Non-Hormonal Management of the Menopause

15

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Menopause is defined by the World Health Organization (WHO) and STRAW Working Groups as the permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy or radiation [1].

With improved health care and increased life expectancy, women spend a considerable proportion of their lives (30 years on average) after the menopause, and it is estimated that within the next 25 years, more than one billion women worldwide will be older than 50 years, and approximately two million women in the US will reach menopause annually.

There are a number of symptoms associated with menopausal transition, and it is estimated that approximately 75% of women will experience some symptoms related to oestrogen deficiency during this time, although some women will experience none of these.

Symptoms include hot flushes and night sweats (vasomotor symptoms), vaginal symptoms, depression, anxiety, irritability and mood swings (psychological effects), joint pains, migraines or headaches, sleeping problems and urinary incontinence.

Vasomotor symptoms (VMS) are the most commonly reported and often the most difficult to manage effectively with non-hormonal therapies; we have attempted to cover the most commonly used alternatives in this chapter. We will also briefly touch on vulvovaginal symptoms, but it is simply not possible, within the remit of this chapter, to cover all possible treatments for mood disturbance.

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A. Cano (ed.), *Menopause*, DOI 10.1007/978-3-319-59318-0_15

15.1 Vasomotor Symptoms

The most commonly reported symptoms are vasomotor symptoms, characterised by a feeling of intense warmth, often accompanied by profuse sweating, anxiety, skin reddening, palpitations and sometimes followed by chills. It was previously thought that they resolve spontaneously in most women after 2 years, but may persist for up to 15 years; however, recent research suggests that median duration is in fact 7.4 years [2]. The sleep disturbance, fatigue and decreased cognitive function associated with hot flushes and night sweats have been shown to lead to a significant reduction in HRQoL and an increased use of medical resources.

The exact pathophysiology of flushing is not well characterised, although it is generally accepted that falling oestrogens play a main role; flushes generally occur at times of relative oestrogen withdrawal and replacing it will result in improvement in most women. However, whilst oestrogen concentrations remain low after the menopause, most vasomotor symptoms will diminish with time, and therefore a fall in oestrogen concentration does not seem to provide the complete answer. It has also been found that circulating levels of oestrogen do not differ significantly between symptomatic and asymptomatic postmenopausal women.

Furthermore, it is thought that withdrawal of oestrogen, rather than low circulating oestrogen levels, is the central change that leads to hot flushes, and there are several observations to support this theory. The abrupt oestrogen withdrawal due to bilateral oophorectomy in premenopausal women is associated with a higher prevalence of flushes than in those women who experience a gradual physiological menopause, and young women with gonadal dysgenesis, who have low levels of endogenous oestrogen, do not experience hot flushes unless they receive several months of oestrogen therapy and then abruptly discontinue its use.

A hot flush closely resembles a heat dissipation response (sweating and peripheral vasodilation), and as such, dysfunction in the central control of thermoregulation remains our best understanding of the mechanism of flushing [3].

Changes in core temperature may also be associated with alterations in neuroendocrine pathways involving steroid hormones, noradrenaline (NA), the endorphins and serotonin. Noradrenaline and serotonin, particularly, are thought to play a key role.

The recently published NICE guideline (NG23) [4] has recommended that women should be offered HRT for vasomotor symptoms after a discussion of the short-term (up to 5 years) and longer-term benefits and risks. However, there are of course a group of women for whom hormonal therapy is not suitable. Fifty percent of the more than half million women living with breast cancer in the UK will not adhere to the recommended 10 years of tamoxifen, often as a result of the severity of the hot flushes that are associated with taking this drug. It is essential that we are able to safely and accurately advise women on treatment alternatives for symptoms of the menopause, particularly for these women to help them continue a potentially life-saving treatment.

15.1.1 Cooling Techniques and Avoiding Triggers

Hot flushes can be triggered by small increases in core body temperature, and therefore, it seems logical to suggest practices that lower body temperature or prevent it from rising. These might include loose clothing, made from natural fibres, fans and cool packs. There is no clinical evidence for either these interventions or the avoidance of triggers, which might be reported by some; spicy or hot food and drinks; and alcohol.

15.1.2 Lifestyle Modifications

There is evidence that body mass index (BMI), smoking, alcohol consumption and sedentary lifestyle are associated with reports of vasomotor symptoms; however, there are few papers reporting the direct effect modifications have on flushes.

It may be safe to assume, though, that there will be an improvement in symptoms if a risk factor for exacerbation of those symptoms is removed. Smoking cessation and weight loss have numerous other health benefits, not exclusively alterations in endothelial function, which may be involved in the hot flush mechanism.

15.1.3 Exercise

As well as having significant physiological benefits (e.g. cardiovascular and bone health), exercise may be one of the promising alternatives to HRT and, if demonstrated to be effective in the treatment of vasomotor symptoms, is an inexpensive intervention that typically has few known side effects.

The Cochrane Collaboration carried out a systematic review [5] to examine the effectiveness of any type of exercise intervention in the management of vasomotor symptoms in symptomatic perimenopausal and postmenopausal women. Only one very small trial was considered suitable for inclusion, which found, not unexpectedly, that HRT was more effective than exercise. There is no available evidence examining whether exercise is an effective treatment relative to other interventions or no intervention. Weight loss, however, has been shown to have a beneficial effect on vasomotor symptoms [6].

15.1.4 Pharmacological Preparations

15.1.4.1 Clonidine

Monoamines have been shown to play an important role in the control of thermoregulation, and animal studies have shown that noradrenaline (NA) acts to narrow the thermoregulatory zone. Noradrenergic stimulation of the medial preoptic area of the hypothalamus in monkeys and baboons causes peripheral vasodilation, heat loss

and a drop in core temperature, similar to changes which occur in women during hot flushes.

It has also been shown that plasma levels of a noradrenaline metabolite are significantly increased both before and during hot flush episodes in postmenopausal women.

Clonidine is an alpha$_2$-adrenergic agonist licensed for the treatment of hypertension, migraines and postmenopausal vasomotor symptoms. It is also used for postoperative shivering because it is thought that, like general anaesthetic agents and sedatives, it decreases shivering thresholds by a generalised impairment of central thermoregulatory control. It has also been demonstrated to increase the sweating threshold.

When used for the treatment of flushing, it has been shown to be more effective than placebo but less effective than SSRIs, SNRIs and gabapentin [7, 8]. However, it may not be well tolerated, because of adverse effects, including dry mouth, insomnia and drowsiness.

15.1.4.2 Selective Serotonin (and Noradrenaline) Reuptake Inhibitors

Serotonin is involved in many bodily functions including mood, anxiety, sleep, sexual behaviour and thermoregulation. Oestrogen withdrawal is associated with decreased blood serotonin levels, and short-term oestrogen therapy has been shown to increase these levels.

Selective serotonin reuptake inhibitors (SSRIs) are a group of drugs typically used as antidepressants, which are thought to function by blocking the reuptake of serotonin to the presynaptic cell. This increases the amount of serotonin in the synaptic cleft available to bind to the postsynaptic cell. SSRIs were commonly prescribed for the treatment of depression in women undergoing treatment for breast cancer. Anecdotally, these same women were noted to have an improvement in their vasomotor symptoms, which occurred as a side effect of treatment. Studies were then carried out to determine the efficacy of these as an effective treatment for flushing.

Meta-analyses [7, 9, 10] and a Cochrane review [7, 8] have demonstrated mild to moderate improvements in flush frequency and severity in symptomatic postmenopausal (surgical and natural) women. Statistically significant reductions in flushing were seen with paroxetine, escitalopram, citalopram, venlafaxine and desvenlafaxine. Sertraline and fluoxetine appear to be less consistent, although there was still a trend towards improvement.

SNRIs may produce significant nausea, but this typically improves in 2–3 days, and can be reduced by titrating the dose slowly.

Use of these drugs in women with breast cancer using tamoxifen is common; therefore, consideration must be given to potential interactions. Tamoxifen must be metabolised by the cytochrome P450 enzyme system, predominantly cytochrome P450 isoenzyme 2D6 (CYP2D6), to become active, and CYP2D6 is inhibited to varying degrees by SSRIs. Paroxetine is an exceptionally potent inhibitor, whereas sertraline inhibits to a lesser degree and citalopram and escitalopram are only weak

inhibitors. Evidence is conflicting on the success rates of tamoxifen in preventing recurrence of breast cancer when using a concurrent SSRI. For those women who need to begin treatment with an SSRI for depression, citalopram or escitalopram may be the safest choice; however, improvements in flushing are better with venlafaxine and desvenlafaxine, and these appear to be safe choices.

15.1.4.3 Gabapentin

The mechanism of action of gabapentin in the amelioration of vasomotor symptoms is unknown, but it is thought to involve a direct effect on the hypothalamic thermoregulatory centre.

Two double-blind randomised placebo-controlled trials, examined in a meta-analysis [7], both conducted in women with breast cancer, showed a significant reduction in the frequency and severity of hot flushes when taking 900 mg/day but not when taking 300 mg/day. Titration to 2400 mg/day continued to be superior to placebo but was not significantly different to oestrogen 0.625 mg/day. However, dizziness, unsteadiness and fatigue were reported in the gabapentin-treated group and resulted in a higher dropout rate than in the control group.

15.1.5 Non-Pharmacological Therapies

15.1.5.1 Phytoestrogens

Phytoestrogens are chemicals that resemble oestrogen and are present in most plants, vegetables and fruits. There are three main types of phytoestrogens: soy isoflavones (the most potent), coumestans and lignans. Soybean and red clover are also rich in phytoestrogens. These compounds are converted into weak oestrogenic substances in the gastrointestinal tract.

Isoflavones are the most researched, and Nelson's meta-analysis included 17 RCTs. From six trials comparing Promensil (red clover isoflavone) with placebo, only one fair-quality trial found a reduction in flush frequency with Promensil, although there was no overall reduction in the meta-analysis, and no improvement in flush severity was demonstrated in any of the included trials.

Soy isoflavones were compared with placebo in the remaining 11 trials. The meta-analysis revealed an improvement in hot flushes after 12–16 weeks (4 trials) and after 6 months (2 trials) but not significant decrease in studies examining 4–6 weeks use.

A systematic review [11] was also carried out by the Cochrane Collaboration. They included five trials in a meta-analysis, which demonstrated no significant decrease in the frequency of hot flushes with phytoestrogens.

Thirty trials were also studied comparing phytoestrogens with control. Some of the trials found that phytoestrogens alleviated the frequency and severity of hot flushes and night sweats when compared with placebo, but many of the trials were of low quality or were underpowered. The great variability in the results of these trials may result in part from the difference in efficacy of the various types of phytoestrogens used, the exact treatment protocol and the fraction of equol producers in

the cohort. It is claimed that only 30–40% of the US population possess the gut microflora responsible for converting isoflavones to the active oestrogenic equol. It should also be noted that there was also a strong placebo response in most trials, ranging from 1 to 59%.

15.1.5.2 Black Cohosh

Black cohosh (*Actaea racemosa*) is a species of flowering plant of the family Ranunculaceae. It is native to eastern North America, and it is thought to behave as a selective oestrogen receptor modulator (SERM) with mild central oestrogenic effects, although the active ingredients are unknown.

A 2012 Cochrane review [12] analysed 16 RCTS of 2027 perimenopausal and postmenopausal women. All studies used oral monopreparations of black cohosh at a median daily dose of 40 mg, for a mean duration of 23 weeks. There was no significant difference between black cohosh and placebo in the frequency of hot flushes. Evidence on the safety of black cohosh was inconclusive, owing to poor reporting, and there were insufficient data to pool results for health-related quality of life, sexuality, bone health, vulvovaginal atrophic symptoms and night sweats.

A meta-analysis of several short-term and relatively small RCTs comparing black cohosh use with placebo 'revealed a trend towards reducing vasomotor symptoms' but only in cases of mild to moderate symptoms [13]. This was particularly notable when hot flushes were associated with sleep and mood disturbances. This was confirmed in another 12-week study of 304 women in addition to improvements in mood, sleep disorders, sexual disorders and sweating. In contrast, however, the recent Herbal Alternatives for Menopause Trial (HALT) [14] which compared black cohosh to both placebo and oestrogen replacement over 12 months suggested that black cohosh was ineffective in relieving vasomotor symptoms.

Whilst there has been no confirmation of its efficacy, many women, both cancer-free and breast cancer patients and survivors, will use black cohosh to relieve vasomotor symptoms since describing a drug as no more effective **t**han placebo may mean that it may bring relief to over 30% of women. However, it is important to exercise caution as there is limited information on its potential to influence breast cancer development or progression. No effect has been seen on mammary tumour development, which would suggest that black cohosh would not influence breast cancer risk if given to women before tumour formation, but there has been an increase in the incidence of lung metastases in tumour-bearing animals when compared with mice fed with an isoflavone-free control diet. Additional studies will be needed to correlate these findings to women taking different black cohosh products at various times during breast cancer development; however, these results suggest caution for women using black cohosh, especially for extended periods of time.

Reports of possible hepatotoxicity associated with black cohosh began to appear after 2000; however, a recent critical analysis and structured causality assessment has shown no causal relationship between treatment by black cohosh and liver disease.

15.1.5.3 Dong Quai

Also known as *Angelica sinensis*, dang gui and tang kuei, dong quai is the root of the Angelica polymorpha Maxim var. sinensis Oliv. *Angelica sinensis* grows in high altitude mountains in China, Japan and Korea, and the yellowish brown root of the plant had been used in traditional Chinese medicine for thousands of years. It is reputed to be oestrogenic based on reports of uterine bleeding with use and uterotrophic effects in ovariectomised rats, but there is no evidence of oestrogenic activity in human studies [15].

Dong quai does not appear to be effective for hot flushes, and there may be some safety concerns, including possible photosensitisation, anticoagulation and possible carcinogenicity [16].

15.1.5.4 Vitamin E

Three trials show varying evidence for vitamin E for treatment of vasomotor symptoms. A randomised placebo-controlled trial, in which 105 women with a history of breast cancer received placebo and vitamin E 800 IU daily for 4 weeks in a crossover design [17], demonstrated no improvement in the frequency or severity of hot flushes. One-hundred and fifteen women were randomised to vitamin E or gabapentin in a further trial, with significant improvements in symptoms with gabapentin and a 35% dropout rate in the vitamin E group [18]. However, in another crossover trial of 50 postmenopausal women, 4 weeks of vitamin E (400 IU) followed by placebo, or vice versa, demonstrated a small reduction in hot flushes of two flushes per day and a reduction in severity with vitamin E [19]. Care must always be taken when a toxic vitamin is ingested in excessive amounts.

15.1.5.5 Evening Primrose Oil (*Oenothera biennis*)

Oenothera biennis is a flowering plant rich in linolenic acid and ý-linolenic acid. It is a widely used product for the treatment of menopausal symptoms, although the exact mechanism of action is not fully understood. Its effectiveness has been analysed in a double-blind randomised placebo-controlled trial of 56 postmenopausal women [20]. This trial used a combination of evening primrose oil (2000 mg/day) with vitamin E (10 mg/day) versus placebo and showed a significantly greater reduction in daytime flushes in the placebo group than in the treatment group. Unsurprisingly, there was a high dropout rate; only 18 women given in the EPO group and 17 in the placebo group completed the trial, due to unrelieved symptoms, and precluded reliable conclusions.

There are a number of other over-the-counter and herbal therapies that are reported to be effective in reducing vasomotor symptoms, and a comprehensive review of these can be found in the 2015 North American Menopause Society Position statement on non-hormonal management of menopause-associated vasomotor symptoms [16]. It is important to remember that herbal supplements are not as closely regulated as prescription drugs, and the amount of herbal product, quality, safety and purity may vary between brands or even between batches of the same brand. We must make it clear to women that these therapies may also interact with prescription drugs, and as such these must be declared health-care providers and may need to be stopped before any planned surgery.

15.1.6 Alternative Treatments

15.1.6.1 CBT

Cognitive behavioural therapy (CBT), group and self-help, has been developed to help women self-manage VMS. It has been shown to be effective in reducing the impact, but not frequency, of flushing in two randomised, double-blind controlled trials: MENOS 1 [21] and MENOS 2 [22]. Improvements were maintained 26 weeks after randomisation, and there were additional benefits to quality of life, with no adverse effects.

A follow-up study [23] has revealed that beliefs about coping and control over VMS, and belief about sleep and night sweats, mediated the effect of CBT on VMS problem ratings.

NAMS has recommended CBT as an effective non-hormonal management option for vasomotor symptoms for both breast cancer survivors and menopausal women, and NICE (NG23) has recommended CBT to alleviate low mood or anxiety due to menopause.

15.1.6.2 Acupuncture

Acupuncture is a traditional component of Chinese medicine in which thin needles are inserted into the skin at key points in the body to balance the flow of energy or *chi*. Western medical acupuncture is the use of acupuncture following a medical diagnosis, and it involves stimulating sensory nerves under the skin and in the muscles of the body. This causes the production of endorphins, which may be responsible for the beneficial effects experienced.

Sham acupuncture is a placebo treatment involving needles inserted into unrelated points on the body or of special needles that do not pierce the skin.

A Cochrane review [24], and other systematic reviews [25, 26], concludes that although acupuncture is superior to no treatment, or a wait-list control, acupuncture is not superior to sham acupuncture. NAMS concluded, in their recently published position statement, that needling at acupuncture points does not appear to reduce VMS frequency or intensity independently of the superficial touch of a sham needle [16].

15.1.6.3 Stellate Ganglion Blockade

Stellate ganglion blocks (SGB) have been carried out safely for more than 60 years, for pain syndromes and vascular insufficiency. 0.5% bupivacaine is injected on the right side of the anterolateral aspect of the C6 vertebra under fluoroscopy and an effective block confirmed by the presence of Horner's syndrome. Adverse events, such as transient seizures, or a bleeding complication, occur rarely.

A case report published in 1985 of a 77-year-old gentleman with flushing after orchiectomy for infarction in his remaining testis was treated with SGB based on the belief that the flushing centre has a sympathetic outflow to the stellate ganglion. This abolished his attacks of flushing.

Four uncontrolled, open-label studies [27–30] have shown that SGB reduced vasomotor symptoms, with effects ranging from a 45 to 90% reduction 6 weeks to several months after blockade. A pilot study of 13 women (age range 38–71 years), with a history of breast cancer, who suffered with severe hot flushes, demonstrated reductions in flush episodes and an improvement in sleep quality following stellate ganglion blockade [28]. A more recent study [27] revealed a benefit in only half of the 20 women in the study. The exact mechanism of action of SGB is unknown, but findings suggest that it may be an effective non-hormonal treatment for flushing. Larger trials are needed.

15.1.7 New Research

It is well accepted that reduced secretion of oestrogen at the time of menopause is associated with increased GnRH secretion from the hypothalamus, resulting in high luteinising hormone (LH) and follicle-stimulating hormone (FSH) concentrations.

The kisspeptin/neurokinin B/dynorphin (KNDy) signalling system in the hypothalamus is the proximate and obligate stimulus to GnRH secretion [31]. These KNDy neurons also project to the medial preoptic area (MPOA) [32], the hypothalamic site of thermoregulatory neuronal pathways.

Recent data demonstrate induction of hot flushes in healthy premenopausal women with administration of NKB [33]; therefore, it is possible that the mechanism of flushes may be tied to the hypothalamic control of pulsatile GnRH secretion by NKB and that an NKB antagonist may be an effective new therapy for hot flushes. There is a clinical trial currently recruiting to investigate this.

15.2 Vaginal Symptoms and Sexual Dysfunction

Vaginal symptoms become apparent 4–5 years after the menopause and objective changes as well as subjective complaints are present in 25–50% of all postmenopausal women [34]. Symptoms may include vaginal dryness (75%), dyspareunia (38%), vaginal itching, burning and pain (15%). Dyspareunia can adversely affect a postmenopausal woman's sexual quality of life or intensify pre-existing sexual disorders [35].

Vaginal oestrogens are effective in the treatment of menopause-related vulval and vaginal symptoms and a Cochrane review reported equal efficacy across all products tested: creams, pessaries, tablets and vaginal rings [36]. Local oestrogen therapy will lower vaginal pH, thicken the epithelium, increase blood flow and improve vaginal lubrication.

Vaginal oestrogen is controversial in women with a history of breast cancer, in whom vulval and vaginal symptoms are common, particularly those on endocrine therapy. In a case–control study, there was no documented increase in recurrence in those women receiving endocrine therapy and use of local oestrogen compared to

non-use [37]. However, in another study of breast cancer survivors, there was an initial, albeit unsustained, increase in circulating oestrogen levels [38].

Non-hormonal treatment options include lubricants and moisturisers. Lubricants are non-physiological, but may reduce friction-related irritation of vaginal tissues, whilst moisturisers are hydrophilic, insoluble, cross-linked polymers which reduce vaginal pH [34]. In a trial of vaginal moisturiser compared to low-dose vaginal oestrogen, both preparations were found to be effective, but the moisturiser provided only temporary benefit [39].

Ospemifene is a non-oestrogen, tissue-selective oestrogen receptor agonist/antagonist or selective oestrogen receptor modulator (SERM). It has recently been approved in the USA for dyspareunia secondary to menopause-related vulvovaginal atrophy. Studies have shown improvements in vaginal pH and dryness [40, 41]; however, it should not be used in women with, or at high risk of, breast cancer.

Conclusion

Clonidine, SSRIs and gabapentin have all shown a significant improvement in flushing, whilst vitamin E and evening primrose oil have been shown to be of no benefit. Adverse effects may limit the use of clonidine and gabapentin, but SSRIs and SNRIs have a well-established safety profile and appear to have only minor adverse effects.

The evidence surrounding the efficacy of phytoestrogens and black cohosh is contradictory. Soy isoflavones may be more effective with longer term use than other phytoestrogens, but black cohosh, or any compound with oestrogenic properties, should be used with extreme caution in women with a history of breast cancer or any other oestrogen-dependent disease.

The effectiveness of stellate ganglion blockade for vasomotor symptoms is unconfirmed; therefore, further studies are required. It is also worth considering that the uptake of this treatment may be limited as it is costly and invasive, and the short-term side effects of Horner's syndrome may be unacceptable to some.

NKB antagonist, as a potential novel treatment, is an exciting new development which may offer relief to many women with severe flushing who cannot use hormonal therapy.

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