Managing menopause in Primary Care and recent advances in HRT

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Content of today’s talk

• Aims
  – To feel confident in discussing the management of menopausal symptoms with patients
  – To be able to diagnose menopause and know when it is appropriate to investigate and consider referral
  – To be able to prescribe HRT safely

• Objectives
  – Review subject of menopause – why it is important?
  – Controversies and Available evidence
  – Discuss management of menopausal symptoms
  – Look in more depth at HRT preparations
  – Look at the first consultation for HRT
  – Discuss different clinical situations
Demographic revolutions — rapidly changing population structures

Increase of elderly ≥ 60 population
8% to 21%

Decrease of children ≤ 14 population
34% to 20%
Demographic revolutions – rapidly changing population structures in Europe

Increase of elderly ≥ 60 population
13% to 46%

Decrease of children ≤14 population
26% to 14%
Elderly population by 2050
UN projection

- A large proportion of women will live in postmenopausal age

£335 million
One billion by 2050
Knowledge and scientific evidence

- Preventive measures
- Quality of life
- Social and emotional
- Activity
Review of HRT studies confirms health dangers

By Jeremy Laurence Health Editor

Friday, 20 September 2002

Hormone replacement therapy is not a risk-free treatment for menopausal symptoms, a large-scale review of its safety has concluded.

Hormone replacement therapy is not a risk-free treatment for menopausal symptoms, a large-scale review of its safety has concluded.

Women using the treatment long term are more likely to contract a life-threatening disease than be protected against one, a study of 20,000 postmenopausal women who had taken HRT for about five years shows.

British scientists reviewed seven life-threatening conditions linked with HRT after an American trial in July showed that it increased the risk of breast cancer by 26 per cent and the risk of heart disease by 29 per cent.

Although the risk of breast cancer with HRT has been known in the last couple of years, the surprise from the American trial was the increased risk of heart disease. HRT had been thought to protect against it.
"A 51-year-old postmenopausal woman has occasional hot flushes attends your clinic to discuss HRT. She is otherwise healthy."
Would you consider prescribing HRT?
“A 51-year-old woman has frequent and distressing hot flushes that interfere with her work and sleep, and vaginal dryness that makes sexual intercourse with her husband uncomfortable. She is otherwise healthy.”
Would you consider prescribing HRT?
Why women come to you for HRT?

They want relief from hypo-oestrogenic symptoms or they want to gain the long term benefits of HRT
Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial.
The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.
Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial.
Combined HRT vs Placebo

TABLE 1
Women’s Health Initiative Trial Results Disease Rates (Number of Cases Per Year in 10,000 Women) for Women on Estrogen Plus Progestin or Placebo

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estrogen + Progestin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart attacks</td>
<td>37</td>
<td>30</td>
</tr>
<tr>
<td>Strokes</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>Blood clots</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Deaths</td>
<td>52</td>
<td>53</td>
</tr>
</tbody>
</table>

A possible reduction in breast cancer risk requires further investigation. The burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit. Thus, CEE should not be recommended for chronic disease prevention in postmenopausal women.
Symptoms

- Hot flushes
- Palpitations
- Night sweats
- Sleep disturbances
- Vaginal dryness
- Urinary urgency
- Depressed mood
- Irritability
- Lethargy
- Forgetfulness
- Loss of concentration
- Loss of libido
To date oestrogen is the most effective treatment for hot flushes
Menopause: diagnosis and management

NICE guideline
Published: 12 November 2015
nice.org.uk/guidance/ng23
Strategies for hot flushes – non estrogenic substance

- High dose progesterone only is effective – perhaps not appropriate with current evidence
- Modest benefit on paroxetine, inconsistent result with venlafaxine
- SSRI found most effective with breast cancer
- Gabapentine was found to be modestly effective
- Clonidine is inconsistent with some side effects
Non estrogenic treatment for vasomotor symptoms

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>SSRI</th>
<th>SNRI</th>
<th>Extensive list of side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>30 mg</td>
<td>No</td>
<td>No benefit over placebo³³</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg</td>
<td>Mixed</td>
<td>Improvement of 24% over placebo among breast cancer survivors³⁴</td>
</tr>
<tr>
<td></td>
<td>30 mg</td>
<td></td>
<td>No benefit among women without breast cancer³³</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10 to 20 mg</td>
<td>Yes</td>
<td>Improvement of 30% over placebo among breast cancer survivors³⁵</td>
</tr>
<tr>
<td></td>
<td>12.5 to 25 mg CR</td>
<td></td>
<td>Improvement of 25% over placebo among women without breast cancer³⁶</td>
</tr>
<tr>
<td>Sertraline</td>
<td>No</td>
<td></td>
<td>No benefit over placebo among breast cancer survivors³⁷</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75 or 150 mg</td>
<td>Mixed</td>
<td>Improvement of 34% over placebo among breast cancer survivors³⁸</td>
</tr>
<tr>
<td></td>
<td>75 mg ER</td>
<td></td>
<td>No benefit over placebo among women without breast cancer⁴⁰</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300 mg 3 times daily</td>
<td>Yes</td>
<td>Improvement of 31% over placebo among breast cancer survivors³⁹</td>
</tr>
<tr>
<td>Alpha-blockers</td>
<td>Clonidine 0.1 mg transdermal</td>
<td>Mixed</td>
<td>Little or no benefit⁴⁴ or improvement of 27% over placebo⁴⁵</td>
</tr>
<tr>
<td></td>
<td>Metyldopa 375 to 1125 mg daily in divided doses</td>
<td>No</td>
<td>No benefit over placebo⁴⁶</td>
</tr>
</tbody>
</table>

Same side effects as for SSRIs, but minimal effect on cytochrome P-450 enzymes (only slightly inhibits conversion of tamoxifen to active metabolites)⁴⁷; possible hypertension.

Nausea, vomiting, somnolence, dizziness, rash, ataxia, fatigue, and leukopenia.

Dry mouth, drowsiness, dizziness, hypotension, and rebound hypertension.
Centrally active nonhormonal hot flash therapies

Charles L. Loprinzi, MD, a Vered Stearns, MD, b Debra Barton, PhD, RN a

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bThe Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland, USA

KEYWORDS:
Hot flashes; Newer antidepressants; Nonhormonal therapies

Given the problems associated with hormonal therapy, and the prominent problem of hot flashes in menopausal women, there is a need for nonhormonal agents to alleviate hot flashes. Several compounds that appear to act on the central nervous system have been investigated. Potential mechanisms for their effects on hot flashes have been described. Bellerpaq (no longer available in the US market, where it was known as Bellerpaq-S), a combination preparation sedative that consists of low-dose phenobarbital, ergotamine tartrate, and levorotatory alkaloids of belladonna, is an old agent that was popular approximately 20 years ago; however, there is limited suggestion of efficacy for this agent. Clonidine, an older antihypertensive drug, is another centrally active agent that has been studied. Randomized trials have demonstrated that it clearly works for reducing hot flashes, but the magnitude of efficacy is somewhat limited. Toxicity from this agent limits its utility in the clinic. Metyrapol is another centrally active agent that has been studied to a more limited degree. It appears to have minimal efficacy and too much toxicity to make it clinically useful. Anecdotal observations from a number of sources suggested that newer antidepressants can alleviate hot flashes. This led to pilot trials of venlafaxine and paroxetine, with results suggesting benefit from both drugs. Subsequently, randomized, placebo-controlled, double-blind clinical trials of venlafaxine, paroxetine, and fluoxetine were conducted. All 3 of these clinical trials demonstrated statistically significant reductions in hot flashes with these newer antidepressants compared with placebo. Pilot trials of citalopram and mirtazapine, 2 other newer antidepressants, have also suggested efficacy. Toxicity evaluations have suggested that these agents are, again, well tolerated by the majority of patients. A recent trial, however, was unable to demonstrate any benefit for fluoxetine or citalopram over a placebo. Anecdotal observations also suggested that gabapentin was helpful for alleviating hot flashes. This led to pilot trials that again suggested efficacy. Subsequently, 2 large placebo-controlled, randomized, double-blind clinical trials were conducted. Both of these demonstrated statistically significant efficacy for gabapentin compared with a placebo. This drug is relatively well tolerated by most patients. Thus, centrally active nonhormonal agents clearly do decrease hot flashes in women. The most efficacious and clinically appropriate agents to use are newer antidepressants and gabapentin. Continued evaluation of the efficacy and toxicity of these agents is ongoing.

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Strategies for vaginal symptoms

- Topical estrogenic cream, tablet and ring all are very effective.
- Does not raise the serum level of estrogen significantly for short term use.
- Polycarbophil-based vaginal moisturiser.
Risk of unscheduled vaginal bleeding after HRT

- Unscheduled vaginal bleeding is a common side effect of HRT within the first 3 months of treatment.

- Specifically mention to the woman that if bleeding persists at the 3-month should be referred for further investigation.
HRT and breast cancer

- Tibolone or progestogens are not recommended for women with menopausal symptoms who have breast cancer.

- The selective serotonin re-uptake inhibitor antidepressants paroxetine[14] and fluoxetine[14] may be offered to women with breast cancer for relieving menopausal symptoms, particularly hot flushes, but not to those taking tamoxifen.
Strategies for hot flushes

- Estrogen is effective in 80-95%
- Non hysterectomy patient requires progesterone
- Different routes could be considered – appropriate for a particular patient
- Usually takes 4 wks to achieve substantial relief
Behavioural and alternative therapy

- Lowering temp.
- Regular exercise
- Breathing exercise
- Stop smoking
- No evidence in support of Acupuncture, black cohos, primrose oil, red clover
- Phytoestrogens
NICE Guideline on complimentary therapy

- Explain to women that there is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms. However, explain that:
  - Multiple preparations are available and their safety is uncertain. Different preparations may vary.
  - Interactions with other medicines have been reported.
What should you do during follow up

- Reassess after 3 months then annually
- Follow up consultations should cover;
  - How effective has been the primary management?
  - Enquiring about side effects
  - Enquire about bleeding pattern any abnormal bleeding?
  - Check weight and BP
  - Ensure she examines her breasts regularly
- If on cyclical treatment, consider changing to continuous if she is considered to be postmenopausal > 1yr. This is usually considered to be
  - If she has previous raised FSH levels on two occasions or amenorrhoea > 1yr
  - If she has been on cyclical regimes for at least 2 years
Royal College of Physicians guidance on risk factors for osteoporosis

- Premature menopause (before the age of 40)
- Family history of osteoporosis
- Taken steroids for more than 6 months
- Premenopausal amenorrhoea for more than 6 months (due to low body mass index or excessive exercise)
- Liver, thyroid, or renal disease
- History of excessive alcohol intake
- Taken gonadotrophin agonists
Strategies for women prone to develop osteoporosis

- To offer bone density scan (DEXA)
- Consider biphosphonates and/or HRT
- Supplement - Calcium and Vitamin D3
- Role of Raloxifene (SERM)
- Life style changes – regular exercise, cessation of smoking
Levonorgestrel 20 micrograms/24 hours
Special situation

- Thromboembolic disease
- Cardiovascular disease
- Breast cancer
- Endometrial cancer
- Ovarian cancer
- Cervical cancer
## HRT Risk

<table>
<thead>
<tr>
<th>Risk</th>
<th>Age range (years)</th>
<th>Background incidence per 1000 women in Europe not using HRT</th>
<th>Additional cases per 1000 women using oestrogen only HRT (estimated)</th>
<th>Additional cases per 1000 women using combined (oestrogen-progestogen) HRT (estimated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Over 5 years</td>
<td>Over 10 years</td>
<td>For 5 years’ use</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>50–59</td>
<td>10</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>15</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>50–59</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>50–59</td>
<td>2</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>3</td>
<td>6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>50–59</td>
<td>5</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>8</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>50–59</td>
<td>4</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>9</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>70–79</td>
<td>29–44</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

**Note:** Where background incidence or additional cases have not been included in the table, this indicates a lack of available data. NS indicates a non-significant difference.

Taken from MHRA/CHM (Drug Safety Update 2007: 1 (2): 2–6) available at [www.mhra.gov.uk/drugsafetyupdate](http://www.mhra.gov.uk/drugsafetyupdate)
Alternative medicine

- They are often not regulated by a governing body.
- General rule is to advise against herbal medications.
- Many may contain estrogenic compounds.
- Women may be taking more hormones by using these than they would with HRT.
- Some studies suggest diet high in soy and isoflavones reduces severity and frequency of symptoms. They are safe.
- Acupuncture – no evidence
- Foot massage, reflexology – no evidence
- Evening primrose oil – no evidence
- Black Cohosh – limited evidence
- Red Clover – limited evidence, no health concerns
- Dong Quai – no evidence
It is a beginning of a journey

Understanding, knowledge and joint co-operation
Thank you