

Leading Article

Vasomotor Symptoms (VMS): Pharmacological Management and Updates

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Vasomotor symptoms

Hot flushes and night sweats are the most common symptoms seen in peri and postmenopausal women and known as vasomotor symptoms (VMS). Hot flushes originate as a sudden onset sensation of heat, arising from the neck and the central chest, and then rapidly generalized into the other parts of the body¹. Hot flushes are usually last for 1-5 minutes, but it can be last up to 15-60 minutes². The occurrence of hot flushes during sleep is termed night sweats¹. Other symptoms associat-

ed with VMS include headache, chest discomfort, nausea, anxiety, tachycardia, and tachypnoea.

VMS are common in postmenopausal women, though they can be appeared in perimenopausal period and rarely in premenopausal period³. It is evident that 60%-80% of postmenopausal women are experiencing VMS^{4,5}. Median duration of occurrence of VMS is about 5.2 years⁶. 15%-20% of postmenopausal women experience VMS for longer duration (up to 15 years)².

Pathophysiology

Despite extended research on occurrence of VMS, exact pathophysiology is not established yet. Currently, it is believed to be associated with reduction in estrogen levels during menopause, which is causing disturbances in thermoregulatory center in the brain⁷.

Core body temperature (CBT) homeostasis is regulated between the upper and the lower thresholds, which is called thermoregulatory zone or

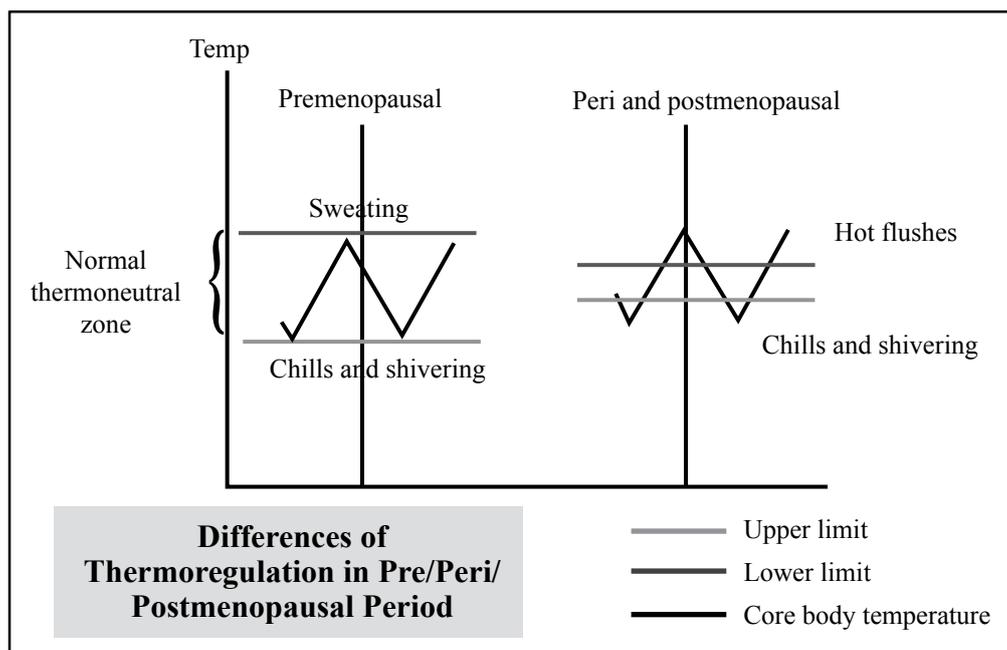


Figure 01 - The differences of thermoregulation during pre/peri/postmenopausal periods



thermoneutral zone. Vasodilatation and sweating occur when the upper threshold (upper limit) of normal thermoregulatory zone is exceeded. Chills and rigors occur when the lower threshold (lower limit) of normal thermoregulatory zone is exceeded⁸. Small changes in CBT are regulated by peripheral blood circulation.

Lower level of estrogen during peri and postmenopausal period is associated with narrowing of thermoregulatory zone in the hypothalamus due to several mechanisms⁷. This causes frequent hot flushes and sweating due to minor changes in the core body temperature (Figure 01). However reduced estrogen level alone does not explain the occurrence of vasomotor symptoms^{9,10}.

Several hypotheses have been postulated to discuss the reduced estrogen levels causing narrowing of thermoregulatory zone. These hypotheses include,

1. Role of serotonin and endorphins
2. Role of hypothalamic Kisspeptin, Neurokinin-B and Dynorphin (KNDy) signalling system
3. Role of CGRP (Calcitonin Gene-Related Peptide)

During premenopausal period, estrogen stimulate the production of serotonin and endorphins, and there is a decreased serotonin level after menopause, corresponding to declining estrogen levels. Hypothalamic thermostat is disturbed by the reduced levels of serotonin and reflectively increased level of norepinephrine, resulted in narrowing of thermoregulatory zone¹¹.

Kisspeptin/Neurokinin-B/Dynorphin Neurones (KNDy Neurones), which is located in infundibular nucleus of hypothalamus, secrete Kisspeptin, Neurokinin-B and Dynorphin. Kisspeptin act on GnRH neurones stimulating the secretion of GnRH, which in turn stimulate the secretion of LH and FSH. Neurokinin-B and Dynorphin have a autoregulation mechanism on the KNDy neurons. Neurokinin-B act on median preoptic nucleus and thereby thermoregulatory center, increasing

its sensitivity and narrowing the hypothalamic thermoregulatory Zone¹². Estrogen has a negative feedback on KNDy neurones. During menopause, lack of estrogen and its negative feedback on KNDy neurons cause increased Neurokinin-B signalling, resulted in narrowing of thermoregulatory zone causing VMS¹².

CGRP is a potent vasodilator seen in peripheral circulation. Serum CGRP levels are significantly higher in postmenopausal women who experienced VMS than premenopausal women¹³. 24-hour urinary excretion of CGRP level is found to be higher in women who experienced VMS than who did not experience VMS¹⁴. There are no differences of serum CGRP levels between premenopausal and postmenopausal women who did not experience VMS¹³. Some studies have found an increased serum CGRP levels during the onset of hot flushes¹⁵. These findings suggest that serum CGRP levels are regulated by serum estrogen level and reduction of serum estrogen level is associated with increased serum CGRP levels. The occurrence of VMS induced by CGRP may be mediated by increased peripheral vasodilatation following increased serum CGRP levels¹⁶. However, exact association of serum CGRP levels with occurrence of VMS is yet to be studied.

Effects of VMS

VMS are negatively affected on work productivity, interpersonal relationships, sleep quality and overall quality of life in menopausal women. Persistent symptoms have caused increased health-care resource utilization and increased healthcare related cost.

Treatment options

Treatment options of VMS include pharmacological therapies and complimentary therapies. Pharmacological therapies include Menopausal Hormone Therapy (MHT) and non-hormonal therapies like SSRIs, SNRIs and Gabapentinoids. Complementary therapies include herbal and nutrient supplements, lifestyle changes and mind body techniques. In addition, emerging therapies



include selective Neurokinin-3 (NK-3) receptor antagonists and dual Neurokinin-1 (NK-1) and Neurokinin-3 (NK-3) receptor antagonists.

Pharmacological therapies and emerging therapies are discussed in this review.

Menopausal Hormone Therapy (MHT)

MHT is the most effective standard treatment for VMS¹⁷. Cochrane review of randomized control trials on MHT concluded that it is highly effective, with a 75% reduction of frequency and severity of VMS¹⁸. Current recommendation is to start MHT within 10 years of menopause or under the age of 60 years (within window period).

However, MHT is associated with multiple adverse effects including venous thrombosis, transient ischaemic attacks, stroke, myocardial infarction, pulmonary embolism, and breast cancer¹⁹. These systemic adverse effects can be minimized by local application of estrogen preparations by the means of transdermal estrogen patches, which has desirable serum estrogen concentration with small doses. Despite of the mode of administration, it is associated with increased risk of breast cancers, and in some patients MHT is contraindicated. Absolute contraindications of MHT include current breast cancer, current venous thromboembolism (VTE), active liver disease and SLE with renal involvement. History of breast cancer, history of VTE, migraine, epilepsy and other gynaecological cancers are considered as relative contraindications for MHT.

According to the newer evidence, MHT with combined equino estrogen (CEE) and medroxyprogesterone acetate (MPA) is not associated with increased risk of all cause, cardiovascular and cancer mortality for a median of 5.6 years²⁰. Further, MHT with CEE alone is not associated with increased risk of all cause, cardiovascular and cancer mortality for median of 7.2 years²⁰.

Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)

SSRIs and SNRIs are non-hormonal pharmacological treatment options which are effective in reducing symptoms of VMS²¹. Statistically significant reduction of VMS severity with SSRIs (Paroxetine, Citalopram and Escitalopram) and SNRIs (Venlafaxine and Desvenlafaxine) has been shown by large, randomized control trials (RCTs)²². However, recent evidence has shown low dose estrogen therapy has superior efficacy than SSRIs and SNRIs²³.

SSRIs and SNRIs are contraindicated in patients with a history of neuroleptic syndrome or at risk of serotonin syndrome, and in patients who are using monoamine oxidase inhibitors concomitantly. Patients with liver or renal impairments, uncontrolled hypertension, and bipolar disorders, should be treated cautiously. Main side effects of SSRIs and SNRIs include nausea, fatigue, headache, dry mouth, and other gastrointestinal symptoms.

Paroxetine

Paroxetine mesylate 7.5 mg is the only non-hormonal pharmacological therapy approved by the United States Food and Drug Administration (US FDA) for treating moderate to severe vasomotor symptoms²⁴. Paroxetine mesylate 7.5mg or paroxetine hydrochloride 10-12.5 mg/day is recommended as the first line treatment option for VMS when MHT is not applicable²⁵.

Two phase III randomized clinical trials conducted in 2013 have found that paroxetine mesylate 7.5mg is effective in reduction of frequency and severity of moderate to severe VMS in postmenopausal women²⁶. This clinical trial had two study arms. Patients in both study arms were randomly given with paroxetine mesylate 7.5mg and a placebo at night for 12 weeks and 24 weeks respectively. Improvement of symptoms were assessed after 4 weeks and 12 weeks. In both studies, patients with paroxetine mesylate 7.5mg had report-



ed significantly reduced frequency and severity of VMS.

Citalopram

A phase III randomized clinical trial conducted in 2010 to evaluate the efficacy of citalopram in the management of VMS has found promising results ($p < 0.002$)²⁷. Patients were randomly given citalopram 10mg/day, 20mg/day, 30mg/day and a placebo. Effects were assessed after 6 weeks, and 30mg/day group has recorded 55% reduction of VMS severity score, while 20mg/day group and 10mg/day groups have recorded 50% and 49% reduction compared to placebo (recorded as 23% reduction).

Escitalopram

A randomized double-blind placebo controlled clinical trial conducted in 2011 to evaluate the efficacy of escitalopram for VMS has concluded that escitalopram is significantly effective in reducing frequency ($P < 0.001$) and severity ($P < 0.001$) of VMS²⁸. 205 postmenopausal women have participated in the study and the candidates were given with escitalopram 10mg/day, 20mg/day and a placebo and the effects were assessed in 8 weeks.

Sertraline

Sertraline has not shown consistent or significant improvements in severity or frequency of VMS and therefore it is not recommended for the treatment of VMS^{29,30}.

Fluoxetine

Fluoxetine has not shown consistent or significant improvements in severity or frequency of VMS and therefore it is not recommended for the treatment of VMS^{29,30}.

Venlafaxine

A study was done to evaluate the efficacy of 37.5mg, 75mg and 150mg Venlafaxine against a

placebo³¹. It has found that 37.5mg dose had 37% reduction of VMS whereas 75mg and 150mg had 61% reduction of VMS. However, 150mg Venlafaxine has associated with significant side effects including dry mouth, decreased appetite, nausea, and constipation.

Venlafaxine is not superior to MHT, but it is a good option for treatment of VMS.

Desvenlafaxine

Desvenlafaxine is the major active metabolite of Venlafaxine. In animal studies, Desvenlafaxine significantly increased the secretion of serotonin and norepinephrine in the hypothalamus³².

Evidence has found that 100mg Desvenlafaxine or higher doses has significant reduction of frequency of moderate to severe VMS³³. It also found that 100mg Desvenlafaxine is not associated with significant side effects. However, there is insufficient evidence to recommend it over other non-pharmacological treatments. Therefore, clinical trials comparing the efficacy of Desvenlafaxine compared to other nonhormonal treatments are needed to be established.

Gabapentinoids

Gabapentin

Gabapentin is a gamma-aminobutyric analogue, and the exact mechanism of alleviating VMS is still unclear. Studies has shown affinity of gabapentin for calcium channels in the hypothalamus, widening the thermoregulatory zone, resulting in the reduction of hot flushes^{34,35}.

Recent evidence has shown favorable effects of gabapentin in relieving VMS compared to controls³⁶. A meta-analysis has shown that reduction in severity and frequency of VMS were between 20%-30% and the doses used to treat VMS were between 900-2400mg³⁷. However, the effect is less superior than those of estrogen³⁶. When compared to SSRIs and SNRIs, gabapentin showed equal efficacy in alleviating hot flushes³⁸.

Major side effects of gabapentin include dizziness and somnolence. The recommended starting dose is 100mg/day and dose can be increased up to 900mg/day (three divided doses). These side effects can be reduced by starting with lower dose and gradually increasing and by prescribing the drugs at bedtime.

Clonidine

Clonidine is an alpha-2 adrenergic agonist and the mechanism of action of alleviating hot flushes is postulated as widening of thermoregulatory zone by reducing norepinephrine levels¹¹. Its effects are modest compared to placebo but inferior to SSRIs, SNRIs and Gabapentinoids^{11,22,39}. Few placebo-controlled trials has shown a reduction of severity of VMS over placebo but significant reduction of frequency of VMS has not shown^{40,41}.

Clonidine is a less preferable option due to its side effects profile, which includes hypotension, light headedness, dry mouth, and dizziness.

Pregabalin

Pregabalin is a Gabapentinoid, and it is used as an anticonvulsant and anxiolytic agent used to treat generalized anxiety disorder, epilepsy, fibromyalgia, restless leg syndrome, neuropathic pain, and opioid withdrawal.

A three-arm, double-blinded, placebo-controlled randomized trial was done in 2009 to assess the effectiveness of Pregabalin in the management of VMS⁴². Pregabalin, 75 mg twice a day, shown to be effective in the reduction of median score (severity and frequency) of VMS by 60% compared to placebo (50%)⁴². There was a 65% reduction with the dose of 150mg. But higher doses of Pregabalin is associated with more side effects and it is no more effective than lower doses. Side effects of Pregabalin includes changes in coordination, sleepiness, concentration difficulties, and visual changes.

However, the treatment of Pregabalin in the management of VMS is still inconclusive.

Oxybutynin

Oxybutynin has anticholinergic effects which has shown to be effective in the reduction of VMS. Recent RCT done in 2016 has found that Oxybutynin is an effective, nonhormonal therapy for moderate to severe VMS in postmenopausal women⁴³. 73% of women had statistically significant symptom improvement compared to 26.1% in placebo group. In addition, women treated with Oxybutynin showed significant improvement in sleep quality, sleep disturbance, and the global sleep index. 52.1% participants had reported dry mouth and 6.8% of the participants had discontinued the treatment. However, current evidence is still not conclusive to recommend Oxybutynin for the treatment of VMS.

Oxybutynin should be used with caution in elderly women who have multiple comorbidities or polypharmacy due to drug interactions.

Emerging Therapies: Neurokinin-B Antagonist

Recent evidence has found that Neurokinin-B (NK-B) involved in the pathophysiology of VMS¹². NK-B has the affinity to Neurokinin-3 (NK-3) receptors located on median preoptic nucleus and thereby thermoregulatory center resulted in narrowing of thermoregulatory zone. During postmenopausal period, lack of estrogen causes increased secretion of NK-B, overstimulating its action, resulted in VMS. Studies have been done on NK-B antagonists to assess the efficacy of its use in the treatment of VMS. NK-B antagonists are divided in to two categories as selective NK-3 antagonists and dual NK-1 and NK-3 receptor antagonists⁴⁴.

Fezolinetant

Fezolinetant is a NK-3 receptor antagonist and is currently under clinical trials. Fezolinetant act by binding to NK-3 receptor and inhibiting the action of NK-B.



A phase 2-a randomized clinical trial was conducted in 2019 to assess the efficacy of Fezolinetant 90mg compared to placebo, in the treatment of VMS⁴⁵. One arm was given with Fezolinetant 90mg two times a day for 12 weeks and the second arm was given a placebo. First arm, who was treated with Fezolinetant, had significant reduction of severity and frequency of moderate to severe VMS and there was a 74%-87% reduction of frequency of VMS compared to 55% reduction with a placebo⁴⁶.

Common side effects of Fezolinetant include headache, fatigue, nausea, diarrhoea, sinusitis, and cough. Rare but serious side effects include retinal detachment, cholelithiasis, elevated liver function values, and adjustment disorders.

Elinzanetant (NT-814)

Elinzanetant (NT-814) is a dual NK-1 and NK-3 antagonist and still under clinical trials. A placebo-controlled, randomized clinical trial done in 2020 found that Elinzanetant 150mg has shown a greater reduction (84%) of frequency of VMS compared to other treatment doses (24% with 50mg, 100mg and 300mg) and placebos (37%)⁴⁴. Another randomized, double-blind, placebo-controlled, dose-finding study done in 2020 found that 120mg and 160mg of Elinzanetant has shown the greatest mean reduction of VMS compared to lesser doses of 40mg and 80mg⁴⁷. It also has shown statistically significant reduction of mood and sleep disorders⁴⁷.

Summary

VMS symptoms are bothersome and affecting 60-80% postmenopausal women and median duration of VMS is 5.2 years. Exact pathophysiology of VMS is not established yet and currently, it is believed to be associated with reduction in estrogen levels causing disturbances in thermoregulatory center during menopause. Treatment options of VMS includes MHT, non-hormonal options and complimentary therapies. MHT considered to be the standard treatment option with 75% efficacy. Paroxetine mesylate 7.5 mg is the only non-hor-

monal pharmacological therapy approved by US FDA for treating moderate to severe vasomotor symptoms. Newer, emerging therapies, such as neurokinin 3 receptor antagonists and dual Neurokinin 1 and 3 receptor antagonists show promising effects in reduction of vasomotor symptoms.

Author declarations

Conflicts of interest: No conflicts of interest.

Group	Drug	Dose	Evidence	Recommendation
MHT – Estrogens and Progestogens	MHT		<ul style="list-style-type: none"> • Most effective standard treatment for VMS • 75% reductions of frequency and severity of VMS 	Recommended Start within 10 years of menopause or under the age of 60 years
Gabapentinoids	Gabapentin	100 - 900mg/day	<ul style="list-style-type: none"> • Has shown that reduction in severity and frequency of VMS • Less superior than those of estrogeni • Equal efficacy when compared to SSRI and SNRI 	Can be recommended
	Clonidine	Patch - 0.1-0.3mg/week	<ul style="list-style-type: none"> • Effects are modest compared to placebos but inferior to SSRIs, SNRIs and Gabapentinoids • Has shown a reduction of severity of VMS • Significant reduction of frequency of VMS has not shown 	Can be recommended but it is a less preferable option due to its side effect profile
	Pregabalin	-	<ul style="list-style-type: none"> • Shown to be effective in the reduction of median score (severity and frequency) of VMS • Higher doses associated with more side effects 	Inconclusive evidence to recommend
	Oxybutynin	-	<ul style="list-style-type: none"> • Has shown improvements in hot flush frequency and severity 	Inconclusive evidence to recommend
SSRI	Paroxetine	7.5-12.5mg/day	<ul style="list-style-type: none"> • Statistically significant reduction of VMS severity but less superior than estrogen 	Only non-hormonal pharmacological therapy Recommended by the US FDA
	Fluoxetine	-	<ul style="list-style-type: none"> • Not shown consistent or significant improvements in VMS 	Not recommended
	Sertraline	-	<ul style="list-style-type: none"> • Not shown consistent or significant improvements in VMS 	Not recommended
	Citalopram	10-20mg/day	<ul style="list-style-type: none"> • Statistically significant reduction of VMS severity but less superior than estrogen • Reduction of sleep disturbances 	Can be recommended
	Escitalopram	10-20mg/day	<ul style="list-style-type: none"> • Statistically significant reduction of VMS severity but less superior than estrogen • Similar efficacy in the reduction of frequency of VMS compared to estrogen 	Can be recommended
SNRI	Venlafaxine	37.5-75mg/day	<ul style="list-style-type: none"> • Statistically significant reduction of VMS severity but less superior than estrogen • Similar efficacy in the reduction of frequency of VMS compared to estrogen 	Can be recommended
	Desvenlafaxine	75-100mg/day	<ul style="list-style-type: none"> • Has significant reduction of frequency of moderate to severe VMS • less superior than estrogen 	Can be recommended but insufficient evidence to recommend over the other non-pharmacological methods
Selective NK-3 Antagonists	Fezolinetant	90 mg/day	<ul style="list-style-type: none"> • Significant reduction (74%-87%) of severity and frequency of moderate to severe VMS 	Still under clinical trials (Phase 2-a)
Dual NK-1 and NK-3 Antagonists	Elinzanetant	120-160 mg/day	<ul style="list-style-type: none"> • 120mg and 160mg has shown mean reduction of VMS • Significant reduction of mood and sleep disorders 	Still under clinical trials (phase 3)

Table 01 - Pharmacological Management of VMS – Summary Table

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