Menopause

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Menopause is the time of life when menstrual cycles cease, and is caused by reduced secretion of the ovarian hormones oestrogen and progesterone. Although menopause is a normal event for women, individual experiences vary, and some women seek medical advice for the management of symptoms. Many symptoms have been attributed to menopause, but only vasomotor dysfunction and vaginal dryness are consistently associated with this time of life in epidemiological studies. Other common symptoms such as mood changes, sleep disturbances, urinary incontinence, cognitive changes, somatic complaints, sexual dysfunction, and reduced quality of life may be secondary to other symptoms, or related to other causes. Trials of therapies for vasomotor dysfunction have shown improvements with oestrogen, gabapentin, paroxetine, and clonidine, but little or no benefit with other agents; adverse effects of these treatments must also be considered. Many questions about menopausal transition and its effects on health have not been adequately addressed.

Introduction

The transition to menopause is a complex physiological process, often accompanied by the additional effects of ageing and social adjustment. Historically, much medical knowledge of menopause drew on convention rather than on rigorously designed studies, which led to inappropriate care. Moreover, at times serious symptoms were regarded as normal concomitants of the time of life and not addressed further, and mild symptoms were overmedicalised.

Menopause results from reduced secretion of the ovarian hormones oestrogen and progesterone, which takes place as the finite store of ovarian follicles is depleted. Natural menopause is diagnosed after 12 months of amenorrhoea not associated with a pathological cause. Menopause can also be induced by surgery, chemotherapy, or radiation. Initially, the menstrual cycle lengths become irregular, and follicle-stimulating hormone (FSH) concentrations rise in response to decreased concentrations of ovarian hormones. As the menopausal transition progresses, menstrual cycles are missed and ultimately stop, as does ovulation. For some women, 3 consecutive months of amenorrhoea, or mean cycle lengths longer than 42 days, are predictors of impending menopause.[2,3]

Several terms have been used to describe the events that take place during the menopausal transition. A model developed at the Stages of Reproductive Aging Workshop (STRAW)[4] described seven stages of reproductive ageing (figure 1), which were subdivided into reproductive stages, characterised by regular menstrual cycles; menopausal transition stages, with variable menstrual cycles and high FSH values; and postmenopause stages, beginning with the final menstrual period, and lasting until the end of life. Definitions and models continue to be assessed and refined for clinical and research applications.[5–7] Although models are useful to describe the general progression of events leading to menopause, substantial individual variation exists, including skipping stages and moving back and forth between stages.[8]

The menopausal transition usually begins when women are in their mid-to-late 40s, and can last several years, most commonly 4–5 years.[9] The final menstrual period generally happens when women are between 40 and 58 years old,[9] and a final menstrual period before 40 years of age is regarded as premature. Population studies suggest that smoking and low socioeconomic status are associated with premature final menstrual periods.[10] Other factors can affect the age at which women have their final menstrual period, including age at menarche, parity, previous oral contraceptive use, body-mass index, ethnic origin, and family history.[11] The age at which women have their final menstrual period varies across large surveys done in different countries. Mean ages of 50–51 years were reported in Italy, Iran, Slovenia,[11] and the USA;[12] and of 47–50 years in Korea, Lebanon, Singapore, Greece, Morocco, Mexico, Taiwan, and Turkey.[11]

Search strategy and selection criteria

Relevant studies were identified from comprehensive searches of MedLine (1966 to December, 2006) and the Cochrane database of systematic reviews and controlled trials (last accessed December, 2006). Search strategies focused on menopausal symptoms and therapies for symptoms using the terms climacteric and menopause with terms depression, depressive disorder, affect, mood disorders, quality of life, sex disorders or dysfunction, sleep disorder, urination disorder, vasomotor symptom, somatic symptom, and vaginal dryness, and with specific terms for treatments such as, estrogen, androgen, progestin, tibolone, antidepressants, gabapentin, etc. Specific searches are described in a previous publication[1] and were updated for this Seminar. Additional articles were obtained by searching recent systematic reviews, reference lists of related articles, and websites, and by consulting experts. Non-English studies were included if they were sufficiently described in English-language abstracts. For symptoms, prospective cohort studies of the menopause, examining at least one potential menopausal symptom, were included; cross-sectional studies with similar criteria were examined for contributory data, such as prevalence rates of symptoms. For therapies, randomised, double-blind, placebo-controlled trials, providing data on the treatment of menopausal symptoms with one or more therapies, were included, as were meta-analyses of relevant trials. Trials without a placebo group, comparing therapies, were excluded, because of difficulty in interpreting their results. Studies were included whether the women were recruited from health-care settings, or the general population.

Clinical manifestations

Many clinical manifestations have been attributed to menopause. Vasomotor episodes manifest as spontaneous sensations of warmth, usually felt on the chest,

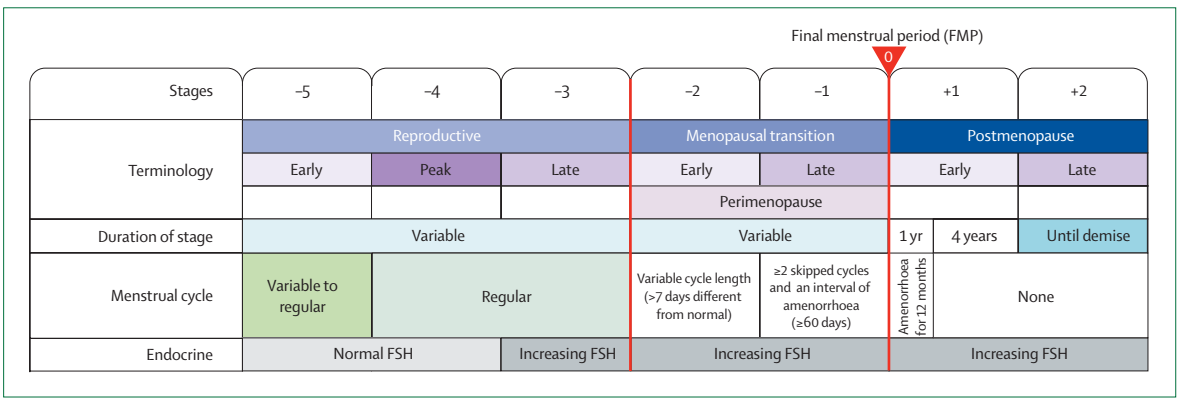

Figure 1: **Stages of normal reproductive ageing in women**
Reproduced with permission from Soules and colleagues.[4] FSH=follicle-stimulating hormone.

neck and face, and often associated with perspiration, palpitations, and anxiety. These episodes are described as hot flushes, hot flashes, and night sweats. The term "hot flush" indicates the sensation of heat; "hot flash" describes episodes with sweating, sometimes followed by a chill; however, the terms are often used interchangeably. Vasomotor episodes are variable in frequency, duration, and severity, are sometimes recurrent, and usually last less than 5 min. They can be triggered by warm environments, hot food or drinks, and stress. For some women, these episodes interfere with activities or sleep to such a degree that medical advice is needed. The mechanisms causing vasomotor symptoms are not fully understood. One theory is that reduced oestrogen concentrations cause decreased endorphin concentrations in the hypothalamus, which increases the release of norepinephrine and serotonin; these neurotransmitters lower the set point in the thermoregulatory nucleus, and trigger inappropriate heat loss.[13–15]

Urogenital problems, such as vaginal dryness, itching, and dyspareunia, are caused by physiological responses to low concentrations of oestrogen and androgens. These responses include reduced vaginal blood flow and secretions, tissue changes, and a change in the pH of vaginal fluid, from acidic to neutral. Additional symptoms, such as anxiety, depression, and mood changes, urinary incontinence and leakage, sleep disturbances, cognitive changes, somatic complaints, and sexual dysfunction have been associated with the menopausal transition. Some of these symptoms are secondary to vasomotor and urogenital symptoms, and others are related to other causes. Factor analysis studies showed that menopausal status is more consistently associated with vasomotor than with psychological or physical symptoms, arguing against a universal menopausal syndrome that includes all of them.[16]

Distinction between clinical signs related specifically to the menopausal transition, and those related to ageing in general, is difficult. Studies of menopausal dysfunctions need to be carefully interpreted, because of methodological inconsistencies and limitations. Many methods have been developed to assess menopausal symptoms, but only a few are standardised, valid, and reliable. Some methods are based on self-reports of the presence, severity, and frequency of individual symptoms, such as hot flashes. Others use cumulative scores, based on lists or scales of symptoms that are thought to be associated with the menopause, such as changes of mood, cognition, quality of life, sexual function, and somatic symptoms. The Green climacteric scale,[17] Kupperman index,[18] and menopause-specific quality of life questionnaire[19] are examples of commonly used scores of menopausal symptoms. The multitude of symptoms studied and methods used often does not allow comparisons between studies, and the populations they represent. Most studies fail to adjust or stratify for potentially important variables such as age,

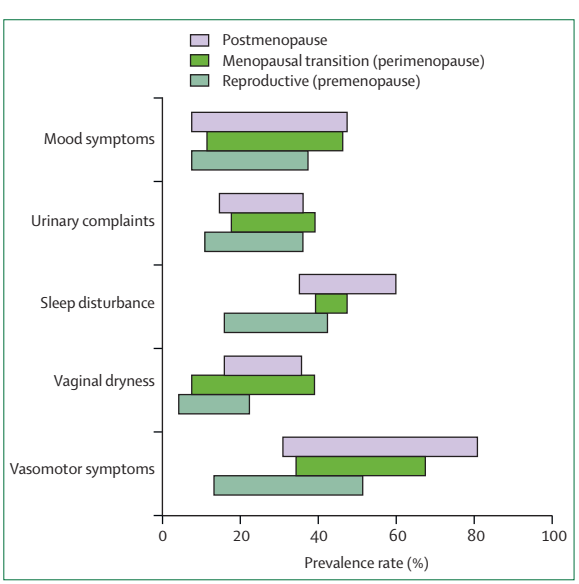

Figure 2: **Prevalence rates of symptoms**
51 population studies showed wide ranges of prevalence rates. Rates of vasomotor symptoms, vaginal dryness, and sleep disturbances are higher for women in menopausal transition and postmenopause than for women in reproductive stages.

pre-existing disorders, and the use of hormone therapy.

In epidemiological studies, the reproductive stages are often defined by terms that predate the STRAW model.[4] In general, premenopause corresponds to the STRAW reproductive stages; perimenopause corresponds to the STRAW menopausal transition stages; and postmenopause begins at the time of the final menstrual period. However, studies vary in: how these terms are used; the data used to assess menopausal status;[6] which stages are compared; and when and how frequently symptoms are measured. Most studies, including those from prospective cohorts, report cross-sectional data and compare results for premenopausal, perimenopausal, and postmenopausal groups of women, whereas others provide serial measures from individuals as they progress through stages.

Prevalence rates of symptoms, such as vasomotor dysfunctions, vaginal dryness, sleep disturbance, urinary complaints, and mood changes, vary greatly (figure 2).[1] Differences between studies might result from inconsistencies in methods, or from true differences between populations.

Cohort studies have shown that only a few clinical manifestations are significantly associated with the menopausal transition (table 1). Vasomotor dysfunctions, including hot flashes (odds ratio [OR] 1·3–13) and night sweats (OR 2·4–4·3), substantially increase in frequency and severity during the menopausal transition:[20–22] these symptoms are experienced by more than 50% of menopausal women.[1] Although most symptoms resolve within a few months for many women, they can persist for several years after the final menstrual period. About 29% of 60-year-old women report persistent hot flashes.[23] Studies of factors that might affect vasomotor dysfunction are inconclusive, but suggest that body-mass index, exercise, age of onset of menopausal transition, surgical menopause, smoking, and depression might all be implicated.[1]

Vaginal dryness is also associated with the menopausal transition[22] and is reported by up to a third of menopausal women.[1] Additionally, menopausal women have more sleep disturbances than non-menopausal women (OR 1·3–1·5),[20,22] sometimes because of vasomotor symptoms.[23] About 40–60% of women have sleep disturbances during menopause and postmenopause stages.

Several symptoms are inconsistently associated with menopause. Some studies have reported no correlation

	Description (length of follow-up in studies)	Transition from premenopause to perimenopause	Perimenopause stage	Transition from perimenopause to postmenopause	Postmenopause stage
Australian Longitudinal Study on Women's Health	8236 women (45–50 years of age) enrolled in 1996 in Australia (2 years)	Increased hot flashes, night sweats, sleeping disturbances, severe tiredness, and stiff painful joints. No associations with back pain, body pain, headache, urinary leakage, general health perception, general mental health, quality of life, or constipation	Increased hot flashes, night sweats, sleeping disturbances, severe tiredness, stiff painful joints, back pain, body pain, urinary leakage, worse general health perception, and quality of life. No associations with general mental health, headache, or constipation	Increased night sweats and sleeping disturbances. No associations with hot flashes, somatic symptoms (severe tiredness, stiff painful joints, back pain, body pain, headache), urinary leakage, general health perception, general mental health, quality of life, or constipation	Increased night sweats, decreased general mental health. No associations with hot flashes, difficulty sleeping, somatic symptoms (severe tiredness, stiff painful joints, back pain, body pain, headache), urinary leakage, general health perception, quality of life, or constipation
Eindhoven	2103 women born between 1941 and 1947 recruited on the basis of responses to an osteoporosis screening study in Eindhoven, Netherlands (5 years)	No association with depression	No association with depression	Increased depression based on EDS score	
Gothenburg	899 women (38–60 years of age) randomly selected in 1968–1969 and followed up for more than 25 years in Gothenburg, Sweden (6 years)	No associations with development of mental disorder			
Manitoba Project on Women and Their Health in the Middle Years	469 women (40–59 years of age) from Manitoba, Canada (3 years)	No associations with depression (based on CES-D score 16 and over)			
Massachusetts Women's Health Study	231 premenopausal women (45–55 years of age) from Massachusetts, USA (8 years)	No associations with depression (based on CES-D score 16 and over)			
Medical Research Council (MRC) National Survey for Health and Development	1572 women identified from a socially stratified sample of all births in March 1943 in Britain (52 years)	No associations with vasomotor symptoms, anxiety, or depression	Increased vasomotor symptoms; no associations with anxiety or depression	No associations with vasomotor symptoms, anxiety, or depression	

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	Description (length of follow-up in studies)	Transition from premenopause to perimenopause	Perimenopause stage	Transition from perimenopause to postmenopause	Postmenopause stage
(Continued from previous page)					
Melbourne Women's Midlife Health Project	494 women (45–55 years of age) from Melbourne, Australia enrolled in 1991 (4–5 years)		Increased sleeping disturbances, decreased quality of life. No association with hot flashes, vaginal dryness, mood, somatic symptoms, urinary symptoms, incontinence, or sexual dysfunction (early perimenopause). Increased hot flashes and night sweats, vaginal dryness, sleeping disturbances, sexual dysfunction, and general wellbeing; decreased breast soreness, and quality of life. No association with mood changes, somatic symptoms, urinary symptoms, or incontinence (late perimenopause)		Increased hot flashes and night sweats, vaginal dryness, sleeping disturbances, and general wellbeing; decreased breast soreness, and quality of life. No association with mood changes, somatic symptoms, urinary symptoms, or incontinence
National Health Examination Follow-up Study	3049 women (40–60 years of age) from the US National Health and Nutrition Examination Survey (NHANES) (10 years)	No associations with depression or quality of life			
Ohio Midlife Women's Study	208 women (40–60 years of age) from a community in Ohio, USA, including 57% white and 43% African-American women (2 years)	No associations with anxiety or depression			
Pennsylvania Ovarian Aging Study	436 women (35–47 years of age) from Pennsylvania, USA, including 50% white and 50% African-American women (4 years)	Increased depression (CES-D score 16 or higher) (transition from premenopause to early and late perimenopause)		No increase in depression score	
Seattle Midlife Women's Health Study	11 222 premenopausal and perimenopausal women (35–55 years of age) from Seattle, USA, census tracts, including different ethnic groups (2–3 years)	No associations with vasomotor symptoms, insomnia, dysphoric or depressed mood, or neuromuscular or somatic symptoms			
Study of Women's Health Across the Nation (SWAN)	3306 women (40–55 years of age), from different community sites in the USA, followed up since 1995 (6 years)	Increased vasomotor symptoms	Increased depressive symptoms (based on CES-D score 16 or higher)		Increased depressive symptoms (based on CES-D score 16 or higher)

EDS=Edinburgh depression scale. CES-D=center for epidemiologic studies depression scale. PRIME-MD=primary care evaluation of mental disorders. *Summarised from reference 1.

Table 1: **Associations of symptoms with menopausal stages* reported in cohort studies**

between menopausal transition and mood changes, development of mental disorders, or general mental health;[21,24,–34] others—including the Pennsylvania Ovarian Aging Study,[35] the Study of Women's health Across the Nation (SWAN),[36] and the Eindhoven Perimenopausal Osteoporosis study[37]—have shown associations. The inconsistent results probably indicate methodological differences, especially in how symptoms are measured.[38] No associations have been reported between cognitive change and menopause, in the few studies that have been done;[1] increased somatic symptoms are sometimes reported.[1]

Urinary complaints, including incontinence and leakage, were related to menopause in some,[20] but not all,[22,39] investigations. Women reported decreased sexual responsivity, libido, and frequency of sexual activity with menopause;[40,41] depression and vaginal dryness were reliable predictors of low sexual desire. Although decreased oestradiol concentrations were associated with low sexual function in an Australian cohort, previous sexual and partner issues have more substantial effects than hormonal factors.[42] Studies of quality of life during menopause are conflicting: some have indicated decline, others an improvement, and others no association.[1]

Large cohorts provide useful information about the menopausal transition. However, individual experience can be affected by many additional factors; ethnic origin and culture are important, but whether biological or sociocultural factors have the biggest effect is unclear. Genetics, dietary practices, parity, body-mass index,

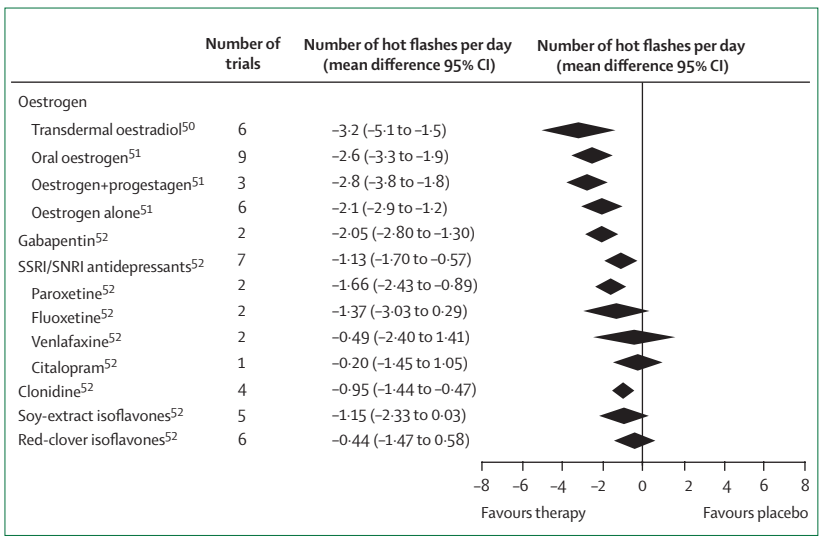

Figure 3: **Results of trials of therapies for hot flashes**
Hot flashes were reduced by two to three flashes per day with oestrogen, two with gabapentin, about one with paroxetine, and one with clonidine in double-blind, randomised, placebo-controlled trials. Isoflavones had slight or no effect.

physical activity, and environmental exposures differ with ethnic origin and culture, and are likely to affect the menopausal transition as they do other phases of reproductive life,[11] and health in general. Additionally, the perception and description of symptoms vary with cultural context and language. Some women might interpret a vasomotor symptom as a warm sensation, whereas others might describe dizziness or other sensation because it is more culturally meaningful to them.[43]

In SWAN,[36] done in the USA, African-American women reported more frequent vasomotor dysfunctions than did white women, who in turn reported more than did Hispanic, Chinese, and Japanese women.[44,45] White and Hispanic women had sleep difficulties more often than did African-American, Chinese, and Japanese women.[46] Hispanic women reported body pain more frequently than did white women.[47] In surveys done in Asia, most Asian women had body or joint pain rather than vasomotor symptoms, although proportions varied with ethnic group.[48]

Management and treatment

Many questions about the menopausal transition and its effects on health have not yet been adequately answered. Considerable differences exist between individuals from different countries. Even in homogeneous populations, individual experiences of menopause vary, as do experiences of pregnancy. The best possible approach to the management of menopausal symptoms is to address each woman's unique needs.

Surveys in the USA indicate that physicians underestimate their patients' concerns about menopausal symptoms.[49] A correct diagnosis of clinical manifestations and their association with menopause is crucial. Symptoms should be assessed and treated individually and specifically. If treatments for menopausal symptoms are prescribed, understanding their effectiveness and safety is essential.

Many investigators have reported on the treatment of symptoms associated with the menopausal transition. Most randomised, placebo-controlled trials focus on the treatment of vasomotor symptoms. These trials provide useful information for the management of highly symptomatic women, although not all proposed therapies have been sufficiently assessed. Effectiveness varies between therapies; evidence of substantial clinical benefit exists only for a few (figure 3).

Hormones

Oestrogen has been used for many years as a hormonal supplement to treat menopausal symptoms, and is the most effective treatment for vasomotor dysfunction in most women. This hormone is no longer recommended for prevention of chronic conditions,[53] although it is effective and approved for osteoporosis prevention.[1] Oestrogen is provided in several formulations, and is most commonly given by oral, transdermal, or vaginal routes. Women with an intact uterus are prescribed the "combined" or "opposed" regimen, in which oestrogen is combined with progestagen: this is intended to avoid the development of endometrial hyperplasia and endometrial cancer. The combined regimen can be administered on a cyclical basis, in which components are provided on specific days of the month, or on a continuous schedule, in which women take both hormones daily. Women without a uterus can take a daily dose of oestrogen without progestagen (the "unopposed" regimen). Doses vary by formulation, but present recommendations suggest the use of the lowest possible dose, for the shortest duration needed to relieve symptoms.[1] Periodic attempts to taper and discontinue oestrogen treatment are encouraged, to reduce to a minimum potential adverse events, although the best method of discontinuing oestrogen is not known. The interruption of oestrogen therapy can be difficult for many women, who experience a recurrence of symptoms.[54]

The use of oestrogen to treat hot flashes has been studied in many randomised controlled trials; the results are summarised in recent systematic reviews and meta-analyses.[50,51,55,56] Most trials were done in the USA or western Europe, and assessed forms of oestrogen that are common in these countries, especially oestradiol and conjugated equine oestrogen. Trials often recruited participants from primary care or gynaecology practices, focusing on healthy menopausal women in their early 50s; the baseline symptoms varied from study to study.

A Cochrane meta-analysis of randomised controlled trials found that symptomatic women treated with various forms of oral oestrogen had 2·6 fewer hot flashes

	Dose (mg/day)	Number of trials	Number of trials including women with breast cancer	Difference in number of daily hot flashes (95% CI)	Difference in severity or composite score (%)*	Potential adverse effects (selected)†
Gabapentin[68,73,74]	100–300 mg three times a day	3	1	−2·05 (−2·80 to −1·30); two trials‡	Improved 17–30%	Somnolence, fatigue, nausea, vomiting, and dizziness
SSRI/SNRI						
Paroxetine[75,76]	10–20 and 12·5–25 controlled release	2	2	−1·66 (−2·43 to −0·89); two trials‡	Improved 25–35%	Headache, nausea, drowsiness, and insomnia
Fluoxetine[52]	20–30	2	1	−1·37 (−3·03 to 0·29); two trials‡	Improved 25%	Nausea and dry mouth
Citalopram[52]	20–30	1	None	−0·20 (−1·45 to 1·05)	Improved	Nausea and dry mouth
Sertraline[77,78]	50–100	3	1	Reduced by <1 per day in 2 trials	Improved in 2 trials	Headache, nausea, drowsiness, dry mouth, and dizziness
Venlafaxine[52,79,80]	37·5–150 extended release	3	1	−0·49 (−2·40 to 1·41); 2 trials‡	Improved 10–35%	Dry mouth, nausea, decreased appetite, constipation, and insomnia
Veralipride[52]	100	3	None	Not reported§	Improved 45% in 2 trials	Mastodynia and galactorrhea
Moclobemide[52]	150–300	1	None	Not reported§	Not reported§	Somnolence
α blockers						
Clonidine[52]	Oral 0·025–0·075 mg twice a day; transdermal 0·1	10	2	−0·95 (−1·44 to −0·47); 4 trials at 4 weeks‡ −1·63 (−2·76, to −0·05); 2 trials at 8 weeks‡	Improved 13–26% in 4 of seven trials	Dry mouth, nausea, constipation, insomnia, drowsiness, skin irritation with transdermal form
Methlydopa[52]	375–1125	3	None	No difference	Improved in 1 of 2 trials‖	Dry mouth, nausea, and fatigue
Bellergal Retard[81]	One tablet twice a day (0·6 mg ergotamine, 40 mg phenobarbital, 0·2 mg levorotatory alkaloids)	1	None	No difference	No difference	Dry mouth, dizziness, and sleepiness

SSRI/SNRI=selective serotonin reuptake inhibitor/selective noradrenergic reuptake inhibitor. *Frequency and severity. †Additional adverse effects are described in other sources. ‡Based on meta-analysis of trials.[52] §Between-group differences not reported. ‖Data presented in graphs.

Table 2: **Efficacy of non-hormonal prescribed therapies in placebo-controlled trials**

per day (95% CI 1·9–3·3) than did women given placebo.[51] This effect was equivalent to a 75% reduction in frequency (0·64–0·82).[51] Oestrogen users also had significantly reduced hot-flash severity, compared with placebo users. The decrease in frequency of hot flashes was similar in women treated with opposed and unopposed oestrogen regimens, than in those treated with placebo, although severity decreased slightly more in women treated with the opposed regimen.

In a systematic review, hot-flash frequency, severity, or both, improved with oral and transdermal forms of oestradiol more than it did with placebo.[50] Oral oestradiol reduced hot flashes by 2·4 per day (1·5–3·2), and transdermal oestradiol by 3·2 per day (1·5–5·1); and results were similar for opposed and unopposed regimens.[50] Trials of oral conjugated equine oestrogen reported similar improvements in hot-flash frequency, severity, or both. Trials comparing oestrogen agents head-to-head (conjugated equine oestrogen *vs* oral or transdermal oestradiol) showed reduced number and severity of hot flashes for all treatment groups, with no substantial differences between them.[50]

Adverse effects of oestrogen have been well studied. Breast tenderness and uterine bleeding are the most common side-effects from short-duration treatment trials.[50] Others include nausea and vomiting, headache, weight change, dizziness, venous thromboembolic events, cardiovascular events, rash and pruritus, cholecystitis, and liver disorders.[50] Oestrogen users have increased breast density, leading to higher rates of biopsy of lesions detected by mammography.[57] Results of the Women's Health Initiative (WHI), a large trial of conjugated equine oestrogen alone or combined with medroxyprogesterone acetate versus placebo, reported increased risks of stroke and venous thromboembolic events with both regimens.[58,59] Risks of coronary heart disease and invasive breast cancer were also higher for those treated with conjugated equine oestrogen and medroxyprogesterone acetate than for those treated with placebo,[58] but not for those treated with conjugated equine oestrogen alone.[59] Secondary analysis of WHI data suggested that women starting hormone therapy within 10 years from the onset of menopause had a reduced risk of coronary heart disease, compared with those who started later.[60] Oestrogen should not be prescribed to women with cardiovascular disease, a history of thromboembolic events, breast or uterine cancer, or liver disease. The effects of other forms of oestrogen, including customised and bioidentical formulations, have not been well studied and are not known.

Few trials of progestagen or progesterone have described their effectiveness as single agents for the treatment of hot flashes; these trials have conflicting[61,62] or inconclusive results.[63–65] In a trial of women with breast cancer, the use of megestrol reduced hot flashes

by 73% compared with 26% with placebo (p<0·001).[66] Few trials have reported comparisons of testosterone and oestrogen combinations versus oestrogen alone or placebo. One trial showed no differences between treatment with testosterone and oestrogen versus treatment with oestrogen alone for hot-flash severity.[67] Tibolone is a synthetic steroid with progestogenic, androgenic, and oestrogenic effects. Some trials comparing the effect of tibolone with that of placebo showed decreased severity of hot flashes[68,69] and a decreased score on Kupperman's scale;[70] other trials did not.[1] Common adverse effects of tibolone include uterine bleeding, body pain, weight gain, and headache.[1]

Non-hormonal agents

Concerns about the adverse effects of oestrogen, after the results of the WHI trial were published in 2002,[58] have led to increased interest in non-hormonal therapies for menopausal symptoms. These agents have not been approved by drug-regulating agencies for menopause; moreover, they are associated with adverse effects that are well described (see US Food and Drug Administration). Several trials of non-hormonal therapies enrolled women with vasomotor symptoms who have breast cancer, for whom oestrogen is contraindicated. Whether women with breast cancer have responses to these agents that are different from those of women without cancer is not clear, because of the small number of trials. Trials that compare tamoxifen users and non-users showed similar results;[71] however, whether vasomotor symptoms of women with breast cancer are induced mainly by menopause or by use of tamoxifen is not known.

Use of gabapentin, a γ-aminobutyric acid analogue for treatment of seizures, reduced hot-flash frequency[72,73] and severity[72–74] compared with placebo in three trials (table 2). This reduction is equivalent to about two fewer hot flashes per day.[52] Women reported improvement when treated with 900 mg per day gabapentin,[73,74] but not with 300 mg per day.[73]

Two trials of paroxetine,[75,76] a selective serotonin reuptake inhibitor (SSRI), and two of venlafaxine,[79,80] a serotonin norepinephrine reuptake inhibitor (SNRI), showed a reduction in hot-flash frequency of at least one hot flash per day (table 2).[52] This effect was not significant in other trials of SSRIs and SNRIs. Although some trials of sertraline suggest potential benefits in reducing hot flashes,[77,78] others do not.[82] It has been postulated that hot flashes are linked to an overloading of serotonin-receptor sites in the hypothalamus, which are then blocked by SSRIs or SNRIs.[75] In treatment trials, hot flashes improved earlier than did psychiatric symptoms, and irrespective of coexisting depression and anxiety.[76] For some women, treatment of underlying depression might improve their ability to cope with their hot flashes. Trials of other antidepressants, veralipride and moclobemide, have been inconclusive because of methodological limitations.[52]

50% of trials of clonidine, a centrally active antihypertensive α-adrenergic agonist, showed substantially reduced hot-flash frequency or severity, and the other 50% did not.[52] In combination, results from all trials suggest a reduction of about one hot flash per day (table 2).[52] Clonidine might relieve hot flashes by decreasing peripheral vascular reactivity. Trials comparing methyldopa, an α-adrenergic antihypertensive agonist, with placebo showed no significant differences in hot-flash frequency.[52]

Non-prescribed therapies

Trials of non-prescribed therapies are often difficult to interpret because of variability of components and doses. Adverse effects, especially long-term effects, are not as well known as those of prescribed medications. Clinicians should access reliable sources to assess potential benefits and harms of individual agents (for an example, see US National Institutes of Health Office of Dietary Supplements).

Phyto-oestrogens are plant-based substances that bind to oestrogen receptors, and have weak oestrogenic and anti-oestrogenic activities. Soy isoflavone extracts, containing predominantly daidzein, genistein, and their glucoconjugates, show mixed effects on hot flashes in placebo-controlled trials (table 3).[52] In combination, results indicated about one hot flash less per day compared with placebo, although some estimates were not significant.[52] Other systematic reviews drew similar conclusions.[113–115] Few trials of dietary forms of soy—including soy in beverages, powder, flour, protein, cereal, and muffins—reported improvements in frequency or other hot-flash measures (table 3).[1,83,84]

Red-clover isoflavones, containing genistein, daidzein, formononetin, and biochanin, did not improve frequency or severity of hot flashes in placebo-controlled trials (table 3).[52,85,116–121] Similarly, phyto-oestrogens from hop extract,[85] flax,[84,87] and in topical forms,[88,89] did not show benefit in the treatment of hot flashes.

Black cohosh is a herbal therapy (*Cimicifuga racemosa*) believed to have oestrogenic properties. Black cohosh does not reduce the frequency of hot flashes, and although some trials showed improvement of other hot-flash measures,[90–92] others did not[93–96] (table 3). Results are also ambiguous when black cohosh is added to soy isoflavones[97,98] or St John's wort.[99] Black cohosh has been associated with liver damage.[122]

Several trials assessing Chinese herbs showed no differences in hot flashes compared with placebo.[1,83] Single trials of other supplements, such as evening primrose oil,[100] phospholipid liposomes,[101] and pollen extract[102] reported some improvements in hot-flash measures, but most did not (table 3).[103–107] One small trial of osteopathic manipulations reported improved hot flashes and night sweats.[108] Trials of reflexology,[109] magnets,[110] and aerobic exercise[111] showed no improvement in hot-flash measures compared with

	Types and doses (mg/day)	Number of trials (including women with breast cancer)	Difference in number of daily hot flashes (95% CI)	Improvement in severity, composite score,* or other measures†
Phyto-oestrogens				
Soy isoflavone extract[52]	Various components and doses	12 (4)	−1·15 (−2·33 to 0·03); 5 trials at 4–6 weeks‡ −0·97 (−1·82 to −0·12); 4 trials at 12–16 weeks‡ −1·22 (−2·02 to −0·42); 2 trials at 6 months‡	Improved in 4 of 9 trials
Dietary soy[83,84]	Soy beverage, powder, flour, protein, cereal, and muffin	10 (1)	Improved in 1 of 7 trials	Improved in 2 of 10 trials
Red-clover extract[52,85]	Promensil (40–160); rimostil (57)	7 (none)	−0·44 (−1·47 to 0·58); 6 trials‡	Improved in 1 of 6 trials
Hop extract[86]	Hop-derived flavonoids	1 (none)	Not reported§	No difference
Flax[84,87]	Lignans (20– 50)	2 (none)	No difference	No difference
Topical agents[88,89]	Phyto-oestrogen cream, wild yam cream	2 (none)	No difference	No difference
Black cohosh[90–96]	(40–160)	7 (2)	No difference	Improved in 3 of 7 trials
Dietary combinations[97–99]	Soy isoflavones and black cohosh; St John's Wort and black cohosh	3 (none)	No difference	Improved in 2 of 3 trials
Chinese herbs[83]	Ginseng, ginkgo, dong quai, pueraria lobata, combinations	6 (none)	Not reported§	No difference
Other supplements[100–107]	Vitamin E, kava, phospholipid liposomes, evening primrose oil, botanical formulas, guar gum, pollen extract, DHEA	8 (1)	No difference	Improved in 3 of 8 trials
Manual therapies[108]	Osteopathic manipulations	1 (none)	Not reported§	Improved hot flashes and night sweats
Energy therapies[109,110]	Reflexology, magnets	2 (1)	Improved with placebo *vs* magnets	No difference
Behavioural interventions[111]	Aerobic exercise	1 (1)	No difference	Not reported§
Acupuncture[83,112]	Various treatments	3 (none)	No difference	No difference

DHEA=dehydroepiandrosterone. *Frequency and severity. †Additional measures of hot flashes are included in this column because few trials of non-prescribed therapies provided severity and composite measures comparable to trials of prescribed therapies. ‡Based on meta-analysis of trials.[52] §Between-group differences not reported.

Table 3: **Efficacy of non-prescribed therapies in placebo-controlled trials**

placebo. A pilot study of acupuncture reduced night-time hot flashes,[112] but other trials of acupuncture did not show benefit.[1,83]

Therapies for non-vasomotor symptoms

Vaginal dryness and dyspareunia improved in trials of oral and vaginal forms of oestrogen.[123] For vaginal symptoms, the intravaginal oestradiol ring, oestradiol tablet, and conjugated equine oestrogen vaginal cream are similarly effective for relief of vaginal dryness, dyspareunia, resolution of atrophic signs, improvement in vaginal mucosal maturation indices, and reduction in vaginal pH.[123] Some women report reduced vaginal dryness with non-oestrogen moisturisers. Oestrogen does not improve urinary frequency and incontinence.[1] A few trials comparing oestrogen plus testosterone with oestrogen alone, or placebo, showed improved scores on sexual questionnaires addressing sexual interest and desire, responsiveness, and frequency of sexual activity, among other topics.[1] Tibolone could improve sexual interest and performance.[1]

Treatment of other symptoms, including sleep disturbances, mood changes, somatic complaints, and quality of life, have been assessed in trials for most therapies,[1] but results are inconclusive. This ambiguity might be due to the insensitivity and non-comparability of various measures and outcomes considered; the eventual resolution of symptoms as women progress through the menopausal transition; the placebo effect; or different effects in different groups of women (for instance, a positive effect only in women with the most severe symptoms, or comorbidities). Some symptoms could be secondary to others and improve as the primary symptom is treated, such as sleep disturbances arising from night sweats. As the epidemiological evidence indicates, some symptoms might not be related to menopause; if so, they would not be expected to improve with menopause-specific therapies such as oestrogen.

Conclusions

Menopause is an expected life event for midlife women. Most women have transient symptoms that are manageable with self-care approaches, such as wearing layers of clothing, and lowering stress. Some women ask health providers for help to manage menopausal symptoms, especially frequent and severe vasomotor symptoms and vaginal dryness, that interfere with healthy living. Coexistent health concerns can complicate the presentation, and require independent assessment. Social changes that are common in midlife, such as children leaving home, parents becoming ill or disabled, and the patient's changing role in society, can also affect the experience of menopause. Studies of menopause are vast in number, but incomplete in what they uncover.[124] Nonetheless, these results inform the recommendations of medical professional organisations,

and influence standards of practice.[125,126] Improved understanding of the menopausal transition, its symptoms, and therapies will permit a better response to the needs of patients.

Conflict of interest statement
I declare that I have no conflict of interest.

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