact menopause was going to have on my relationship with my partner. It took a long time for us to find our balance again."

JD: "I wish someone had explained to me about the importance of self-care as my body started to go through all these changes. I really had a lot of anxiety about the whole process."

GF: "My doctor never talked with me about menopause. Everything I knew came from friends who were going through it. I wish she had been able to help me understand what it was going to be like…what I should expect…, because it wasn't anything like my friends."

Some suggestions when having a conversation with the patient:

- Start with open-ended questions to assess their symptoms
- Remind them that the symptoms they are experiencing are common and can be managed successfully
- Assess their treatment goals
- Promote effective non-pharmacological strategies (i.e., adequate sleep, formal exercise, paced beathing, smoking cessation)
- Review their treatment options, including potential benefits, risks, and side-effects
- Objectively discuss the latest evidence about herbal therapies/supplements
- Assess and address their fears and beliefs about their symptoms and treatment options
- Set realistic expectations
- Make a clear management and follow up plan together
- Perform Teach-Back, when possible, to confirm understanding
- Provide clear, easy to understand handouts and written instructions in the patient's preferred reading language

Conclusion

As healthcare clinicians we need to counsel and support women who experience disruptive changes through their perimenopausal and menopausal years. This involves educating our patients, promoting conversation, offering therapeutic options, and being sure that follow up surveillance is provided. Recognizing the complexity of the physical and psychosocial changes our perimenopausal and menopausal patients may experience, and developing individualized evidence-based treatment approaches tailored to their needs is the best medical practice. This is so very well exemplified in the treatment of depression in this population, which may be impacted both by the physiologic changes of menopause and its subsequent physical symptoms alone or in addition to mood symptoms associated with major depressive disorder (MDD).

CASE STUDIES

Regina

Regina is a 42-year-old woman with no history of depression who presents to you with significant vasomotor symptoms, mood changes, and irritability. She also tells you that her periods are bothersome and that irregular menses with intermenstrual spotting, which is interfering with her sex life. She uses condoms inconsistently and does not want to be pregnant. She has no history of hypertension, CVD, or VTE, and does not smoke. After further discussion, you ask her to complete the PHQ-9. Her score was 10. She has no suicidal or homicidal ideations.

What would be the most effective initial treatment option for this patient?

A. Low dose hormone therapy (HT)
B. An SSRI or SNRI
C. Combined hormonal contraceptive

ANSWER: C – A combined hormonal contraceptive delivered by oral, ring, or patch will likely improve her vasomotor symptoms, while also regulating her menses, and preventing unintended pregnancy. Combined hormonal contraception, especially given continuously, has also been shown to potentially improve depressive symptoms in perimenopausal women. It would also be appropriate to recommend Cognitive Behavioral Therapy (CBT) with a licensed behavioral therapist. Low-dose estrogen-containing HT would likely improve Regina's vasomotor symptoms and may improve her depressive symptoms. However, postmenopausal dose of estrogen and progestin are insufficient to regulate menses in a pre/perimenopausal patient and may actually make Regina's irregular bleeding worse. These doses are also insufficient to provide effective contraception. An SSRI/SNRI would help manage her depressive and vasomotor symptoms, though it is not necessary to start with an SSRI/SNRI based on Regina's presentation and PHQ-9 score (10). An SSRI/SNRI would also not address her menstrual irregularity, which is a significant concern for her, nor would it help prevent an unintended pregnancy.

When should you ask Regina to return for a reassessment?

A. 4 weeks
B. 2 – 3 months
C. 6 months

Answer: A – Most vasomotor symptoms should improve within four weeks of initiating estrogen therapy. It would also be prudent to reassess her depressive mood symptoms with CHC in about four weeks, rather than waiting a longer period of time.

Regina returns in four weeks for follow-up. Her vasomotor symptoms have significantly improved, but depressive symptoms persist (PHQ9 score remains 10). The best option at this point would be to:

A. Increase the estrogen dose of the Combined Oral Contraceptive (COC)
B. Add an SSRI/SNRI
C. Local Vaginal Estrogen

B. Adding an SSRI or SNRI, along with CBT, would be most appropriate to manage her persisting depressive symptoms while continuing her current COC since it has improved her vasomotor symptoms and menstrual irregularity while providing effective contraception. It may take up to three months to determine if the current COC effectively improves her menstrual symptoms. Increasing the estrogen dose of her COC might increase estrogen side effects (i.e., nausea, breast tenderness) without improving her persisting depressive symptoms. Local Vaginal Estrogen has very little systemic absorption and offers no benefit to the patient’s vasomotor symptoms.

Cassandra

Cassandra is a 49-year-old high school guidance counselor. She has come to see you due to increased irritability, insomnia, and feeling less empathetic with her students for the past six weeks. Her LMP was 4 months ago. For the past year, her periods have been irregular, only occurring about every three or four months, with lighter flow and shorter duration. She notes occasional, intermittent hot flashes, but no other vasomotor symptoms. She has a history of depression following her divorce, over 5 years ago, and was treated with sertraline for six months with resolution. She smokes about 10 cigarettes a day. She is not currently in a relationship and has not been sexually active for over a year. After evaluation, including PHQ-9 (score:15), and discussion, what would you recommend to treat Cassandra's symptoms?

A. Local Vaginal Estrogen
B. Combined Oral Contraceptives
C. SSRI

Answer: C – Given her recurrence of MDD and PHQ9 score consistent with moderately severe depression (10-19), an SSRI or SNRI would be a good initial treatment for this patient, especially sertraline given the fact that she had success with it in the past. Also, encourage smoking cessation and non-pharmacologic management of her mild vasomotor symptoms. Local Vaginal Estrogen therapy will not relieve her hot flashes, regulate her menstrual cycles, or improve her depressive symptoms. Combined Oral Contraceptives are contraindicated in women over 35yrs who smoke. This patient should also be encouraged to consider Cognitive Behavioral Therapy (CBT) with a licensed therapist.

On her 4-week and 3-month follow-up telehealth visits, Cassandra was feeling well. However, she comes to see you after 6 months on sertraline, and while her mood symptoms have improved with the SSRI and CBT (PHQ-9:2), she is now experiencing worsening hot flashes occurring 6 to 8 times a day along with bothersome night sweats. Her LMP was 6 months ago. She is losing sleep due to these vasomotor symptoms and feels tired all the time. What would you do now to treat Cassandra's symptoms?

A. Increase SSRI dosage
B. Add postmenopausal doses of systemic HT
C. Add a Local Vaginal Estrogen

Answer: B – Adding postmenopausal doses of HT - oral/transdermal HT is the most effective option to alleviate her vasomotor symptoms and, and these doses of estrogen are not contraindicated in smokers, though she should still be encouraged to stop smoking and if motivated, she should be offered methods to assist in tobacco cessation. Titrate the dose to alleviation of symptoms. Increasing her SSRI dosage is not necessary given the significant improvement of her depressive symptoms, and higher doses are often not associated with improved vasomotor symptoms. Local vaginal estrogen will not alleviate her vasomotor symptoms, and she is not complaining of any urogenital symptoms. Since the patient still has a uterus, she will need progestin/progesterone with estrogen therapy to prevent endometrial hyperplasia.

References

1. Deeks AA. Psychological aspects of menopause management. *Best Pract Res Clin Endocrinol Metab*. 2003;17(1):17-31. doi:10.1016/S1521-690X(02)00077-5
2. Talaulikar V. Menopause transition: Physiology and symptoms. *Best Pract Res Clin Obstet Gynaecol*. 2022;81:3-7. doi:10.1016/j.bpobgyn.2022.03.003
3. Goodman N, Cobin R, Ginzburg S, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of menopause. *Endocr Pract*. 2011;17(6):1-25. doi:10.4158/EP.17.S6.1
4. Kagan R, Kellogg-Spadt S, Parish SJ. Practical treatment considerations in the management of genitourinary syndrome of menopause. *Drugs Aging*. 2019;36(10):897-908. doi:10.1007/s40266-019-00700-w
5. Parish SJ, Nappi RE, Krychman ML, Kellogg-Spadt S, Simon JA, Goldstein JA, Kingsberg SA. Impact of vulvovaginal health on postmenopausal women: a review of surveys on symptoms of vulvovaginal atrophy. *Int J Womens Health*. 2013;5:437-447. doi:10.2147/IJWH.S44579
6. Harper JC, Phillips S, Biswakarma R, et al. An online survey of perimenopausal women to determine their attitudes and knowledge of the menopause. *Women's Health (Lond)*. 2022;18:17455057221106890. doi:10.1177/17455057221106890
7. Dutton PJ, Rymer JM. Physiology of the menstrual cycle and changes in the perimenopause. In: Panay N, Briggs P, Kovacs G, eds. *Managing the Menopause: 21st Century Solutions*. Cambridge University Press; 2015:1-10.
8. Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: Addressing the unfinished agenda of staging reproductive aging *J Clin Endocrinol Metab*. 2012;97(4):1159-1168. doi:10.1210/jc.2011-3362
9. El Khoudary SR. Age at menopause onset and risk of cardiovascular disease around the world. *Maturitas*. 2020;141:33-38. doi:10.1016/j.maturitas.2020.06.007
10. Monteleone P, Mascagni G, Giannini A, Genazzani AR, Simoncini T. Symptoms of menopause — global prevalence, physiology and implications. *Nat Rev Endocrinol*. 2018;14(4):199-215. doi:10.1038/nrendo.2017.180
11. Thasneem K, Kalarani IB, Jayaprasad P, Mohammed V, Veerabathiran R. Genes linked with early menopause and the pathogenesis of its associated diseases: a systematic review. *Middle East Fertil Soc J*. 2022;27(1):2. doi:10.1186/s43043-021-00093-0

12. Eum KD, Weisskopf MG, Nie LH, Hu H, Korrick SA. Cumulative lead exposure and age at menopause in the Nurses' Health Study cohort. *Environ Health Perspect*. 2014;122(3):229-34. doi:10.1289/ehp.1206399
13. Mishra GD, Pandeya N, Dobson AJ, et al. Early menarche, nulliparity and the risk for premature and early natural menopause. *Hum Reprod*. 2017;32(3):679-686. doi:10.1093/humrep/dew350
14. Wang X, Ding N, Harlow SD, Randolph JF, Mukherjee B, Gold EB, Park SK. Urinary metals and metal mixtures and timing of natural menopause in midlife women: The Study of Women's Health Across the Nation. *Environ Int*. 2021;157:106781. doi:10.1016/j.envint.2021.106781
15. Popovic M, McNeill FE, Chettle DR, Webber CE, Lee CV, Kaye WE. Impact of occupational exposure on lead levels in women. *Environ Health Perspect*. 2005;113(4):478-484. doi:doi:10.1289/ehp.7386
16. Forman MR, Mangini LD, Thelus-Jean R, Hayward MD. Life-course origins of the ages at menarche and menopause. *Adolesc Health Med Ther*. 2013;4:1-21. doi:10.2147/ahmt.S15946
17. Namazi M, Sadeghi R, Behboodi Moghadam Z. Social determinants of health in menopause: an integrative review. *Int J Womens Health*. 2019;11:637-647. doi:10.2147/IJWH.S228594
18. Velez MP, Alvarado BE, Rosendaal N, da Câmara SM, Belanger E, Richardson H, Pirkle CM. Age at natural menopause and physical functioning in postmenopausal women: the Canadian Longitudinal Study on Aging. *Menopause*. 2019;26(9):958-965. doi:10.1097/gme.0000000000001362
19. Whitcomb BW, Purdue-Smithe AC, Szegda KL, et al. Cigarette smoking and risk of early natural menopause. *Am J Epidemiol*. 2017;187(4):696-704. doi:10.1093/aje/kwx292
20. Zhu D, Chung H-F, Pandeya N, et al. Relationships between intensity, duration, cumulative dose, and timing of smoking with age at menopause: A pooled analysis of individual data from 17 observational studies. *PLoS Med*. 2018;15(11)(e1002704). doi:10.1371/journal.pmed.1002704
21. Paramsothy P, Harlow SD, Nan B, et al. Duration of the menopausal transition is longer in women with young age at onset: the multiethnic Study of Women's Health Across the Nation. *Menopause*. 2017;24(2):142-149. doi:10.1097/gme.0000000000000736
22. Zhu D, Chung H-F, Dobson AJ, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *The Lancet Public Health*. 2019;4(11):e553-e564. doi:10.1016/S2468-2667(19)30155-0
23. Williams M, Richard-Davis G, Weickert A, Christensin L, Ward E, Schrager S. A review of African American women's experiences in menopause. *Menopause*. 2022;29(11):1331-1337. doi:10.1097/GME.0000000000002060
24. Perlman B, Kulak D, Goldsmith LT, Weiss G. The etiology of menopause: not just ovarian dysfunction but also a role for the central nervous system. *Global Reproductive Health*. 2018;3(2)(e8). DOI: 10.1097/GRH.0000000000000008
25. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *Am J Public Health*. 2006;96(7):1226-35. doi:10.2105/ajph.2005.066936
26. Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: evidence from the Penn Ovarian Aging Study cohort. *Menopause*. 2014;21(9):924-32. doi:10.1097/gme.0000000000000196
27. Green R, Santoro N. Menopausal symptoms and ethnicity: the Study of Women's Health Across the Nation. *Women's Health (Lond)*. 2009;5(2):127–133. doi:10.2217/17455057.5.2.127
28. Avis NE, Crawford SL, Green R. Vasomotor symptoms across the menopause transition: Differences among women. *Obstet Gynecol Clin North Am*. 2018;45(4):629-640. doi:10.1016/j.ogc.2018.07.005
29. Melby MK, Anderson D, Sievert LL, Obermeyer CM. Methods used in cross-cultural comparisons of vasomotor symptoms and their determinants. *Maturitas*. 2011/10/01/ 2011;70(2):110-119. doi:10.1016/j.maturitas.2011.07.010
30. Dotlic J, Markovic N, Gazibara T. Patterns of smoking and menopause-specific quality of life: smoking duration matters more. *Behav Med*. 2021;49(1):1-11. doi:10.1080/08964289.2021.1958739
31. Anderson DJ, Chung HF, Seib CA, et al. Obesity, smoking, and risk of vasomotor menopausal symptoms: a pooled analysis of eight cohort studies. *Am J Obstet Gynecol*. 2020;222(5):478.e1-478.e17. doi:10.1016/j.ajog.2019.10.103
32. Greendale GA, Sternfeld B, Huang M, et al. Changes in body composition and weight during the menopause transition. *JCI Insight*. 2019;4(5)doi:10.1172/jci.insight.124865
33. Davis SR, Castelo-Branco C, Chedraui P, Lumsden MA, Nappi RE, Shah D, Villaseca P. Understanding weight gain at menopause. *Climacteric*. 2012;15(5):419-29. doi:10.3109/13697137.2012.707385
34. Santoro N, Komi J. Prevalence and impact of vaginal symptoms among postmenopausal women *J Sex Med*. 2009;6(8):2133-2142. doi:10.1111/j.1743-6109.2009.01335.x
35. Nappi RE, Kokot-Kierepa M. Women's voices in the menopause: Results from an international survey on vaginal atrophy. *Maturitas*. 2010;67(3):233-238. doi:10.1016/j.maturitas.2010.08.001

36. Mili N, Paschou SA, Armeni A, Georgopoulos N, Goulis DG, Lambrinoudaki I. Genitourinary syndrome of menopause: a systematic review on prevalence and treatment. *Menopause*. 2021;28(6):706-716. doi:10.1097/gme.0000000000001752
37. Avis NE, Brockwell S, Colvin A. A universal menopausal syndrome? *Am J Med*. 2005;118(12, Supplement 2):37-46. doi:10.1016/j.amjmed.2005.09.057
38. Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. *Arch Gen Psychiatry*. 2004;61(1):62-70. doi:10.1001/archpsyc.61.1.62
39. Bromberger JT, Schott LL, Kravitz HM, et al. Longitudinal change in reproductive hormones and depressive symptoms across the menopausal transition: Results from the Study of Women's Health Across the Nation (SWAN). *Arch Gen Psychiatry*. 2010;67(6):598-607. doi:10.1001/archgenpsychiatry.2010.55
40. Maki PM, Kornstein SG, Joffe H, et al. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause*. 2018;25(10):1069-1085. doi:10.1097/gme.0000000000001174
41. Shea AK, Wolfman W, Fortier M, Soares CN. Guideline No. 422c: menopause: mood, sleep, and cognition. *J Obstet Gynaecol Can*. 2021/11/01/ 2021;43(11):1316-1323.e1. doi:10.1016/j.jogc.2021.08.009
42. Freeman EW, Sammel MD, Boorman DW, Zhang R. Longitudinal pattern of depressive symptoms around natural menopause. *JAMA Psychiatry*. 2014;71(1):36-43. doi:10.1001/jamapsychiatry.2013.2819
43. Maki PM, Kornstein SG, Joffe H, et al. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause*. 2018;25(10):1069-1085. doi:10.1097/gme.0000000000001174
44. Maki PM, Kornstein SG, Joffe H, et al. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *J Womens Health (Larchmt)*. 2019;28(2):117-134. doi:10.1089/jwh.2018.27099.mensocrec
45. Freeman EW, Sammel MD, Lin H. Temporal associations of hot flashes and depression in the transition to menopause. *Menopause*. 2009;16(4):728-34. doi:10.1097/gme.0b013e3181967e16
46. Gordon JL, Rubinow DR, Eisenlohr-Moul TA, Leserman J, Girdler SS. Estradiol variability, stressful life events, and the emergence of depressive symptomatology during the menopausal transition. *Menopause*. 2016;23(3):257-266. doi:10.1097/GME.0000000000000528
47. Gordon JL, Peltier A, Grummisch JA, Tottenham LS. Estradiol fluctuation, sensitivity to stress, and depressive symptoms in the menopause transition: a pilot study. *Front Psychol*. 2019;10(1319)doi:10.3389/fpsyg.2019.01319
48. Bromberger JT, Epperson CN. Depression during and after the perimenopause: Impact of hormones, genetics, and environmental determinants of disease. *Obstet Gynecol Clin North Am*. 2018;45(4):663-678. doi:10.1016/j.ogc.2018.07.007
49. Bromberger JT, Kravitz HM. Mood and menopause: findings from the Study of Women's Health Across the Nation (SWAN) over 10 years. *Obstet Gynecol Clin North Am*. 2011;38(3):609-25. doi:10.1016/j.ogc.2011.05.011
50. Gronewold J, Duman EE, Engel M, et al. Association between life events and later depression in the population-based Heinz Nixdorf Recall study-The role of sex and optimism. *PLoS One*. 2022;17(7):e0271716. doi:10.1371/journal.pone.0271716
51. Hickey M, Schoenaker DAJM, Joffe H, Mishra GD. Depressive symptoms across the menopause transition: findings from a large population-based cohort study. *Menopause*. 2016;23(12):1287-1293. doi:10.1097/gme.0000000000000712
52. Van Dole KB, DeVellis RF, Brown RD, Jonsson Funk ML, Gaynes BN, Williams RE. Evaluation of the Menopause-Specific Quality of Life Questionnaire: a factor-analytic approach. *Menopause*. 2012;19(2):211-215. doi:10.1097/gme.0b013e31822817f9
53. Minkin MJ. Menopause: hormones, lifestyle, and optimizing aging. *Obstet Gynecol Clin N Am*. 2019;46(3):501–514. doi:10.1016/j.ogc.2019.04.00
54. Cagnacci A, Venier M. The controversial history of hormone replacement therapy. *Medicina (Kaunas)*. 2019;55(9)doi:10.3390/medicina55090602
55. Wilson RA. *Feminine Forever*. M. Evans & Company; 1966.
56. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women principal results from the women's health initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333. doi:10.1001/jama.288.3.321
57. Fournier A, Mesrine S, Dossus L, Boutron-Ruault M-C, Clavel-Chapelon F, Chabbert-Buffet N. Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort. *Breast Cancer Res Treat*. 2014/06/01 2014;145(2):535-543. doi:10.1007/s10549-014-2934-6
58. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the women's health initiative randomized clinical trials. *JAMA*. 2020;324(4):369-380. doi:10.1001/jama.2020.9482
59. Shifren JL, Gass MLS, for the Nams Recommendations for Clinical Care of Midlife Women Working Group. The North American Menopause Society recommendations for clinical care of midlife

women. *Menopause*. 2014;21(10)doi:10.1097/GME.0000000000000319
60. World Health Organization. Menopause. 2022. Accessed August 8, 2023. https://www.who.int/news-room/fact-sheets/detail/menopause
61. Stanzel KA, Hammarberg K, Fisher J. Experiences of menopause, self-management strategies for menopausal symptoms and perceptions of health care among immigrant women: a systematic review. *Climacteric*. 2018/03/04 2018;21(2):101-110. doi:10.1080/13697137.2017.1421922
62. Stanzel KA, Hammarberg K, Fisher J. Challenges in menopausal care of immigrant women. *Maturitas*. 2021/08/01/ 2021;150:49-60. doi:10.1016/j.maturitas.2021.05.008
63. Blount JG. *Communication with women in the menopause transition*. Each Woman's Menopause: An Evidence Based Resource: For Nurse Practitioners, Advanced Practice Nurses and Allied Health Professionals. Springer; 2022.
64. Obermeyer CM. Menopause across cultures: a review of the evidence. *Menopause*. 2000;(3):184-192. doi:10.1097/00042192-200007030-00009
65. Carolan M. Menopause: Irish women's voices. *J Obstet Gynecol Neonatal Nurs*. 2000;29(4):397-404. doi:10.1111/j.1552-6909.2000.tb02062.x
66. Stewart DE. Menopause in highland Guatemala Mayan women. *Maturitas*. 2003;44(4):293-297. doi:10.1016/S0378-5122(03)00036-7
67. Menopause Steering Committee. Menopause. In: Barrett TJ, ed. Trenton, NJ: NJAFP; 2022.
68. Richard-Davis G, Wellons M. Racial and ethnic differences in the physiology and clinical symptoms of menopause. *Semin Reprod Med*. 2013;31(5):380-386. doi:10.1055/s-0033-1348897
69. Newhouser LM, Maneval M, Rayalam K, Sabeeh G, Varela L. SSRIs vs. SNRIs for vasomotor symptoms of menopause. *Am Fam Physician*. 2022;105(4):430-431.

CME Accreditation Procedures

Accreditation Statements:

AFP Accreditation Statement:

The AAFP has reviewed The Menopause Transition: Optimally Protecting Emotional Health and deemed it acceptable for up to 2.00 Enduring Materials, Self-Study AAFP Prescribed credits. Term of Approval is from 06/23/2023 to 05/22/2024. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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