New Interventions for Menopausal Symptoms

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MEETING SUMMARY

National Institute on Aging
National Institute of Child Health and Human Development
National Institute of Mental Health
National Center for Alternative and Complementary Medicine
NIH Office of Research on Women's Health
NIH Office of Dietary Supplements

National Institutes of Health
Department of Health and Human Services

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New Interventions for Menopausal Symptoms
Meeting Summary

Introduction

A variety of symptoms may be experienced during the menopause transition including hot flashes, night sweats, and problems sleeping, reduced sexual desire and sexual dysfunction, depression, vaginal dryness, and urinary and bleeding complaints. While some women have few or mild symptoms, for others the discomfort of severe symptoms greatly diminishes their quality of life.

To better understand options for symptom management, on March 21-23, 2005, the National Institute on Aging (NIA) with the Office of Medical Applications of Research (OMAR), the National Center for Complementary and Alternative Medicine (NCCAM), the NIH Office of Research on Women's Health (ORWH) and other NIH institutes and centers sponsored an NIH State-of-the-Science (SoS) Conference on Management of Menopause-Related Symptoms in Bethesda, MD.

The independent SoS panel prepared and presented a state-of-the-science statement summarizing its findings after weighing all the scientific evidence from 1) a systematic review of the evidence prepared by the Agency for Healthcare Research and Quality (AHRQ) through its Evidence-based Practice Program; and 2) one and one-half days of expert testimony. The panel statement examined the nature of menopause-related symptoms in the context of ovarian aging and senescence and the surrounding biologic, and psychosocial milieu of the menopause transition. The panel then reviewed the efficacy, acceptability, safety, and risk/benefit profile of mainstream and promising hormonal and non-hormonal approaches for ameliorating menopause-related symptoms. Lastly, the panel identified opportunities for future research aimed at developing new strategies to treat menopause-related symptoms. The SoS panel statement[1] was published in the Annals of Internal Medicine in 2005.[2]

To follow up, the NIA in collaboration with NCCAM, NICHD, NIMH, NIH ORWH and the Office of Dietary Supplements (and other NIH institutes and offices) convened an advisory panel on July 11-12, 2006 and November 20-21, 2006 to:

- Review the statement of the independent panel of the March 2005 NIH SoS Conference on Management of Menopause-Related Symptoms and

- Make recommendations regarding the next steps to be undertaken by interested NIH institutes and offices to address priorities and new research opportunities targeted by the SoS expert panel. Such priorities and opportunities would be focused on developing and/or testing current or new interventions to reduce the burden of a number of menopause-related symptoms (to be identified by the panel).

The advisory panel included 10 investigators with expertise in reproductive endocrinology, epidemiology, hot flash physiology, psychometrics, psychiatry, quality of life, management of

menopause-related symptoms, complementary and alternative medicine, and clinical trials. Two FDA representatives with expertise in reproductive and urologic products also participated.

The purpose of this document is to review the key symptoms associated with the menopause transition, and to report recommendations issued by the advisory panel regarding needs for further research on the etiology and characteristics (e.g., severity, duration, etc.) of symptoms, as well as promising new strategies for managing menopausal symptoms. The following summary statement presents the results of the panel's deliberations as well as its recommendations.

Key Symptomatology

Perhaps the most significant challenge in studying the menopause transition and its associated symptomatology involves making a correct attribution of symptomatology to the menopausal process itself. Since menopause occurs against a background of aging, it is difficult -- if not impossible -- to make definitive attributions in many cases. Natural history studies of the menopause have provided data on the prevalence and incidence of symptoms in association with the process and progression of the menopause transition.[3] Based upon the proceedings of the 2005 NIH SoS Conference on Management of Menopausal Symptoms, and subsequent epidemiologic findings, the following symptoms were considered to be attributable to the process of the menopause transition with good evidence[4] and will be addressed in this statement:

1. Vasomotor symptoms (hot flashes and night sweats)
2. Vaginal dryness and dyspareunia
3. Sleep disturbances
4. Mood disorder and depression

Symptoms with mixed or inconclusive evidence for attribution to menopause that will be discussed in this statement include:

5. Sexual dysfunction
6. Quality of Life

   The concept that the menopause transition causes diminished "quality of life" and that this reduction in quality of life is a rationale for treatment was not addressed as a specific item in the NIH SoS Conference but will be briefly discussed within this document.

Symptoms found not to be directly linked to the menopausal process (and not addressed in this statement) but worthy of further exploration include:

7. Joint aches and muscle pain
8. Metabolic changes (weight gain, metabolic syndrome)

Key symptoms 1-5 will be addressed with respect to their clinical impact and natural history, pathophysiology, and clinical management.

Few studies have focused on the etiology of the most common symptoms of the menopause transition. Current measurement methodologies are of questionable relevance for evaluating some symptoms. For example, general menopause scales may not adequately measure many associated elements such as sleep or mood disorders. For other symptoms, measurements (e.g., which include polysomnography to diagnose fatigue due to sleep apnea), though excellent in their discriminatory power to separate affected from non-affected individuals, are so specialized or detailed that they are seldom deployed in large-scale epidemiological studies. Moreover, successful treatment of menopausal symptoms involves patient self-assessment and patient reported outcomes [PROs]. The use of PROs for menopausal symptoms requires special consideration when designing either etiologic or intervention trials.

I. VASOMOTOR SYMPTOMS

A. Clinical Impact and Natural History: Vasomotor symptoms (VMS, hot flashes and night sweats), are of very high priority for research for several compelling reasons. Of all menopause-associated symptoms, VMS are highly prevalent, vary by race/ethnicity, and are most clearly related to the menopause transition. Up to 80% of American women experience VMS at some time during the menopause transition or post-menopause.[2,3]

In the SWAN longitudinal study, depending on race/ethnicity, participant reporting of "any" VMS ranged from 28-55% during the early perimenopause and 52-85% during the late perimenopause. Reporting of VMS occurring >6 days ranged from 5-20% during the early perimenopause and 25-50% during the late perimenopause. African American women reported the highest prevalence, while Chinese and Japanese women had the lowest prevalence of symptoms.[5]

About 67% of all women naturally traversing the menopause report symptoms and seek at least one medical consultation for their symptoms.[6,7] Women with hysterectomy and ovarian preservation have a 70% greater likelihood of having moderate to severe hot flashes compared to same-aged naturally menopausal women, (64.8% vs. 49.2%), and 50% more likely to have moderate to severe sweating.[8] Similarly, among premenopausal women at risk for ovarian cancer, approximately 40% of those with a prophylactic bilateral salpingo-oophorectomy who do not use menopausal hormone therapy (MHT) experience VMS.[9] About 1-2% of women experience premature ovarian failure and an early onset of the menopause and these women appear to have worse symptomatology than age-appropriate, naturally menopausal women.[10]

It is unclear why VMS occur in some women and not others. Although VMS subside in most women (even without intervention), some 4.8% of women in their 60's-70's report moderate-to-severe VMS.[11] In general, currently known risk factors do not provide strong predictors for an individual woman, but African-American race, increased body mass index (BMI), cigarette smoking, low educational level and financial stress all predict a greater likelihood of VMS.[12,13] An improved understanding of the natural history of VMS is a critical research priority.

Additional populations of women are prone to VMS. Up to 13% of women in the U.S. may develop breast cancer over their lifetime. In 2005, 211,000 new breast cancers occurred with 40,000 deaths[14] and in 2007, 178,480 new cases and 40,460 deaths are expected.[15] Approximately 75% of women diagnosed with breast cancer are postmenopausal[16] and most will be diagnosed with tumors overexpressing estrogen or progesterone receptor.[17] Hormonal intervention strategies in the form of tamoxifen, aromatase inhibitors, or a sequential administration of the two for a total of 5-10 years is recommended to almost every woman with a hormone receptor-expressing tumor.[18] Tamoxifen and aromatase inhibitors are commonly associated with menopausal symptoms such as vasomotor symptoms, vaginal dryness or discharge, and musculoskeletal complaints. Hot flashes were reported by 37-40% of women on tamoxifen and 32-35% of women on aromatase inhibitors.[19,20]

About 25% of women with breast cancer will be premenopausal at diagnosis. These women may receive chemotherapy (which may induce menopause), hormonal therapy (which may include tamoxifen), or both. Up to 90% of premenopausal women who receive both chemotherapy and anti-estrogen hormone therapy experience VMS[21] and the menopausal symptoms experienced by these women may be greater in frequency and/or more bothersome than those in naturally menopausal women.[2] These women may also suffer other gynecological symptoms, and are at greater risk for accelerated bone loss.[22] Menopausal symptoms may also be problematic in women at high risk of breast cancer who are prescribed tamoxifen for risk reduction.

Menopausal hormone therapy (MHT, or estrogen with or without progestin) is the gold standard for treating VMS because of its high efficacy and general acceptability. However, the release of the controversial WHI findings in July 2002[23,24] resulted in an immediate and substantial decline in MHT use. In the first 6-8 months after the WHI estrogen plus progestin study findings were published, 56% of MHT users surveyed at a large California HMO reported attempting to quit MHT;[25] 74% quite successfully, while 26% resumed MHT.[26] Among women enrolled in the San Francisco Mammography Registry, there was a decline in MHT use of 18% per quarter in the year following the WHI report(s),[27] and, in one multicenter study, estrogen plus progestin use declined 46% while, in another study, use of unopposed estrogen declined 28%.[28] These studies indicate that many women will choose to tolerate their symptoms rather than take a medication that has significant risks. Nevertheless some 8-9% of women overall, and 17% of perimenopausal women, continue using MHT despite the risks, perhaps due to intolerable symptoms.[28] This intolerability may relate to VMS, impaired sleep or diminished feelings of well being.[29,30,31] Although a recent subgroup analysis of WHI data showed that 50-59 year old women initiating MHT closer to menopause had no increase in CHD risk and a 30% decrease in total mortality (compared to older women who were more than 10 years from their menopause),[32] it is unclear how these findings will affect women's decisions to use MHT. Importantly, many women whose symptoms could be relieved by MHT are unable to use estrogen due to contraindications or side effects. Thus, the problem of VMS affects large numbers of women, has substantial clinical impact, and is directly attributable to the cessation of, or interference with, ovarian function and endogenous estrogen production. Finding new efficacious and safe therapies would significantly improve quality of life for women who find their symptoms intolerable.

B. Pathophysiology: While the fundamental etiology of vasomotor symptoms is poorly understood, reports that behavioral therapies such as paced respiration may be effective, suggest that a cortical pathway influences the onset of VMS, and that this pathway may potentially be exploited to modulate the occurrence or severity of these symptoms.[33] The efficacy of some selective serotonin reuptake inhibitors (SSRIs; e.g., paroxetine) and particularly serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g. venlafaxine) further implies that serotonergic and noradrenergic pathways are also involved.[34] Linkage of the onset of VMS to estrogen withdrawal is strong. Women who are administered agents that abolish endogenous estrogen production, such as GnRH agonists or antagonists, as well as aromatase inhibitors or mixed estrogen agonists like tamoxifen, experience VMS.[35] One study showed that some 90% of breast cancer patients treated with GnRH agonists reported VMS.[36] Men administered GnRH agonists for prostate cancer report similar prevalence of VMS as do women using these agents.[37]

Even though withdrawal of, or interference with, estrogen action elicits VMS, there is not a strong linkage of circulating estradiol levels to VMS. Thus, some menopausal women with very low measurable endogenous estradiol will not report VMS, whereas others with higher measurable levels (as may occur in late perimenopausal women) appear to suffer from severe VMS. The hormonal basis underlying VMS is clearly worthy of further exploration and may be due to individual mitigating factors such as estrogen receptor status and subtypes and other genetic considerations.

Women who take hormone therapy and then discontinue its use have about a 50% risk for recurrence of their vasomotor symptoms.[38] This is especially true for women who had a hysterectomy or who had vasomotor symptoms prior to initiating hormone therapy.[26] Women should be informed in advance about the potential risk of vasomotor symptoms recurrence after exogenous hormones are withdrawn. The mechanisms underlying the recrudescence of vasomotor symptoms upon discontinuation of exogenous estrogen, while not known, are believed to be similar to those operating after abrupt endogenous hormonal withdrawal, such as after bilateral oophorectomy.

The current inadvisability of long term menopausal hormone therapy makes the development of non-hormonal interventions for VMS a major research priority. Further etiologic research is imperative to elucidate the exact neural circuitry involved in VMS. The pathophysiological construct of VMS in the causal pathway of sleep disorders which in turn further exacerbates the bothersomeness of the VMS also merits further exploration, because methods to improve sleep, even in the face of persistent VMS, might also hold promise for reduction of vasomotor symptomatology.

C. Clinical Management. Treatment trials for VMS in women commonly suffer from methodological shortcomings. Clinical trial outcomes have often focused on frequency of vasomotor symptoms, due to its relative ease of measurement. However, the frequency of vasomotor symptoms experienced may not correlate with the degree to which they disrupt a woman's life. There is no universally accepted criterion for the measurement of 'bothersomeness' and thus categorizing the personal impact of VMS is problematic. The degree of relief or efficacy called for in certifying new therapeutic agents has typically been based on that of estradiol, which is over 80% effective in relieving VMS.[39] This level of effectiveness may not be necessary with treatments (such as paced respiration) that have low or no risk and

which may be readily deployed for widespread use. The degree of relief observed in a clinical trial that would generate enthusiasm as "clinically meaningful" is not clear on the basis of known PROs.

***Recommendations**: The New Interventions for Menopausal Symptoms (NIMS) Advisory Panel enthusiastically endorsed the recommendation of the NIH SoS panel to increase research focused on developing new strategies for combating VMS. Potential new therapies for vasomotor symptoms should be based on: 1) an understanding of the biologic and physiologic causes of symptoms; 2) identification of modifiable risk factors; 3) secondary data analyses of existing databases from clinical trials and natural history studies of the menopause transition; 4) more pertinent information from new focus groups of symptomatic women; 5) traditional and alternative behavioral and non-pharmacologic therapies; 6) MHT with estrogen; 7) approved drugs (such as SSRIs, SNRIs) that may impede activation of pathways proposed to mediate vasomotor symptoms; and 8) new and potentially safer drugs, including estrogen receptor-beta selective agonists.*

Data from existing natural history cohorts should be scrutinized to better understand the characteristics, concomitants and risk factors for VMS. Basic research into the physiology of VMS should be conducted to provide leads for the development of targeted therapies. The current FDA guidelines for the design of pharmaceutical trials for the therapy of VMS should be reconsidered with the aim of facilitating the testing of mono- and multiple modality therapies that may be of lesser efficacy than estrogen. Although current methods for self-measurement of VMS frequency are adequate, agreement is lacking on suitable methods for evaluating the severity (i.e., 'bothersomeness') of VMS. The development of an appropriate conceptual framework and more relevant assessment tools and questions (e.g., "How much of your time or energy was spent controlling, planning for, or reacting to, your hot flashes today?") is strongly encouraged. A common language and standardized approach should be developed in assessing VMS and reporting related outcomes in a uniform manner across studies. More extensive use of objective measures of VMS (e.g., from physiologic monitors) would help inform self-report measures and increase the scientific value of treatment trials as well as etiologic studies.

***There are currently no FDA-approved pharmaceuticals for VMS apart from estrogen-containing preparations. Multicenter clinical trial research designed to determine the efficacy of alternatives to estrogen in a broad and representative range of women of diverse race/ethnicity should be considered a high priority.** There are many agents that have been used 'off-label' for VMS, and appropriate testing and establishment of safety and efficacy for these agents in the management of VMS is a top priority. Existing agents appropriate for further testing include: SSRI/SNRI drugs and gabapentin. Additional promising strategies of interest are: ER beta receptor modulators and other SERMs with profiles appropriate for alleviating VMS; behavioral therapies (such as paced respiration), and complementary and alternative medicine (CAM) remedies. Research should incorporate objective as well as self report measures of symptoms. Subgroups of women of particular interest for study of VMS include women with moderate to severe symptoms, women with prolonged symptoms that have not improved many years postmenopause, and, in etiologic studies, women who have never experienced VMS. Women who discontinue hormone therapy and then experience a recurrence of VMS are also a priority for further study.*

II. SLEEP DISTURBANCE

A. Clinical Impact and Natural History. Although sleep disturbance increases with age in both men and women, this disorder rises dramatically from approximately 12% to 40% in women only, during midlife,[40] consistent with the typical age of the menopause transition and early postmenopause. The term 'sleep disturbance' describes any difficulty sleeping, including a perception of unrefreshing sleep or poor sleep quality. Sleep disturbance can range from mild to severe and can be transient or persistent. In contrast, insomnia is a clinically defined disorder involving persistent difficulty initiating or maintaining sleep for at least one month *and* evidence that this sleep disturbance has a significant deleterious impact on daytime function or induces marked distress.[41] The clinical disorder of insomnia is a debilitating condition that burdens personal relationships, diminishes workplace productivity, and causes motor vehicle accidents. An important potential consequence of sleep disturbance is persistent daytime sleepiness, which is a major mediator of risk for motor vehicle accidents. For the approximately 70 million Americans estimated to have insomnia, direct costs are $14 billion annually and indirect costs (e.g., work loss, property damage from accidents) are $28 billion annually.[42] Insomnia is also associated with important medical conditions and morbidities, including cognitive decline, congestive heart failure, chronic obstructive pulmonary disease, back/hip problems, falling, and major depression.[2]

Sleep disturbance was identified by the NIH SoS Panel as an important symptom associated with the menopause transition and early postmenopause.[2] Several large epidemiologic studies have consistently shown that the menopause transition is associated with more sleep disturbance than is reported in late reproductive-aged women.[43,44] In the Study of Women's Health Across the Nation (SWAN), 42% of women in the menopause transition and early postmenopause reported sleep disturbance.[43] Another epidemiologic study of women 18 years and older reported that 26% of perimenopausal (defined as having one or more irregular cycles in the past 12 months) women and 14.4 % of postmenopausal (12 or more months of amenorrhea) women, compared to13 % of premenopausal women reported symptoms consistent with the clinical disorder of insomnia that persisted for six or more months.[31]

However, despite strong evidence of an association of the menopause transition and early postmenopause with sleep disturbance and the disorder of insomnia—both of which were defined by self-report-- studies measuring sleep objectively (with polysomnography) have not found measurable differences in sleep continuity (i.e., sleep efficiency, sleep latency, wake-time after sleep-onset, number of awakenings) or sleep architecture (i.e., percent time in light sleep, deep sleep, and REM, time to first REM).[50] However, self-reports of sleep disturbance and objective measurements of sleep are often not well correlated.

B. Pathophysiology. A critical limitation to developing optimal therapies for women with insomnia that arises during the menopause transition and the early postmenopausal years is the incomplete understanding of the pathophysiology of this disorder in midlife women. Nocturnal VMS (or night sweats) have been considered the primary factor leading to sleep disturbance and insomnia during the menopause transition and early postmenopause, but evidence supporting the etiologic role of VMS in sleep disturbances and insomnia is limited and controversial. Several large epidemiologic studies have found a strong association of self-reported VMS with self-

reported reduction in sleep quality[44] and with the clinical disorder of insomnia.[31] However, results of studies in which sleep is measured objectively are contradictory.[44,45,46,47,48]

Sleep apnea (a sleep disorder characterized by frequent pauses in breathing during the night) may also contribute to the increase in sleep disturbance and insomnia during midlife. Sleep apnea increases with age and body-mass index (BMI), and is more common in men than in women. Among middle-aged individuals, sleep apnea occurs in 4% of men and 2% of women.[49] However, the prevalence of sleep apnea (apnea-hypopnea index ≥ 15) is increased substantially in postmenopausal women (to 29.1%), compared with women who are in the menopause transition (18.4%) or who are of late reproductive age (10.8%).[50] It is not known why the prevalence of sleep apnea increases in postmenopausal women, but it is thought not to be primarily related to age or increasing BMI with age.

C. Clinical Management. Several important therapies to treat insomnia occurring in women during the menopause transition are available and have been tested. Estrogen therapy improves subjectively measured sleep disturbance,[51,52,53] particularly in women with VMS. However, results of studies examining the effects of estrogen (in mixed groups of peri- and postmenopausal women) on objectively measured sleep parameters are inconsistent, with estrogen improving varying parameters of sleep architecture and sleep continuity.[54,55,56, 57,58,59] Selective GABA-A non-benzodiazepine hypnotic agents such as zolpidem[60] and eszopiclone[61] have been shown to improve subjective measures of sleep quality and continuity in women with insomnia during the menopause transition. However, estrogen and hypnotic agents may not have broad acceptability for long-term use. Non-pharmacological behavioral therapies (e.g., sleep hygiene) used to treat insomnia in other populations may be widely acceptable in menopausal women, but have not been studied in this population. Although, one prospective study in breast cancer survivors showed that women randomized to low dose paroxetine had a statistically significant improvement in sleep scores compared to placebo (P=0.01),[62] little is known about the effect of non-hormonal agents (e.g., serotonergic and serotonergic-noradrengergic agents) used to treat VMS on sleep disturbance in women with VMS.

Recommendations: *Detailed data on sleep disturbance in association with the stages of the menopausal transition should be extracted from existing natural history studies of the menopausal transition. Advances from pathophysiologic research are necessary to inform the design of intervention studies of remedies for menopause-associated sleep disturbance and insomnia. As indicated by the NIH SOS conference panel, research focused on the relationship between VMS and insomnia is highly warranted, given the uncertainty about the impact of VMS on this disorder. Methods for screening participants into sleep studies that isolate stage of the menopause transition as the variable of interest (and e.g., exclude or stratify women with sleep apnea and depression) are needed.* ***Multicenter clinical trial research in a broad and representative range of women designed to determine the efficacy of promising sleep agents should be considered a priority. Hypnotic agents (e.g., zolpidem, eszopiclone and older generation agents), non-hormonal treatments for VMS, and non-pharmacological behavioral therapies should be specifically evaluated for their efficacy and acceptability as sleep therapies during the menopausal transition.***

III. MOOD DISTURBANCE

A. Clinical Impact and Natural History: Studies of mood during the menopause transition have mostly focused on depressive symptoms. The occurrence of these symptoms does not necessarily represent a clinical problem requiring treatment unless they are persistent and interfere with social or occupational functioning. More recent studies have focused on the clinical disorder of depression (major depressive disorder or MDD), a serious medical illness that requires medical attention. MDD is diagnosed when sadness and/or loss of interest are present most days, most of the day, persist for at least 2 weeks, interfere with function, and are associated with neurovegetative features (poor sleep, poor concentration, appetite changes, low interest, low energy, and/or suicide thoughts). MDD affects 15 million American adults, approximately 5–8% of adults, each year. MDD is the 3rd highest leading cause of burden of disease in the US.[63] Depression also precedes many medical illnesses by 6-8 years and may be a modifiable risk factor for disorders such as cardiovascular disease, metabolic syndrome, and dementia. MDD affects twice as many women as men over the course of the lifetime. It is not known why there is an increased likelihood of MDD in women, but fluctuating reproductive hormones during the reproductive years are hypothesized to be a factor.[64]

In 2005, the NIH SoS Conference panel concluded that there was not a clear relationship between the menopausal transition and either mood symptoms or MDD because available data were lacking or inconsistent.[2] A relationship with MDD would have been difficult to establish given that data available at that time were focused primarily on measures of depressive symptoms, and not MDD. Moreover, epidemiologic studies examining the association between the menopause transition and depression symptoms used highly variable methodology, including the definitions of both stages of the menopause transition and depressive symptoms. In addition, few studies have examined the association between the menopause transition and other mood symptoms, such as anxiety or irritability.

However, since the 2005 NIH SoS Conference panel report, two epidemiologic studies have since demonstrated that the menopause transition is associated with a significant risk for MDD, even among women without a history of prior MDD.[65,66] These prospective cohort studies followed women with annual structured psychiatric evaluations for MDD as they transitioned from late-reproductive age into the menopause transition. In both studies, women with a history of MDD occurring at any time in their life prior to baseline were excluded. One study examining within-woman risk for depression found an increased likelihood of a first onset of MDD in the menopause transition in women who had no previous depression (OR 2.50, CI 1.25, 5.02 in unadjusted analyses).[66] Results from another study of women who had not had prior MDD, showed a trend towards a statistically significant increase in the risk of developing a first-ever episode of MDD during the menopause transition (odds ratio [OR] 1.8; 95% confidence interval [CI] 1.0-3.2) relative to women in the late-reproductive years, after adjusting for age and stressful life events. After restricting the sample to women with VMS, there was a significant effect of being in the menopause transition on MDD (adjusted OR 2.2, CI 1.1-4.2).[65]

B. Pathophysiology. It is not known why there is an increased risk of MDD during the menopause transition. One theory is that MDD during the menopause transition is a consequence of VMS and associated sleep disruption. However, data supporting an association

between VMS and depression are mixed. Some studies show an association between depression and hot flashes[29,30,65,68] whereas others do not show an independent contribution of hot flashes after adjusting for other risk factors.[66,67]

Another theory is that withdrawal of estradiol or variability in the levels of estradiol[67,68,69] lead to MDD in some women through changes in neurotransmitters involved in mood regulation.[64,69] This is supported by recent data from a population-based cohort showing that the onset of a first MDD episode is associated with variability of estradiol and increasing FSH.[66] Because all women experience an increase in FSH and a fall in estradiol during the menopause transition, but the majority does not experience MDD, it has been hypothesized that there is a differential sensitivity to the effects of these hormonal changes in a subset of susceptible women.[69]

Several other characteristics have also been shown to be associated with depressive symptoms or a clinical diagnosis of MDD during the menopause transition. Women with a prior history of depression are at increased risk.[30] Other risk factors include longer duration of the menopause transition, history of premenstrual syndrome or postpartum depression, stressful life events, as well as complaints of poor health, history of smoking, disturbed sleep, reduced parity, and absence of a partner.[30,66,70,71] Many of these risk factors are not specific to the menopause transition and apply to MDD during other stages of life as well. Several proposed risk factors, such as insomnia, increased stress, and complaints of poor health may be symptoms of, and not necessarily a cause of, a current MDD episode. Finally, while many of these factors are frequent accompaniments of MDD, none are uniformly present in women with MDD during the menopause transition.

C. Clinical Management: Treatment studies of clinical depression during the menopause transition are limited to a series of small clinical trials of estrogen therapy, including open-label studies of estrogen and antidepressants, and two placebo-controlled randomized trials of estrogen therapy. Several small placebo-controlled randomized trials have shown that short-term administration (3-8 weeks) of estradiol therapy (transdermal patches either 0.05 or 0.1 mg/day) effectively treats MDD and other depressive disorders (dysthymia and minor depression) in women during the menopause transition.[72,73] The effectiveness of estradiol appears to be limited to the menopausal transition and early postmenopausal period because randomized studies of older women who were 5-10 years postmenopause did not demonstrate efficacy compared to placebo.[74] Similarly, several small open-label trials have demonstrated that perimenopausal and recently postmenopausal women with MDD and other depressive disorders (dysthymia and minor depression) improve when treated with traditional antidepressants such as citalopram,[75] mirtazapine,[76] escitalopram,[77] and duloxetine[78] alone or in combination with estradiol therapy. No studies have identified specific characteristics of women who are more likely to benefit from traditional antidepressants versus hormonal therapies.

Recommendations**: Because the menopause transition may be a pivotal event in the development of an episode of MDD (first-ever in lifetime or recurrent), studies addressing the treatment of MDD during the menopause transition are of high priority. Careful characterization of the stages of menopause transition as well as detailed, structured interviews to determine a clinical diagnosis of MDD are essential components of such studies.* ***Treatment algorithms for women with depression occurring in relation to the menopause transition need to be developed.

Multi-center clinical trial research in a broad and representative range of women designed to determine the efficacy of low-dose estrogen, antidepressants, and adjunctive use of estrogen with antidepressants should be considered the first priority. Treatment studies should include women with clinically diagnosed depression (MDD) and also those with mood symptoms, such as depressed mood, anxiety, and irritability that do not meet criteria for MDD or other depressive disorders. Previously untested interventions (e.g., psychotherapy, ER beta agonists) are also of interest*. In order to design optimal treatment studies for depression in this population, additional data are needed to describe the pathophysiology of depression during the menopause transition. Understanding the course and biological basis of depression during the menopause transition will determine which specific populations (e.g., within specific stages in the menopause transition or with co-occurring VMS and/or insomnia) should be prioritized for study and the optimal duration of therapy. The optimal treatment for menopausal women may vary depending upon menopausal status as well as the severity of depression and presence of other menopausal symptoms or stressful life events.* ***Studies evaluating whether there is a differential response of depressive disorders to different treatment interventions depending on the presence or absence of vasomotor symptoms, the type and severity of the depression (MDD, minor depression, mood symptoms), and whether the index episode is a first lifetime episode or recurrent episode of MDD, should also be considered a priority.***

IV. Vaginal Dryness

A. Clinical Impact and Natural History. Vaginal dryness and dyspareunia are common complaints among middle-aged women with an estimated prevalence of vaginal dryness ranging from 4% to 22% in reproductive-aged women, from 7% to 39% in women in the menopause transition, and from 17% to 30% postmenopause.[2]

The term "vaginal dryness" is frequently used in conjunction (or even interchangeably) with the term "dyspareunia." Patients and clinicians often assume that vaginal dryness symptom(s) in the peri and postmenopausal woman are due to estrogen deficiency without consideration of other conditions or cofactors. In clinical practice and in research, vaginal dryness that exists apart from sexual activity should be distinguished from vaginal dryness which is exclusively associated with sexual activity (and that might be better described as lack of adequate lubrication) and include an evaluation of the contribution of estrogen deficiency and alternative or co-existing conditions to the overall problem.

Vaginal symptoms as reported by patients often differ from the degree of vaginal atrophy objectively assessed by clinicians. Symptoms are sometimes more and sometimes less severe than the apparent objective findings. Other conditions (such as vaginal infections or reactions to local irritants) with overlapping symptoms of vulvar and/or vaginal dryness may be overlooked, and the extent to which this occurs is unknown.[79] Hyperplastic skin disorders of the vulva (i.e., lichen sclerosis) can sometimes produce symptoms that are similar to vulvovaginal atrophy caused by estrogen deficiency. Clearly, misdiagnosis can result in inappropriate treatment. Vaginal atrophy due to estrogen deficiency is characterized by a maturation index showing a low level of superficial epithelial cells and a high vaginal pH.[80] However, symptoms do not always

correlate with these objective findings, and there are currently no validated scales to assess vaginal symptomatology, greatly limiting research as well as accurate and reliable clinical assessment. Thus, research is greatly needed to identify the various underlying causes and cofactors of the symptom of vaginal dryness during and after the menopausal transition and to develop better means of diagnosis. The development of validated clinical algorithms for efficient and effective diagnosis and management strategies would be highly valuable for clinicians across many specialties (obstetrics-gynecology, family practice, internal medicine, etc.).

B. Pathophysiology. In the presence of estrogen, urogenital tissues thicken and become cornified. With the lack of estrogen (in prepubertal and postmenopausal women), the vaginal wall is thinner. Following the menopause transition, the vulvar tissues also thin, and labia may become reduced in size and sensation, lessening enjoyment during intercourse, and, for many women, making it difficult to tolerate. Although the dermatologic changes associated with vulvovaginal atrophy have been described, the subdermal collagen changes and their responses to therapies other than estrogen are poorly understood and worthy of investigation.

C. Clinical Management. Estrogen is highly effective for vulvovaginal atrophy due to estrogen deficiency.[81] Thus, when this particular condition is diagnosed, the traditional approach to treatment has focused on systemic estrogen, usually to the exclusion of other alternatives except when estrogen is absolutely contraindicated or refused by the patient. Low dose systemic estrogen (e.g. 0.3 mg conjugated equine estrogens) has been shown to be effective for this symptom.[82] Although systemic estrogen may be reasonable as a short-term treatment for many women, because there are many subgroups of patients for whom it is contraindicated, and many women are no longer willing to use any form of menopausal hormone therapy, even in women at low risk, non-estrogen forms of treatment are needed, particularly for long-term use.

In sexually active women, vaginal estrogen preparations to treat vaginal dryness and alleviate pain with intercourse may be an attractive alternative to systemic therapy.[83, 84] Local estrogen use is known to increase circulating estrogen levels, but by much smaller amounts than oral estrogen therapy. However, because these topical estrogen therapies have not been studied in trials of adequate size or duration, actual levels of risk for long-term complications, such as breast cancer occurrence or recurrence, while presumed to be lower than those of oral therapy, remain unknown. Also while estrogen therapy may eliminate vaginal dryness, it may cause vaginal discharge and genital irritation in elderly women.[85]

While there are a variety of non-prescription products on the market targeting inadequate lubrication for sexual intercourse in women with symptoms of vaginal dryness, the effectiveness of these products is not established and needs further study.[86] Importantly, because inadequate lubrication is often narrowly addressed as exclusively a hormonal problem, optimal management should consider other commonly overlooked and understudied causes and cofactors (e.g., problems with arousal) specifically contributing to inadequate lubrication.

***Recommendations**: In middle-aged women, clinical management of vaginal atrophy with or without dyspareunia is highly problematic because of the lack of appropriate definitions for menopause-related vaginal symptoms (which precludes an adequate characterization of vaginal symptoms at menopause), the frequent presence of confounding conditions, and the unavailability of therapeutic agents other than OTC lubricants and moisturizers (of suboptimal*

efficacy) or prescription therapy with estrogen. ***A research imperative in this area is the development of a validated scale and algorithm which will allow the clinician to correctly attribute vulvovaginal symptoms to menopause and estrogen deficiency while ruling out confounding conditions. Estrogen therapy, while well studied for systemic use, lacks long-term efficacy and safety data for low-dose, local use. Thus, the benefits and risks of low dose vaginal estrogen preparations should be evaluated for treating menopause-associated vaginal atrophy in multicenter clinical trial research in a broad and representative range of women. Because there is a paucity of data endorsing the usefulness of currently available over the counter lubricants, an evaluation of such non-hormonal strategies as well as the development of other alternatives to estrogen should be considered a priority. Additional agents of potential effectiveness for vaginal dryness include SERMs with ER beta activity.***

V. SEXUAL FUNCTION.

A. Clinical Impact and Natural History. Sexual dysfunction is common among men and women in midlife.[87] In a recent population-based multinational study, 40-45% of women reported dissatisfaction with at least one aspect of sexual functioning[88] and this data is consistent with other surveys among US women.[87,89] The domains of sexual function are well known in women and there are numerous scales for self-reported sexual function. Categories of sexual dysfunction in women include problems with desire/interest, arousal, pain, and orgasm, and more than one of these complaints may be present simultaneously. [90]

While sexual function declines with aging, an independent effect of menopause on sexual function has been observed in some population based studies.[91,92] Longitudinal studies of the menopause transition have found that prior sexual function was the single best determinant of sexual function during and after the menopause transition, and that endogenous estradiol levels were the best hormonal predictor of sexual function in peri- and postmenopausal women.[93] Testosterone, and particularly the free androgen index, have been associated with sexual desire in two epidemiologic cohort studies.[93,94]

Despite the enthusiasm for androgen therapy for women with sexual dysfunction, the strongest rationale and proof of efficacy appear to currently exist only for oophorectomized women[95] who appear to have twice the risk for sexual dysfunction as their naturally menopausal counterparts.[96] Two randomized clinical trials in surgically menopausal women reported a significant improvement in sexual function and an increase in sexual frequency of one episode per month in women treated with transdermal testosterone.[97,98]

B. Pathophysiology. Despite a large body of knowledge on the female sexual response[99,100] and well-standardized measures of overall sexual function, little is known about the biological basis for changes in sexual motivation and responsiveness in women traversing the menopause

transition. Specific menopause-related changes in vaginal physiology, such as increased pH, reduced cornification, and reduced engorgement in response to sexual stimuli have all been shown to approach parameters in reproductive-aged women when estrogen is administered either vaginally or systemically, confirming a local role for estrogen on vulvovaginal tissues and on physiological responses associated with optimal sexual functioning.[101]

The role of the CNS as an important source of sexual motivation and sensation is underscored by the ability of SSRI drugs to profoundly decrease sexual motivation and to induce anorgasmia. Studies of sexual function in menopausal women should be viewed as high priority, given the large numbers of women who are affected.

C. Clinical Management. Therapy for sexual dysfunction is fragmented into approaches which seem to operate almost to the exclusion of each other. For example, even though "the brain is the most important sexual organ in the body" is a widely espoused aphorism, psychological approaches to sexual dysfunction seem to be neither widely available nor or proven efficacy.[102] More commonly, in the peri- and postmenopausal woman, female sexual dysfunction seems to be viewed as a primarily hormonal problem. Importantly, while women with a bilateral oophorectomy have markedly reduced circulating androgens, positive responses to androgen therapy and thus at least a physiologic rationale for androgen "replacement," therapy with androgens has been widely advocated (without compelling evidence) to encompass intact perimenopausal and naturally menopausal women who would otherwise seem to have an adequate endogenous source of androgens.

Androgen therapy for sexual dysfunction in women has been studied but not well enough to fully understand the potential short- and long-term benefits and risks and the subgroups of women who might benefit the most. Beyond menopausal hormones (without or with androgens) and psychotherapy, there is little else in the way of currently available empiric approaches to mind-body therapy. Given the very high prevalence of sexual dysfunction in the female population, not all of which is limited to menopause, research in this area should be viewed as a priority.

Recommendations*: The large number of women who complain of sexual dysfunction make this an area that should be considered for further investigation in studies of menopause-related symptoms, despite the currently inconclusive nature of its association with the menopause transition. Anorgasmia, either spontaneous or SSRI-induced, and dyspareunia secondary to vaginal atrophy are areas that are priorities for investigation. Secondary analyses of existing data sets are essential to best identify fruitful avenues of further investigation.* ***Existing remedies for sexual dysfunction, including estrogen and testosterone as well as new biobehavioral approaches should be investigated for both long-term efficacy and safety. Intervention studies with new agents including locally active nitric oxide inhibitors and CNS active dopamine agonists should also be considered.***

VI. QUALITY OF LIFE

A. Clinical Impact and Natural History: Many studies of symptomatology in menopausal women rely upon global scales or overall measures collectively purported to represent "quality of life." The validity of such methods of measurement and their ability, when used alone, to justify whether or not a specific treatment should be attempted has not been established. The NIMS panel felt that this was an area worthy of further investigation.

B. Pathophysiology: There are several models suggested for conceptualizing quality of life across the menopausal transition. The simplest construct proposes that symptoms attributable to the transition may act in an additive manner to produce distress. However, it is also possible that symptoms synergize to further intensify distress. In the latter case, vasomotor symptoms might exacerbate pre-existing anxiety, which might, in turn, increase vasomotor symptoms in a feed-forward fashion. Finally, a 'cascade' model has been suggested, in which an initiating symptom highly specific to the menopausal transition, such as vasomotor symptoms, disrupts sleep, which leads to adverse mood, and the subsequent chain reaction leads to a significant loss of quality of life. **The overarching sense is that menopausal symptoms do not occur in isolation, but rather that symptoms interact with each other in potentially complex ways. Given that the vast majority of women who traverse the menopause experience at least one symptom (usuallyVMS), and that many will experience at least one or two more, an improved understanding of the timing and sequelae of symptoms and their relationship to each other is considered a high priority for research.**

The trajectory of self reported quality of life is believed to differ markedly between women undergoing a natural versus surgical menopause. Abrupt production of a "menopausal transition" (induced surgically with bilateral salpingo-oophorectomy or another medical intervention) has been reported to cause more severe overall symptomatology. A determination of whether these induced symptoms appear together or progress in a predictable fashion could help to clarify the potential existence of a 'menopausal syndrome' and would elucidate whether symptoms erode quality of life in an additive fashion, a synergistic fashion, or in the manner of a 'cascade; (e.g., whether the emergence of vasomotor symptoms leads to sleep deprivation which precipitates adverse mood and ultimately leads to erosion of quality of life). Analysis of the changes in quality of life between women with a natural versus induced menopause would be expected to be highly informative. Selective study of women with abrupt (surgical or medically induced) menopause would be useful for the study of key symptom clusters (e.g., vasomotor symptoms) or for populations of interest (e.g., women with breast cancer taking aromatase inhibitor therapy). Such study designs would avoid some of the difficulties inherent in longitudinal naturalistic studies such as the lengthy duration of study, high participant burden and increased variability or 'noise' from other concurrent life events.

C. Clinical Management: Current management of menopausal symptoms does not routinely take into account the potential interactions between symptoms. Rather, symptoms are usually treated one at a time, on a prioritized basis. While some studies have used quality of life measurements as outcomes, the sensitivity of such measures may represent a major challenge for the detection of small differences in response to treatment. Very simple and/or global measures are likely to be sufficient to detect differences when an intervention has a very large

effect size in a highly symptomatic population (such as estrogen versus placebo treatment in women with severe vasomotor symptoms). More sensitive scales are usually needed to detect smaller or more subtle differences between groups or within a single individual. "All purpose" scales which attempt to assess multiple symptom dimensions using a very limited number of items are often inadequate for the assessment of the various domains of interest in studies where large differences are not expected.

***Recommendations**: There is a need to develop better methods for the measurement of quality of life and its improvement or change with various interventions. Appropriate scales should have:*

1. *Established reliability (internal consistency and test-retest reliability).*
2. *Evidence of construct validity (similar findings from similar study cohorts suggest that investigators are measuring what they purport to be measuring).*
3. *Good validity with respect to sensitivity to detect differences in severity between women and within women.*
4. *Limited number of "target" symptom dimensions in order to avoid excessive subject burden.*

Such instruments generally use a group of items (versus a single item) to measure various aspects of a particular symptom dimension (e.g. subjective severity, timing of occurrence, duration, frequency, bothersomeness, change in behavior due to symptom, etc.). They usually describe a feature of the dimension of interest, and, rather than using a dichotomous rating of "present/absent," have provision for ratings of multipoint references to levels of severity or frequency and are summed (with or without weights) items within particular dimensions to provide a composite score for the dimension. Measures should be administered as frequently as feasible to enhance detection of change over time, and sequence of changes, and increase the representativeness of any "last evaluation carried forward" if a subject drops out. ***Given the very large number of women affected by at least one menopausal symptom, development and utilization of sensitive, specific and relevant measurement instruments for quality of life for all menopausal symptoms in clinical trials is a priority. Before developing and testing new scales (which are highly time-consuming) it would be useful to have a small group of experienced investigators examine the evidence regarding the reliability, validity, and sensitivity to change, of the available scales (both published and unpublished).***

Appendix 1: Considerations in Conducting Menopausal Symptoms Intervention Studies

Populations: There should not be a priori restrictions to the populations of menopausal women to be studied. Although the largest single constituency of women which will be most affected by treatment consist of middle aged women who have not had a hysterectomy, a variety of populations should be studied, either because they comprise a large number of burdened women, they experience particularly severe symptoms or because their data may provide unique insights into the physiology of symptoms. These include but are not limited to women with:

- Premature ovarian failure
- Surgical menopause (hysterectomy with or without oophorectomy)
- Chronic reproductive conditions that result in irregular menses
- Still menstruating and in the menopausal transition prior to final menses
- Radiation or chemotherapy induced menopause
- Chemoprevention induced menopause (e.g. with aromatase inhibitors, tamoxifen) in reproductive-aged women
- GnRH agonist, SERM, or aromatase inhibitor induced menopause in reproductive aged women
- Plans to discontinue hormone therapy
- Prolonged symptoms (>5 yrs post final menses)
- No menopausal symptoms

Test agents for vasomotor symptoms, sleep disorders, mood symptoms or vaginal dryness that are now ready for testing include:

- Vaginal lubricants
- Very low dose estrogen vaginal or systemic
- "Bioidentical" or customized compounded hormones
- New SERMs with ER beta selective activity (two are currently in phase III trials)
- Phytoestrogens and other botanicals
- Hypnotics
- Gabapentin
- SSRI/SNRI drugs
- Cognitive behavioral therapy
- Biobehavioral therapies
- Traditional Chinese Medicine (TCM)

Appendix 2: Sources for Secondary Data Analyses for increasing knowledge on risk factors for and interactions between symptoms (VMS, sleep disturbance, mood disorder, vaginal symptoms and sexual dysfunction):

- ✓ SWAN: natural history of VMS, mood symptoms, vaginal dryness and dyspareunia, sleep disorders, weight gain and distribution, DNA and genetic data
- ✓ WHI: persistent symptoms
- ✓ Health Professions Cohort
- ✓ Nurses Health Study
- ✓ STAR and NSABP
- ✓ Harvard Study of Moods and Cycles
- ✓ Penn Ovarian Aging Study
- ✓ Melbourne Healthy Women's Study
- ✓ NHANES
- ✓ CDC Surveys
- ✓ National Health Interview Survey

Appendix 3: Essential Characteristics for Clinical Field Sites Performing Intervention Studies to Reduce Menopausal Symptoms:

A cost-effective way to achieve the goal of reducing the burden of menopausal symptoms would be to develop a consortium of researchers who will share multidisciplinary expertise, study design, measurement strategies, definitions of outcomes, study coordination, and data management while addressing underlying mechanisms and testing new treatments. The consortium should 1) include researchers focused on the pathophysiology and clinically meaningful assessment of vasomotor symptoms, sleep disturbance, mood disorders and vaginal dryness and 2) develop an on-going series of pilot clinical trials to identify the most promising treatments for full-scale trials. The use of uniform measures, and standardized definitions of outcomes and adverse effects will facilitate comparisons of efficacy and safety across treatments and help expedite the discovery of acceptable new options. Other essential characteristics include:

- Multi-site studies
- Access to a broad base of populations of interest, including multi-ethnic samples
- Placebo control for all studies
- Ability to conduct focus groups
- Access to appropriate consultants (i.e., biostatistics, psychiatry, oncology, gynecology, sleep) and technologies (vasomotor and/or sleep lab for clinical sites proposing objective assessments and mechanistic studies)
- Measures of clinical effectiveness against which risks can be balanced (FDA)
- Test agent with potential 50% efficacy (assume 30-40% reduction in VMS with placebo): need 80 women per arm=160 per study, or 20 per site per study, if 8 sites existed. Study duration of 6 months.. For biobehavioral interventions, smaller effect sizes are expected and therefore these studies may require larger sample sizes
- Placebo-controlled pilot studies of short duration (6-12 weeks)
- Demonstrated ability to successfully recruit and retain participants for clinical trials
- Capitated payments to sites per recruited participants in trials
- Concurrent etiologic and mechanistic research
- Linkage of etiologic studies with clinical trials when appropriate
- Coordinating Center for data
- Ability to store blood
- Ability to conduct assays for reproductive hormones
- Areas of welcome expertise: BMD, imaging, LC-mass spec ultrasensitive hormone analyses, sleep laboratory

Appendix 4: Strategies to Advance the Field and Encourage Further Research:

- Initiatives to conduct secondary data analyses
- Etiologic research on VMS, sleep, vaginal atrophy, mood (first episode of depression in menopausal women), aches & pains
- Development of sensitive and reliable assessment tools for vaginal symptomatology

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