Managing menopause

1. Controlling menopause symptoms
   a) Flushes
   b) Genitourinary problems

2. Long-term disease prevention
   a) Bones
   b) Heart
   c) Breasts
   d) Uterus

Aetiology of flushes
- Unstable thermoregulatory center
- Thermostat “resets”
  - Sweat & shiver more easily
- Noradrenaline is thought to be the main neurotransmitter that regulates temperature.
- Serotonin, endorphins and catecholestrogens have a role

Flushes – non-oestrogen treatments
- Avoid aggravators
  - Overheating, spicy foods, hot drinks, stress
  - Stop Tamoxifen for 4 wks
- Placebo effect
  - 25% at 4 weeks and 50% at 12 weeks
- Herbals
- SSRIs and SNRIs
- Clonidine
- Gabapentin

Herbals
- Safety of phytoestrogens?
- Herbals with negative RCTs:
  - Evening Primrose Oil
  - Promensil
  - Wild Yam Cream
  - Dong Quai
  - Low dose progesterone cream
  - A Chinese herbal mixture
Remifemin

- Extract of black cohosh; high quality product. Dose – 1-2 twice daily
- First therapeutic effect seen at 2W, maximum at 12W
- Breast culture & mammogram studies show no effect
- Osmers study (Obstet Gynecol 2005:105, 1074-83)
  - RCT Remifemin 2/d v. placebo, n=304
  - Remifemin more effective than placebo for total MRS (p<0.001)
  - Effective for the hot flush & psychological sub scores. No difference for adverse effects

St John’s Wort

- Linde (1996) BMJ – meta-analysis. St John’s Wort significantly better than placebo for mild-moderate depression
- Hypericum depression trial (2002) N=340 with major depression. 11-160 extract/placebo
- The only high quality & clinically tested St John’s Wort extract available in Australia is REMOTIV (www.flordis.com.au)
  - Beware of drug interactions (CYP450)

Non-hormonal therapies for menopausal hot flashes. Systematic Review and Meta-analysis

Nelson et al. JAMA 2006; 295, 17 :2057-2071

SSRIs and SNRIs

- Venlafaxine for hot flushes in survivors of breast ca: A RCT
  - 191 women with breast ca. w/ >14 flushes/wk. 4 groups treated for 4 wks
    - Placebo (n=50)
    - Venlafaxine 37.5mg daily (n=56)
    - Venlafaxine 75mg daily (n=43)
    - Venlafaxine 150mg daily (n=49)
  - 69% were on Tamoxifen
SSRIs and SNRIs

Results at 4 weeks

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>37.5mg</th>
<th>75mg</th>
<th>150mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>% in flushes</td>
<td>27%</td>
<td>37%</td>
<td>61%</td>
<td>61%</td>
</tr>
</tbody>
</table>

- All doses sig. better than placebo
- 75mg & 150mg equivalent
- Main side effects – dry mouth, nausea, constipation
- 69% on Tamoxifen, & Venlafaxine still effective

Clonidine

- Clonidine is a centrally acting α-adrenergic agonist that is used primarily to treat hypertension. It has central nervous system activity and is believed to inhibit adrenergic pathways.
- Often need higher doses with high rate of side effects (at least 50%)
  - Dry mouth, eyes, nose; insomnia; depression

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Red Clover Isoflavones

- Red Clover Isoflavones
  - Soy Isoflavones
  - Red Clover Isoflavones
  - Other agents
Gabapentin

- Gabapentin is a γ-aminobutyric acid (GABA) analogue that is used to treat a variety of neurologic disorders including epilepsy and neuropathic pain. Its precise mechanism of action is unclear. Notably, the agent is not a GABA agonist, does not inhibit GABA uptake, and acts independently of GABA receptors.

- 2 trials identified
  - Significant improvement in flush scores in both studies
- Side effects:
  - dizziness, disturbed sleep, fatigue, tremor, nausea, ataxia, nystagmus, and peripheral oedema

Gabapentin

Lancet 2005; 366:818-824

- 420 women with breast cancer
- RCT – placebo, 300mg, 900mg GP/d
- Only the 900mg dose was significantly better than placebo at 8 weeks (46% reduction in flushes vs 15%)
- 6 withdrew in placebo group, 10 in the 900mg group. ?side effects?

Other agents

Trials underway
1. Blue Moonstone
   - “Metabolite of an antidepressant”
2. “Derivative of gabapentin”
3. LIBERATE trial
   - RCT of Livial after breast cancer

LIVERATE trial

- RCT of Livial or placebo for menopause symptoms after breast cancer. Duration 4 years.
- N = 3,100; fully recruited
- Inclusion criteria
  - Sx treatment for invasive Br Ca <5y
  - Menopausal with at least 1 symptom
HRT or not to HRT?

Associate Professor John Eden
Royal Hospital for Women

Hormone Therapy

- Highly effective for menopause symptoms but women fear breast cancer
- Cyclical HT for perimenopausal women
- Continuous combined HT for post-menopausal woman
- Much of the side-effects of HT are from the progestin (PMT etc)
- Mirena plus and oestrogen

Combined HRT – summary of WHI 2002

- Very low risk for women 45-55y
- In older women (mean age 68y), after 5y usage there are 8 extra BrCA/10,000/y but also 8 fewer bowel & uterus cancers
- HT did lower the risk of hip fracture
- HT did not improve well being of asymptomatic women

Oestrogen only – summary of WHI 2004, 2006

- No effect on breast or heart risk
- ET group had lower risk Br CA (p=0.06, WHI 2004);
  - CCE reduced risk of intraductal CA (HR, 0.71; 95% CI, 0.52-0.99; WHI 2006)
  - neutral on lobular CA.
  - The equine oestrogens are SERMs

Oestrogen only – summary of WHI 2004, 2006

- Oral ERT slightly prothrombotic (doubling of risk).
  - DVT risk: 50y 10/10,000
  - DVT risk: 70y 100/10,000
- Less effect for transdermal.
  - Estradot;
  - Sandrena gel;
  - Aerodiol nasal ERT;
  - Oestradiol implants

Stroke risk

- All hormone therapies appear to slightly increase the risk of stroke (6-8/10,000/year)
  - HT
  - Oestrogen only
  - Tamoxifen
  - Raloxifene
  - Livial
Dementia and CVS risk

- WHI studies indicate 'early-benefit' and 'late harm'
  - HT started around 45-55y, decreases the risk of dementia & CVD
  - HT started after 65y increases the risk of both

Perimenopausal women

HRT often causes irregular bleeding

- Only use HRT if symptoms severe
  - Mostly use cyclical HRT
- Oral Contraceptive Pill
- Moderate dose of progestin with/without oestrogen
- Mirena device
- Endometrial ablation

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Menopausal women

Bleeding, periods, progestin side effects

- Only use HRT if symptoms severe
- Livial
- Try different progestins or Mirena
- Unopposed ERT & endometrial Bx
  - Should be very few now
- Topical oestrogens

HRT – how long to treat?

- 2 years and wean off, in cooler months.
- Don’t abruptly stop HRT
- Some flush forever (1/8–1/10)
- The breast cancer issue
- WHI
- NH&MRC patient information

The Future

- Specific agents to turn off flushes are probably 3-5 years away.
- More SERMs coming
- More and more osteoporosis treatment choices.
  - PTH
  - Cement vertebroplasty

Bones

- HRT still a valid option for some with osteoporosis
  - Early menopause
  - Those <55y
  - Any age if symptomatic too
- If z scores low
  - Investigate (FBC, ESR, biochemistry, Ca, vitamin D, PTH, TSH; Xray spine)
Summary

- Some women still need HRT
  - Short-term (most)
  - Long-term (some). Consider Mirena plus oestrogen
- Those with significant medical history (e.g. breast cancer, major thrombosis). Consider SNRI first.
- Ask about vaginal dryness and bladder problems