OPTIONS FOR MEDICATION

Keywords: Menopause medication, complementary therapy for menopause, HRT, hormone replacement therapy

KEY POINT

1. The management of menopausal symptoms after breast cancer is a clinical problem as no treatments are guaranteed to be both safe and effective. A number of specialists are likely to be managing each woman, and symptoms are best treated with a multidisciplinary approach.

INDICATIONS FOR TREATMENT

The treatment of menopausal symptoms following breast cancer should be based on:

- the severity of the symptoms and their impact on quality of life
- evidence for safety following breast cancer (if available)

HORMONAL MEDICATIONS

HORMONE REPLACEMENT THERAPY (HRT)

HRT containing oestrogen is the most effective treatment for menopausal symptoms in healthy women. The evidence suggests that HRT improves vasomotor symptoms, vaginal dryness and reduces the risk of fractures.

Unless hysterectomy has been performed, oestrogen should be given in combination with progesterone to prevent an increased risk of endometrial hyperplasia or cancer.

In postmenopausal women long-term use (greater than five years) of combined HRT (oestrogen and progesterone) appears to increase the risk of breast cancer. This risk is around 26% increased relative risk which translates to approximately eight new breast cancers per 10,000 women per year.

Both oestrogen only and combined HRT increase mammographic density, potentially reducing the efficacy of mammogram in detecting breast cancer and increasing the number of false positive recalls. This effect is more pronounced with combined compared to oestrogen only HRT.

Previous History of Breast Cancer and HRT

In women with a history of breast cancer, taking HRT appears to increase the risk of recurrence / or development of new breast cancers with a relative risk of 3.4. There is a lack of high quality research because of difficulty in recruiting for randomised controlled trials of HRT versus placebo.

The largest randomised control trial to address this question showed that, after a median follow up of 2.1 years, 14.9% of HRT users and 4.09% taking placebo had either a recurrence or development of a new breast cancer.

Note:

It is not known whether the type or regimen of HRT and the oestrogen/progesterone receptor status of the breast cancer have implications for the safety of use of HRT. Similarly, very little is known about the interaction between HRT and endocrine therapy for breast cancer. However, since endocrine therapy is essentially anti-oestrogen, it is certainly possible that HRT may undermine the effects of endocrine therapy.
Recommendations for Practice

- HRT should not be used as first line management for menopausal symptoms following breast cancer.
- HRT may be justified to improve quality of life reasons when all other interventions have failed and the woman is clearly informed of the potential increased recurrence risk.
- HRT may be considered for women with metastatic disease where attainment of quality of life overrides all.

2. PROGESTOGENS

High doses of progestogens have been used to treat advanced breast cancer. Progestogens at lower doses are effective in reducing menopausal hot flushes, but are not as effective as oestrogen or oestrogen and progestogen in combination. A recent small study suggests that one dose of depomedroxyprogesterone acetate (DMPA) may also be effective.

The safety of progestogens for the treatment of menopausal symptoms following breast cancer is not known.

Recommendations for Practice

Progestogens are not recommended for the treatment of vasomotor symptoms as safety is uncertain and efficacy is likely to be less than that of oestrogen and progestogen in combination, or oestrogen alone.

3. TIBOLONE

Tibolone (Livial) is a synthetic compound with weak oestrogenic, progestogenic and androgenic properties. There have been no large studies assessing the impact of tibolone on the risk of breast cancer in healthy women. Tibolone does not appear to:
- stimulate breast cells in vivo
- increase mammographic density or increase the false positive recall rate for mammograms.

Tibolone has an unfavourable effect on serum cholesterol by reducing HDL cholesterol. While it has been known to improve bone density, its effect on fracture reduction is yet to be confirmed.

The researchers from the LIBERATE Trial (Organon) 2008, conclude “tibolone increases the risk of recurrence in breast cancer patients, while relieving vasomotor symptoms and preventing bone loss”. Therefore the use of tibolone for women with a known, past or suspected breast cancer will remain contraindicated.

4. TESTOSTERONE / ANDROGEN THERAPY

Testosterone may exert biological effects by acting directly on the androgen receptors or indirectly through conversion to oestrogen by the aromatase enzyme. This mechanism is blocked by aromatase inhibitors. Levels of testosterone reduce gradually throughout adult life. Early or surgical menopause may be associated with a greater reduction in testosterone and its effects.

The Endocrine Society’s Clinical Guidelines recommend against making a diagnosis of androgen deficiency in women at this time because there is neither a well-defined clinical syndrome nor normative data on testosterone or free testosterone levels in women across their lifespan that can be used to define the disorder.

The safety or efficacy of testosterone supplementation following breast cancer is not known.

Recommendations for Practice

The generalised use of testosterone by women is NOT recommended because the indications are inadequate and evidence of safety in long term studies is lacking.
NON HORMONAL MEDICATIONS

1. **GABAPENTIN**

Gabapentin is a gamma-aminobutyric analogue approved for the treatment of seizures and chronic pain. Use of 900mg per day has been found to be effective in reducing menopausal hot flushes for at least 12 weeks when compared to a placebo \(^7\) (Level 2).

Gabapentin’s use is limited by:

- the cost incurred by the woman as not being approved for the treatment of hot flushes
- side effects including somnolence and dizziness

**Recommendations for Practice**

- Gabapentin can be considered for treating hot flushes following breast cancer but women should be advised regarding cost and potential side effects.

  **Recommended dose:** 900mg/ day in three divided doses. 
  Start at 300mg daily - initial night time dosing is preferable due to possible excessive sleepiness and dizziness.
  Increase to 300mg three times a day over three to seven days.
  Gabapentin dosing should be tapered over a 1 week period when it is discontinued. (See patient information sheet available)

2. **CLONIDINE**

Clonidine is an alpha adrenergic agonist, which acts centrally to reduce vasoconstriction. Primarily used in the treatment of hypertension, clonidine has a modest effect in reducing hot flushes following breast cancer \(^8\) (Level 2).

It is poorly tolerated by some women who experience side effects of:

- constipation
- dry mouth
- drowsiness
- difficulty in sleeping.

Clonidine is approved for the treatment of menopausal flushing in Australia.

**Recommendations for Practice**

- Clonidine can be considered for hot flushes following breast cancer but women should be warned about side effects.

  **Recommended Dose:** Oral, initially 25 micrograms twice daily.
  Increase after two weeks to 50–75micrograms twice daily, if necessary.
  Clonidine is only available in the oral form in Australia as Catapres 100 (100 micrograms) and Catapres 150 (150 micrograms). Both of these tablets are scored.

  - Stop if no benefit is noted after two to four weeks of treatment or if a woman experiences significant side effects. (See patient information sheet available)

3. **SELECTIVE SEROTONIN / NORADRENALINE RE-UPTAKE INHIBITORS (SSRI / SNRI)**

SSRI / SNRI are licensed in Australia for the treatment of depression. Preliminary evidence from a small randomized controlled trial with short follow up – less than eight weeks - suggested that venlafaxine (75mg SR) is effective in reducing hot flushes following breast cancer \(^9\).
Subsequent studies with longer follow up - to 12 weeks - have not shown any beneficial effect of venlafaxine on hot flushes.

NB: Paroxetine has been shown to reduce the effectiveness of Tamoxifen when given to patients taking tamoxifen.

The safety of SSRI/SNRI in breast cancer women taking endocrine therapy is not known and they may interfere with the metabolism of tamoxifen. The clinical implications of this are not known.

Recommendations for Practice

- SSRI/SNRI have not been shown to be effective in reducing vasomotor symptoms for clinically significant duration (>8 weeks).
- Women should be advised that the use of SSRI/SNRI is likely to be associated with anticholinergic side effects and that it may interfere with metabolism of tamoxifen.
- **Recommended Dose**: Venlafaxine (Effexor) is started at 37.5mg per day for a week. Increase up to 75mg per day if well tolerated. Higher doses have not been shown to be useful for the treatment of hot flusheds and may be associated with increased adverse reactions. Venlafaxine as well as SSRIs should be slowly tapered to minimize the occurrence of discontinuation symptoms. It is suggested to reduce the dose over at least two weeks. (See patient information sheet available)

COMPLEMENTARY OR NON PHARMACOLOGICAL THERAPIES

1. **PHYTOESTROGENS**

Phytoestrogens are polyphenol compounds of plant origin with weak oestrogenic activity. They have not consistently been shown to be superior to placebo in the treatment of vasomotor symptoms. No clinical trials have been located that address the efficacy or safety of phytoestrogens following breast cancer\(^{10}\) (Level 1).

Recommendations for Practice

Not recommended as safety and efficacy has not been established.

2. **BLACK COHOSH**

Most trials have been conducted on Remifemin\(^{®}\). Black cohosh has not consistently been shown to be superior to placebo in the treatment of vasomotor symptoms\(^{11}\). Small studies in breast cancer patients have shown mixed results.

Recommendations for Practice

Not recommended as safety and efficacy has not been established. Recent reports of liver failure following the use of black cohosh have raised concerns about safety.

3. **VITAMIN E**

Vitamin E is effective in the treatment of hot flusheds following breast cancer but the magnitude of the effect is very small - mean reduction of one hot flushed per day. Although safety has not been established, there is currently no biological reason to suspect adverse effects.

In one study of 120 women no toxicity was shown\(^{12}\).

Recommendations for Practice

- Can be used as a “natural” therapy but advise women that the benefits are likely to be marginal.
- **Recommended Dose**: 800 – 1000 international units per day in divided doses.
**NON HORMONAL MEDICATIONS**

**What is the appropriate length of therapy?**
Non hormonal treatments for hot flushes appear to be effective in 1 to 2 weeks. If no clinical response is seen over this period treatment approaches should be modified. Most studies have only shown efficacy for 4 to 12 weeks duration (13). The mean duration of hot flushes is around 5 years for spontaneous menopause, with resolution of the most troublesome symptoms - in the first year of menopause (14). It is not known whether hot flushes after breast cancer treatment have a similar duration.

<table>
<thead>
<tr>
<th>Name</th>
<th>Reduction in hot flashes (vs placebo)</th>
<th>Duration of effect</th>
<th>Side effects</th>
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<tbody>
<tr>
<td>Desvenlafaxine (pristiq) 100mg</td>
<td>64% (vs 51%) Improved sleep</td>
<td>12 weeks</td>
<td>Nausea, dry mouth, constipation, dizziness, somnolence</td>
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<td>Venlafaxine (effexor) 75mg SR</td>
<td>60% (vs 27%)</td>
<td>6 weeks</td>
<td>Headache, nausea, anxiety, sleep and sexual dysfunction</td>
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<td>Escitalopram (10-20mg)</td>
<td>55% (vs 36%)</td>
<td>8 weeks</td>
<td>Initial shakiness, nausea, and dry mouth</td>
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<tr>
<td>Citalopram (cipramil) 10mg</td>
<td>49% (vs 23%)</td>
<td>6 weeks</td>
<td>Initial shakiness, nausea, and dry mouth</td>
</tr>
<tr>
<td>Fluoxetine (prozac) 20mg</td>
<td>50% (vs 36%)</td>
<td>6 weeks</td>
<td>Drowsiness, weight gain, sexual dysfunction</td>
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<tr>
<td>Paroxetine (paxil) 12.5mg</td>
<td>56% (vs 28%)</td>
<td>6 weeks</td>
<td>Drowsiness, weight gain, sexual dysfunction, dry mouth</td>
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REFERENCES / STANDARDS


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3. Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer - is it safe?), a randomised comparison. 


13. Politi MC, Schleinitz, M.D., Col, N.F. Revisiting the duration of vasomotor symptoms of menopause: a meta-analysis. 

    *Climacteric*, 6, 112-117.

Bibliography

- Hickey M, Davis S, Sturdee D. Treatment of menopausal symptoms: what shall we do now? 


National Standards – 1- Care provided by the clinical workforce is guided by current best practice
4- Medication Safety

Legislation - Nil
Related Policies - Nil
Other related documents – KEMH Clinical Guidelines Section Management of Menopause

RESPONSIBILITY

<table>
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<th>Policy Sponsor</th>
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