RESOURCES AND REFERENCES

The National Institutes of Health (NIH) held a conference in 2005 that focused on identifying menopausal symptoms and evaluating treatments for these symptoms [National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. Ann Intern Med 2005;142(12 Pt 1):1003-13]. This conference formed the basis for much of the information found in this information booklet. We have supplemented the conference findings with a review of the literature as listed below and from knowledge gained by caring for post-menopausal women.

1. Tice JA, Grady D. Alternatives to estrogen for treatment of hot flashes: are they effective and safe? Jama 2006;295(17):2076-8.
2. National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. Ann Intern Med 2005;142(12 Pt 1):1003-13.
3. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. Jama 2003;289(21):2827-34.
4. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause 2004;11(1):11-33.
5. Shanafelt TD, Barton DL, Adjei AA, Loprinzi CL. Pathophysiology and treatment of hot flashes. Mayo Clin Proc 2002;77(11):1207-18.
6. Stearns V, Loprinzi CL. New therapeutic approaches for hot flashes in women. J Support Oncol 2003;1(1):11-21; discussion 14-5, 9-21.
7. Stearns V. Management of hot flashes in breast cancer survivors and men with prostate cancer. Curr Oncol Rep 2004;6(4):285-90.
8. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. Jama 2006;295(17):2057-71.
9. Loprinzi CL, Kugler JW, Barton DL, et al. Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. J Clin Oncol 2007;25(3):308-12.
10. Pandya KJ, Morrow GR, Roscoe JA, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. Lancet 2005;366 (9488):818-24.
11. Fugate SE, Church CO. Nonestrogen treatment modalities for vasomotor symptoms associated with menopause. Ann Pharmacother 2004;38(9):1482-99.
12. Sicat BL, Brokaw DK. Nonhormonal alternatives for the treatment of hot flashes. Pharmacotherapy 2004;24(1):79-93.
13. Fitzpatrick LA. Alternatives to estrogen. Med Clin North Am 2003;87(5):1091-113, x.
14. Loprinzi CL, Barton DL, Rhodes D. Management of hot flashes in breast-cancer survivors. Lancet Oncol 2001;2(4):199-204.
15. National Center for Complimentary and Alternative Medicine. *Do CAM Therapies Help Menopausal Symptoms*? Available at http://nccam.nih.gov/health/menopauseandcam. Accessed June 15, 2007.
16. Barton DL, Loprinzi CL, Quella SK, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. J Clin Oncol 1998;16(2):495-500.
17. Miller ER, 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142(1):37-46.
18. Pockaj BA, Gallagher JG, Loprinzi CL, et al. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1. J Clin Oncol 2006;24(18):2836-41.
19. Keefer L, Blanchard EB. Hot flash, hot topic: conceptualizing menopausal symptoms from a cognitive-behavioral perspective. Appl Psychophysiol Biofeedback 2005;30(1):75-82.
20. Keefer L, Blanchard EB. A behavioral group treatment program for menopausal hot flashes: results of a pilot study. Appl Psychophysiol Biofeedback 2005;30(1):21-30.
21. McKee J, Warber S. The patient page. Symptom relief for menopause. South Med J 2005;98 (3):399.
22. Hickey M, Saunders CM, Stuckey BG. Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. Lancet Oncol 2005;6(9):687-95.

Non-hormonal alternatives for the treatment of early menopause symptoms

Information for Women Enrolled in GOG-0215 and their Health Care Providers

GOG-0215: A Phase II randomized study of the effect of zoledronic acid versus observation on bone mineral density of the lumbar spine in women who elect to undergo surgery that results in removal of both ovaries

Gynecologic Oncology Group

Managing Hot Flashes and Night Sweats

Many postmenopausal women have hot flashes and night sweats. Typically, women describe these symptoms as a sudden increase in perceived body temperature that occurs along with sweating, flushing, and occasionally, heart palpitations (irregular heartbeats). Cigarette smoking increases the risk of experiencing hot flashes. For most women, hot flashes resolve over a period of several years, but in a small minority of women (10-15%), the symptoms may persist for extended periods of time [(1)].

These symptoms frequently occur at night. Many women report waking up drenched in sweat. When severe, these night-time symptoms can interfere with restful sleep. Hot flashes can significantly reduce quality of life for postmenopausal women, both as a direct result of the symptoms, and indirectly, from insufficient sleep.

Women who undergo premature menopause as a result of surgery that results in the removal of both ovaries are usually younger than women who undergo natural menopause; these younger women may experience hot flashes or night sweats that are more bothersome than those that occur at the time of natural menopause.

Many women opt to mange hot flashes with menopausal hormonal therapy (MHT). Menopausal hormone therapy (MHT) is the use of medications (or medical products) which contain estrogen and/ or progesterone to replace the hormones previously made by the ovaries. However, as with any medication, there are risks with MHT, some of which are potentially very serious. If you choose to use MHT, please discuss the risks and benefits with your health care provider.

Alternatives to Hormone Therapy

Because MHT can affect bone mineral density, we ask that women who are enrolled in GOG-215 not use them while on the study. There are a number of non-hormonal alternatives to MHT for managing hot flashes. This booklet provides a brief overview of the non-hormonal medications available for hot flashes and night sweats (pages 3– 9) and for vaginal symptoms (pages 10-14) that may be associated with early menopause.

Helpful Tips

Some women find it is useful to keep a **diary of symptoms**. This may help identify triggers of menopausal symptoms, and what remedies are most helpful. Some triggers of hot flashes/menopausal symptoms may include alcohol, diet pills, hot food, saunas, caffeine, smoking, hot tubs/ saunas, and smoking. Stress is also commonly a trigger of menopausal symptoms.

If you are experiencing hot flashes, there are ways to **prepare yourself** to handle them throughout your day. Dressing in layers is helpful so you can take some clothing off when you get warmer. Cotton, linen or rayon are more comfortable fabrics than wool, synthetics or silk when experiencing hot flashes. Turtleneck shirts are likely to become uncomfortable; choose loose, open necked shirts instead. Use cotton sheets for your bed and take a cool shower before you go to sleep. Keep ice water on hand throughout the day to cool yourself when you start feeling warmer. Some women like to carry a hand-held battery operated fan.

NOTES:

IUDs

Although intrauterine devices (IUDs) are prescription devises used for contraception, there is some evidence that they may alleviate the symptoms of menopause. Two such IUDs include **Mirena** and **Progestasert.** IUDs deliver hormones directly to the tissue of the vagina. IUDs contain progestin and can remain in place for up to five years (Mirena) or for one year (Progestasert). Women using IUDs for menopausal symptoms may experience side effects.

The choice between vaginal tablet, cream, gel or IUD largely depends on the treatment needs and medical condition of an individual woman. As with any prescription medications, the IUD has possible risks that must be weighed against the benefits. It is important to discuss these and other options with your health care provider. In general, it is best not to start off with the strongest treatment possible, but to start slow, and only do what is needed for your body to manage the symptoms of menopause. The least aggressive approach should always be the first choice.

Summary

If you would like more information or if you would like to try any of the suggestions in this booklet, please be sure to discuss them with your physician first. This booklet was not intended to provide women with medical advice, but rather to be sure that participants enrolled to GOG-215 are informed of the wide variety of options available to treat menopausal symptoms. As stated previously, always begin with the least aggressive approach to treating your symptoms.

It is important to remember to inform your physician and the study staff of all new medications, whether herbal/natural remedies, over-the-counter, or prescription. If symptoms persist and do not improve, please discuss them with your physician. Some vaginal symptoms may be caused by an infection that may require prescribed medication treatment.

Selective Serotonin Re-uptake Inhibitors (SSRIs)

SSRIs are antidepressant medications that can be very effective in reducing the severity and frequency of hot flash episodes[3-7]. Examples of SSRIs include Effexor® (Venlafaxine), Effexor XR, and Paxil® (Paroxetine HCl). A recent combined analysis of published randomized controlled studies of SSRIs supports the effectiveness of these medications[8].

Benefits

SSRIs have been shown to substantially decrease hot flash frequency and severity. Typically, short-term use (1 or 2 weeks) is sufficient to determine if an SSRI is going to be beneficial. More prolonged therapy is generally required to obtain maximum symptom control. SSRIs are an appropriate first-line treatment for women who decline or cannot take MHT. A possible bonus effect is an improvement in clinical depression, should that be a co-existing medical problem.

Risks

Possible side effects of SSRIs may include restlessness, fatigue, dry mouth, decreased appetite, constipation, difficulty sleeping and nausea. The chances of experiencing side effects are greater at higher medication doses.

Common SSRI treatment approaches for hot flash control

- **Effexor® (Venlafaxine)**
- **Paxil® (Paroxetine HCl):**

Duration of therapy:

No data are available regarding optimum duration of treatment. Decision-making should be individualized, based on discussions with your health care provider about possible benefits and risks.

Gabapentin (Neurontin®)

This medication is generally used to treat epilepsy and related neurological conditions, but it also may reduce the frequency and severity of hot flash episodes[7, 9-11]. Gabapentin can be used in combination with or instead of an SSRI[9]. A recent combined analysis of published randomized controlled studies of gabapentin supports the effectiveness of this medication[8].

Benefits

Neurontin is reported to decrease hot flashes.

Risks

Side effects may include lightheadedness, mild swelling of the ankles, or difficulty achieving orgasm.

Common Treatment Schedule for Hot Flash Control

- Start at a relatively low dose, such as 100 mg/day.
- May gradually increase the dose to as much as 300 mg, three times a day.
- The greatest improvement in hot flash frequency was observed in women taking the 900 mg/day dose.

Duration of therapy:

No data are available regarding optimum duration of treatment. Decision-making should be individualized, based on discussions with your health care provider.

Vaginal Creams

Estrogen creams allow direct administration of estrogens to the vagina while minimizing the levels of estrogen that circulate throughout the body. Because the level of circulating estrogens is so small, they will not affect bone density and are permitted for women enrolled on GOG-215.

Vaginal estrogen creams are available by prescription and include:

- **Dienestrol**
- **Estrace**
- **Ogen**
- **Ovestin**
- **Premarin,** and
- **Ortho Dienestrol cream.**

Each of these creams have some similarities and differences, so it is important to talk to your health care provider to determine which, if any, of these treatments may be right for you.

Vaginal creams, like all medications, have some possible risks as well as benefits. Similar to the vaginal tablets and rings, vaginal creams deliver medication to the nearby tissues, so that some of the estrogen previously produced by the ovaries is replaced. This alleviates some of the symptoms experienced during menopause.

Moisturizers and Lubricants

Moisturizers can be used for everyday dryness. **Replens** is a gel that is inserted into the vagina and lasts for three days. **Gye-Moistrin** is another commonly used vaginal moisturizer.

To reduce discomfort during sex, couples should use lubricants before vaginal penetration. Water-soluble (not oil-based) lubricants should be used. Examples of these include: **KY Jelly, Ortho Personal Lubricant,** and **Astroglide**. Other useful lubricants include **Lubrin vaginal suppositories** or **Lubafax,** which can be inserted about five minutes before intercourse.

Some women also have found that **Vitamin E oil** is useful. Vitamin E capsules can be broken open, and the oil applied directly to the vagina. Vitamin E oil should be applied once a day for 1-2 weeks, then applications should decrease to one or two times per week.

Vaginal Tablets and Rings

Vagifem is a vaginal tablet that is available by prescription. It is used to treat vaginal dryness, soreness and pain that is caused by the decrease in vaginal lubrication during menopause. Although this tablet does contain estrogen, very little estrogen enters the bloodstream. Therefore, the estrogen can treat the symptoms of menopause without affecting bone density.

Estring and **Femring** are two similar types of estrogen-containing rings that are inserted into the vagina. Vaginal rings are available by prescription to treat the vaginal symptoms associated with menopause. Once the ring is placed, it is to remain in place for three months, at which time it should be removed or replaced. A vaginal ring is placed in such a way that you should not be able to feel it, and the rings should not interfere with intercourse. The ring works by delivering a small dose of estrogen directly to the vagina. The estrogen only minimally enters the bloodstream, so does not affect bone density.

All medications carry some possible risk as well as benefit, as both estrogen tablets and rings deliver medication to the nearby tissues. The differences between Vagifem, Estring and Femring, as well as the risks and benefits of each medication, should be discussed with your health care provider.

Clonidine Hydrochloride (Catapres®)

This blood pressure medication has been found to reduce the frequency and severity of hot flash episodes[2, 5, 12]. A recent combined analysis of published randomized controlled studies of clonidine supports the effectiveness of this medication, although the benefits are smaller than those seen with MHT[8].

Benefits

Clonidine has been shown to decrease hot flashes. It may be an appropriate second-line treatment for women who decline or can't tolerate MHT or SSRI treatment.

Risks

Side effects may include dry mouth, dizziness, drowsiness, tiredness, lightheadedness, constipation, decreased sexual desire, lethargy, low blood pressure, and difficulty sleeping. Some patients find it difficult to take this medication over a long period of time. Among women participating in clinical trials of clonidine, there have been high dropout rates because of its numerous side effects.

Common Treatment Schedule for Hot Flash Control

- Apply transdermal patch of 0.1 mg/day.
- May increase the dose to 0.2 to 0.3 mg/day, if needed and if tolerated.
- Take oral doses in the range of 0.1 to 0.4 mg/day.
- May take an extra dose at night to prevent awakening.

Duration of therapy:

No data are available regarding optimum duration of treatment. Decision-making should be individualized, based on discussions with your health care provider

Belladonna-phenobarbital-ergotamine preparations (Bellergal-S®)

Some women report that belladonna preparations help them cope with hot flashes[5, 13, 14]. A recent combined analysis of published randomized controlled studies of hot flash management identified only one trial of this preparation. It was judged to be of poor quality, and did not support the value of belladonna in treating hot flashes[8].

Benefits

Belladonna is reported to decrease hot flashes, and is an FDA-approved treatment for menopausal symptoms.

Risks

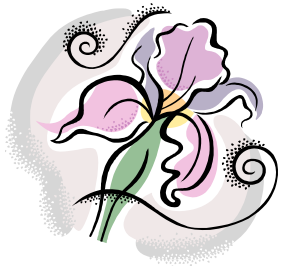
This combination medication has the potential for abuse and addiction because it contains a barbiturate. It may be difficult to take during the day because of its sedative effect. Side effects include dry mouth, dizziness and sleepiness.

Common Treatment Approach for Hot Flash Control

- 1 tablet once or twice daily.

Duration of therapy:

No data are available regarding optimum duration of treatment. Decision-making should be individualized, based on discussions with your health care provider, with careful consideration of the potential for abuse or addiction.



Kegel exercises

Kegel exercises are used to strengthen the muscles of the pelvic floor. These exercises, when done regularly, can increase sensation in the pelvic area and strengthen the muscles that support the bladder.

Instructions:

1) Find the pelvic floor muscles by trying to start and then stop the flow of urine. The muscles that control this activity are the pelvic floor muscles. Do not make a habit of starting/stopping urination, as this may increase the risk of a urinary tract infection. This activity is simply to help you to identify the pelvic floor muscles.

2) Tighten/draw up the pelvic floor muscles and hold for 3 seconds, then relax. Repeat this 10 times.

3) Start by doing 10 Kegels a day, and work up to 30 per day

4) Be sure to relax and breathe while doing these exercises.

5) Try doing these exercises in different positions: lying down, sitting, and standing. You can exercise while lying on the floor, sitting at a desk, or standing in the kitchen. Using all three positions makes the muscles strongest.

Kegel exercises should be done on a daily basis. Be sure not to tighten other muscles while doing Kegels. Results can be seen in as few as 3-6 weeks. Be sure to tighten the pelvic floor muscles before (and hold until after) sneezing, lifting or jumping to prevent muscle damage.

For more information on Kegel exercises, you can request NIH publication number 02-4188 from the National Institutes of Health (1–800–891–5388).

Managing Vaginal Symptoms

Some women who experience early menopause experience vaginal dryness as a result of the loss of estrogen that had been produced by the ovaries. As estrogen decreases, the walls of the vagina become thinner and more fragile, and vaginal pH level may increase. This may also result in an increased likelihood of infection. Vaginal dryness can range from a mild annoyance to having a negative impact on sexual functioning and overall quality of life.

Many women opt to mange vaginal dryness with menopausal hormonal therapy (MHT). Because these medications can affect bone mineral density, we ask that women who are enrolled in GOG-215 not use hormonal therapies while on the study.

In general, it is important to keep yourself well hydrated by drinking at least eight 8-ounce glasses of water each day. Women **should avoid** the use of feminine hygiene sprays, perfumed toilet paper, vasoline, baby oil, tight-fitting clothes, scented laundry products, perfumed soaps, douches, and any other oil based products, as these may increase irritation and/or infection. Many women find that a warm bath can relieve the itching and discomfort. Excess sugar, chocolate, or alcohol may increase the risk of a yeast infection; therefore, women may want to moderate their intake following the onset of menopause.

There are a number of non-hormonal alternatives to MHT for managing vaginal dryness that may be used to reduce the risk of vaginal irritation and infection. We have listed these below and describe each in more detail in the pages that follow.

- **Kegel exercises**
- **Lubricants and moisturizers**
- **Vaginal tablets/rings**
- **Vaginal creams/gels**
- **Intrauterine devices (IUDs)**

Do not try to self-diagnose your vaginal symptoms. Some symptoms may not be caused by dryness alone, but could be bacterial or yeast infections, which may require prescribed treatment from your physician.

Complementary and Alternative Medicines (CAM)

As is generally the case with most CAMs, the safety and/or efficacy of the approaches listed below are unknown, as most are not regulated by FDA. If women choose to use these approaches in an effort to reduce hot flashes or night sweats, it is recommended that they first discuss this with their health care provider, to avoid unexpected side effects from interactions with other medications[2, 15].

Phytoestrogens

Phytoestrogens are plant-derived substances that possess some of estrogen's biological effects[2, 15]. The active ingredients in these products are thought to be members of a family of chemicals called "isoflavones." Red clover and soy products are among the common sources used to create these medications. Others include tofu, tempeh, whole-grain cereals, seeds, certain fruits/vegetables. In commercial supplements, phytoestrogens have been either extracted from the plants in which they occur, or made in the laboratory, and turned into pills or capsules that can be taken as a medication[2, 15].

Benefits

A recent combined analysis of published randomized controlled studies of isoflavones showed no benefit related to the red clover-derived preparations, and provided mixed evidence regarding the effectiveness of the soy-derived preparations, although the benefits from soy are smaller than those seen with MHT[8]. Other experts, reviewing these and additional data, have concluded that the overall evidence does not show benefit from phytoestrogens in the treatment of hot flashes[1].

Risks

Side effects were similar between subjects taking phytoestrogens and those taking placebo in several clinical trials. Although these are considered to be benign, natural, herbal preparations, they do in fact have at least some estrogen-like biologic effects. It is possible that estrogen-like side effects might occur as well. One long-term study did suggest an increased rate of endometrial thickening after 5 years of soy isoflavone use. Be sure to discuss with your Health Care Provider how much phytoestrogen you can safely take.

CAM, continued

Vitamin E
Vitamin has been evaluated for the treatment of hot flashes in one randomized, placebo-controlled crossover clinical trial. In that study, there was a decrease of 1 hot flash/day in patients on the Vitamin E arm compared with the placebo arm. This difference was statistically significant, but is unlikely to be of clinically meaningful. In addition, at the end of the study, participants did not prefer Vitamin E use over placebo. There was no toxicity associated with Vitamin E use in this study[16].

Common treatment approach for hot flash control
- Start at a relatively low dose, such as 100IU per day.
- The daily recommended dose for treatment of hot flashes is 800IU per day.

Risks
The long-term safety of vitamin E is unknown – a recent meta-analysis of randomized controlled trials of Vitamin E supplementation suggested an increase in mortality among users of high dosage (>400 IU/d) Vitamin E[17].

Black Cohosh
Some women report an improvement in hot flashes associated with the use of this herbal preparation, but the English language medical literature does not contain evidence of a consistent benefit[11, 12]. A recent NIH-sponsored clinical trial studied the effectiveness of black cohosh *versus* placebo pills for hot flash control, and found no evidence of benefit for black cohosh[18].

Common treatment approach for hot flash control
- Daily doses range from 20 to 40mg/day for 6 months.

Risks
In clinical trials, few side effects were reported (side effects included: headaches, gastric complaints, heaviness in the legs, and weight problems). Black cohosh may have estrogen-like effects, some of which may be undesirable.

CAM, continued

Miscellaneous CAM treatments
Small studies, generally of poor quality, have been performed to evaluate the value of a wide variety of other preparations, including flaxseed, kava, Dong Quai root, ginseng, evening primrose oil, and wild yam[2, 15]. The available data do not show evidence of benefit in the treatment of hot flashes.

Relaxation techniques
Relaxation techniques include yoga, massage, meditation, leisure bath, and slow, deep, paced respiration. Several reports have suggested that women may experience some relief of hot flashes with the use of these techniques[19-21].

Acupuncture, Biofeedback, Hypnosis
There are no data supporting the efficacy of acupuncture, biofeedback, or hypnosis in the treatment of hot flashes or night sweats[2].

Lifestyle and Environmental Changes

Women can adopt healthy behaviors in an effort to minimize hot flashes and night sweats[22].

- Keep a diary of when hot flashes and night sweats occur. This will help identify triggers to their occurrence or times when medication loses its effectiveness.
- Keep body temperature cool:
  - dress in layers
  - use a fan
  - choose cold food and drinks
  - sleep in cool room
- Exercise regularly. Physically active women report fewer hot flashes than do sedentary women.
- Do not smoke.
- Eat a healthy diet, and avoid dietary triggers to hot flash occurrence (such as spicy/hot foods, caffeine, and alcohol).