Managing menopause symptoms

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Conflict of interest: none declared
Options

1. HRT/ MHT
2. Non-hormonal pharmacological interventions and laser therapy (VVA,GSM only)
3. Behavioral therapies
4. Lifestyle modifications and diet
5. Alternative and complementary medicine

AND What should employers be doing

Guidance on menopause and the workplace
What is systemic HRT/MHT

- **Estrogen alone** for women who have had a hysterectomy
- **Estrogen plus a progestogen or progesterone** for women who have not had a hysterectomy to reduce the risk of endometrial cancer if estrogen was given alone
- **Progestogen** can be given intermittently (usually monthly) and cause withdrawal bleeds or every day leading to ‘no bleed HRT’
Types and routes of administration: availability depends on country

- Estrogen
- Estradiol
- Conjugated estrogens (equine or plant-based)
- Tablet/ patch/ gel

- Progestogen
- Progesterone
- Dydrogesterone
- Medroxyprogesterone acetate
- Norethisterone
- Levonorgestrel/ norgestrel
- Drospirenone
- Tablet/ patch / intrauterine
Conjugated estrogens /bazedoxifene

- Conjugated estrogens /bazedoxifene is a tissue selective estrogen complex (TSEC).
- In Europe, it is indicated for the treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate.
- The FDA has approved the combination ‘for women who suffer from moderate-to-severe hot flashes (vasomotor symptoms) associated with menopause and to prevent osteoporosis after menopause’.
- It is a ‘no bleed HRT’
Tibolone

- Is a synthetic steroid compound that is in itself inert, but whose metabolites have estrogenic, progestogenetic and androgenic actions.
- It is classified as HRT.
- It is used in postmenopausal women and is a ‘no bleed HRT’
Bioidentical hormones

- The term “bioidentical hormone therapy” began as a marketing term for custom-compounded hormones.
- A bioidentical hormone is a compound that has the same chemical and molecular structure as hormones that are produced in the body e.g. estradiol and progesterone.
- There are many approved HRT products containing estradiol and progesterone.
- Concerns regarding custom-compounded HRT: lack of regulation, rigorous safety and efficacy testing, batch standardization, and purity measures.
Duration of systemic HRT treatment

- Depends on the endpoints of treatment.
- For women with a premature/early menopause it is recommended that treatment is continued until the average age of the natural menopause (ie early 50s) and then reassessed.
- Vasomotor symptoms are the commonest indication for MHT and treatment should be continued for up to 5 years and then stopped to see if they are still present.
- There are no arbitrary limits regarding the duration of use of MHT - it can be used for as long as the woman feels the benefits outweigh the risks for her and decisions must be made on an individual basis. Routine discontinuation after 5 years or at age of 65 is not recommended.
Estrogen based therapies: stopping systemic treatment

- The main issue is that it is impossible to predict whether individual women will still be symptomatic or not when they stop systemic HT.
- The limited evidence available shows no advantage of tapering down or stopping abruptly. Anecdotally, older women need less estrogen to control their symptoms and thus a lower dose can be tried before stopping.
- A Finnish cohort study found that discontinuation of systemic HT is associated with an increased risk of cardiovascular deaths especially within the first year and in those aged under 60 years.

Premature ovarian failure

- In women with POF, systemic estrogen-based HRT is recommended at least until the average age of the natural menopause, unless it is contraindicated.
- Untreated it increases the risk of osteoporosis, cardiovascular disease, dementia, cognitive decline and Parkinsonism.
- In women under the age of 50 HRT use is not associated with an increased risk of breast cancer compared to that found in normally menstruating women.
Topical/ vaginal estrogens

- Estradiol
- Estriol
- Tablet, ring/ cream/ pessaries
- No need to add a progestogen as for systemic HRT, if the recommended low dose regimes are used
- VVA/ GSM is a chronic condition and symptoms will return when treatment is stopped
Hormonal Alternatives for VVA

- Ospemifene oral tablet
  - Indicated for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy
- Vaginal dehydroepiandrosterone
  - Indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms
ESTROGEN THERAPY—A WARNING
JAMA. 1939;113(26):2323-2324.

Physician and Pharmacopeia

The Journal of previous occasions has explained the machinery for the production of the U. S. Pharmacopeia, pointing out that the decision of a convention is not binding upon the pharmacists from the United States. The convention is a mere meeting of the Board of Pharmacy and Chemistry and that the resulting treatment is binding upon no one and is not binding upon no one. The convention is a mere meeting of the Board of Pharmacy and Chemistry and that the resulting treatment is binding upon no one and is not binding upon no one.

Estrogens were synthetised in the 1930s. HRT was first made available on prescription in North America in 1941.
MHT: history

- 1929/30 Adolf Butenandt, Germany / Edward Doisy, US (both Nobel laureates) isolate estrone, estriol and estradiol
- 1934 estradiol synthesised (Schering in Berlin)
- 1936 estrone synthesised (Pennsylvania State University supported by Parke Davis)
- 1938 Ethinyl estradiol synthesised (Schering in Berlin)
- 1938 Diethyl stilbestrol synthesised (Middlesex Hospital London)
- 1939 Ayerst, McKenna and Harrison isolated estrogens from pregnant mares’ urine
- Ayerst introduced Premarin in 1941 in Canada and 1942 in the US
- 1938-1940 Marker degradation synthetic route in steroid chemistry used for production of estradiol and progesterone from plant steroids developed and commercialized 1940s (Parke Davis/ Syntex)
Health scare 'clouded views on HRT'

"Thousands of women have had a 'bleak decade' of suffering once the HRT scare, according to an international panel of experts," the Daily Mail has reported.

The new is based on a major re-evaluation of the Women's Health Initiative (WHI) study, the results of which prompted safety alerts in 2002. The review analysis comes in a series of papers reporting which the results of the WHI were presented and the media's interpretation of them. The authors state that the evidence could have a significant impact on the potential benefits of the well-being of thousands of women worldwide.

The authors of one review concluded, "While HRT is certainly not appropriate for every woman, it may be for those with symptoms or other indications. In that setting, with a suitable health practitioner, the weight of evidence supports benefits over risks."

What is HRT?

Hormone replacement therapy (HRT) is a treatment used to relieve the symptoms of menopause. It replaces the female sex hormones that women's bodies stop producing after menopause. Reduced production of the hormone oestrogen is associated with many of the symptoms of menopause, including:

- Hot flashes
- Night sweats

Related articles
- Antibiotic resistance 'hitlist' launched (March 7 2014)
- "Pausing" in pill may create harmful side effects (March 7 2014)
- "HRT gone hack" offers new treatment hope (March 5 2014)
- WHO says harmful sugary drink has extra benefit (March 6 2014)
- Claims of anti-aging pill may be premature (February 28 2014)

Useful links

HRT Choices Links

The menopause

The menopause

The menopause

The menopause

HRT breast cancer link in doubt

Read more and advice on the menopause

Menopause: self-help

Five simple ways to help you cope with menopause symptoms

Menopause: how your GPs can help

Find out how your GP can help if you have symptoms such as hot
Benefits and risks: global consensus statement 2016

- Are all HRTs the same? No
- Estrogen alone systemic HRT does not increase the risk of breast cancer
- Patch or gel estrogen HRT does not increase the risk of deep vein thrombosis
- MHT, including tibolone and the combination of conjugated equine estrogens and bazedoxifene (CE/BZA), is the most effective treatment for vasomotor symptoms (VMS) associated with menopause at any age, but benefits are more likely to outweigh risks if initiated for symptomatic women before the age of 60 years or within 10 years after menopause.
Non-hormonal pharmacological interventions and laser therapy

- SSRIs and SNRIs
- Clonidine (licensed in UK)
- Gabapentin
- Vaginal lubricants and moisturisers
- Laser therapy for VVA and GSM
SSRIs and SNRIs for hot flushes

- SSRIs eg paroxetine, escitalopram, citalopram and sertraline effective in decreasing both frequency and severity of hot flushes
- 28 June 2013 FDA approved paroxetine to treat moderate to severe hot flashes
- Paroxetine (Cytochrome P450 2D6 inhibitor should be avoided in tamoxifen users as it affects tamoxifen metabolism)
- SNRIs eg venlafaxine and desvenlafaxine effective in randomised trials

Fig 1 Risk of breast cancer mortality associated with increasing proportions of antidepressant use during tamoxifen treatment

- Paroxetine
- Citalopram
- Sertraline
- Fluvoxamine
- Fluoxetine
- Venlafaxine

Kelly, C. M et al. BMJ 2010;340:c693
Clonidine

- Clonidine is a centrally acting alpha-adrenoceptor agonist that was developed originally for the treatment of hypertension. It is licensed for the treatment of hot flushes in some countries.
- It has been shown modestly more effective than placebo in a meta-analysis of 10 trials.
- It does not inhibit cytochrome P450.

Gabapentin

- Gabapentin is a gamma-aminobutyric acid analogue indicated for epilepsy and neuropathic pain.
- It reduces hot flushes at a dose of 900mg/day by about 50%. Side effects include dry mouth, dizziness and drowsiness which may improve with continued use.
- It is not approved for the treatment of hot flushes. It does not inhibit cytochrome P450 and thus can be used in women taking tamoxifen. Different doses have been studied (600-2,400mg daily). Combined therapy with gabapentin and an antidepressant (SSRI or venlafaxine) does not appear to be more effective for hot flashes than gabapentin alone.

Loprinzi et al. Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. J Clin Oncol. 2007;25:308.
Stellate ganglion blockade

Methods: RCT 40 women of bupivicaine versus saline injections

Results: There were no significant group differences in overall VMS frequency, but the frequency of moderate to very severe VMS was reduced more in the active group compared with the sham treatment group. The frequency of objective VMS was also reduced to a greater degree in the active than in the sham group.

Conclusions: SGB may provide effective treatment of VMS in women who seek nonhormonal treatments because of safety concerns and personal preference. A larger trial is warranted to confirm these findings.

Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized controlled clinical trial in postmenopausal women
Walega et al Menopause 2014; 21: 807–814
Vaginal lubricants and moisturisers

- Moisturisers used on a regular basis and lubricants during intercourse can alleviate symptoms of vaginal dryness.
- Moisturisers are typically used on a regular basis, rather than episodically associated with sexual activity. They may contain a bioadhesive polycarbophil-based polymer, which attaches to mucin and epithelial cells on the vaginal wall and retains water.
- Lubricants are typically used episodically to correspond to sexual activity. Lubricants, in general, give only temporary relief of symptoms.
- Lubricants such as petroleum-based products and baby oil can compromise the integrity of condoms.
Laser therapy

- Two types: fractional CO$_2$ laser and the non-ablative Er:YAG laser
- No randomized trials to date
- FDA Warns Against Use of Energy-Based Devices to Perform Vaginal 'Rejuvenation' or Vaginal Cosmetic Procedures: FDA Safety Communication 30 July 2018
Cognitive behavioural therapy

- Randomized controlled trial data are available both in women from the general population and in breast cancer survivors.
- CBT can be delivered in various ways: group, self-help or internet-based.

- Self-help cognitive behavior therapy for working women with problematic hot flushes and night sweats (MENOS@Work): a multicenter randomized controlled trial. Hardy et al. Menopause. 2018;25:508-519
For hot flushes and night sweats, advise:

- Taking regular exercise.
- Weight loss if applicable
- Wearing lighter clothing and sleeping in a cooler room.
- Reducing stress.
- Avoiding possible triggers, such as spicy foods, caffeine, smoking, and alcohol.
Weight loss and dietary components

- Weight loss
- Phytoestrogens/ isoflavones
- Mediterranean diet/ sugar and fat intake
- Spicy foods no studies with documented Scoville heat units (subjective scale) or HPLC measurement of capsaicinoid content

- Self-administered questionnaires were used to assess bothersome hot flushes in a 6-month randomized controlled trial of an intensive behavioral weight loss program (intervention) vs a structured health education program (control) in 338 women who were overweight or obese and had urinary incontinence.

- Among women who were overweight or obese and had bothersome hot flushes, an intensive behavioral weight loss intervention resulted in improvement in flushing relative to control.
Effects of a dietary intervention and weight change on VMS in the Women’s Health Initiative.

- 17,473 women, aged 50–79 at baseline who participated in the Women’s Health Initiative Dietary Modification (DM) trial and were not taking MHT. Dietary intervention designed to reduce fat intake and increase intake of fruit, vegetables, and whole grains.
- 65% of respondents reported no; 25% mild; 8% moderate; and 2% severe VMS.
- Women who lost weight reported a reduction or elimination of VMS over one year. The dietary intervention appeared to ameliorate symptoms over and above the effect of weight change.
- BUT Women in the intervention who gained >10 lbs also had reduced VMS suggesting that the beneficial impact of healthy diet was not restricted to those who lost weight.
- These results support the use of weight loss and healthy dietary change as alternative approaches to hormone therapy for the relief of vasomotor symptoms.
Fat, Fit or Famished? No clear answers from the WHI about diet and dieting for long-standing hot flashes


- It turns out that the dietary change interventions included nutrition classes every 1–2 weeks, individualized dietary goals, culture-based cooking classes, professional-facilitated group sessions for sustaining lifestyle change, a regular newsletter, follow-up telephone calls and the use of a host of self-monitoring diaries, pictograms and other tools rolled out during the 5 year start-up phase when adherence rates began falling. No wonder the intervention group lost three times as much weight and reported fewer mild hot flashes vs controls with such focused attention and support.

- The problem is we have yet to clearly define a self-management intervention that works without an army of highly-trained lifestyle coaches

- Although these results are unlikely to create a “tsunami of uncertainty” they have produced more questions than answers.

- Use of phytoestrogens was associated with a decrease in the number of daily hot flashes but not in the number of night sweats

- Individual phytoestrogen interventions such as dietary and supplemental soy isoflavones were associated with improvement in daily hot flashes
Fruit, Mediterranean-style, and high-fat and -sugar diets are associated with the risk of night sweats and hot flushes in midlife: results from a prospective cohort study

- Australian Longitudinal Study on Women's Health: prospective cohort study of 6040 women with a natural menopause were followed up at 3-y intervals over 9 y.
- A higher consumption of the fruit or Mediterranean-style diet was inversely associated with VMSs.
- The high-fat and -sugar pattern increased the risk of VMSs.
Vegans report less bothersome vasomotor and physical menopausal symptoms than omnivores

- Compared vasomotor and physical symptoms in omnivores (n = 304, consumed meat and/or poultry at least monthly) and vegans (n = 125, abstained from all animal proteins)

- Among perimenopausal women, vegans reported less bothersome vasomotor (p < 0.01) and physical symptoms (p < 0.01) than omnivores.

- For both symptom types, more vegetables and less flesh food were associated with less bothersome symptoms (p values < 0.05).
We included five RCTs (733 women) comparing exercise with no active treatment, exercise with yoga and exercise with HT. The evidence was of low quality: Limitations in study design were noted, along with inconsistency and imprecision. In the comparison of exercise versus no active treatment (three studies, n = 454 women), no evidence was found of a difference between groups in frequency or intensity of vasomotor symptoms (SMD -0.10, 95% CI -0.33 to 0.13, three RCTs, 454 women, I(2) = 30%, low-quality evidence). Nor was any evidence found of a difference between groups in the frequency or intensity of vasomotor symptoms when exercise was compared with yoga (SMD -0.03, 95% CI -0.45 to 0.38, two studies, n = 279 women, I(2) = 61%, low-quality evidence).

Evidence was insufficient to show whether exercise is an effective treatment for vasomotor menopausal symptoms.

- Three-group randomised controlled 6 month trial, two exercise interventions and a control group. N=261, 87 per group

- Participants in both exercise interventions groups were offered two face-to-face consultations with a physical activity facilitator to support engagement in regular exercise.

- In addition, one exercise group received a menopause-specific information DVD and written materials to encourage regular exercise and the other exercise group was offered the opportunity to attend exercise social support groups in their communities.
Neither of the exercise intervention groups reported significantly less frequent hot flushes/night sweats per week than controls (exercise-DVD versus control: -8.9, 95% CI -20.0 to 2.2; exercise-social support versus control: -5.2, 95% CI -16.7 to 6.3).

Exercise is not an effective treatment for hot flushes/night sweats. Contrary to current clinical guidance, women should not be advised that exercise will relieve their vasomotor menopausal symptoms.
Complementary and alternative therapies

- Herbals
- Phytoestrogens
- Vitamins and minerals
- Functional foods
- DHEAS
- Progesterone creams
- Homeopathy
- Reflexology
- Acupuncture
- Magnets
- Relaxation
- Yoga
- Exercise
Herbals

- No good RCTs
- Active ingredient?
- What part of the herb: leaf or root
- Mode of action? via oestrogen/serotonin (black cohosh) receptors
- Contaminants: heavy metals, pesticides, carcinogens
- Herb-drug interactions e.g. anticoagulants, antidepressants, anti-epileptics, chemotherapy, tamoxifen
- Herb-herb interactions

Herbal options

- Black cohosh
- Ginseng
- St John’s Wort
- Oil of Evening Primrose
- Wild Yam cream
- Dong Quai
- Agnus Castus
- Liquorice
- Valerian
- Ginkgo Biloba

- Not all preparations are the same
- Many different *Cimicifuga* species exist.
- These include three North American species, *C. racemosa*, *C. americana*, *C. rubifolia*, and seven Asian species, *C. acerina*, *C. biternat*, *C. dahurica*, *C. heracleifolia*, *C. japonica*, *C. foetida*, and *C. simplex*.
- Their chemical composition is different.
Acupuncture

- the workings of the human body are controlled by a vital force or energy called "Qi" which circulates between the organs along channels called meridians.
- There are 12 main meridians, which correspond to 12 major functions or "organs" of the body. The acupuncture points are located along the meridians and provide one means of altering the flow of Qi.
Acupuncture

- No convincingly inert 'placebo' needle has yet been designed.
- Insufficient evidence to determine whether acupuncture is effective for controlling menopausal vasomotor symptoms.
- Low quality evidence
- Data on adverse effects lacking.
EMAS recommendations for conditions in the workplace for menopausal women

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ARTICLE INFO

Keywords:
Menopause
Workplace

ABSTRACT

Women form a large part of many workforces throughout Europe. Many will be working throughout their menopausal years. Whilst the menopause may cause no significant problems for some, for others it is known to present considerable difficulties in both their personal and working lives. During the

Chart 2. Employment rates by 5-year age bands, Women

- 50-54
- 55-59
- 60-64
- 65-69
- 70-74
Highlights

- Many women in today’s workforces will be working throughout their menopausal years.
- While the menopause may cause no significant problems for some women, for others it may present considerable difficulties in both their personal and working lives.
- Greater awareness among employers, together with sensitive and flexible management can be helpful for women at this time.
- Working conditions should be assessed to consider the specific needs of menopausal women and ensure that the working environment will not make their symptoms worse.
Recommendations

1. Raise awareness
2. Allow disclosure of troublesome symptoms
3. Review control over workplace temperature and ventilation
4. Reduce work-related stress
5. Allow flexible working arrangements
6. Provide access to cold drinking water
7. Ensure access to toilets
The Workplace Wellness Issue No One Is Talking About

Employers need to support their female workers during menopause.

01/13/2016 12:34 pm ET

Lisa Rapaport
12th European Congress on Menopause and Andropause
15 – 17 May 2019 | Berlin, Germany
Managing Midlife Health and Beyond in the Era of e-Medicine