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# Vasomotor Symptoms: Natural History, Risk Factors, and Treatment Options

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The menopause is a universal transition experienced by all women. It is characterized by menstrual cycle irregularity and ultimately cessation, reproductive hormone fluctuations, and for many women, symptoms such as vasomotor symptoms (VMS). In fact, VMS, or hot flashes and night sweats, are considered the cardinal symptoms of the menopause transition. VMS are episodes of profuse heat accompanied by sweating and flushing, experienced around the head, neck, chest, and upper back.[1] Most (60-80%) women living in the United States experience VMS at some point during the menopause transition, with prevalence rates varying by racial/ethnic group.[2] For a third of women, VMS are frequent or severe.[2-6]

The occurrence and frequency of VMS peak in the late perimenopause and early postmenopausal years,[2] or the several years surrounding the final menstrual period. This final menstrual period, defined retrospectively after 12 months of amenorrhea, marks a woman's entry into the postmenopause. The years preceding the final menstrual period, often accompanied by menstrual irregularity and skipping, are considered the perimenopause, which is further categorized into the early perimenopause, the period of marked menstrual cycle irregularity, and the late perimenopause, the time between 2 and 12 months of amenorrhea.[7] Notably, menopause stages are defined based upon menstrual cycle criteria rather than reproductive hormone levels, as gonadotropins such as follicle stimulating hormone (FSH) and ovarian hormones such as estradiol (E2) can fluctuate dramatically from month to month as well as among women during the perimenopause, making them somewhat unreliable markers during this transition period.[8]

Accumulating data indicate that women are typically the most symptomatic during the perimenopausal and early postmenopausal years,[2] yet a large minority of women report VMS earlier in midlife, when they are still cycling regularly.[9] Newer data also indicate that VMS last much longer than once thought, on average 7-10 years,

and milder symptoms persist much longer.[10,11] For 30% of women, moderate-severe VMS continue for >10 years after the final menstrual period.[12] VMS are common well into a woman's sixth and seventh decades of life.[4,13,14] However, it is also notable that there is wide variability in the experience of VMS across women. In an recent analysis of 1,455 women followed for 15 years, women followed one of four distinct trajectories of VMS: VMS primarily early in the pre- and perimenopause and declining at the time of the final menstrual period (18%), VMS starting right around the final menstrual period and persisting for years (29%), persistently high levels of VMS over the 15 years of the study (26%), and for a lucky minority of women (27%), few or no VMS over the transition.[15] Thus, for many women, VMS are a persistent experience for a decade or more.

## Impact of VMS

VMS are well known to have an important impact on quality-of-life, and are associated with reduced health-related quality-of-life across studies.[16,17] VMS are also consistent predictors of poor sleep, mood, and possibly cognition in midlife.

### Sleep

Many (35-60%) midlife women report problems with sleep, including trouble falling asleep, waking in the middle of the night, and waking up earlier than desired (early morning wakening).[18,19] In fact, sleep problems are so common during the menopause that they have been dubbed a core menopausal symptom.[18] Sleep problems can persist for years[20] and can cause considerable distress and impairment.[21]

VMS are a consistent predictor of poor sleep. VMS are associated with poorer reported sleep in cross-sectional epidemiologic studies,[19] longitudinal studies following women across the transition,[22] and in studies using daily diaries.[23] VMS have been associated with all aspects of sleep disturbance, including falling asleep, staying asleep, and early-morning awakening.[22] Notably, the majority of this evidence has come from studies using self-reported VMS and sleep. Studies using objective measures of both VMS and sleep have shown more mixed results, calling into question the causal nature of relations between VMS and sleep problems.[24] There is some evidence that women who report frequent VMS may have physiologic evidence of greater arousal during sleep or more disturbed sleep.[25] However, further work is needed to clarify whether VMS actually impact sleep, whether women with poor sleep recall more VMS upon awakening, or whether a third factor contributes to both poor sleep and VMS among midlife women. However, it is clear that the women reporting VMS are also those at risk for poor sleep during the menopause.

### Mood

The risk of elevated depressive symptoms[26-28] and clinical depression[29-31] increases during the perimenopause and early postmenopause relative to the premenopause. VMS may be a risk factor for negative mood during the menopause transition.[26,29-34] Notably, VMS can precede, follow, and occur concurrently with depression.[35,36] VMS may be distressing themselves or mood disturbance may be secondary to the impact of VMS on sleep. Alternatively, VMS may be a symptomatic manifestation of perturbations in neural systems that underlie depression. Serotonergic and noradrenergic systems, neurotransmitter systems often linked to depression, may be involved in the etiology of VMS.[37-41,42] VMS appear additionally to be associated with alterations in brain default mode network function[43] and changes in the hypothalamic pituitary axis,[44,45] changes also seen with depression. Thus, it is possible that central nervous system processes contribute to both VMS and depression. Further investigation is warranted to understand the causal relationship between these two common midlife symptoms.

### Cognitive Function

Some aspects of cognition, and specifically verbal learning and memory performance, may degrade as women transition through the menopause, effects not driven by chronologic aging.[46-48] While some work suggests that performance might bounce back in the postmenopause,[48] other data indicate that effects persist.[46] One contributor to these cognitive changes may be VMS, as women who report VMS have more memory complaints.[49] Further, physiologically-measured VMS have been related to poorer memory performance, differences not driven by sleep.[50] Some preliminary data indicate that when treating VMS, memory may improve with the reduction in VMS.[51]

## Physiology of VMS

The physiology of VMS is not fully understood, and likely represents an interplay between multiple physiologic systems. The menopause transition is characterized by dramatic fluctuations, and ultimately by decreases in the ovarian estrogen E2 and increases in the gonadotropin FSH. These hormones play an important role in VMS, as evidenced by the onset of VMS occurring during the

dramatic reproductive hormonal changes of the menopausal transition and by the fact that exogenous estrogen is an effective treatment. Further, lower E2 and higher FSH levels are associated with a greater reporting of VMS.[52,53] However, these hormonal changes do not solely predict VMS, and recent analyses indicate relatively weak relations between sex hormones and VMS.[15,49,50] Further, while all menopausal women experience these hormonal changes, not all women have VMS. Therefore, other physiologic systems must be at play.

Leading models characterize VMS as hypothalamic thermoregulatory heat dissipation events. The thermoneutral zone is the zone in which core body temperature is maintained, and mechanisms such as sweating or shivering are employed to keep the core body temperature in this range. Symptomatic menopausal women may have a very narrow thermoneutral zone;[54] among these women, small fluctuations in core body temperature can exceed this zone and trigger heat dissipation mechanisms such as sweating, flushing, and peripheral vasodilation (i.e., a hot flash). While some data support this thermoregulatory model, other systems have been implicated. VMS are believed to originate in the brain, and some data employing brain imaging point to several neural networks in the occurrence of VMS.[43,55] Further, serotonergic, noradrenergic, opioid, adrenal, and autonomic systems have all been implicated in VMS.[37-41] For example, reductions in parasympathetic nervous system control may be involved in the acute triggering of VMS,[56] and elevations in the stress hormone cortisol or altered hypothalamic pituitary gonadal axis function are also observed among women with VMS.[44,45] Some data further suggest genetic influences in VMS, including polymorphisms in genes encoding for estrogen receptors and enzymes involved in synthesis of and conversion between estrogens,[57,58] and select single nucleotide polymorphisms involved in synthesis and metabolism of steroid hormones.[59-63] Thus, many different systems have been implicated in VMS, and a comprehensive understanding of the physiology of VMS remains to be established.

## Risk Factors for VMS

### Race/Ethnicity

VMS show pronounced racial/ethnic variations in the United States. African-American women are most likely to report frequent, bothersome, and persistent VMS over the transition.[2,15,64] Caucasian and Hispanic women have broadly similar rates of VMS, with variation across different ethnic groups of Hispanic women.[65] Asian women in the United States are least likely to report VMS.[2,64]

The reasons for racial/ethnic differences in VMS are varied and not fully understood. Risk factors for VMS, including smoking, hormone use, socioeconomic position, adiposity, and hormone levels, show pronounced racial/ethnic variation yet racial/ethnic differences in VMS persist after controlling for these factors.[2] It has been suggested that the relative protection from VMS among Asian women is due to Asian women's high soy intake, yet epidemiologic data do not support this explanation.[2,66] Cultural variations in how women experience, interpret, label, and report VMS to others may also play a role in racial/ethnic differences in VMS.[67]

### Overweight/Obesity

The majority of women living in the United States are overweight or obese,[68] and weight gain is common during midlife.[69] Adiposity was once thought to be universally protective against VMS. Because androgens are aromatized into estrogens in body fat,[70] women with more adipose tissue would be expected to have higher levels of estrogen and thus a lower risk of VMS, or conversely thin women would be more likely to have VMS due to lower peripheral estrogen sources (aka, the "the hypothesis"). However, subsequent findings challenged this idea, indicating that higher adiposity may be a risk factor for VMS[2,71] and that body fat gain over midlife may increase the likelihood of VMS.[72]

Recent work has provided a more nuanced understanding of these associations, indicating that the direction of the association between adiposity and VMS appears to depend on chronologic or ovarian age. Adiposity appears to act as a risk factor for VMS earlier in the menopausal transition (e.g., in the perimenopause), yet protective later in the postmenopause.[73-78] Notably, the reversal of associations between adiposity and VMS by ovarian aging parallels that of the associations between BMI and endogenous E2: higher BMI is associated with lower E2 levels in the pre- and perimenopause, yet higher levels after the final menstrual period.[79] One perspective is that excess adipose tissue has a deleterious effect on ovarian function early in the transition, yet becomes the primary source of estrogen (estrone) after ovarian function ceases.

### Health Behaviors

The potential role of health behaviors in VMS has been of particular interest. One of the most consistently observed health behaviors associated with VMS is smoking. In one large cohort study, smokers had an over 60% increased likelihood of reporting VMS relative to nonsmokers,[2] adjusted for confounding factors. Both active smoking and passive smoke exposure are associated with VMS[66] possibly due in part to the anti-estrogenic effects of cigarette smoking.[80]

Other health behaviors, such as diet and physical activity, have shown weaker associations with VMS. Dietary factors (e.g., total kilocalorie, fat, fiber, caffeine, alcohol) are not reliably associated with VMS after accounting for confounding factors.[2,66] Phytoestrogen supplements may have a modest effect on VMS.[81] Physical activity has not been consistently associated with VMS after adjustment for confounding factors,[2,82] and moderate physical activity does not appear to improve VMS.[83]

### Negative Affect

Negative mood (affect) has consistently been associated with VMS. Not only can VMS impact mood, mood can impact VMS occurrence or reporting. In cohort studies, higher levels of anxiety, depressive symptoms, and perceived stress have been associated with an increased likelihood of reporting VMS occurring over the subsequent years.[2] Women with greater negative affect also tend to rate their VMS as more bothersome, even after accounting for the frequency of their VMS.[64] Anxiety appears particularly associated with VMS.[84,85] Whether negative affect has a direct physiologic impact to increase VMS occurrence is not known. However, it is known that negative affect can influence symptom reporting,[86] as women with a greater sensitivity to physical symptoms may be more likely to report VMS,[2] and research with physiological VMS monitors shows that negative affect predicts a greater likelihood of reporting VMS that are not detected physiologically.[87,88]

### Other Social and Demographic Factors

Child abuse and neglect is prevalent and associated with a range of health outcomes, including VMS. In one large cohort study, women who endorsed a history of child abuse or neglect (38% of the sample) were more likely to report VMS over midlife even after controlling for multiple factors.[89] Further, women who are in lower socioeconomic positions, including women with lower educational attainment, lower income, or who endorse difficulty paying for basics are more likely to report VMS.[2] The reasons for associations between socioeconomic position and VMS are not well understood, but they are not accounted for by potential confounders such as smoking, adiposity, negative affect, or race/ethnicity.[90,91] The influence of low socio-economic position or child abuse on health is likely the result of multiple psychosocial and physiologic processes operating over a life course.

## Emerging Links Between VMS and Disease Outcomes

VMS are known to be important quality-of-life issues during the menopausal transition, yet they have generally not been assumed to have implications for physical health. However, emerging research has begun to call this assumption into question.

### Cardiovascular Disease Risk

Recent research has begun to link VMS to indicators of cardiovascular disease (CVD) risk. Initial work came from several large trials of hormone therapy (HT) in which the elevated coronary heart disease event risk associated with HT use was highest among older women reporting moderate-severe VMS at study entry.[92,93] Subsequent findings from large cohort studies tested relations between VMS and subclinical cardiovascular disease (CVD). These indices are important to understanding CVD risk among midlife women, as midlife is typically before the onset of clinical CVD in women, and have been prospectively associated with CVD events among individuals without clinical CVD.[94-96] Evidence from cohort studies has indicated that women reporting VMS had poorer endothelial function, greater aortic calcification, and greater carotid intima media thickness (IMT), a marker of atherosclerosis, as compared to their counterparts without VMS; these associations were not explained by standard CVD risk factors or estradiol levels.[97,98] Subsequent research seeking to further refine our understanding of these associations has suggested that women with early onset VMS or with some level of existing CVD risk factor burden may be most at greatest CVD risk.[99-101] However, contradictory findings exist,[102-104] and associations between VMS and CVD risk require further investigation and explication in rigorously designed studies employing the most advanced measures of VMS. One such study is an NIH-funded study currently

underway in our laboratories (MsHeart), and initial findings support positive associations between VMS and subclinical CVD.[105] Should findings continue to replicate, VMS may be a symptomatic manifestation of underlying adverse changes in a woman's vasculature.

### Bone Health

Emerging research has linked VMS and bone mineral density and bone turnover. In one study, women reporting VMS had lower bone mineral density, particularly at the lumbar spine and hip for postmenopausal women and at the femoral neck for women earlier in the menopausal transition.[106] Studies next indicated that women with VMS had higher bone turnover as assessed by a highly sensitive marker of bone turnover, urinary N-telopeptide.[107] In both studies, associations largely persisted after controlling for confounders, although E2 and FSH levels accounted for some but not all of these associations. Potential reasons for associations between VMS and bone health require further investigation, with consideration of the hypothalamic pituitary adrenal axis and the sympathetic nervous system.[106] It is possible that VMS may be an important indicator of some aspect of declining ovarian function that is not captured by menstrual cycle changes or reproductive hormone levels.

## Treatments for VMS

Data indicate that menopausal symptoms such as VMS are a leading driver of midlife gynecology ambulatory care visits[108] and out-of-pocket expenditures.[109] Traditionally, VMS were treated with HT, the most effective treatment for VMS. However, secondary to widely publicized findings from large trials, such as the Women's Health Initiative (WHI) suggesting some health risk with hormone therapy (HT) for certain women,[110] many women have discontinued HT.[111] There has been great interest in other treatment options. In the wake of the WHI, many treatments are being used by the public or tested for the management of VMS, with varying degrees of evidence to support them. Notably, several recent position statements regarding treatment options for VMS have been released from leading international menopause organizations (North American Menopause Society, European Menopause and Andropause Society), and the reader is referred to these publications for more in-depth coverage.[112,113] The North American Menopause Society has also developed a free MenoPro app designed to assist patients and providers in decisions about menopausal symptom treatment.[114]

One important consideration in interpreting the literature on VMS is the pronounced placebo response of VMS, typically a 30% reduction in reported VMS in response to placebo. Thus, adequate blinding and inclusion of a control group is critical to testing VMS treatments. Second, mood and affect can influence the perception, experience, recall, and reporting of VMS. Since the majority of trials measure VMS solely via self-report, the degree to which many of these therapies impact the experience of the VMS rather than the physiologic occurrence of VMS remains to be clarified.[115]

### Prescription Pharmacologic and Supplements

#### *Hormone Therapy (HT)*

HT is typically a combination of estrogens and/or progesterone delivered orally or transdermally (e.g., ring, patch). HT is an effective treatment for VMS, is a U.S. Food and Drug Administration (FDA)-approved treatment for VMS, and has traditionally been the mainstay of VMS treatment. However, HT is not indicated for all women, such as those with a history of breast cancer. Recommendations surrounding the use of HT (e.g., dose, type, duration of use, patient characteristics) are evolving, and the reader is referred elsewhere for more in-depth coverage.[116, 135]

#### *Selective-Serotonin Reuptake Inhibitors (SSRI)/Serotonin Norepinephrine Reuptake Inhibitors (SNRI)*

Low-dose paroxetine salt (7.5mg/d), an SSRI, is the only non-hormonal pharmaceutical approved by the FDA for the treatment of VMS. Improvements can occur within several weeks and be maintained up to 24 months without negative effects on libido. A range of other SSRIs (escitalopram, citalopram) as well as SNRIs (venlafaxine, desvenlafaxine) have also been shown to be effective in reducing VMS relative to placebo. These treatments are typically not as effective as HT, yet one trial showed that venlafaxine (75 mg/day) was as effective as a low-dose oral estradiol (0.5 mg/day).[117] Some concerns about sexual side effects have been noted, but recent data on venlafaxine for VMS suggest that any changes are subtle.[118] Contraindications to SSRI/SNRI use are detailed elsewhere.[112] However, one notable contraindication is tamoxifen use. For these women, paroxetine and fluoxetine should be avoided due to their potent inhibition of CYP2D6, the enzyme that converts tamoxifen to its most active metabolite, critical for the efficacy of tamoxifen. SSRI/SNRIs may be useful for women experiencing some associated mood or anxiety symptoms, but in many cases doses for VMS are lower than that which is recommended for psychiatric use.

### *Other Pharmacologic*

Several other prescription pharmacologic medications have been tested for the treatment of VMS. Gabapentin, an antiepileptic drug, at doses of 900 mg/day (300 mg 3x/d) has been shown to reduce VMS. However, drop out from these studies has been high due to adverse effects such as dizziness, headache, and drowsiness, particularly at higher doses, which limits some conclusions about its efficacy and tolerability. Pregabalin has also received some consideration but evidence supporting its use at this time is limited. Clonidine, a central alpha-2 adrenergic agonist, has some efficacy in reducing VMS, but it is typically is less effective than other pharmacologic agents and may have other undesirable side effects.

### *Supplements*

A large range of supplements has been considered for the management of VMS in studies of varying size and quality. As supplements are not regulated by the FDA, investigators and consumers must carefully consider the source and purity of the product. One supplement that has received a great deal of attention is phytoestrogens/isoflavones (e.g., genistein, daidzein, glycitein, biochanin A, formononetin), which may have weak estrogenic properties. Although not entirely consistent,[119] recent data indicate that isoflavone supplements may have some modest efficacy in reducing VMS, particularly for women with the intestinal flora to adequately metabolize them (i.e., equol producers).[81] Thus, they may be useful for some women, particularly those with mild symptoms (and without a soy allergy). Another widely used supplement is black cohosh, the most commonly purchased botanical for VMS. However, a comprehensive review concluded that black cohosh was comparable to placebo in reducing VMS.[120] Given this lack of efficacy paired with concern of potential hepatotoxicity, black cohosh is not recommended for the treatment of VMS. Other supplements (crinum, dioscorea, dong quai, evening primrose, flaxseed, ginseng, hops, maca, omega-3s, pine bark, pollen extract, puerperia, Siberian ginseng, vitamin supplements) are not recommended for treating VMS at this time.

## Behavioral

Several behavioral techniques have been tested to manage VMS. Behavioral approaches are particularly appealing to women who hope to avoid taking medications. Further, these approaches have a relatively low risk of adverse events, and several approaches may have the potential for additional salubrious health effects. However, the majority of this research has been characterized by single trials, and much more research, including replication of findings and extension to larger trials, is urgently needed.

### *Hypnosis*

One of the most effective behavioral approaches to reducing VMS is clinical hypnosis. A six-session protocol reduced reported VMS by as much as 80% and physiologic VMS by 57%, significantly more than placebo.[121,122] This work on hypnosis is notable in the use of physiologic measures of VMS, demonstrating that hypnosis appeared to impact the actual physiologic occurrence of VMS rather than simply their report. However, this work has largely been conducted at a single site by a single investigative group, and whether this approach can be exported more widely is in need of investigation.

### *Exercise and Weight Loss*

Traditional lifestyle approaches, such as aerobic exercise and weight loss have received some limited investigation as approaches to reduce VMS. Some early observational studies indicated that more physically active or fitter women were less likely to report VMS, however, later findings have been more mixed.[123] Although physical activity is critical to overall health and well-being, little data supports it as an approach to reducing VMS. One well-designed study of 248 midlife women compared a moderate intensity aerobic exercise intervention to usual activity for the reduction of VMS, and found no difference in reported VMS with exercise relative to control.[83] Notably, physical activity may have opposing roles, positively impacting mood and body composition, which may improve VMS, but also acutely raising core body temperature, which may increase VMS.

Another potential lifestyle change that may improve VMS is weight loss, given observations that excess adipose tissue may be associated with increased VMS among perimenopausal women. Some evidence from post-hoc analyses suggests that weight loss may reduce VMS.[124] Another small trial designed to test weight loss for VMS reduction suggested that behavioral weight loss may help reduce VMS for women early in the peri- and early postmenopause.[125] However, the impact of weight loss on VMS has yet to be investigated in a large, well-powered trial.

### *Cognitive-Behavioral, Mindfulness, Paced Respiration, Yoga*

Other behavioral approaches to reducing or managing VMS include cognitive behavioral therapy, mindfulness-based stress reduction, yoga, paced respiration, and relaxation. Cognitive behavioral therapy[126] and mindfulness-based stress reduction[127] appear to be quite effective in helping women cope with their VMS. These interventions also may positively impact sleep. Cognitive behavioral approaches help women test and challenge maladaptive cognitions about their VMS and engage in behaviors that may help reduce stress and enhance coping with their VMS. Mindfulness-based approaches foster a non-judgmental awareness of bodily experiences and thoughts, and may additionally act to directly reduce physiologic arousal. These promising approaches are critical to test in other settings, with larger samples, and with rigorous consideration of associated mechanisms. Additional studies have tested yoga, which showed initial promise in helping women manage their VMS,[128] yet a later large study of a 12-week yoga practice showed little benefit to VMS.[129] However, the diversity of yoga practices is notable and warrants consideration. Finally, small studies indicated potential efficacy of paced respiration or of relaxation therapy,[130,131] yet later more rigorously designed studies provided little evidence for the efficacy of these approaches alone to reduce VMS.[132,133]

## Other Modalities

Several other modalities have been considered for managing VMS. One notable approach is acupuncture, a traditional Chinese medicine modality in which needles are inserted into the skin at key points to balance the flow of energy (chi). A large body of literature has examined acupuncture's efficacy in treating VMS. As a whole, this literature indicates that acupuncture is effective in reducing reported VMS frequency and severity, but only when compared to no treatment. Importantly, sham needling, a common placebo for acupuncture studies, shows similar efficacy as acupuncture in reducing VMS.[134] These data suggest that the effects observed with acupuncture are largely placebo responses (or supports the efficacy of sham needling), and acupuncture is not recommended for treating VMS at this time. Stellate ganglion blockade, a widely used anesthesia treatment for pain management in which a local anesthetic is injected at the C6 level of the cervical spine, has shown some promise in reducing VMS,[51] but further study of this approach is required.

In summary, women are using a range of approaches to attempt to reduce their VMS. At this time, the most effective pharmacologic approaches for reducing VMS appear to be HT and SSRI/SNRI medications; providers should refer to guidelines in prescribing these therapies. Most supplements are ineffective in reducing VMS, with possible evidence for isoflavones, although the purity of the supplement and a woman's equol status must be considered. A range of behavioral approaches may be effective, including clinical hypnosis, cognitive behavioral therapy, and mindfulness-based stress reduction. Given their low risk of adverse side effects and other potential beneficial effects, these should be considered first line approaches, depending on their availability, cost, and patient preference. For overweight/obese women early in the transition, weight loss may help ease symptoms. However, further investigation of treatments for VMS is imperative.

## Conclusions

VMS are the cardinal symptom of menopause, and a burgeoning body of research has yielded unique insights about this common midlife symptom. VMS are experienced by the majority of midlife women, and newer data indicate that they typically last a decade or more. VMS are associated with poorer quality of life, negative mood, and sleep problems during the menopause transition. Low education, smoking, negative affect, and for younger women, obesity are risk factors for VMS. VMS also show pronounced racial/ethnic differences, with African-American women particularly affected. Emerging work indicates that VMS may be linked to certain physical health indices, including subclinical cardiovascular disease and lower bone density. VMS spur many women to seek treatment from health care providers. Treatments to reduce or manage VMS are rapidly evolving and include pharmacologic options, including HT and SSRI/SNRIs, and behavioral options, such as clinical hypnosis, cognitive behavioral therapy, and mindfulness. However, there is an urgent need for further investigation and development in this area to make a range of effective treatment options available. Ongoing research will continue to yield critical information about VMS and their treatment in the years to come.

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