Over the Counter Options
For
Perimenopause and Menopause

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Learning Objectives

Participants will be able to:

1) Discuss the use of over-the-counter therapies for “menopause” symptoms
2) Identify potential health related problems associated with transitional years and hormonal changes
3) Identify common interventions that may optimize the patient’s care
“I have this menopause thing happening, what should I do?”

Clarifying the terminology:

- Peri-menopause
- Menopause
- Post-menopause
<table>
<thead>
<tr>
<th>Stages:</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>+1</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology:</td>
<td>Reproductive</td>
<td>Menopausal Transition</td>
<td>Postmenopause</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early*</td>
<td>Late*</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Duration of Stage:</td>
<td>variable</td>
<td>variable</td>
<td>a 1 yr</td>
<td>b 4 yrs</td>
<td>until demise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual Cycles:</td>
<td>variable to regular</td>
<td>regular</td>
<td>variable cycle length (&gt;7 days different from normal)</td>
<td>intervals of amenorrhea (&gt;42 days)</td>
<td>none</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine:</td>
<td>normal FSH</td>
<td>↑ FSH</td>
<td>↑ FSH</td>
<td>↑ FSH</td>
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</tbody>
</table>

*Stages most likely to be characterized by vasomotor symptoms*
What Happens in Peri/Post Menopause?

• Symptoms are usually divided into three categories:
  – **Vasomotor symptoms (VMS):** hot flashes, night sweats
  – **Somatic symptoms:** headaches, joint pain
  – **Psychological symptoms:** depression, irritability

• Most North American women will spend the last 1/3 of their lives post-menopause.

• Many women are seeking alternative approaches to their menopausal symptoms

Meet Mrs. Jones:

“I have this menopause thing happening...

What should I do?”

Mrs Jones has been suffering from menopausal symptoms. She does not want to take any prescription medications.

– She would like your advice on other options.
– Is there anything she can take to help her symptoms?
Involving the Patient in the Decision-making Process

1. Acknowledge patient’s role in decision-making
2. Discuss clinical issue that needs to be addressed
3. Discuss alternative treatment options
4. Discuss the pros and cons of each alternative
5. Discuss real and perceived risks
6. Assess patient’s understanding of the available options
7. Explore patient’s preferences

Vasomotor Symptoms (VMS): Therapeutic options

- Lifestyle modification
- Complementary and alternative medicine (CAM) approaches
- Nonprescription remedies
- Prescription drugs
Alternative Approaches for Vasomotor Symptoms:

NAMS Lifestyle Adaptations Guidelines

- Lowering body core temperature
- Exercise
- Paced respirations (catecholamine control)
- Relaxing activities
  - Yoga, massage, meditation, leisurely bath
- Avoid triggers
  - Spicy food, hot drinks, caffeine, alcohol

Benefits of Regular Exercise

- Decreases hot flashes
- Improves mood and sleep
- Decreases/maintains weight
- Supports joint/muscle flexibility
- Prevents bone loss
- Decreases risk of many other diseases
Evidence for Different Types of Exercise in Menopause

- Mixed results with regards to studies for VMS and exercise
- **In summary:** Moderate and regular exercise has positive effects on central thermoregulation, unless associated with obesity, sweating or severe VMS

Other Modalities

Deep breathing exercises, paced respiration

• Diaphragmatic breathing for 15 min BID, with 5 seconds inhalation and 5 seconds exhalation was found effective in reducing the severity and frequency of hot flashes

Other Modalities

Meditation, applied relaxation, yoga

- Yoga decreases climacteric symptoms, perceived stress and neuroticism in perimenopausal women
- Most studies have participants practicing yoga once a week for 8-10 weeks

Other Modalities

Acupuncture

• Studies show mixed results
• Acupuncture seems to reduce hot flash frequency
• Additional studies with adequate controls needed

Other Modalities

Homeopathy, magnetic therapy and reflexology

- Studies show mixed results
- In RCTs, none of these therapies performed better than placebo
- Most of the tested modalities have very low potential for harm

Mrs Jones

- She tried all lifestyle modifications you just mentioned, and nothing seems to work
- She would like to try something over-the-counter for her vasomotor symptoms, irritability, insomnia...
Over-the-counter options

– Vitamin E
– Phytoestrogens/isoflavones
  – Dietary or supplements (soy-derived)
  – Red clover
– Black cohosh
– Vitex
– Siberian rhubarb
– Studies show no effect compared to placebo for the following:
  – Dong quai
  – Ginseng
  – Evening primrose oil

Vitamin E

- Tocopherol (Vitamin E) has been reported as an agent that improves VMS
- Modest benefits observed in a trial with 120 women who have a history of breast cancer
- 800IU per day (higher than RDI)
- Decrease of 1 HF/day observed
- No adverse effects observed

Botanical (Herbal) Medicine
Current terminology in Canada: Natural Health Products (NHPs)

Potential problems:

• Mislabeled and under-labeling
• Substitution of herbs
• Presence of toxic metals in a number of traditional Chinese medicines
• Presence of conventional Western pharmaceuticals
• Inconsistent preparations

Update on Canadian Natural Health Products Regulations

• Regulations came into effect on January 1, 2004, with transition period ranging from 2-6 years.

• NAPRA Advisory from January 21, 2010:
  “Pharmacists SHOULD NOT sell NHP without NPN, DIN or HM-DIN...”
Botanical Medicines in Menopause

- Phytoestrogens: Soy and Red clover
- Black cohosh
- Vitex or chasteberry
- Siberian rhubarb
- Dong quai
- Evening primrose oil
Phytoestrogen: Definition

- **Phytoestrogen** is any plant compound structurally and/or functionally similar to ovarian and placental estrogens and their active metabolites.

- Compounds may have agonistic, partial agonistic, and antagonistic interactions with estrogen receptors and other targets of estrogenic steroids involved in estrogen transport, synthesis and metabolism.
Soy Protein/Isoflavones

• Genistein and daidzein have estrogen-like effects on select target tissues
• Doses used in studies: 36-80 mg up to TID
• Estrogenic activity, ERβ>ERα
• No dramatic effects compared to placebo found (~15% over placebo in only one study)
• Unknown long-term effects on estrogen-sensitive tissues; soy components stimulate breast tumors in nude mice

Soy and Hot Flashes

- Double-blind 6 month study on menopausal symptoms
- 69 perimenopausal women
- Treatments:
  - Isoflavone rich soy protein
  - Isoflavone poor soy protein
- No effect on vasomotor or menopausal symptoms

A S Germain et al Menopause:8, 17 (2001)
Soy supplement in menopause: Summary

• The evidence to date is mixed but suggests that soy protein and isolated isoflavones do not reduce hot flashes substantially.

• The long-term safety of soy supplements, especially in patients with a history of breast or uterine cancer remains to be established.
Isoflavones in food

Isoflavone Amount In Food (mg/100g)

• Soybeans, green, raw 151.17
• Soybeans, dry roasted 128.35
• Instant beverage soy, powder, not reconstituted 109.51
• Miso soup mix, dry 60.39
• Soybean chips 54.16
• Tempeh, cooked 53.00
• Tofu, silken 27.91
• Tofu, yogurt 16.30
• Soymilk 9.65

http://www.webmd.com/menopause/guide/menopause-alternative-therapy
Reviewed by Mikio A. Nihira, MD on September 16, 2009
Red clover (Trifolium pratense)

- Contains isoflavones similar to soy
- Two systematic reviews suggested that red clover did not significantly improve hot flashes
- Large trial compared two different red clover extracts (82mg/day and 57mg/day) with placebo:
  \[\text{Improvement observed only in women with high BMI}\]
- Caution – potential anticoagulant effect; not to be combined with warfarin

Flaxseed
*(Linum usitatissimum)*

- Flaxseed is an edible seed that contains lignans, another class of phytoestrogens.
- Some research suggests that 40 grams/day of flaxseed in place of other dietary fats can reduce mild VMS.
- Flaxseed is available in whole seed, ground up meal, and seed oil forms.
- Only the crushed or ground forms of flaxseed provide lignans that our body can digest.
- Caution – flaxseed can decrease platelet aggregation.

Black cohosh
(Acta racemosa, formerly Cimicifuga racemosa)

Mechanism of action:
• Appears to have estrogen-like effects, but it does not directly bind to estrogen receptors, nor does it up-regulate estrogen-dependent genes or stimulate growth of estrogen-dependent tumours
• It might act as an agonist at serotonin receptors
• Increases markers of bone formation
Black Cohosh

- Approved and is reimbursed in EU countries
- Daily dose of 20 to 40 mg for 6 months

Duration of administration: 6 months is predicated on the Commission E desire to ensure that women return to their healthcare provider at six-month intervals; the limitation is not based on any concerns about the long-term safety

- 25-30% improvement in hot flashes over placebo
- Properties probably not due to estrogen-like effects
- Preparations vary widely

Liske E. *Adv Ther* 1998;15:45-53
Black cohosh

- The most consistent evidence is for a specific commercial extract called Remifemin™ or NuFem™ in Canada (1mg triterpene glycosides, calculated as 27-deoxyacetin, per 20 mg tablet)
  - Significantly reduces menopausal indices and frequency of hot flashes compared to placebo
  - Comparable to low-dose transdermal estradiol (25mcg q7ds) for relieving hot flashes
Black cohosh

- Recent, high-quality study found that a non-commercial black cohosh extract (2.5% triterpene glycosides) did not significantly reduce VMS
- *Note*: Problem with comparing different standardization products
Black cohosh

• Safety issues: based on clinical trials, Black cohosh appears to be safe

• However, there have been reports of liver damage, sometimes requiring liver transplant in patients taking Black cohosh
  
  • Safety of Black cohosh was reviewed at “Workshop on the Safety of Black Cohosh in Clinical Studies”, sponsored by NIH Office of Dietary Supplements, Bethesda, Maryland, Nov 22, 2004

Black cohosh

• In 2005, Health Canada issued an advisory to healthcare professionals with regards to reports of liver damage THOUGHT to be associated with black cohosh

• January 2010, Canadian Adverse Reaction Newsletter: 6 serious cases reported in Canada between Jan 2005 and March 2009
  - 2 cases – Involved products not authorized for sale in Canada
  - 4 remaining cases – Products DID NOT contain Black cohosh (products withdrawn from the market, eg Swiss Herbal)

CPJ/RPC, March/April 2010, Vol 143, No 2:pg 67
Chaste berry or Vitex (Vitex agnus-castus)

- *German E Commission* approves Vitex for menstrual irregularities and mastodynia
- May raise progesterone levels
- Proposed mechanisms of action:
  - Increases secretion of luteinizing hormone
  - Improves “progesterone deficiency”
  - Inhibits prolactin

Vitex

• Mechanism of action:
  - Acts centrally, at pituitary level, by inhibiting release of FSH and promoting release of LH
  - Reduction of prolactin secretion by the pituitary gland (dopamine antagonism)

• Uses:
  - Dysmenorrhea
  - Hyperprolactinemia
  - Premenstrual syndrome

Vitex

• Most studies used proprietary extracts:
  - Agnolyt™ (liquid or capsules)
  - Ze440 or PreMens™

Not commercially available in Canada, closest equivalent is Femaprim™ distributed by Nature’s Way.
Siberian rhubarb
*(Rheum rhaponticum L.)*

- Similar to garden rhubarb (*Rheum rhabarbarium*)
- Most studies used standardized extract ERr 731
- Active ingredients: hydroxystilbenes (rhaponticin, desoxyrhaponticin)
- Does not exhibit estrogenic properties
- Studies used MRS (MRS) to assess efficacy: reduction in VMS reported within 28 days, improvement in overall mood in 12 weeks

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Measurement</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaskzin-Bettag, <em>Alt Ther Health Med</em>, 2009</td>
<td>N=112 perimenopausal women (symptomatic) (N=56 ERr 731; N=56 on placebo).</td>
<td>MRS after 12 weeks</td>
<td>↓ MRS score</td>
</tr>
<tr>
<td>Kaskzin-Bettag et al., <em>Alt Ther Health Med</em>, 2008</td>
<td>N=252 peri/post menopausal women from 70 gynecological centers</td>
<td>MRS at 6 months</td>
<td>↓ in MRS score</td>
</tr>
<tr>
<td>Hasper et al., <em>Menopause</em>, 2008</td>
<td>Of 109 perimenopausal women from previous study, 28 that were on ERr 731 and 31 on placebo were put on ERr 731 as an observational trial for 48 weeks. For another 48 weeks, 23 from the ERr group and 28 from the original placebo group were continued for the second phase of the trial.</td>
<td>MRS II after 48 and 96 weeks</td>
<td>↓ MRS score</td>
</tr>
<tr>
<td>Kaskzin-Bettag et al., <em>Menopause</em>, 2007</td>
<td>N=109 perimenopausal (symptomatic) women (n=54 on ERr 731)</td>
<td>Hamilton Anxiety Scale at 12 weeks</td>
<td>↓ anxiety correlated with no hot flushes</td>
</tr>
<tr>
<td>Heger et al., <em>Menopause</em>, 2006</td>
<td>N=109 perimenopausal (symptomatic) women (n=54 on ERr 731)</td>
<td>MRS II at 12 weeks</td>
<td>↓ occurrence and severity of climacteric complaints</td>
</tr>
</tbody>
</table>
Siberian rhubarb

- ERr 371 available in Canada as Estrovera™
- Dose: 1 tablet daily (4mg of root extract, providing 2.2mg rhaponticin and 1mg desoxyrhaponticin)
- Should be taken with food (breakfast)
- Duration of treatment: individualized; 2-year observational studies demonstrate long-term safety
- Used in Europe since 1993, recently became available in Canada
Evening primrose oil
(Oenothera biennis)

- Evening primrose oil (Oenothera biennis)
  - No effect on VMS
  - Anecdotal evidence in mastodynia
  - GI upset, diarrhea, potential interaction with anticonvulsants
Other Herbal Preparations
With Little or No Evidence

• Dong quai (*Angelica sinensis*)
  - Promoted to relieve menopause symptoms such as hot flashes and night sweats; there is little scientific evidence to support this claim
  - **Caution**: Photosensitising; antiplatelet action; potential stimulation of the breast cancer cells

Clinical Management Series: Natural Medicines in the Clinical Management of Menopausal Symptoms, accessed on line www.naturaldatabase.com 26/03/2010
Vaginal Health in Menopause

- Urogenital aging affects > 50% of postmenopausal women
- Atrophic changes secondary to estrogen decline
- Symptoms occur gradually
- ↓ QOL

<table>
<thead>
<tr>
<th>Vulvovaginal</th>
<th>Urinary</th>
<th>Prolapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dryness</td>
<td>Dysuria</td>
<td>Pelvic heaviness</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Nocturia</td>
<td>Incomplete emptying on voiding</td>
</tr>
<tr>
<td>Pain during intercourse</td>
<td>Frequency</td>
<td>Constipation</td>
</tr>
<tr>
<td>Post-coital bleeding</td>
<td>Urgency</td>
<td>Low back pain</td>
</tr>
</tbody>
</table>

Management of Vaginal Atrophy

Choices for atrophic vaginitis treatment include:

• Vaginal moisturizers
  – Polycarbophil gel – as effective as local hormone therapy for short term relief

• Vaginal lubricants
  – Useful for reducing immediate irritation but no long-term effect on vaginal atrophy

• Local hormone therapy
  – Recommended early, before permanent changes occur
Treatment Options for Vaginal Yeast or Bacterial Infections

• Conventional OTC: clotrimazole (vaginal or oral), miconazole (vaginal)

• Novel therapies:
  1. Probiotic preparations
     - **Rephresh ProB™** (L. rhamnosus GR-1, L. reuteri RC-14) oral capsule
     - **Provacare™** (L. rhamnosus Lcr35) – vaginal capsule
     - **Purfem™** (L. rhamnosus PB01, L. gasseri EB01) – vaginal ovule
  2. Vitamin C vaginal ovule: **Prevegyne™** (for recurrent bacterial vaginosis)
Back to Mrs Jones........

• What questions should you ask Mrs. Jones?
• If she is still menstruating = perimenopausal; what are possible recommendations?
• If she has not had her period for more than 12 months = postmenopausal; what is the next step?
• MedsCheck?
• Pharmaceutical opinion?