Indian Menopause Society

**Guideline Number 1 : August 2010**

# Management of Vasomotor Symptoms

The symptoms of vasomotor instability associated with menopause are called hot flushes. They are recurrent, transient episodes of flushing, perspiration & a sensation ranging from warmth to intense heat on the upper body & face & may be sometimes followed by chills. Most hot flushes stop over time without therapy. Incidence of hot flushes increases during peri-menopause, reaching its highest rate during the first 2 years post menopause & declining over time. A consistent pattern of hot flushes in a woman & a circadian rhythm has been observed. The circadian rhythm of core body temperature is well known and hot flushes are most frequent when core temperature is highest. Though Indian data is lacking, according to Western data, hot flushes are experienced by 10 – 83% of women. After surgical menopause hot flush rate of up to 90% have been reported. But with passage of time symptom rate, becomes similar to women with naturally acquired menopause [1].

Various factors seem to be related to hot flush frequency. Warm temperatures increase a women's core body temperature & makes her more likely to reach the sweating threshold. Cooler air temperatures are associated with a lower incidence of hot flushes.

In peri menopausal women, a high BMI (>30 kg/m2) is associated with an increased risk for hot flushes as compared to women with low BMI (<24.9kg/m2). But in postmenopausal women this association is not found [2]. Strenuous exercise may trigger hot flushes, however daily exercise is associated with an overall decreased incidence. Women who have less physical activity have an increased relative risk of hot flushes. Women of low socioeconomic status also have an increased relative risk of hot flushes.

Cigarette smoking (past & current) is associated with an increased relative risk of hot flushes [2].There is no significant association between alcohol intake and rate of hot flushes.There is no evidence supporting relationship of hot flushes with emotional stress & consumption of caffeine, hot or spicy food.

## Etiological Considerations

Although the exact etiology of hot flushes is not known, a hypothalamic origin has been suggested.

## Endocrinology

An acute decrease in the level of estrogens plays a role in the genesis of hot flushes rather than low levels per se and an acute increase in luteinizing hormone levels has been refuted as a cause for hot flushes. No causal relationship has been associated between opiodergic system & hot flushes.[3]

## Thermoregulation

Elevated brain nor-epinephrine levels narrows the thermoregulatory zone in symptomatic women & small elevations on core body temperature triggers a hot flush when sweating threshold is crossed [4].

**Recommendations for Management of Vasomotor Symptoms**

Treatment of vasomotor symptoms due to menopause is a common clinical challenge. Before starting treatment a detailed history of woman regarding frequency and severity of hot flashes & their effect on the woman's daily activities should be enquired into.

No treatment is required unless hot flushes are bothersome to the patient and disrupt her day to day activities. Therapy should be tailored to each woman's needs. The decision to start treatment should be based on the severity of symptoms, individual woman's attitude towards menopause & medication & assessment of risks related to treatment.

There is a tendency of natural regression of symptoms over time in most women. In majority of women treatment for hot flushes can be discontinued within a year.

Since obesity & sedentary lifestyle are related to hot flushes patient should be advised to maintain a healthy weight & to do regular exercise. Use of fans, air conditioners & light cotton clothing may be helpful.[5]

1.For mild vasomotor symptoms, the first strategy should be life style changes like regular exercise, keeping the core body temperature cool & paced respiration (Slow Controlled diaphragmatic breathing). [6]

2. When the desired relief from hot flushes is not achieved addition of non prescription remedies may be considered, as these are comparatively free of side effects. Vitamin E, 800 iu/day is nontoxic at this doses, inexpensive & can be tried for relief of hot flushes. Use of evening primrose oil & Ginseng is not superior to placebo. When therapy is required various non-pharmacologic & pharmacologic options are available. [7]

3. For women who cannot or do not wish to use estrogen for control of severe vasomotor symptoms, life style modification should be the first step. [8]

4. Soy may have some estrogen agonist activity. A healthy diet incorporating soy protein seems reasonable . Women should be encouraged to use whole food sources, rather than supplements, because of the risk of overdosage and lack of known long term effects of soy supplements. Data regarding the estrogenic effects of soy are inconclusive.
Clinical trials are insufficient to support or refute efficacy of soy foods & iso flavones supplements (soy or red clover) i.e. Phyto estrogens, Black cohosh, Vitamin E, dong quai, evening primrose oil, ginseng, acupuncture or magnet therapy. The adverse effects reported with red clover isoflavones seem minimal, although the long – term safety of red clover has not been confirmed. [7]

**WHEN TO START HORMONE THERAPY( HT)?** [9]

No therapy other than Estrogen has been approved by FDA for treatment of vasomotor symptoms.

For patients with persistent and severe hot flushes HT is the most effective intervention.

HT should be used for the shortest duration of time necessary to control symptoms at the lowest dose.

The short-term use (5 years or less) of estrogen & progestin does not seem to be associated with significant risk Estradiol is the first-line estrogen (orally or transdermally).In a cyclic regimen-progestational agent should be added for 10-14 days in women with intact uterus .

Use of progestegen for 14 days every 3 months has not been validated for effectiveness, but it has been proposed to reduce exposure of breast tissue to progestogen .

Only very small percentage of women continue to suffer from hot flushes ten years after the onset of menopause therefore longer HT may be appropriate in these women depending on the benefit versus risk profile.

Treatment should be periodically evaluated to determine if it is still necessary, as in almost all women, menopause related vasomotor symptoms will abate over time without any intervention.

While prescribing HT its contraindications & adverse effects should be kept in mind.

**Contraindications**

1. Current, past, or suspected breast cancer
2. Known or suspected estrogen-sensitive malignant conditions
3. Undiagnosed genital bleeding
4. Untreated endometrial hyperplasia
5. Previous idiopathic or current venous thromboembolism (deep vein thrombosis, pulmonary embolism)
6. Active or recent arterial thromboembolic disease (angina, MI)
7. Untreated hypertension
8. Active liver disease
9. Known hypersensitivity to the active substances of HT or to any of the excipients
10. Porphyria cutanea tarda (absolute contraindication)

**Terminology defining types of EPT regimens**

| Regimen | Estrogen | Progestogen |
|---|---|---|
| Cyclic | Days 1-25 | 10-14 days of ET cycle |
| Cyclic- combined | Days 1-25 | Days 1-25 |
| Sequential combined | Daily | 10-14 days every month |
| Continuous-combined | Daily | Daily |
| Continuous long-cycle | Daily | 14 days every 3-6 months |

**Commonly Used Preparations[10]**

**Oral Estrogens**

Conjugated equine estrogens: 0.30/0.625mg/d

Micronized estradiol 1/2 mg/d

**Vaginal**

| | |
|---|---|
| Conjugated equine estrogen | 0.625 mg, 7days/wk foll by 2days/wk |
| 17 ß estradiol tablet | 0.025mg 7days/wk foll by 2days/wk |
| Estriol cream | 1mg 7days/wk foll by 2days/wk |

Continuous ET is recommended over cyclic therapy since in the cyclic therapy, hot flushes may return by the end of hormone free week.

**Progestogen**

The primary indication for their use is for endometrial protection from unopposed ET.

Use of progestogen contributes substantially to increased Breast Cancer risk.

| **Drug** | **Cyclic** | **Continuous** |
|---|---|---|
| Oral | (Daily ≥12 days/month) | (Daily) |
| MPA | 5mg | 2.5 mg |
| Norethisterone | 1mg | 0.3 mg |
| Norethindrone | 2.5 mg | 0.5mg |
| Dydrogesterone | 10mg | 10mg |
| Micronized progesterone | 300 mg | 200mg |
| Vaginal | | |
| Micronized progesterone | 200mg | 100mg |
| Progesterone gel | 45 mg | 45 mg |
| Intrauterine system | | |
| Levonorgestrel | ___ | 20μgm |

If vasomotor symptoms persist after 2-3 months of therapy, other differential diagnosis should be considered.

On discontinuation of HT abruptly, hot flushes often return within days. So gradual reduction in dose is recommended for avoiding rebound hot flushes or the time between the doses may be increased

Progestogen alone can be used to treat hot flushes. DMPA, MPA & Megesterol acetate are efficacious.

**Tibolone** may also be prescribed in a single daily dose of 2.5 mg orally. Recent data have shown a lower dose of 1.25 mg to be equally effective in many cases.

Subgroups of postmenopausal women with vasomotor symptoms in whom tibolone might have added value include women with sexual dysfunction, mood disorders, fibroids and urogenital complaints, as well as those with breast tenderness or high mammographic breast density with HT use.

Use of **androgens** in women has not been approved by FDA.[9]

**Non hormonal options**[11,12]

In women with vasomotor symptoms in whom hormones are not an option, other drug therapy is available.

Fluoxetine (20mg/day) and Paroxetine (12.5 or 25mg/day) were popular options. However, there are now concerns about their use, due to their potent inhibition of CYP2D6, which is an essential component in the biotransformation of tamoxifen to the potent antiestrogen endoxifen. Thus Citalopram, a selective serotonin re-uptake inhibitor (SSRI) that is a weak inhibitor of the CYP2D6 pathway and does not interfere with tamoxifen metabolism in a clinically significant way is now considered a better option.[13]

Venlafaxine to be started at 37.5mg/day & increased to 75mg/day

Gabapentine (900mg/day) side effects may include fatigue, dizziness, and peripheral edema.

Side effects of these agents may include nausea, dry mouth, insomnia, fatigue, sexual dysfunction, and gastrointestinal disturbances.

Antihypertensives [14]

Clonidine (0.1mg/day) side effects, including dry mouth, postural hypotension, fatigue, and constipation, often limit the use of this medication.

Methyldopa (500 – 1000mg/day) causes significant reduction in hot flushes.

**CONCLUSION**

Vasomotor symptoms can be very distressing. The full range of choices from lifestyle modification to non-hormonal and hormonal options should be offered to the woman. Low dose hormone therapy for the shortest duration is the most effective modality of treatment in women who do not have any contra-indications to HT.

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