Non-Hormonal Treatment of the Menopause

Tania Adib
Menopause

- Pre-menopause
- Transition
- Post-menopause
Women Affected

- Natural menopause
- Surgical menopause
  - Benign disease
  - Cancer
- Anti-oestrogen treatment
Menopausal symptoms

- Physical
- Urogenital
- Psychosomatic
Menopausal Symptoms

- Incidence of hot flushes
  - China 18%
  - Japan 15%
  - Singapore 14%
  - Europe & America 85%
  - Brazil 70%
Mechanism of Hot Flushes

- Exact mechanism unknown
- Drop in oestrogen levels rather than absolute levels
- Central thermoregulatory dysfunction
- Noradrenaline main neurotransmitter
Menopausal Symptoms

- Vasomotor symptoms
  - Hot flushes
  - Night sweats
  - Sleep disturbances

- Impaired sexual functioning
  - Vaginal dryness
  - Painful intercourse
  - Loss of libido
HRT

WHI 2002

Oestrogen & progesterone:

Increased rates of:

- Breast cancer
- Cardiovascular disease
- Pulmonary embolism
- Strokes
Online Survey

- 166 women
- 70% hot flushes, mood swings & sleeplessness
  - 50% wanted natural supplements
  - 39% wanted lifestyle advice

Provision of menopause information: do we get it right? A web-based surgery on provision of menopause treatment...
Online Survey

What are the most important attributes for natural treatment?

• 70% recommended by a health care professional
• 75% good symptom control & safety profile
• 70% strong evidence base
Treatments for the Menopause

- Medication
- Lifestyle advice
- Supplements
- Supportive interventions
Non-Hormonal Drug Treatments

- Clonidine
- SSRIs
- Venlafaxine
- Gabapentin
- Pregabalin
Clonidine

- Alpha adrenergic receptor agonist
- Inhibits adrenergic neurotransmitter release
- Oral or transdermal
- 25mcg od, 50mcg bd
- 10 RCTs
- Most decade ago
- 2 included women on tamoxifen
Effect of Clonidine

Mean difference in no. of hot flushes per day (95% CI)

-6 -4 -2 0 2 4 6

Favours clonidine

Favours placebo

Mean difference in no. of hot flushes per day (95% CI)
Clonidine - Summary

- Effective in <40%, but not if symptoms severe
- Dose 25mcg bd or tds
- Side-effects, mainly postural hypotension & insomnia in 50%
- Patches may be more effective than tablets
- Must be tailed off gradually
Selective Serotonin Reuptake Inhibitors: SSRIs

- Fluoxetine
- Paroxetine
- Sertraline
- Citalopram
SSRIs

- Meta-analysis
- 11 RCTs
- 2,069 women
- Follow-up 9 months
- Decrease in hot flushes 20%
- Main side-effects nausea & loss of libido

Paroxetine

- Reduction in hot flushes of 40% vs 14% placebo
- Reduction in hot flushes 60% vs 40% placebo
- 10mg sufficient, increasing dose not more effective but more side-effects
- Controlled release better tolerated
- 20mg if anti-depressant
SSRIs

- Contra-indicated in women with breast cancer on tamoxifen

- SSRIs inhibit cytochrome P450 (CYP2D6), enzyme important in metabolism of tamoxifen into active metabolite endoxifen
Selective Nor-Epinephrine Re-uptake Inhibitors - venlafaxine

- 37.5mg can be increased to 75mg
- Less likely to interfere with tamoxifen metabolism
- 20% side-effects
  - Decreased libido
  - Insomnia - take in the morning
  - Nausea - long-acting
- Caution in patients with cardiovascular risks eg recent MI/arrhythmia
GABA Analogues

- Gabapentin & pregabalin
- Exact mechanism of action unclear, may have direct affect on hypothalamic temperature regulation centre
- Patients using for neurological conditions observed to have reduction in hot flushes
# Gabapentin

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>Length of trial</th>
<th>Outcome</th>
<th>SE’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guttuso et al 2003</td>
<td>59</td>
<td>Gabapentin 300mg tds Placebo</td>
<td>12wk</td>
<td>Reduced freq 54% vs 31% vs placebo</td>
<td>19 withdrawals, dry mouth, sleeplessness, decreased appetite</td>
</tr>
<tr>
<td>Pandya et al 2005</td>
<td>420</td>
<td>Gabapentin 100mg tds Gabapentin 300mg tds</td>
<td>8wk</td>
<td>Reduced freq 44% vs 15% (p&lt;0.001) &amp; reduced severity (46% vs 15%)</td>
<td>39 withdrawals, dry mouth, nausea, constipation, decreased appetite</td>
</tr>
<tr>
<td>Butt et al 2008</td>
<td>200</td>
<td>Gabapentin 300mg tds Placebo</td>
<td>4wk</td>
<td>Reduction 51% vs 26% (p&lt;0.001)</td>
<td>Dizziness, unsteadiness, but SE returned to baseline after 4wk</td>
</tr>
<tr>
<td>Reddy et al 2006</td>
<td>60</td>
<td>Gabapentin 2400mg CEE 0.625mg Placebo</td>
<td>12wk</td>
<td>72%, 71% vs 54%</td>
<td>Fatigue, somnolence</td>
</tr>
</tbody>
</table>
Gabapentin

- Many studies in breast cancer patients on tamoxifen
- Small numbers, followed up for short periods of time 12 weeks
- 45% reduction in hot flush frequency
- 54% reduction in symptom severity

Guttuso et al. Gabapentin’s effects on hot flashes in postmenopausal women: a randomised controlled trial. Obstet
Gabapentin

- Dose 900mg/day
- 50% side-effects - dry mouth, nausea, constipation, decreased appetite, fatigue
- Titrate up slowly
- 300mg od, bd, tds every 2 weeks
- If drowsiness a problem, take 900mg at night
Pregabalin

- Decreases hot flushes 50-70%
- Dose 75mg bd
- Small numbers, short follow-up time
- Safe in breast cancer
- Significant side-effects - dizziness, drowsiness, difficulty concentrating
### Pregabalin

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<th>Treatment</th>
<th>Length of trial</th>
<th>Outcome</th>
<th>SE’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presant et al 2007</td>
<td>6</td>
<td>Pregabalin 50mg od to tds</td>
<td>4wk</td>
<td>Reduced freq by 53%</td>
<td>3 withdrawals, drowsiness, dizziness, lethargy, constipation, flatulence</td>
</tr>
<tr>
<td>Loprinzi et al 2010</td>
<td>207 women</td>
<td>Pregabalin 75mg bd, 150mg bd</td>
<td>6wk</td>
<td>50%, 65%, 71% reduction</td>
<td>Drowsiness, altered cognition</td>
</tr>
</tbody>
</table>
General Lifestyle Changes

- Diet
- Reduce acidic foods & drink
- Exercise
- Reduce coffee
- Stop smoking
General Measures

Avoid triggers -

- spicy food
- hot drinks
- caffeine
- hot weather
- smoking
- stress
General Measures

• Dress in layers
• Hand fan
• Tepid bath
• Keep bedroom temperature low & use cool packs
• Keep healthy weight
• Cut down/stop smoking
• Regular moderate exercise
Diet

- Few Chinese & Japanese women experience hot flushes
- Japanese consume around 30g soy/day
- Western women consume around 1g - added to processed food
Diet

- Study of Greek & Mayan women
- American Anthropologist
  - Greek women subsistence farmers
    - Average age menopause 47
    - 75% developed menopausal symptoms
  - Mayan women
    - southeastern part of Yucatan, Mexico
    - menopause age 42
    - No hot flushes reported, didn’t have a word for them, like Japanese
Diet

• Difference in diet -

• Mayan - corn, corn tortillas, beans, tomatoes, squash, sweet potatoes, radishes, vegetables, very little meat and no dairy

• Greek - rich in vegetables & legumes, also high in meat, fish, cheese & milk
Phytoestrogens

• Plant compounds
• Resemble oestrogen
• Selective $\beta$ oestrogen receptor
• Found in food and supplements
Phytoestrogens

• 3 groups
  • isoflavones - soy products, beans, red clover
  • lignans - fruit, vegetables & grains
  • coumestans - sprouting seeds eg alfalfa
Phytoestrogens

Genistein

Daidzein

Estradiol

Equol
Phytoestrogen Subclasses

Phytoestrogens

- Lignans
- Isoflavones
- Coumestans
- Stilbens

Glucosides (biologically inactive)

Aglycones (biologically active)

Intestinal bacteria

Genistein

Diadzein

Glycitein
Soy & Menopausal Symptoms

• Marked heterogeneity between studies
• Pre-, peri-, post-menopausal
• Different formulations
• Diet vs supplements
Phytoestrogens
ER-Independent Effects

- Inhibition of vascular endothelial growth factor (VEGF)
- Apoptosis
- Inhibition of tyrosine kinase
- Induces tumour suppressor protein PTEN
- Reduction several chronic diseases
- Reduction risk certain cancers
Red Clover

- 2 RCTs Promensil® (40mg red clover)
- Effect on hot flushes & oestrogen responsive tissues
- Atkinson et al, 205 women 1 year, at increased risk of breast cancer due to increased breast density
- Powles et al 401 women 3 years, with FHx breast cancer
- No significant difference menopausal symptoms
- No significant effect on serum hormone profile
- No significant change breast density or endometrial thickness

Isoflavones, Lactobacilli, Magnolia Bark Extract, Vitamin D3 and Calcium

- Mucci et al 2006
- RCT 89 women
- Estromineral serena or Calcium & vitamin D3
- Symptoms at 2,4,8,12,24 weeks

  Hot flushes          Depression
  Night sweats        Anxiety
  Palpitations        Vaginal dryness
  Asthenia            Dyspareunia
  Insomnia            Loss of libido

Soy isoflavones, lactobacilli, Magnolia bark extract, vitamin D3 and calcium. Mucci et al Minerva Gynecol 2006;58:1-10
# Results

## Disappearance Rate

<table>
<thead>
<tr>
<th>Symptom</th>
<th>ES</th>
<th>Ca+D</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td>55.3</td>
<td>19.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Night sweats</td>
<td>68.6</td>
<td>7.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Palpitations</td>
<td>72.4</td>
<td>16.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Insomnia</td>
<td>56.8</td>
<td>21.6</td>
<td>0.0002</td>
</tr>
<tr>
<td>Asthenia</td>
<td>78.6</td>
<td>20</td>
<td>0.0001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>65.8</td>
<td>27.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>64.3</td>
<td>25</td>
<td>0.01</td>
</tr>
<tr>
<td>Irritability</td>
<td>63.3</td>
<td>17.9</td>
<td>0.006</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>40.7</td>
<td>13.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>44.8</td>
<td>7.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>42.4</td>
<td>12.9</td>
<td>0.01</td>
</tr>
</tbody>
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Soy isoflavones, lactobacilli, Magnolia bark extract, vitamin D3 and calcium. Mucci et al Minerva Gynecol 2006;58:1-10
Herbs & Supplements

- Black cohosh
- Hop
- Wild yam
- Flaxseed
- Maritime bark extract
- Sage
- Maca
Supportive Treatments

- Acupuncture
- Yoga
- CBT
- Mindfulness
Acupuncture

- Increases central beta-endorphin activity
- Stabilising thermoregulation in hypothalamus
- Reduces vasomotor symptoms
Acupuncture

- 6 RCTs
- Breast cancer
- 38-94 women
- Acupuncture vs placebo
- 3-21 months
- Almost 50% reduction in hot flushes
Yoga

- Joshi et al 2011
- Randomised trial 200 women
- 3 months yoga (asana, pranayam, meditation)
- Menopause rating scale & 3 subscales showed >50% reduction in score in all subscales

Effect of yoga on menopausal symptoms. Joshi et al Menopause Intl 2011;17:78-81
Meta-analysis

- 4 RCTs with 582 postmenopausal women
- Standardised mean differences
- SMD = -0.37 (p=0.02) short-term psychological symptoms
- No evidence for total menopausal symptoms, somatic, vasomotor, or urogenital symptoms
- No adverse events
Cognitive Behavioural Therapy

- RCT
- CBT weekly 90 minute sessions 6 wk
- PE 3 hours/wk for 12 weeks
- 422 women with breast cancer
- CBT (n=109), PE (n=104), CBT+PE (n=106) WL (n=103)
- 12wk & 6m

Efficacy of Cognitive Behavioral Therapy and Physical Exercise in Alleviating Treatment-Induced Menopausal Symptoms in Patients With Breast Cancer: Results of a Randomized, Controlled, Multicenter Trial Duijts et al J Clin Onc 2012;30(33):4124-4133
Results CBT+PE

- 50% reduction hot flushes vs 30 placebo
- 33% reduction urogenital symptoms vs 29%
- Improved physical functioning 46% vs 37%
- CBT groups showed signify decrease in perceived severity of hot flushes & night sweats 56% vs 39%
- CBT groups increase in sexual activity
- Sustained at 6 months
- However, high lack of compliance

Efficacy of Cognitive Behavioral Therapy and Physical Exercise in Alleviating Treatment-Induced Menopausal Symptoms in Patients With Breast Cancer: Results of a Randomized, Controlled, Multicenter Trial Duijts et al J Clin Onc 2012;30(33):4124-4133
Mindfulness

- Increase insight into how automatic, habitual patterns of over-identification and cognitive reactivity to sensations, emotion and thoughts increase stress and emotional distress
- Mindfulness based stress reduction
- Mindfulness based cognitive therapy
Mindfulness-Based Stress Reduction (MBSR)

- RCT
- 229 women with breast cancer
- 8wk program 3hrs/wk then 1 day
- Significant differences at 8 weeks vigour, fatigue, confusion
- Significant differences at 12 weeks hot flushes & depression

Effectiveness of Mindfulness-Based Stress Reduction in Mood, Breast- and Endocrine-Related Quality of Life, and Well-Being in Stage 0 to III Breast Cancer: A Randomized, Controlled Trial Hoffman et al J Clin Onc 2012;30(12):1335-42
Which Treatment?

- Combination
- Depends what suits each individual
- Support from health care professional