Maturitas 86 (2016) 53–58

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

Managing the menopause: An update

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ARTICLE INFO

Article history:
Received 4 January 2016
Received in revised form 12 January 2016
Accepted 13 January 2016

Keywords:
Menopause
Hormone therapy

ABSTRACT

Vasomotor symptoms (VMS), genito-urinary syndrome of menopause (GSM), sleep disturbance, sexual dysfunction and mood disturbance are common during the menopause transition. The degree of "bother" from symptoms should guide discussions about treatment. Moderate dose estrogen-containing hormone therapy (HT) is currently the most effective treatment for VMS and also improves vaginal dryness. The indication for HT is moderate to severe VMS in women without contraindications. It should not be prescribed or continued for the treatment of chronic disease. GSM can effectively be treated with vaginal (topical) estrogens. The dose, delivery system and duration of treatment for HT should be individualised to relieve symptoms. For most healthy women aged 50–59 years, the risks of HT are low. Several widely available non-hormonal agents can treat VMS for those who should avoid or do not wish to take estrogen. These include selected antidepressants and gaba-agonists.

Contents

1. What is the menopause?

The "menopause" is the final menstrual period. The menopause transition is the time from the onset of menstrual cycle changes or vasomotor symptoms until one year after the final menstrual period [1]. The menopause transition starts at around 47 years and lasts for 5–8 years on average. Whilst the timing of menopause is relatively constant, both the nature and severity of symptoms varies substantially between women from different ethnicities and geographical locations for reasons that are poorly understood.

Midlife may be a vulnerable period for a number of physical and psychological conditions. In order to manage menopause effectively and not overlook conditions which require different management, clinicians need to be aware what symptoms can be attributed to endocrine changes during the menopause transition. These "core" symptoms of menopause include VMS, vaginal

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http://dx.doi.org/10.1016/j.maturitas.2016.01.007
0378-5122/

Table 1
Recommendations for HT use (6).

Outcome	Recommendation	Level of Evidence
Prevention of CVD	Do not use	I-A
Menopausal symptoms	Moderate dose HT most effective for VMS therapy	I-A
	Progestin alone	I-A
	Selected Antidepressants/clonidine/gabapentin	I-B
Vaginal dryness	Low dose vaginal estrogen.	I-A
	Progestin not required	III-C
Recurrent UTIUrge incontinence	Low dose vaginal estrogen	I-B
		II-1A

Table 2
Recommendations for HT use in women with particular conditions (6).

Medical history	Recommendation to use for symptom relief	Level of Evidence[a]
Personal history or	Do not use oral HT	I-A
high risk of VTE	consider transdermal	III-C
Diabetes	Can use HT	I-A
Breast cancer	Uncertainty re risks of HT	I-B
Surgical menopause	Offer HT	I-A
Premature ovarian insufficiency	Offer HT	I-A
	Recommend use to average age of menopause	III-B

[a] I: Evidence obtained from at least one properly randomized controlled trial. II-1: Evidence from well-designed controlled trials without randomization. III: Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees. A: There is good evidence to recommend the clinical preventive action B. There is fair evidence to recommend the clinical preventive action. C: The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making.

dryness and urinary symptoms (now called "genito-urinary syndrome of menopause") [2], sexual dysfunction, mood and sleep disturbance [3]. The recently published NICE menopause guidelines advises that women presenting with a reduction in menstrual frequency and/or VMS aged >45 years do not need further investigation [4]. Women commonly have more than one symptom at menopause, and clinical evaluation should include discussion of symptom "bother" to guide treatment.

2. What is the duration of menopausal vasomotor symptoms?

Vasomotor symptoms (VMS); "hot flushes" or "night sweats" are normal during the menopause transition and affect around 80% of women [5].The mechanisms of vasomotor symptoms are poorly understood, but are thought to reflect disturbances of the hypothalamic thermoregulatory system after estrogen exposure then withdrawal [6]. Recent longitudinal studies indicate that the average duration of VMS is around 7.4 years and those who start flushing before their final menstrual period may have the most persistent symptoms [7]. Around 10% have symptoms lasting for as long as 12 years [8] and symptoms may persist for many decades in some women [9].

3. How can vasomotor symptoms be treated?

Treatment of moderate to severe VMS and their potential sequelae of sleep disturbance, difficulty concentrating and subsequent reduced quality of life, remains the primary indication for treatment [10]. The key clinical consideration guiding treatment is how "bothersome" symptoms are. This reflects that the frequency and severity of VM and other symptoms, and also psychological and social factors vary substantially between women [11].

Women should be provided with information about VMS and what behavioural and pharmacological treatments are available. For those who require pharmacological therapies, average dose HT is the most effective treatment for VMS with reductions in both frequency and severity in the order of 75% [12] and HT may improve quality of life in symptomatic women [13]. HT should be avoided in those with unexplained vaginal bleeding, active liver disease, previous breast cancer, coronary heart disease, stroke, personal history of thromboembolic disease or known high inherited risk. CVD risk factors do not automatically preclude HT but should be taken into account [4]. There is observational evidence that transdermal estrogen ($\leq$50 μg) is associated with a lower risk of deep vein thrombosis, stroke, and myocardial infarction compared to oral therapy [10] and may be the preferable delivery system, particularly for women with higher thromboembolic risk (Table 2). A mathematical analysis in the NICE guidelines concluded that the VTE risk with transdermal delivery is no different to controls [4]. Dosing of HT should start low and aim to reduce troublesome symptoms. Minimising estrogen exposure reduces VTE risk [14] and may reduce side-effects such as mastalgia and unscheduled bleeding [15]. Some may wish to avoid higher doses of HT and accept ongoing symptoms, and this should be part of the clinical discussion. Younger menopausal women may require higher doses to relieve symptoms, but there is currently little evidence to support this. The inclusion of progestogen appears to increase breast cancer risk, but progestogens are still indicated to prevent endometrial hyperplasia and cancer risk [16]. Low dose HT e.g. 0.3 mg of conjugated equine estrogens, $\leq$1 mg 17 β estradiol [16] may take up to 6–8 weeks before there is adequate symptom relief [6]. Those in the menopause transition [1] may need to consider contraception. Tibolone, a synthetic steroid with weak estrogenic, progestogenic, and androgenic properties, used at the daily dose of 2.5 mg, reduces VMS but may be less effective than combined HT. Tibolone causes less unscheduled bleeding than combined HT [17]. The tissue selective estrogen complex (combination of 0.45 mg of oral conjugated equine estrogen and 20 mg bazedoxifene (a SERM)) has been approved for the management of moderate to severe VMS in the US and Europe [18]. Comparative efficacy and safety with conventional HT is not yet known.

4. What are the risks and benefits of HT?

Discussion of risk should consider absolute rather than relative risk. In general, absolute risks are small in healthy women during the menopause transition or within 10 years of menopause [19]. The 13 year cumulative follow up from WHI gives absolute risks for these women currently taking HT and how these change 7–8 years