Noradrenergic and serotonergic modulation to treat vasomotor symptoms

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Abstract
Hot flushes are a major clinical problem for many menopausal women. Their aetiology is unknown. Centrally acting neurotransmitters are involved, but this involvement is yet to be fully characterized. In clinical trials with optimal patient selection and compliance, estrogen can reduce the frequency of hot flushes by 70–80%, and placebo by 20–40%. For some women, however, there are contraindications to the use of estrogen, and others are unwilling to use it. Furthermore, hot flushes may persist in spite of adequate estrogen replacement, and to improve symptoms physicians then have either to add another drug to the regimen or find an alternative to estrogen. The most commonly used non-hormonal alternatives for climacteric symptoms are neurotransmitter modulators such as the selective serotonin reuptake inhibitors. These reduce the frequency of hot flushes by 60%. The mechanism of this effect appears to differ from that underlying their effect on mood. They are generally well tolerated and rates of adverse events are far lower than those reported in studies of the use of these agents for depression. The limited efficacy of clonidine suggests that adrenergic mechanisms may be involved and data are awaited for more specific selective noradrenaline reuptake inhibitors. Thus, non-hormonal treatments are not as effective as estrogens in relieving hot flushes but may have a place as an alternative.

Keywords: Hot flushes, menopause, neurotransmitters, noradrenaline, serotonin

Introduction
Approximately 75% of perimenopausal women will experience some hot flushes and in 10–20% these symptoms will be enduring and severe. A disturbance in normal thermoregulatory function is thought to be the main underlying cause of hot flushes, but their physiology is not fully understood. They occur most commonly in association with menopausal estrogen withdrawal, but other mechanisms must be involved as endogenous estrogen levels do not correlate with either the presence or the intensity of hot flushes, and many postmenopausal women do not experience any symptoms in spite of low serum estrogen levels. Further, hot flushes occur in 15–25% of regularly menstruating women with normal endogenous estrogen levels. In addition, hot flushes may be experienced by women taking adequate doses of hormone replacement therapy (HRT).

The primary symptom of a hot flush is a subjective transient sensation of heat that usually lasts 4–10 minutes. This may be accompanied by palpitations, anxiety, irritability and panic. Core temperature rises by an average of 0.09°C some 7–20 minutes before a flush, with a consequent increase in energy expenditure and respiratory quotient.

Hot flushes appear to be caused by a small elevation in core body temperature \( T_c \) acting via a narrowed thermoneutral zone. This abnormality is not related to menopausal status and occurs only in symptomatic women – not in asymptomatic women. In other words, those who suffer hot flushes after the menopause do so because their threshold for sweating has been lowered. This narrowing of the thermoneutral zone means that the ‘buffer zone’ that controls temperature homeostasis is reduced, hence small temperature changes result in inappropriate activation of central neurotransmitters such as noradrenaline and serotonin (5-hydroxytryptamine or 5-HT).

It has been hypothesized that elevated brain levels of noradrenaline decrease the sweating threshold in symptomatic postmenopausal women, thereby contributing to the initiation of hot flushes. Serum levels of serotonin are lower in postmenopausal women and estrogen treatment is known to normalize them. It has been suggested that estrogen withdrawal causes a reduction in circulating serotonin, resulting in an up-regulation of the 5-HT\(_{2A}\) receptor in the hypothalamus.

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Methods

Computerized searches on MEDLINE (PubMed) and EMBASE were undertaken. Keywords used were ‘menopause’, ‘hot flushes’, ‘climacteric symptoms’, ‘neurotransmitters’, ‘serotonin reuptake inhibitors’, ‘noradrenaline reuptake inhibitors’ and ‘noradrenaline’. A manual search of reference data was also employed.

Noradrenergic pathways

Noradrenaline plays a major role in thermoregulation, acting partly through $\alpha_2$-adrenergic receptors. When injected into the preoptic hypothalamus, noradrenaline causes peripheral vasodilation and heat loss followed by a decline in core temperature. Gonadal steroids are known to regulate central noradrenaline activity. The plasma level of noradrenaline does not reflect its level in the central nervous system and hot flushes are not associated with variation of peripheral noradrenaline levels.

Plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) is the main noradrenaline metabolite found in plasma. It is derived primarily from the brain and is metabolized peripherally into vanillylmandelic acid (VMA). Plasma levels of MHPG appear to increase in parallel with hot flushes but VMA levels do not change, which suggests that only an elevation of the brain level of noradrenaline and not of its peripheral metabolites is involved in the initiation of hot flushes.

Clonidine, a centrally acting $\alpha_2$-adrenergic agonist that was originally developed as an antihypertensive, reduces central noradrenergic activation. Yohimbine, an $\alpha_2$-adrenergic antagonist, increases central noradrenergic activation. In a small pilot study, intravenous clonidine decreased the length of heating time needed to provoke a hot flush and reduced the number of hot flushes compared with placebo (2 versus 8). Intravenous yohimbine on the contrary produced six hot flushes compared with none occurring during the placebo phase. These, however, occurred only in symptomatic women; yohimbine did not trigger hot flushes in women without symptoms.

Several small studies published in the late 1970s and early 1980s suggested some effect of clonidine in the treatment of hot flushes. Edington et al. in 1980 performed a multicentre, randomized, placebo-controlled, double-blind, cross-over study in 66 patients and found clonidine effective. In another cross-over study, 110 breast cancer survivors receiving tamoxifen were randomized to receive a weekly patch of transdermal clonidine at a daily dose equivalent to 0.1 mg. Each arm of the study lasted four weeks. Clonidine decreased the frequency of hot flushes by about 20% compared with baseline. This was statistically significant but hardly clinically useful. The side-effects most commonly associated with the patch were dry mouth, constipation, itchiness under the patch, drowsiness and dizziness. Oral clonidine (0.1 mg/day for eight weeks) was also studied in 194 breast cancer survivors receiving adjuvant tamoxifen. It reduced the frequency of flushes by 38%, compared with 24% with placebo. The drug was generally well tolerated, although sleeping difficulties were noted.

Other agents affecting noradrenergic transmission include selective noradrenaline reuptake inhibitors. These hinder the reuptake of noradrenaline by neurons and thus more of this neurotransmitter remains in the synapse. They are used to treat depression and attention-deficit/hyperactivity disorder. No data are currently available with regard to hot flushes.

Serotonergic pathways

Given the relationship between serotonin and temperature control it is not surprising that the use of selective serotonin reuptake inhibitors (SSRIs) for the treatment of hot flushes has long attracted attention. SSRIs are a class of antidepressants. They act within the brain to increase the amount of serotonin in the synaptic gap by inhibiting its reuptake. Several SSRIs have been tested for the treatment of climacteric symptoms. Their effect on mood does not appear to predict their effect on hot flushes, which suggests the two effects have different mechanisms of action. However, the underlying mechanism of the reduction in hot flushes is still unknown.

There are three reasons for concern in using SSRIs:

- the occurrence of withdrawal symptoms
- the possible occurrence of dependence
- their negative effect on libido.

The incidence of withdrawal symptoms on cessation of SSRIs has been reported to vary from 0% to over 80% between different compounds. Withdrawal symptoms are compound specific and occur most often with those that have a short half-life, such as paroxetine and venlafaxine. Symptoms most commonly reported after rapid withdrawal of SSRIs are dizziness, lethargy, paraesthesia, nausea, vivid dreams, irritability and lowered mood. It is thought that compounds that have a long half-life, such as fluoxetine, are less likely to produce these symptoms, as they require several weeks to reach a steady state. Thus, stopping treatment leads to slower changes in blood levels and more tolerable withdrawal symptoms. Withdrawal reactions have never been reported in patients taking these agents for hot flushes and this is reassuring; however, a slow withdrawal of these drugs is advised to minimize the occurrence of problems on stopping them.

With regard to dependency, position statements by regulatory bodies state that while all SSRIs are associated with withdrawal reactions, they are not drugs of dependence.

Most SSRIs have been shown to have a negative impact on sexuality during their use, and lack of libido is a side-effect of treatment. Patients using these compounds to treat depression have reported inability to reach orgasm. However, venlafaxine either did not change or improved libido and sexuality when used for the treatment of climacteric symptoms.

Venlafaxine

Venlafaxine is both an SSRI and a selective noradrenaline reuptake inhibitor (SNRI). Four randomized, placebo-controlled studies have been performed with this compound for the treatment of climacteric symptoms. In a pilot four-week study, Loprinzi et al. found that over 28 women receiving venlafaxine 25 mg daily had a reduction of 55% in their median weekly hot flush scores compared with baseline. Venlafaxine was generally well...
tolerated and appeared to alleviate fatigue, sweating and sleeping difficulties. In a larger four-week study (with 221 women) by the same investigators, both 75 mg and 150 mg doses of venlafaxine reduced scores for hot flushes compared with baseline by 61%, while 37.5 mg reduced them by 37% and placebo by 27%. Dry mouth, decreased appetite, nausea and constipation were the reported side-effects and the intensity and prevalence of these were dose related.

Venlafaxine appears to be beneficial for libido and mood. Evans et al., in their study involving 80 women, found that at a dose of 75 mg it improved the subjective perception of hot flushes as recorded monthly on questionnaires, but failed to decrease the number of hot flushes as recorded in patient diaries, compared with placebo. An Italian study with 30 breast cancer survivors suggested that 37.5 mg of venlafaxine reduced hot flushes by 59%, with minimal side-effects.

Because of concerns about cardiotoxicity, venlafaxine should not be used in patients with heart disease or electrolyte imbalance, or those who are hypertensive.

Fluoxetine

Fluoxetine is an SSRI. Two studies have been performed on its use in the treatment of hot flushes. At a dose of 20 mg it has been shown to reduce hot flush scores (frequency × severity) by 50%, compared with 36% by placebo. This was a randomized, double-blind, placebo-controlled, cross-over trial, with each treatment period lasting four weeks. The trial was performed in 81 women with a history of breast cancer or a concern regarding the use of estrogen (because of breast cancer risk). Cross-over analysis demonstrated a significantly greater improvement in scores for hot flushes with fluoxetine compared with placebo (P = 0.02), but a similar profile of adverse effects.

A nine-month study examined fluoxetine and citalopram over nine months in 150 women and showed no benefit of these two SSRIs over placebo. Discontinuation rates at nine months were 40% in the placebo group, 34% in the fluoxetine group and 34% in the citalopram group. Ineffectiveness of treatment was the most common reason for discontinuation, rather than side-effects. Evaluations were made with the RAND-36 quality-of-life questionnaire, the Beck Depression Inventory and the McCoy Female Sexuality Questionnaire. Both fluoxetine and citalopram improved ratings of depression and did not have any adverse effect on sexuality.

So far a positive effect of fluoxetine on hot flushes has been found only in studies lasting 4–6 weeks. The only long-term study so far performed did not show any effect, which suggests that the effect of these compounds on hot flushes is not sustained long term.

Paroxetine

Four studies have examined the effects of paroxetine on hot flushes. In one, 13 women (all breast cancer survivors) took part in a five-week open-label trial of paroxetine (20 mg daily). Significant improvements were seen in the ratings of severity of hot flushes (P = 0.002), as well as in ratings of general, emotional and mental fatigue.

In a second study, after completing daily diaries for one week on no therapy, 27 women received open-label paroxetine, 10 mg daily for one week, followed by four weeks of 20 mg paroxetine daily. The mean reduction in the frequency of hot flushes was 67% (95% CI 56–79%). The mean reduction in severity score for hot flushes was 75% (95% CI 66–85%). There was a statistically significant improvement in scores for depression, sleep, anxiety and quality of life. Furthermore, 25 of the study participants chose to continue paroxetine therapy at the end of the study.

When used for the treatment of depression, a controlled-release (CR) formulation of paroxetine is better tolerated than the standard formulation. This has been examined in 165 women over six weeks. By week 6, mean daily frequency of hot flushes decreased from 7.1 to 3.8 (mean reduction 3.3) for those in the group receiving 12.5 mg CR paroxetine daily and from 6.4 to 3.2 (mean reduction, 3.2) for those in the group receiving 25 mg CR paroxetine daily, and from 6.6 to 4.8 (mean reduction 1.8) for those in the placebo group. Median reductions in the scores for hot flushes were 62.2% for those in the 12.5 mg group and 64.6% for those in the 25.0 mg group, compared with 37.8% for those taking placebo.

The same investigators have also undertaken a stratified, randomized, double-blind, cross-over, placebo-controlled trial to investigate the efficacy of 10 mg and 20 mg paroxetine in 151 women. Women were randomly assigned to four weeks of 10 mg or 20 mg paroxetine followed by placebo for four weeks, or placebo for four weeks followed by 10 mg or 20 mg paroxetine for four weeks. The 10 mg dose of paroxetine reduced the frequency of hot flushes and a composite score (number × severity) by 40.6% and 45.6%, respectively, compared with 13.7% and 13.7% for placebo (P = 0.0006 and P = 0.0008, respectively). The 20 mg dose of paroxetine reduced the frequency of hot flushes and the composite score by 51.7% and 56.1%, respectively, compared with 26.6% and 28.8% for placebo (P = 0.002 and P = 0.004, respectively). Efficacy was thus similar with the two doses but women were less likely to discontinue low-dose paroxetine. Sexual function did not appear to be compromised with any of the doses. The 10 mg dose of paroxetine was associated with a significant improvement in sleep compared with placebo (P = 0.01).

Trazadone

Trazadone is a triazolopyridine antidepressant with relatively small effects on cholinergic conduction. It is an effective antidepressant drug with a broad therapeutic spectrum, including anxiolytic and sedative efficacy. Although trazadone is usually referred to as an SSRI, it may have other pharmacological effects. Only one small, open-label study on its effects on climacteric symptoms has been carried out, in which a 75 mg daily dose of trazadone was given to 25 menopausal patients for three months. No effect was observed on scores for hot flushes (OR 0.52, 95% CI 0.08–1.87), but trazadone was effective in reducing anxiety (OR 0.08, 95% CI 0–0.80), insomnia (OR 0.15, 95% CI 0.02–0.71) and irritability (OR 0.29, 95% CI 0.04–1.48). The average total score of symptoms appearing on the Kupperman scale was reduced (–14%).

Citalopram

A small prospective pilot study described a beneficial effect of citalopram on hot flushes after four weeks of
treatment. During the first week of treatment, 10 mg/day clitopram was taken. The dose was then increased to 20 mg/day for the following three weeks. The frequency of hot flushes was reduced by 58%. Those patients who completed the study also reported decreased anger, tension and depression, as well as improved mood. 39

Clitopram was also tested in its ability to relieve hot flushes in 22 women in whom venlafaxine had previously failed. It reduced scores for hot flushes by 53% at four weeks compared with baseline. 40

However, any benefit of clitopram appears to be short term, as its effectiveness in the treatment of hot flushes was not confirmed in a nine-month placebo-controlled study (see under ‘Fluoxetine’, above). 31

Mirtazapine

Mirtazapine is an antagonist of the α2, 5-HT2, 5-HT3 and H1 receptors. It is also a presynaptic α2 antagonist and it increases both central noradrenergic and serotonergic transmission. It is licensed for the treatment of depression. It has been shown to reduce the tail temperature in ovariectomized rats (a well tested model used to screen compounds for the treatment of the climacteric syndrome). 41

Only two small studies are available on its effect on hot flushes. In one of these, four women reported that their hot flushes disappeared within the first week of treatment with 15–30 mg daily of mirtazapine. 42 The other was a single-arm, pilot trial in which 22 women started with 7.5 mg mirtazapine daily; the dose then increased to 15 mg daily at week 3 and to 30 mg daily at week 4. 43 In the fifth week patients could choose whether to take 15 mg or 30 mg a day. For the 16 women who completed the study, median reductions in the total daily number of hot flushes and weekly scores for hot flushes were 52.5% and 59.5%, respectively.

Conclusion

Serotonin reuptake inhibitors are a useful short-term option for the treatment of hot flushes. Their long-term benefits, however, are not known and as a whole they are less effective than estrogen. Their effectiveness in relation to hot flushes is similar for all the compounds tested and is not related to their effect on mood. The effect on hot flushes is not dose dependent, which means that low doses can be used. When used to treat hot flushes, SSRIs do not seem to affect sexuality adversely. Tolerability is generally good, particularly for low doses, and no withdrawal reactions or dependence has been reported when these compounds are used to treat climacteric symptoms.

Competing interests: None declared.

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