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Review Article

THE EFFICACY AND TOLERABILITY OF SNRI (VENLAFAXINE AND DESVENLAFAXINE) FOR THE TREATMENT OF VASOMOTOR SYMPTOMS IN MENOPAUSAL WOMEN

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ABSTRACT

Vasomotor symptoms are the most troublesome problem among the symptoms of menopausal transition for which women seek treatment. Hormonal therapy is the most widely used and effective one but due to its adverse effects on long-term use, most women seek for alternative. Since the publication of Women's Health Initiative report many health practioners and consumers seek for the alternative. The SSRI/SNRI are the first and the most effective alternative after hormone therapy and most widely studied among all alternatives. The objective of this review is to assess the effectivity and tolerability of SNRI (venlafaxine and desvenlafaxine) treatment for Vasomotor Symptoms.

Keywords: SNRI, desvenlafaxine and venlafaxine, vasomotor symptoms, hot flashes

INTRODUCTION

A majority of perimenopausal women will experience bothersome symptoms due to declining or fluctuating estrogens level in their menopausal transition [2]. Because of a development of medical science, women now live more than one-third of their lifetimes beyond menopausal transition [4]. Symptoms associated with menopausal transition are: changes in menstrual patterns, vasomotor symptoms (VMS), psychological and mental disturbances, sexual dysfunction, somatic symptoms and other symptoms [1]. Among them, vasomotor symptoms affect almost 75% of women in perimenopausal stage [5-7]. VMS symptoms last for 1 to 2 years after menopause in most women, but may last up to 10 years or more in others. Hot flashes are the main reason for seeking the menopause care [8]. Recent past, most women were treated by Hormonal therapy (HT) but after the publication of women's health initiative (WHI) result, there is dramatically declined in the use of HT and breast cancer cases. The health practioners and consumers seek for the alternative therapy. Since then many trials were done for alternative to HT especially SSRI/SNRI. In 2013, Paroxetine became the first SSRI approved by Food and Drug Association (FDA). Although numerous randomized trials have documented that estrogen markedly reduces the frequency and intensity of hot flashes, the results of WHI studies in 2002 have raised concern about long-term adverse effects pertaining to receive HRT [9, 10]. Since the result of WHI, studies of the non-hormonal therapies are intensified. These evidences suggest that treatment should be individualized, taking the consideration of risk/benefit ratio for each women. Data from the meta-analysis of 16 studies demonstrate that prolonged used of estrogen has 30% higher relative risk for breast cancer [19, 20]. So the use of estrogen following the breast cancer is discouraged. Placebo-controlled, randomized control trials have provided conflicting results on the use of progesterone in hot flashes, so its use is controversial [21, 22]. So, despite of higher cure rate, hormone therapy must be overtaken by others in selected cases. There are many alternatives for hormone therapy but in this review we will check for SNRI (serotonin and norepinephrine reuptake inhibitors) for its effectiveness. Desvenlafaxine is the active metabolite of Venlafaxine.

Physiological changes during menopausal transition:

Menopause is an expected transitional life occurrence in women, generally occurs 12 months after the final menstrual period [9]. Although a great increase in the life expectancy of women, the age at menopause remains constant. The age at menopause is genetically determined and not affected by race, socioeconomic status and age at menarche, or a number of previous ovulation [8]. The average age for the final menstrual period is 51.5 years [1]

The menopausal transition is changes in menstrual cycle and endocrine, beginning with irregular menstrual cycle and increase follicle stimulating hormone (FSH) and ends with the Final Menstrual Period. Menopausal transition starts with the loss of follicular activity in wide range of age (42-58 years) [10].

During reproductive life of women, gonadotrophic releasing hormone (G_nRH) is release from arcuate nucleus of the medial basal hypothalamus in a pulsatile fashion. It binds to G_nRH receptors on pituitary gonadotropes to stimulate cyclic release of the gonadotropins i.e. luteinizing hormone (LH) and follicular stimulating hormone (FSH). These gonadotropins, in turn, stimulate to produce ovarian sex steroids estrogen and progesterone and the peptide hormone inhibin. During the reproductive years, estrogen and progesterone exert both positive and negative feedback on pituitary gonadotropins secretion and on the amplitude and frequency of G_nRH release. Inhibin produced in granulosa cells exerts important negative feedback response for FHS secretion from pituitary. This tightly regulated endocrine hormones maintain menstrual cycle regular and predictable.

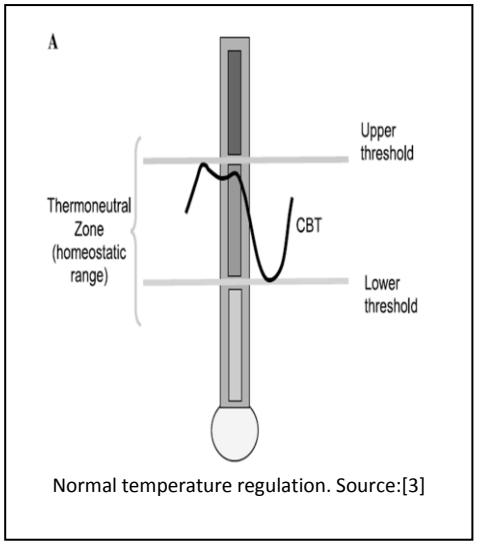
But, as aging progresses and when women reached their menopausal transition state, the number of follicles start declining to the critical stage, so the follicular inhibin starts falling and FSH starts rising. Despite the overall decline in ovarian follicles during, increased FSH stimulates ovary and maintain estrogen level until the late stage of menopausal transition. The changes in the pituitary gonadotropins levels results in intermittent ovulation and variable cycle length-is the characteristics of Menopausal Transition. Although women having regular menstrual cycle in early menopausal transition, the level of progesterone drop below than women in mid-reproductive age. Indeed the only clinical sign for menopausal transition is cycle length.

Vasomotor symptoms:

Vasomotor symptoms are the most common perimenopausal symptoms as if affect 75% of all menopausal women. It presents as hot flashes or hot flushes, night sweat, insomnia, and lethargy. Vasomotor symptoms result from either decline or fluctuation of estrogens level in perimenopausal women. Although menopause is related to changes in hypothalamic and pituitary hormones that regulate the menstrual cycle, menopause is not a central event but rather primary ovarian failure [8]. Vasomotor symptoms are related to temperature dysfunction that occurs due to changes in ovarian hormones. Core Body Temperature (CBT) is controlled by physiological processes that conserve and dissipate heat. The tight regulation of CBT is necessary for optimal internal organ function. Disturbance in this tightly controlled temperature circuit results in exaggerated heat-loss responses and present as Vasomotor Symptoms [3]. Hot flashes disturb women at work, interrupt daily activities and disturb sleep [11]. Hot flashes present as an episodic sensation of heat, intense sweating and flushing effect on face and chest which is followed by palpitation and anxiety [6]. Although each episode last for 3-10 minutes and episodes recur with varying frequency [12], 94% of women experience for 1-5 minutes and remaining few percent will experience, longer than 6 minutes [13]. The Majority of women experiences hot flashes during perimenopausal and early postmenopausal period but the minority of women during the regular menstrual period. Most women have hot flashes for 1-2 years but some percentage of women have persistent hot flashes for 8-30 years after final menstrual period [12, 14]. The assumption for prolonged duration of VMS are onset of VMS in early menopause and in younger age and

African-American women whereas, shorter duration of VMS is associated with obesity [15]. The reasons for the increase in frequency and duration of hot flashes are surgical menopause, race/ethnicity, body mass index, smoking, and breast cancer women taking antiestrogenic medication. African-American ethnical group of women perceive frequent VMS with more troublesome [16] whereas, Asian group of women perceive mild VMS with less troublesome [16, 17]. It is also approved by SWAN (study of women's health across the nation) study [16], but the exact reason is still unknown, as these groups of women are more exposed to smoking, tobacco smoking and higher BMI than Asian women [18].

Maintenance of thermoregulation:

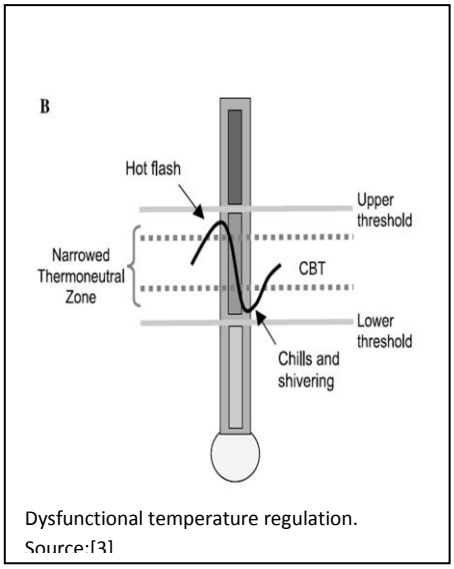


Normal temperature regulation. Source:[3]

The thermoregulatory circuit is made up of three components: brain, internal body cavity, and peripheral vasculature [23]. These components work together to achieve normal thermoregulation. Our body has other thermoregulatory zones that provide temperature inputs in the brain especially hypothalamus. And, the centers in the brain use the signals to maintain optimal core body temperature by inducing vasodilation to dissipate heat or vasoconstriction to conserve heat. The functional MRI of brain has clearly shown that corticosubcortical network of brain is involved in thermoregulation [10]. Hot flashes is a rapid, exaggerated response causing an intense heat sensation, upper body skin flushing and increase skin blood flow resulting changes in blood pressure and heart rate. It is assumed that the body's temperature is not hyperthermic state rather this is miscommunication in temperature signaling to regulate normal temperature responses [3]. So the signal to reduce CBT results extreme vasodilatation resulting perspiration (during night) causing sleep disturbance [12]. Thermoregulation is complex, highly regulated network of neuroendocrine, autonomic and somatomotor responses. The medial preoptic nucleus of hypothalamus is responsible for perspiration and vasodilatation. When exposed to the temperature changes, this nucleus activates and maintains the body temperature accordingly. Thus, maintain the core body temperature in

normal range, called the Thermoregulatory zone [1]. But if the CBT can't be maintained the most commonly encountered thermoregulatory dysfunction is called VMS of menopause [3].

Thermoregulatory dysfunction during menopausal transition/Pathophysiology of Hot Flashes:

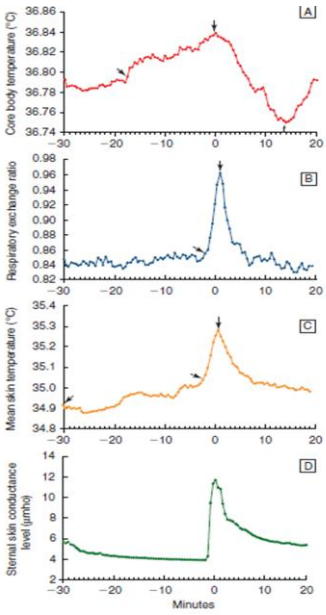


Dysfunctional temperature regulation.
Source:[3]

Thermoregulatory dysfunction occurs due to decline or fluctuation in gonadal hormones years before the menopause [24-28] and present as hot flashes or night-time sweating. Although VMS lead to poor quality of life, its pathophysiology is not clearly understood [29]. The proposed mechanism of thermoregulatory dysfunction is the imbalance in hypothalamic neurotransmitter [5-7]. Now it is proved that HFs are due to decreased estrogens level because HFs are seen in natural or surgical menopause and dramatical improvement with estrogens replacement [30]. Dysfunction of central thermoregulatory centers in the hypothalamus is the most likely cause for VMS. Perimenopausal women had very unpredictable menses, having periods of unpredictable cycles and periods of time when urine estrone level reached almost double the premenopausal state concentration. And, sometimes having acyclic menses with low, tonic estradiol levels are the characteristic of menopause. This fluctuating levels of estrogens is the reason for vasomotor symptoms [31]. Ovarian function began to decline and estrogens fluctuate dramatically, long before final menstrual period [24, 27, 28]. So Menopausal transition and postmenopausal women have rapid decrease in estrogens level.

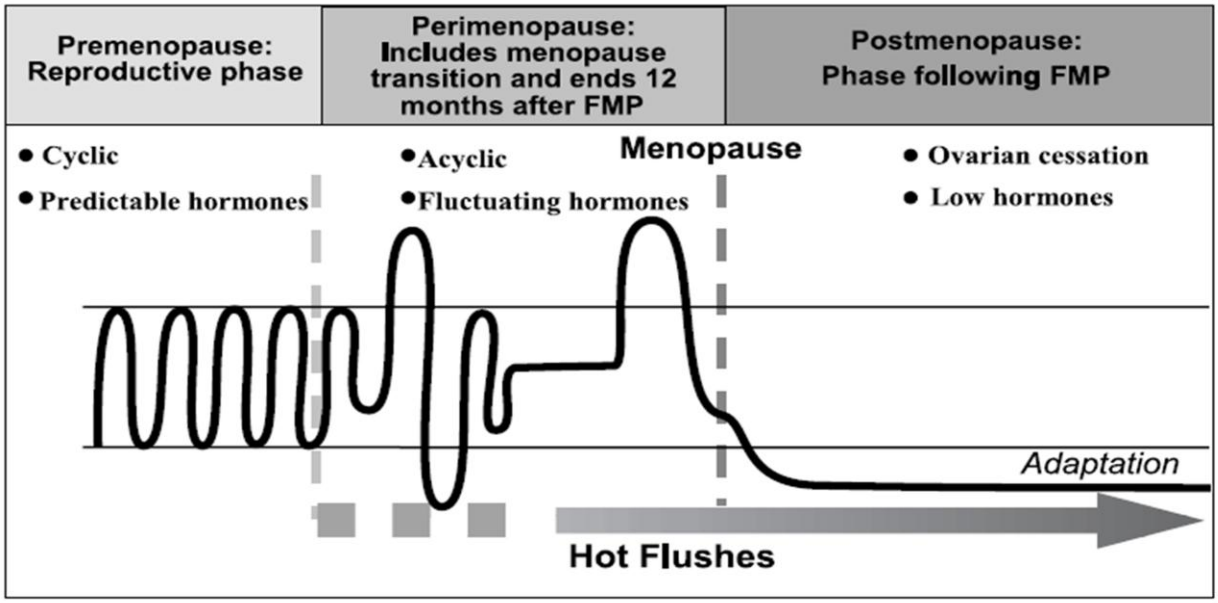
Rapid decrease in estrogen level (estrogen withdrawal) causes increase activities of norepinephrine, serotonin and central opioid peptides. These factors cause narrow thermoregulatory zone in thermoregulatory center in hypothalamus. As a result, there is decrease in upper and increase lower

threshold. The decrease in upper threshold means, smaller increases in CBT can trigger mechanisms to dissipate heat, like vasodilation and sweating. When lower threshold is increased, smaller decreases in CBT trigger mechanisms to preserve heat, like shivers and chills. Estrogens are modulator of adrenergic receptors in many tissues [1]. Menopause associated decrease in estrogens level decrease hypothalamic alpha2-adrenergic receptors. As a consequences of decreased pre-synaptic alpha2-adrenergic receptors increase norepinephrine and serotonin levels, thus causing Vasomotor Symptoms [32].



Physiologic changes during a hot flash.
Source: [1]

Hot flashes start with rising CBT above narrow upper threshold, causing peripheral vasodilation and resulting increase skin temperature and increase systolic BP and tachycardia, tachypnea and followed by anxiety and palpitation. As a reflex cooling from improved skin surface heat dissipation causes chills after the hot flash. Hot flashes frequently occur at night, causing sleep dysfunction and seeking for lethargy [1]. However, hot flashes are related with different reproductive phases of women and estrogens level. During reproductive years, women have regular menses and predictable estrogens level and so no Hot flashes. Although during early perimenopausal period, women have regular menses however all the menses are not ovulatory but during late perimenopausal period, menses become acyclic. Eventually this leads to decline/fluctuate estrogens level and severe and frequent Hot flashes. Perimenopausal period is the peak time for hot flashes. Initially women experience severe and persistent VMS due to declining estrogens and over time VMS diminish [1, 3].



Relationship between women's reproductive phase and estrogen and occurrence of hot flashes. Source: [3].

Neurotransmitter changes in menopause:

As described earlier, the change of gonadal hormones in menopause, alter the activity of neurotransmitters that are responsible for temperature hemostasis in hypothalamus. Neurotransmitters that alter thermoregulatory zone are norepinephrine and serotonin.

Norepinephrine: It is believed that norepinephrine is the primary neurotransmitter that lower [33] thermoregulatory set point and trigger heat loss mechanism associated with hot flashes [34]. Studies have shown that norepinephrine is responsible for central thermoregulation and its increased level narrow the thermoregulatory zone [7, 35]. The metabolite of brain norepinephrine, 3-methoxy-4-hydroxyphenylglycol level increases markedly just before and after the hot flash. This was reported in 9 menopausal women by Freedman [36]. Conversely, norepinephrine antagonists decrease norepinephrine and reduce hot flashes [37]. So decrease estrogen in menopause decreases alpha2-adrenergic receptor, thereby increasing norepinephrine and finally resulting vasomotor symptoms [32].

Serotonin: Serotonin also called 5-hydroxytryptamine (5-HT) is another neurotransmitter for the pathophysiology of hot flashes [33]. Initially it was assumed that changes in thermoregulatory set point was either due to decrease in serotonin level or imbalance between 5-$HT1_a$/5-HT2 receptors [27]. Now it is clear that decreased or fluctuating level of estrogens level may increase the sensitivity of hypothalamic serotonin

5-HT_{2A} receptor. Precisely estrogen withdrawal reduces the plasma serotonin level and result in upregulation of serotonin receptors in hypothalamus. Activation of serotonin receptor contribute for the narrowing of thermoregulatory zone and hot flashes occurrence [38-40]. On other way, as thermoregulatory center is stimulated by either internal or external stimuli, the concentration of ligand bindings are increased and activated serotonin (5-HT_{2A}) receptor. As a result thermoregulatory set point is decrease and occur hot flashes [33]. But the role of serotonin is complex in central regulatory pathways because binding at some serotonin receptors exert negative feedback effect and other serotonin receptors exert positive feedback effect [24]. Therefore, effect of serotonin depends upon the type of receptor activated.

Many studies clearly suggest that reduction and significant fluctuation in estrogens level decline the pre-synaptic alpha2-adrenergic receptors and an increase in hypothalamic serotonin and norepinephrine, which lower the set point in thermoregulatory nucleus and allow heat loss mechanisms to be triggered by subtle changes in core body temperature.

Mood and Sleep dysfunction during menopausal transition:

Although Sleep disruption increases with age but menopausal transition amplifies it [41]. So preserving a good quality of sleep is the most challenging task for women in menopausal transition [42]. Mood and sleep disruption are due to changes in neurotransmitter of CNS, like serotonin, norepinephrine, dopamine and endorphins [43]. The relationship of the serotonin and mood regulation is shown by Rubinow (1998), as blockade of the serotonin receptors with serotonin antagonist (metergoline) reversed the positive effects of estrogen replacement on mood in perimenopausal women [44]. Depressive mood is frequently found during menopausal transition and improved after menopause [45]. Women with menopausal transition may awake several times during the night and may be drenched with sweat. Disturbed sleep can lead to fatigue, irritability, depressive symptoms, cognitive dysfunction, and impaired daily functioning and the reasons to seek for the menopausal care. Women with moderate-severe hot flashes have greater chance to develop sleep disruption than women with mild hot flashes [46]. The prevalence of sleep disruption in early menopausal transition is 32-40% and in late menopausal transition is 38-46% [41]. According to Freedman [47] hot flashes that occur during first half of the night tends to awake than second half due to the reason that the second half of sleep may associated with rapid eye movement more frequently, which inactivate thermoregulation zone.

Degree of severity of Hot Flashes:

According to Jeffrey (2011) the degree of VMS can be mild, moderate and severe.

I. Mild hot flashes: women experience flush without sweating.

II. Moderate: women experience flush with sweating but able to continue their daily activities.

III. Severe: women experience flush with sweating and unable to continue their daily activities.

The severity of hot flashes varies with women and also varies with the same women throughout the day and in certain period of time [13].

Management of vasomotor symptoms:

The diagnosis of hot flashes can be made either by history alone or labelling of the hormones level. The FDA study criteria on intervention of VMS is: 7 severe or moderate hot flashes per day or 50 to 60 moderate to severe hot flashes per week at baseline [48]. The aim of vasomotor symptoms treatment is multiple, as some women want to just to relieve from intensity and frequency of hot flashes and night sweats and others want to eliminate all hot flashes and night sweats and return to a normal live [13]. The PEPI (postmenopausal Estrogen/Progestin Intervention) Trial demonstrates that women taking placebo show decline in vasomotor symptoms from 56% to 30% after 3 years of trail [49]. Before 2002, the gold standard treatment for VMS was hormonal therapy. However, after the publication of WHI trials, the treatment of VMS becomes complex [50, 51]. Although Hot flashes are the most bothersome symptoms as it has negative impact on daily life activities, job performance, sexual life, sleep and quality of life [13], however there is no any best effective option for treatment. Another most shocking thing; despite of high prevalence and deleterious effects of symptoms on quality of life, many women don't report it [52]. The treatment options for vasomotor symptoms:

I. Wait and watch

There are some group of women who don't seek for treatment may be due to lack of knowledge or to avoid the adverse effects from the drug exposure and also may be some women will have mild VMS, that they can tolerate easily.

II. Life style modification and self-care

Always try to keep lower core body temperature like by using fan, wearing in layered, drinking cool water, taking bath before sleep, and avoiding hot environment. Also, women are encourage for to lose weight and exercise when appropriate [48, 49]. Others lifestyle changes include paced abdominal breathing, meditation, yoga, tai chi and others. But there is no any good evidence to implement such therapies [53, 54]. However, Nelson [55] shows that women who are more active and do regular exercises tend to have less VMS. Definitely, not all types of activity lower the VMS intensity but the heavy exercise worsen the symptoms. So some light regular exercise that can help to reduce VMS are aerobic exercises, running and swimming [53, 56-58]. Meanwhile, another study showed that relaxation training reduces moderate hot flashes. Paced respiration (slow and deep

breathing that requires training) can decrease hot flashes by around 50% [59]. The proposed mechanism of action is decreased central sympathetic tone. The WHI's dietary trail suggests that weight loss in postmenopausal women have experience less VMS [60].

III. Complementary and Alternative Medicine (CAM)

In United States and Canada 49% of women used CAM in 2002 and tends to increase in following years [61]. Although many randomized control trials showed that CAM therapies are not effective but still women follow this therapies because of lack of side effects [62, 63].

Acupuncture: In two randomized trails; one study conducted for 6 weeks shows, acupuncture significantly reduces hot flashes and sudden sweating [64]. Next study followed up to 6 and 12 months shows statistically significant which was found on 12 weeks no longer present on 6 and 12 months. This suggest that acupuncture is useful in rapid reduction of VMS but may be not useful for pronged effect [65].

Phytoestrogens: phytoestrogens (isoflavones) are plant derived compounds and that interact with estrogen receptor and show both estrogen agonist and antagonist effects. Soy products and red clover are rich in isoflavones. A meta-analysis of 175 studies show conflicting result for the management of VMS [66]. Also, RCT of 252 women for the effective of red clover shows no significant difference with placebo [67].

Black cohosh: The root of the herb *Cimifuga racemosa* is thought to have estrogenic properties. But very minimal good quality evidence is available for the treatment of VMS [62, 68, 69]. The seven randomized controlled trials fail to show the reduction of VMS with black cohosh [70-76]. Although few adverse effect have been reported, the most serious was hepatotoxicity, even requiring liver transplantation in one case [69]. So, black cohosh is contraindicated in aspirin hypersensitive women as it contains salicylate.

Dong Quai: Dong quai is the perennial plant found in southwest of china, commonly prescribed in traditional Chinese medicine especially for the female problems [1, 13]. Since it is believed that dong quai maintain regular menstruation, increase vascularity and support of uterus. Also, Dong quai express some estrogenic properties, but Hirata and colleagues shows no any effect for the VMS [77]. Interaction with anticoagulants and photosensitization has been reported, due to presence of coumarin and presented as bleeding and sun exposure-related skin cancer.

Vitamin E and Evening Primrose oil: Studies show that both the vitamin E and evening primrose oil is no effective for the VMS.

IV. Hormonal Therapy (HT)

Hormone therapy is defined as an estrogen therapy or estrogen therapy is combined with cyclic or

continuous progesterone therapy. Before 2013, HT is the sole therapy for the vasomotor symptoms approved by FDA. Hormonal therapy has been used for more than 50 years and still remains the most effective treatment for vasomotor symptoms and improved quality of life [5, 78-80]. Although the physiologic mechanism of vasomotor symptoms is exactly not known many studies, suggest that changes in hypothalamic thermoregulatory zone and imbalance in neurotransmitters are due to decreased level of estrogens which provokes hot flashes. And, this proved that the mainstay of treatment is hormonal therapy. According to the first published systemic review on VMS, which included 24 RCTs trials and 3329 participants with age range of 34 to 64 years, suggested 75-79% of VMS frequency and severity is reduced by HT [81]. Despite of these; the initial report of two trials WHI and Heart and Estrogen/progestin replacement dramatically decline in HT therapy [82, 83] because of long-term adverse effects especially breast cancer and coronary heart disease in older postmenopausal women. Therefore, their results couldn't be implemented on the younger perimenopausal women with short-term therapy. Recent studies suggest that treatment should be individualized and should use for the short-term period soon after menopause with lowest effective dose of estrogen and add progestin in women with a uterus to prevent from endometrial cancer. The standard lowest effective doses of estrogen preparation for VMS: 0.625 mg of conjugated equine estradiol, 1mg of oral micronized 17beta-estradiol or 50microgram transdermal estradiol [84]. It begins to work in between 2-12 weeks of therapy and after every 6 months of therapy, tapering of dose and frequency or stopped the HT, to see whether the women's VMS subsiding on their own or not [13]. There is no any good quality evidence for the stoppage of HT, but two study suggest stopping after 4 years of therapy in order to prevent from long-term risks [85, 86]. The recurrence chance of VMS after the discontinuation of HT is >50%, and it is independent with age of women and duration she has taken [87]. Although estrogen can be administered by oral, parenteral, topical, vaginal or transdermal routes with similar effects, however the route and dose varies the risk and benefit ratio. The safest route of administration is transdermal, as it pass the first-pass metabolism in liver that promote prothrombotic homeostatic changes in factor IX, activated protein C resistance and tissue-plasminogen activator [88]. The risk-benefit ratio of estrogen therapy in hysterectomized women is more favorable than combined estrogen and progestin therapy in nonhysterectomized women [89].

V. Central Nervous System Agents

SSRI/SNRIs: The mechanism of action of SSRI/SNRI in reduction of VMS frequency and severity is complex and most probably differ from the mechanism involved in major depressive disorders. It is thought that there is imbalance between the two receptors subtype of serotonin; 5-HT1a and 5-HT2a and cause narrow thermoregulatory zone. These SSRI/SNRI probably maintain balance between them and maintain temperature hemostasis [90-92]. **Paroxetine** became the first FDA proved non hormonal therapy for VMS [90] but **Venlafaxine** is the most widely studied serotonergic agents and

the reports show 75-150mg/d dose is lowest effective dose to treat VMS with less adverse effects [93-95]. Although SSRIs, especially paroxetine and fluoxetine must be used in caution in breast cancer women taking tamoxifen, because SSRI decreased the metabolism of tamoxifen to its active metabolite, endoxifen by inhibiting the enzyme P450 cytochrome, CYP2D but the SNRI, Venlafaxine is safe in such case [96]. According to the latest systemic review on the efficacy and tolerability of SSRI and SNRI, both begin to work after 1 week of therapy and reduce 65% of hot flashes [97]. Importantly, benefits of SSRI/SNRI should be balanced against drug side effects, which can include nausea, diarrhea, headache, insomnia, jitteriness, fatigue, and sexual dysfunction.

Clonidine: Clonidine is the centrally active alpha2-adernergic-receptor agonist, was a popular alternative for VMS in past. The exact mechanism involved for reducing VMS is not known but may be due to reducing peripheral vascular reactivity. Nelson and colleague conducted a meta-analysis including 10 trail of clonidine, and they concluded, clonidine is inconsistent for VMS therapy [53].

Gabapentin: Gabapentin is structurally related to neurotransmitter alpha-aminobutyric acid primarily used for anticonvulsant and neuropathic pain but used as VMS therapy on 2000 by Guttuso [98]. The systemic review including 7 trails conducted in 901 patients, comparing gabapentin with placebo showed 20 to 30% reduction in frequency and severity of hot flashes with gabapentin but the dropout with gabapentin is higher than placebo due to its adverse events [99].

VI. Newer agent

Tissue-selective estrogen complex (TSEC): With better understanding of the estrogen receptor, TSEC is developed. TSEC is a complex of estrogen and selective-estrogen receptor modulator (SERM), to overcome the adverse effect from combination of progestin and estrogen, especially breast cancer [2]. Lately, FDA has approved the combination of 0.45mg estrogen and 20mg bazedoxifene for the management of hot flashes as it also prevent osteoporosis in women with uterus and improve sleep [100].

VII. Others

Exercise, Yoga, Relaxing training, Hypnosis: Although all of these have no any adverse events but none of the trials show it is effective.

DISCUSSION

It is clear that after the WHI report publication, many researchers and consumers are interested in alternative to HT and there are long list of alternative the researchers had trialed of, and above mentioned are only some of them. Without any confusion, the most effective therapy for reduction of severity and frequency of VMS is HT but many practioners and consumers reluctance to take HT and some women are

contraindication for the HT. So, despite of the most effectiveness of HT on VMS treatment, most of the time the alternatives are necessary. In this review, I will discuss about the efficacy and tolerability of SNRI (venlafaxine and desvenlafaxine).

I had found seven trials that are relevant to my topic. Among them three [101-103] trials comparison with placebo but {103} also compared with gabapentin and three [93, 95, 104] trials to see the venlafaxine in women with breast cancer or reluctance to use HT in fear of breast cancer and only one [105] trail actually comparing estrogen with venlafaxine for hot flashes treatment. These all trials are randomized placebo-control trail with double blinding except two [93, 104] are cross over trial and all trials done in United States except [104] is done in Canada and [103] is done in Europe and Mexico.

Joffe et al. 2014, is the first randomized clinical trial that simultaneously investigate the efficacy of low-dose estrogens with SNRI venlafaxine for VMS treatment. This study enrolled 339 women with age range 40 to 62 years and experiencing VMS at least 14times/week and followed for 8 weeks. The results of this study suggest that both low dose estradiol and venlafaxine are effective for reduction of VMS frequency and severity but the treatment decision should out weighted the risk-benefit ratio in each women.

Bouchard et al. 2012 evaluated the efficacy and safety of desvenlafaxine Vs tibolone and placebo. The study enrolled 485 postmenopausal women with age 40-65 years and experiencing hot flashes $\geq$50 per week for 12 weeks. After the 12 week of investigation, the study suggest desvenlafaxine has no statistically significant differences in reduction of frequency of hot flashes as compared with placebo but tibolone is unlike to desvenlafaxine. The adverse effect of nausea is more in desvenlafaxine but resolved within first 2 week but significantly more women experience bleeding with tibolone than desvenlafaxine and placebo.

Leon et al. 2008 investigated for efficacy and tolerability of desvenlafaxine done on 707 healthy postmenopausal women (average age 53.47 years) experiencing 50 or more moderate-severe VMS per week. The duration of trial was for 52 weeks and suggested that 100mg of desvenlafaxine significantly reduced hot flashes frequency at 4 (p=.013) and 12 (p=.005) weeks when compared with placebo. However, the treatment-emergent adverse effects is significantly more in desvenlafaxine-treatment women then placebo-treatment women during the first weeks of therapy only.

Archer et al. 2009 investigated desvenlafaxine for VMS treatment. This was a 26 weeks trial including 567 women having the mean age of 53.7 years and facing hot flashes 50 or more per week. This study suggest that desvenlafaxine significantly reduce hot flashes frequency and severity than placebo but the number of drop out is more in desvenlafaxine-treatment group during first week of treatment only.

Loprinzi et al. 2000 used venlafaxine for the management of hot flashes in survivors of breast cancer. The number of participants were 191 with the history of breast cancer or who were concerned about taking estrogen for fear of breast cancer and experiencing hot flashes 14 times/week. The participants were above

18 years and investigation duration was 4 weeks. This trial found that venlafaxine can alleviate the hot flashes and starting dose is 37.5mg and increase the dose but not above the 75mg.

Bordeleau et al. in 2010 conducted a multicenter, randomized, cross-over clinical trials of venlafaxine Vs gabapentin for the management of hot flashes in breast cancer survivors. The participants were postmenopausal having hot flashes at least 14 times/week and number of preference in venlafaxine were 38 and 18 in gabapentin. After the four weeks of trial both venlafaxine and gabapentin reduced the hot flashes score to a similar extend (66% reduction) but the side effect of nausea, appetite loss, constipation and negative mood changes are more on venlafaxine whereas, gabapentin has more dizziness and increase appetite.

Carpenter et al. in 2007 conducted randomized controlled-crossover trial of venlafaxine for hot flashes after breast cancer survivors. The trial enrolled 57 adult women having $\geq$1 hot flashes for 14 weeks. They concluded that venlafaxine reduced hot flashes moderately with few adverse effects, resulting that the some patients may be intolerable for long-term.

CONCLUSION

With regards of all above seven study most of them suggest SNRIs (venlafaxine and desvenlafaxine) are effective and tolerable for hot flashes but none of them suggest SNRI is highly effective. So, without any dilemma hormone therapy is the best treatment to alleviate VMS but when HT is not the first option we should have other alternatives, and the SNRI can be the most effective and tolerable among them and it is a first choice in breast cancer survivors. In future, more trials comparing HT and SNRI is necessary.

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