safe practical clinical answers - *fast*

What should I advise a woman taking tamoxifen?

- Encourage the woman to continue taking tamoxifen unless told otherwise by her specialist.
- Advise that there is a small risk of endometrial cancer and thrombotic disease (such as deep vein thrombosis).
  - Although the benefits of treatment outweigh the risks, women should be advised to report any abnormal vaginal bleeding, or symptoms of thromboembolism (such as pain in the calf of one leg, and sudden breathlessness).

Basis for recommendation

- The recommendation to advise women to be aware of symptoms of endometrial cancer and thromboembolic disease is based on the British National Formulary [BNF 56, 2008] and a safety bulletin from the Committee on Safety of Medicines [CSM, 1994; CSM, 2002].
- CKS found evidence from two large trials that the risk of endometrial cancer and thromboembolic events is increased in women taking tamoxifen compared with placebo, but the absolute numbers were small.

How should I manage menopausal symptoms?

- Encourage all women to make lifestyle modifications to reduce menopausal symptoms.
  - Hot flushes and night sweats:
  - Take regular exercise, sip cool drinks, wear lighter clothing, dress in layers, sleep in a cooler room, and reduce stress.
  - Avoid possible triggers, such as spicy foods, caffeine, smoking, and alcohol.
  - Sleep disturbances due to hot flushes:
  - Avoid exercise late in the day and maintain a regular bedtime.
- Treat symptomatic atrophic vaginitis with a non-hormonal vaginal lubricant such as Replens MD®.
- If symptoms are still distressing despite trying lifestyle modifications, consider drug treatment.
- If drug treatment is not appropriate or is ineffective, seek specialist advice.

Basis for recommendation

Lifestyle advice

- CKS found no trial evidence on lifestyle modification for women experiencing menopausal symptoms whilst taking tamoxifen.
- It is uncertain whether lifestyle modifications such as exercise, healthy weight loss, and stopping smoking improve hot flushes in menopausal women who are *not* taking tamoxifen.
- Therefore, these recommendations are based on expert opinion found in a review of symptoms and treatment in cancer therapy-induced early menopause [Boekhout et al, 2006], a review on hormonal breast cancer treatments for the primary care provider [Lyon et al, 2006], and recommendations in the CKS topic on Menopause [Rees and Purdie, 2006; ICSI, 2008].

Treatment of atrophic vaginitis

- Symptoms of atrophic vaginitis are less likely to occur with tamoxifen than with aromatase inhibitors. An expert review suggests non-hormonal vaginal lubricants (such as Replens MD®) are helpful for some women, but are not as effective as topical oestrogens [Hickey et al, 2008].
- Gels such as Replens MD® rehydrate the tissues and are a more physiological way of replacing vaginal secretions than with lubricant vaginal gels such as K-Y Jelly® [RCOG, 2006].
- Topical vaginal oestrogens are widely used for atrophic vaginitis in the general population, and are considered to be the most effective treatment for vaginal dryness. However, CKS does not recommend their use in women with breast cancer because their safety in this group is not established, although there is no evidence of harm [Hickey et al, 2008].

Specialist advice

- For severe menopausal symptoms likely to be due to tamoxifen, there may be a place for modifying, or in some cases stopping, endocrine treatment [Hickey et al, 2008].
- Feedback from expert reviewers suggests that this should only be done in secondary care, after lifestyle measures and drug treatments have been tried.
  - Treatment options may include a temporary break from tamoxifen treatment, or a switch to an aromatase inhibitor (for post-menopausal women).

Should I prescribe drug treatment?

- Do not prescribe hormone replacement treatment for women with menopausal symptoms who are taking tamoxifen.
- If hot flushes are not relieved by lifestyle measures, consider prescribing one of the following:
  - A trial of 2–4 weeks of clonidine (licensed use).
  - Start with 50 micrograms twice daily.
  - If after 2 weeks there has been no improvement in symptoms, increase to 75 micrograms twice daily.
  - Stop if no benefit is noted after 4 weeks of treatment, or if the woman experiences unacceptable adverse effects.

- A trial of 2 weeks of venlafaxine 37.5 mg twice a day (unlicensed use).
- A trial of gabapentin 900 mg daily (unlicensed use).
- Titration up to this dose is advised.

- If these are ineffective or unsuitable, seek specialist advice.
- Check regularly (for example every 3–6 months) that the drug is still needed by reducing the dose then discontinuing if symptoms do not return. However, if symptoms persist and adverse effects are not a problem, the drug can be continued as long as the woman is taking tamoxifen.
- For information on contraindications, cautions, drug interactions, and adverse effects, see Prescribing information, and the electronic Medicines Compendium (eMC) (http://emc.medicines.org.uk) or the British National Formulary (BNF) (www.bnf.org).

Basis for recommendation

Hormone replacement treatment

- CKS does not recommend the use of hormone replacement treatment (HRT) in women with breast cancer who are taking tamoxifen, because oestrogen is known to increase the risk of developing breast cancer, and there is a theoretical increased risk of recurrence.
- The use of hormonal treatments for the control of hot flushes is controversial in this group, and women with a history of breast cancer are generally encouraged not to use HRT [Bertelli et al, 2002; Duffy and Cyr, 2003; Bordeleau et al, 2007].

Clonidine

- Clonidine is licensed for the treatment of vasomotor symptoms. A systematic review found limited evidence for the efficacy of oral and transdermal clonidine for hot flushes.
- The recommendation regarding dose and titration is based on the manufacturer's information and the British National Formulary [BNF 56, 2008].

Venlafaxine

- Evidence from a systematic review [Nelson et al, 2006] and subsequent randomized controlled trial [Carpenter et al, 2007] suggests that venlafaxine can reduce hot flushes.
- When effective, antidepressants provide relief from hot flushes almost immediately. A 1-week trial is generally sufficient to determine whether an antidepressant is going to be effective [ICSI, 2008].
- The manufacturer of venlafaxine does not recommend a dose for hot flushes as it is not licensed for this purpose. CKS has therefore based its advice on dosages found to be effective for hot flushes in short-term studies.

▪ Venlafaxine (compared to SSRIs) is only a weak inhibitor of the cytochrome P450 2D6 enzyme (which is involved in the breakdown of tamoxifen to its active metabolite, endoxifen) [Boekhout et al, 2006].

Gabapentin

▪ Gabapentin is not licensed for the treatment of vasomotor symptoms, but CKS found evidence from two randomized controlled trials that suggested it is effective for reducing the frequency and severity of hot flushes [Guttuso et al, 2003; Pandya et al, 2005].

▪ Gabapentin has been less studied for hot flushes than selective serotonin reuptake inhibitors (SSRIs) or serotonin/norepinephrine reuptake inhibitors (SNRIs); current evidence suggests that it may be at least as effective, although head-to-head studies are lacking. It appears to be better tolerated than SNRIs for this indication, although adverse effects are relatively common, and it does not have withdrawal effects. It may be of particular use if sexual dysfunction is a problem or develops on SNRI treatment [Hickey et al, 2008].

Duration of treatment

▪ CKS found no evidence as to how long to prescribe these drugs. Opinion from expert reviewers suggested that:

o Treatment should be for the shortest duration possible.

o As efficacy is not established beyond 3 months, the need for treatment should be reassessed periodically (for example every 3–6 months), but could be continued while the woman is taking tamoxifen if adverse effects are not a problem.

Drugs not recommended

▪ Options which are not recommended by CKS for primary care use (some of which may be considered in secondary care for symptomatic treatment of hot flushes) include progestogens and SSRIs.

o **Progestogens:** there is good evidence that both low-dose megestrol acetate and depot intramuscular medroxyprogesterone acetate can reduce the frequency of hot flushes in post-menopausal women with breast cancer [SIGN, 2005]. However, CKS does not recommend these for primary care use because their effects on breast cancer are uncertain [Shapiro and Recht, 2001]. Some studies discussed concerns that the increased risk of breast cancer with HRT is due to the combination of oestrogen and progestogen (rather than oestrogen alone) [RCOG, 2006].

o **SSRIs** (including paroxetine, fluoxetine, and citalopram) have been extensively tested for menopausal hot flushes in women who have had breast cancer, and results suggest that they are more effective than placebo in short-term studies. They appear to be less effective compared with oestrogen, although there are currently no published head-to-head studies [Hickey et al, 2008].

o SSRIs may reduce the breakdown of tamoxifen to its active metabolite by inhibiting the cytochrome P450 2D6 enzyme [Hickey et al, 2008]. Plasma concentrations of endoxifen (the active metabolite of tamoxifen) were lower in women treated with paroxetine in combination with tamoxifen, compared with tamoxifen alone [Stearns et al, 2003; Boekhout et al, 2006]. In a trial of 80 women with newly-diagnosed breast cancer using tamoxifen, the plasma endoxifen concentration was reduced substantially in women taking paroxetine, but only slightly reduced in women taking venlafaxine (an SNRI) [Jin et al, 2005].

- Adverse effects (particularly nausea, but also headache, decreased appetite, gastrointestinal disturbance, dry mouth, anxiety or agitation, sleep disturbance, and sexual dysfunction) cause 10–20% of people to withdraw from treatment, but are less likely at low doses [RCOG, 2006; Hickey et al, 2008].

- Very few data are available about the safety of SSRIs in breast cancer [Antoine et al, 2007].

What advice should I give about complementary or alternative therapies?

▪ Do not recommend complementary or alternative therapies — explain that there is a lack of evidence of effectiveness and that some products may be harmful.

Basis for recommendation

▪ Many products have been suggested for vasomotor symptoms in women with breast cancer, but CKS cannot recommend them because of limited evidence of efficacy and a lack of safety data [Harris et al, 2002; Duffy and Cyr, 2003; Boekhout et al, 2006; RCOG, 2006; Bordeleau et al, 2007; Hickey et al, 2008]. These include:

- **Black cohosh** — published data are conflicting and the benefit of using black cohosh for treatment of hot flushes is not supported by evidence from methodologically sound clinical trials. There are also safety issues to consider. The Commission on Human Medicines and the Herbal Medicines Advisory Committee have reviewed the available data on liver reactions with black cohosh and, subsequently, advised that these data support a causal association between black cohosh and the risk of liver disorders [MHRA, 2006].

- **Red clover** — studies indicate it may be effective in reducing hot flushes compared with placebo, but there is a lack of statistically significant data. There were no safety concerns in the short-term studies, but longer-term data are needed.

- **Evening primrose oil** — there is no evidence of efficacy for menopausal symptoms, and two trials have found it to be ineffective for treating hot flushes.

- **Phyto-oestrogens** — data from trials are contradictory and long-term safety is unclear. It is difficult to compare studies because of the differences in products and doses.

- **Homeopathy** — well-conducted studies assessing safety and efficacy are needed. Homeopathy appears to be not effective for alleviating hot flushes.

- **Vitamin E** — evidence is limited. Vitamin E is not registered for this indication so it should be used with caution. Supplemental vitamin E at doses of more than 400 IU/day have been linked with an increase in all-cause mortality.

- **Acupuncture** — there is evidence from some studies suggesting electro-acupuncture and acupuncture may decrease the number of hot flushes. However, rare but potentially serious adverse effects (bacterial endocarditis, hepatitis) may occur. Care is needed if the woman has had axillary surgery for lymph node dissection because of the risk of lymphoedema.

Prescriptions

For information on contraindications, cautions, drug interactions, and adverse effects, see the electronic Medicines Compendium (eMC) (http://emc.medicines.org.uk), or the British National Formulary (BNF) (www.bnf.org).

Venlafaxine (2 week trial)

Age from 18 years onwards

Venlafaxine tablets: 37.5mg twice a day

Venlafaxine 37.5mg tablets
Take one tablet twice a day.
Supply 28 tablets.

Age: from 18 years onwards
NHS cost: £11.71
Licensed use: no - off-label indication

Clonidine (2-4 week trial)

Age from 18 years onwards

Clonidine tablets: 50micrograms twice a day

Clonidine 25microgram tablets
Take two tablets twice a day.
Supply 112 tablets.

Age: from 18 years onwards
NHS cost: £15.29
Licensed use: yes
Patient information: If symptoms do not improve after 2 weeks, increase the dose to three tablets twice a day.