

Consumer Reports BEST BUY DRUGS™

PROVEN • EFFECTIVE • AFFORDABLE



Evaluating Prescription Drugs Used to Treat: The Symptoms of Menopause

Comparing Effectiveness, Safety, and Price



Our Recommendations

Medicines containing the female hormones estrogen and progestin are highly effective at reducing the symptoms of menopause. Seventy to 90% of women who have hot flashes or night sweats experience an average 75% reduction in these symptoms within a few months. The drugs also effectively reduce vaginal dryness.

Hormones, however, have been found to increase the risk of heart disease, breast cancer, blood clots, stroke, urinary incontinence, and dementia. Drugs containing estrogen alone pose less risk of breast cancer and possibly heart disease than those containing both estrogen and progestin. However, women who have not had hysterectomies must take both because estrogen-only drugs have been conclusively linked to a much higher incidence of cancer of the uterine lining (endometrial cancer).

We make the following general hormone treatment recommendations:

- Don't take hormones if your symptoms are mild and manageable with lifestyle changes and adjustments.
- Don't take hormones if you have heart disease, or have had a stroke or cancer of the breast, ovaries, or uterus. Don't take hormones if you are at elevated risk of these (for example, if you smoke, have elevated cholesterol, or diabetes).
- If you must take hormones because your symptoms are severe, take the lowest dose possible for the shortest duration possible. The risk associated with such use appears to be quite low, but definitive studies on that are not yet complete.
- Hormones should not be used to treat mood swings, irritability, depression, anxiety, mental lapses, forgetfulness, cognitive difficulties, reduced libido, urinary incontinence, back pain, chronic pain, joint pain, stiffness, or fatigue. They don't help these conditions and could make them worse.
- Herbs, supplements, and "bioidentical" hormone products widely touted as alternatives to estrogen and progestin lack proof of effectiveness and safety and should be used with caution. Consult a physician about them.

The scientific evidence indicates that no one form of estrogen or estrogen plus a progestin is more effective than any other. Taking effectiveness, safety, the choice for mode of

delivery, and cost into account, we have chosen the following as *Consumer Reports Best Buy Drugs* for the treatment of menopausal symptoms:

- *Generic estradiol pills*
- *Gynodiol pills (estradiol)*
- *Estratab or Menest pills (esterified estrogen)*
- *Generic medroxyprogesterone pills (when a progestin alone is needed)*
- *Generic estradiol patch*
- *Alora patch (estradiol)*
- *Vivelle or Vivelle Dot patch (estradiol)*
- *Premarin Cream (conjugated equine estrogen)*
- *Ogen Cream (estropipate)*
- *FemRing (estradiol, vaginal ring)*
- *Estring (estradiol, vaginal ring)*

Most of these products are used to treat all menopausal symptoms. The creams and FemRing are used primarily to treat vaginal dryness.

All our *Best Buys* are as effective as other hormone drugs but less expensive. (See Table 3 on page 15.) In particular, the two estradiol pills could save you \$300 to \$450 a year out-of-pocket compared to brand name Premarin. If you choose an estrogen hormone patch, generic estradiol could save you \$200 to \$400 a year over higher-priced products.

Hormone treatment can cause side effects. The most common are heavier or lighter vaginal bleeding, thickening of the uterine lining, nausea and vomiting, breast tenderness, headache, weight change, and dizziness. Heavier vaginal bleeding and breast tenderness tend to be the most bothersome. Between 20% and 25% of women stop taking hormones because of side effects. Lower doses can reduce your chance of experiencing them.

Welcome

This report on a class of drugs known as female sex hormones (estrogens and progestins, including progesterone) is part of a Consumers Union and *Consumer Reports* project to help find safe, effective medicines that give you the most value for your health-care dollar. To learn more about the project and other drugs we've evaluated, go to www.CRBestBuyDrugs.org.

Female hormones are used primarily in birth control pills and to treat women who experience symptoms associated with menopause – hot flashes, night sweats, sleep disturbance, and vaginal dryness. Contrary to decades of drug marketing, most experts now agree that menopause – the permanent cessation of menstrual periods – is *not* a medical condition that must be treated. It is a normal event that is inevitable as a woman ages.

That said, when the body's production of estrogen and progesterone slows as a woman approaches menopause and then declines more rapidly after the last menstrual period, some women experience symptoms that may reduce their quality of life. Those symptoms can be eased and sometimes completely eliminated by taking prescription estrogen and progestin medicines.

About 25 million women in the U.S. will move through the menopausal transition over the next decade. Studies indicate that about 30% of women will have almost no menopausal symptoms, but 70% will have them. The severity of symptoms and the degree to which they interfere with functioning and quality of life ranges broadly. Most women have mild or moderate symptoms, but about 20% will have severe symptoms.

Treatment with hormones was thrown into almost complete disarray in the summer of 2002. Up until that time, many doctors had recommended that most menopausal women – even those with no symptoms or only mild ones – should use hormones not only to reduce symptoms but also to prevent heart disease, osteoporosis, dementia, and incontinence. In 2002, however, the results of a long-awaited large study (the Women's Health Initiative) showed that after five years of treatment estrogen plus a progestin actually *increased* the risk of heart disease, breast cancer, blood clots, stroke, urinary incontinence, and dementia. The increased risks were small but noteworthy on all counts. Later results from the same study showed that taking estrogen alone increased the risk of stroke and dementia but not breast cancer or heart disease.

Tremendous anxiety and confusion followed the publication (and widespread media reports) of these findings. Many women stopped taking hormones.

Now, three years later, the panic and controversy have subsided and detailed analyses have further clarified the risks and benefits of hormones. A more reasoned, evidence-based approach to their use has begun to emerge. This report will add to other resources available – including many Web sites and

excellent books – to help you and your doctor evaluate whether hormone treatment is right for you, and if so, which medicine to use.


We draw on two systematic evaluations of the scientific evidence to compare the effectiveness, safety, and cost of the estrogen-containing drugs available in the U.S. The drugs we evaluate are listed below. As you can see, there is an array of products to treat menopausal symptoms. These include pills, skin patches, skin creams and gels, vaginal creams, dissolving tablets, and vaginal ring inserts. And all these are divided between products that contain estrogen only, those that contain both estrogen and a progestin, and those that contain a progestin alone.

Generic Name	Brand Name(s)	Available as Prescription Generic Drug?
Estrogen-only pills		
Estradiol	Estrace, Gynodiol	Yes
Conjugated equine estrogens	Premarin	No
Synthetic conjugated estrogens	Cenestin	No
Esterified estrogen	Estratab, Menest	No
Estropipate	Ogen, Ortho-Est	Yes
Estrogen-only skin patches and creams		
Estradiol	Alora, Climara, Esclim, Estrogel, Estroderm, Estrosorb, Menostar, Vivelle, Vivelle Dot	Yes
Estrogen-only vaginal creams, tablets or rings		
Conjugated equine estrogen	Premarin cream	No
Estropipate	Ogen cream	No
Estradiol	Estring, FemRing, VagiFem	Yes

Generic Name	Brand Name(s)	Available as Prescription Generic Drug?
Estrogen plus progesterone pills		
Conjugated equine estrogens plus medroxyprogesterone	Prempro, Premphase	No
Ethinylestradiol plus norethindrone	FemHRT	No
Estradiol plus norethindrone	Activella	No
Estradiol plus norgestimate	Ortho-Prefest	No
Estrogen plus progesterone skin patches		
Estradiol plus norethindrone	CombiPatch	No
Estradiol plus levonorgestrel	Climara Pro	No
Progesterone-only pills		
Medroxyprogesterone acetate	Cycrin, Provera	Yes
Norethindrone acetate	Aygestin, Norlutate	Yes
Progesterone	Prometrium	Yes

As you can see, generic versions of some of these medicines are available. But most are still brand-only products.

Some female hormone products are less used now, notably estrogen pellets and injections. Individualized hormone compounds made by some pharmacists are still available. Such “bioidentical” hormone products can be safe when carefully prepared. But you should know that they lie outside FDA’s regulatory reach and can vary widely in potency. In addition, no studies have assessed their effectiveness or long-term safety. As a result, they are not included in this report and we advise extreme caution in using them.



Female hormones also have been used to prevent bone loss (osteoporosis), which can increase the risk of fractures. Bone loss begins at about age 30 but accelerates during and after menopause. Most experts now advise that hormones *not* be used for this purpose alone until other, safer treatments for osteoporosis have been tried.

Hormones are not the only medicines used to treat menopausal symptoms. Indeed, a range of both prescription and nonprescription treatments have been tried over the years. Prescription medicines used include certain antidepressants such as fluoxetine (Prozac) and paroxetine (Paxil), the high blood pressure medication clonidine (Catapres), and a drug for nerve pain and seizures called gabapentin (Neurontin). Some evidence supports the use of these medicines to reduce menopausal symptoms, and especially hot flashes. But generally, studies show these medicines are not nearly as effective as hormones. And all have their own set of side effects.

Nonprescription dietary supplements are also used. Most notable are products known as phytoestrogens or isoflavones. These occur naturally in some foods, such as soybeans, chick peas, and other legumes. Other products widely touted are black cohosh-containing supplements, ginseng, and vitamin E. So far, studies have yielded mixed results on the effectiveness of these alternative treatments, according to a recent review by a National Institutes of Health expert panel. Safety information is also lacking on these products.

Nevertheless, women who can not or do not want to take hormones should talk with their doctor about these alternatives and other options. We strongly caution against relying on information in advertisements, magazines, books, and on Web sites that promote alternative treatments. The Food and Drug Administration and Federal Trade Commission in November 2005 sent letters to 16 dietary supplement makers and 34 Web sites selling “alternative hormone therapies.” The agencies demanded that the firms stop making any and all medical claims for the products. In several cases, the companies claimed their products prevented heart disease, osteoporosis, and certain cancers.

Some studies suggest that a healthy lifestyle and some simple preventive measures can help ease the discomforts of menopause and reduce the need for hormone treatment. (See box on page 8.) While studies examining the impact of increased exercise and physical activity on menopause symptoms have not yielded conclusive findings, regular exercise has such positive health benefits generally – and enhances one’s sense of well-being – that it is often recommended as one way women may ease the discomforts of menopause.

This report was released and last updated in November 2005.

What are Estrogen and Progestin and Who Needs Them?

Estrogen and progestin are female sex hormones. They are made primarily in the ovaries. Levels of both gradually decline or fluctuate for most women through their forties, and then production typically plummets in the early to mid-fifties after your last period. In the U.S., the average age at which menopause occurs is 51, but it can begin as young as age 40 and as old as age 60. Female hormone pills, patches, creams, and vaginal rings all seek to relieve the symptoms of menopause.

Some simple definitions will help you understand menopause and talk with your doctor about it. The term *perimenopause* refers to the period of time before menopause when menstruation becomes irregular and when you may start experiencing menopausal symptoms. Perimenopause usually lasts several years, with symptoms sometimes increasing over time. The word menopause refers to the point you reach when you have not had a menstrual period for 12 months. The term *postmenopausal* refers to the years after you have reached menopause. *Menopausal transition* refers to the period from perimenopause to menopause.

Table 1 on page 9 describes the main symptoms that can begin in perimenopause and continue well into postmenopause. The severity of these symptoms ranges widely and may fluctuate over time. Most women have very few or mild discomforts while others (about 20%) have severe symptoms. The symptoms last on average about two years, but millions of women experience symptoms for many years.

Importantly, Table 1 also lists symptoms once linked to menopause which, recent studies indicate, are not. Some of these symptoms – such as mood swings, depression, and reduced libido – could be exacerbated by the decline of your hormone levels. But studies have not shown that hormone levels or menopause actually cause them. Indeed, the normal process of aging may bring about several of the symptoms or conditions listed in column 2 of Table 1. The existence of other illnesses and diseases may also precipitate them.

Lifestyle and Environmental Adjustments To Ease The Discomforts and Symptoms of Menopause

- Dress in layers, so you can remove clothes as needed
- Wear natural fabrics, such as cotton and silk
- Keep room temperatures cool or use a fan, especially at night
- Sleep with fewer blankets
- Drink cold beverages rather than hot ones
- Limit intake of caffeine and alcohol, especially at night
- Eat smaller meals and avoid spicy food
- Get regular exercise
- Reduce stress
- Don't smoke
- Try relaxation techniques, meditation, or yoga

Thus, treatment with female hormones is no longer considered appropriate to treat or relieve the symptoms or conditions listed in column 2 of Table 1: *Mood swings, irritability depression, anxiety, mental lapses, forgetfulness, cognitive difficulties, reduced libido, urinary incontinence and urge to urinate, back pain, chronic pain, joint pain and stiffness, and fatigue.* Other, better treatments for these conditions exist. And some studies have actually shown that hormone treatment can worsen some of these conditions.

Treatment with hormones *is* considered appropriate for women who have the discomforts listed in column 1, which are clearly linked to the biological changes triggered by menopause.

Table 1. Is Menopause to Blame?

The Main Symptoms of Menopause	Symptoms Not Clearly Linked to Menopause
<p>Hot Flashes and Flushing – Both involve feelings of intense heat in your face, chest, or over the surface of your body. Your skin may appear flushed, red, or have red blotches. This is caused by blood vessels expanding in your skin; your skin temperature actually rises. This in turn leads to sweating, which can make you feel chilled, and even shiver. You may also feel faint or weak.</p> <p>Night Sweats – These are simply hot flashes that occur at night. Because you are under the covers, your heated skin has produced sweat, sometimes quite a lot. It's not uncommon to awaken to wet sheets and feel chilled.</p> <p>Sleep disturbances – You may find that you are awakened more easily, sleep more lightly or can not get back to sleep easily once you awaken. This can happen with or without night sweats.</p> <p>Vaginal dryness – Reduced estrogen levels bring about changes that result in a lack of vaginal lubrication. Intercourse can be uncomfortable and even painful.</p>	<p>Mood swings, irritability depression, anxiety – May be secondary to the symptoms in column 1. For example, days on end of poor sleep may trigger.</p> <p>Reduced libido – May be secondary to vaginal dryness and pain on intercourse. Could also be associated with other biological changes as the body ages, but that too is in dispute.</p> <p>Mental lapses, forgetfulness, and cognitive difficulties – These increase as we get older. Men experience them, too.</p> <p>Urinary incontinence – Tissues in the bladder and urethra thin as you age. Hormone decline could be partly to blame. Other treatments are available. Hormone treatment may actually increase the risk.</p> <p>Physical changes – Weight gain is common as we age. Distribution of fat may also shift – for example from thighs and hips to abdomen. Hair may also thin.</p> <p>Physical symptoms – Back pain, chronic pain, joint pain and stiffness, fatigue; none of these have been conclusively linked to declining hormones or menopause.</p>

The decision whether to take hormones or not is usually driven by the following factors:

- Your symptoms and their severity
- Your and your family's medical history
- Whether you have had a hysterectomy and/or your ovaries removed
- Your risk of heart disease, certain kinds of cancer, and osteoporosis
- Your tolerance of the risk hormone treatment poses, both short- and long-term
- Your personal circumstances

Your Symptoms and their Severity

Women experience the symptoms of menopause very differently. Some may be bothered mostly by hot flashes, others by vaginal dryness, and still others by sleep disturbances.

If your main problem is vaginal dryness, for example, your doctors may recommend an estrogen-containing gel or cream instead of pills. Most gels and creams contain low doses of estrogen and need to be applied only once or twice a week. Non-drug lubricants may also help. Hormone-containing vaginal rings are another option. The rings have the advantage of convenience: they are inserted and left in place for three months, and some can be changed by a woman herself. (Vaginal creams and rings still release estro-



gen into the blood stream and thus the risks associated with hormone treatment are still presumed.)

If, however, you are struck with many or all the symptoms of menopause, your doctor is more likely to recommend that you consider a hormone pill or patch.

As to severity, if your symptoms are mild and not that bothersome, there may be *no reason to treat them at all*. First, they will go away or ease over time. And they may be controllable with lifestyle or environmental adjustments – such as sleeping in a cool room and wearing loose-fitting layers of clothes. The box on page 8 contains some of these adjustments. Doctors differ in their judgments in prescribing hormones for women with minimal or mild symptoms. Many flat out decline to; others believe it's safe. So, your discomfort level, tolerance, and circumstances can and should help guide treatment.

Generally, you may be a candidate for hormone treatment if:

- Your symptoms are reducing your quality of life or creating real difficulties (such as preventing a good night's sleep for days or weeks on end).
- Lifestyle changes don't ease your symptoms.

Your and Your Family's Medical History

This may be the most important criterion guiding your choice of treatment. If you have a personal or family history of heart disease, stroke, or cancer of the breast, uterus or ovaries, *you are best advised to avoid hormone therapy*.

Of course there are extenuating circumstances. If you are among the 20% of women who have severe debilitating menopausal symptoms, some doctors may be comfortable trying hormones out for short periods even if you have a history of these conditions. You should discuss the benefits and risk carefully with your doctor.

Although hormones raise the risk of dementia, a family history of early dementia is usually not a factor that should prevent short-term (one to two years) hormone treatment. That's because the risk appears to be only for women aged 65 and over. The evidence to date suggests that younger women (50 to 55) do not face any increased risk of dementia with short-term use of hormones.

Hysterectomy and Removal of Ovaries

Whether or not you have had a hysterectomy – removal of your uterus – will substantially affect your treatment options. Contrary to popular belief,

Hormone Treatment Side Effects

Most women experience one or more of these. About one in five stops taking hormones because of side effects.

- Abnormal vaginal bleeding (light or heavy periods, and sometimes both alternating)
- Nausea
- Breast tenderness
- Headaches
- Weight changes
- Dizziness
- Increased need to urinate
- Rash (with skin patches mostly)

hysterectomies that remove only the ovaries do not lead to menopause. However, some women have their ovaries removed at the same time as their uterus and this almost always causes sudden menopause in women who are premenopausal. Quite severe menopausal symptoms can result, and that usually requires treatment.

Women with intact uteruses and ovaries are almost always prescribed hormone pills or patches that contain *both* estrogen and progestin. That's because studies have convincingly shown that such women have a much higher risk of endometrial cancer when treated with estrogen alone. (The endometrium is the lining of the uterus.)

This means that women with intact uteruses must be treated with a regimen (estrogen plus a progestin) that poses a higher risk of other ill effects, such as heart disease and stroke. As you can glean from Table 2 on page 13 and the discussion below, estrogen-only pills, patches, and creams carry fewer risks and are generally considered to be safer.

However, on balance, protection against endometrial cancer is seen as well worth the relatively low risk of other problems for women who require hormone treatment.

Your Risk of Heart Disease, Certain Kinds of Cancer, Osteoporosis

Certain factors and behaviors increase your chances of being at risk for the adverse effects of female hormone treatment. Most are well known: smoking, lack of exercise, excess body weight, poor diet, and excess consumption of alcoholic beverages. But you may also have high blood pressure, elevated cholesterol, or diabetes. All of these conditions put you at higher risk of stroke, heart disease, and heart attack to begin with.

Taking hormones will add to those risks. That's why your doctor may (and should) ask about your risk factors and family history. There's no simple formula. But in general, the more risk factors you have for heart disease and stroke (for example, if you smoke, have diabetes, and high cholesterol), the higher your risk if you take hormones.

Your Tolerance of Risk

Understanding medical risk is not easy. For example, you may read a news report that says that something caused a 50% increase in the risk of cancer or heart disease. That sounds scary. But it could apply to the risk increasing from 1 chance in 100 to 1.5 chances in a 100. Or it could apply to the risk increasing from 50 chances in a 100 to 75 chances in 100. Big difference.

In the case of hormone treatment, the Women's Health Initiative (WHI) study showed the risks associated with hormone therapy going up by around 30%. But the risk started out very low. We present a sampling of the numbers on the next page.

People differ in their psychological response to disease or treatment statistics. You may feel that any elevated risk of developing an illness or dying *from taking a drug* is totally unacceptable while another person may think a small risk of problems is worth it if a drug brings relief.

With this in mind, here's a sampling of what the Women's Health Initiative study found *for every 10,000 women* taking an estrogen-progestin combination drug (Prempro) after 5 years of continuous use, compared to those taking a placebo or dummy pill:

- 8 more cases of breast cancer
- 7 more cases of heart disease
- 8 more strokes
- 18 more cases of blood clots
- 5 fewer hip fractures
- 6 fewer cases of colorectal cancer.

The study also found that for every year of use, 23 more women aged 65 and over taking hormones developed dementia. For every 10,000 women taking estrogen-only hormone pills over almost 7 years, there were:

- 12 more strokes
- 6 more cases of blood clots
- 5 fewer cases of heart disease
(could have statistically been due to chance)
- 1 more case of colorectal cancer
(could have statistically been due to chance)
- 7 fewer cases of breast cancer
(could have statistically been due to chance)
- 6 fewer cases of hip fractures
- 12 more cases of dementia

There's another statistical way to portray what happened to the women in the WHI study. For women taking estrogen plus progestin, their *combined* risk of heart disease, breast cancer, stroke, and blood clots was:

- 1 in 1000 over 1 year
- 1 in 200 over five years
- 1 in 100 over 10 years

For women taking estrogen-only pills, their combined risk for the same adverse outcomes was:

- 0.3 in 1,000 over 1 year

- 1.5 in 1,000 over 5 years
- 3 in 1,000 over 10 years

There are two other very important factors to consider as you weigh the risks of taking hormones: how long to take them and at what dose.

The risks cited above come from studies that followed women taking hormones for an average of four years. For some conditions, the higher risk appeared within a year or so (blood clots, heart disease and stroke). Risk for other conditions, such as breast cancer, did not show up until later.

The general consensus is that there is no absolute "safe period" – say a year or two – in which there is no excess risk. However, the risk of the problems associated with hormones increases the longer you take them.

Treatment with hormones today involves use of lower doses than in the past. Experts and doctors are assuming that lower doses will reduce the risk of ill effects over the long-term. Medically and biologically that makes sense. However, it has *not yet been proven*. A gathering of experts in March 2005 sponsored by the National Institutes of Health made the following relevant statement in their final report: "Little is known about major adverse events that could be associated with 3-year to 5-year exposures to low-dose estrogen and progestins."

Considering both these issues – duration of use and dose – most doctors today usually prescribe hormones *at the lowest dose that relieves your symptoms and for the shortest duration*. Indeed, like many women, you may only need a drug for a year or two. However, some women who want to stop hormone treatment find that symptoms return and that they can not function as they want without the medicines. Many doctors today are open to continuing treatment for such women for another year or two or more.

Your Personal Circumstances

Other factors may affect your decision about hormone use. For example, if you are not sexually active, vaginal dryness – if it does not cause irritation and itching – may not be something that bothers you. If

you live in the hot south, the environment may well exacerbate the discomfort of your hot flashes and night sweats – even if you have air conditioning. More than many other classes of prescription drugs, hormone treatment involves choices that are driven by your risks, personal preferences, and circumstances. Your doctor will hopefully help you sort all this out. But more than likely you will have to use other resources.

Finally, your tolerance of the side effects that hormone treatment can cause – such as breast tenderness and abnormal vaginal bleeding – may not be a factor in your decision to try them, but it may well be a factor in your decision whether to keep taking them, or try them again if your symptoms return. Thus, a critical decision once you start taking hormones is whether the side effects outweigh the benefits in symptom relief. (See the box on page 11 for a list of common side effects.)

Table 2. The Risks and Benefits of Hormone Therapy

Condition or Disease	Increased or Decreased Risk with Estrogen + Progestin ¹	Increased or Decreased Risk with Estrogen Alone ¹
Breast cancer	Increased	Not certain ²
Stroke	Increased	Increased
Heart disease and heart attack	Increased	Not certain ²
Blood clots (legs, lungs)	Increased ³	Increased
Colorectal cancer	Decreased ³	No difference ²
Uterine cancer	No difference ²	Increased
Endometrial cancer	No difference ²	Increased
Osteoporosis or Bone Fractures	Decreased	Decreased
Dementia	Increased	Increased

Source: *Facts About Menopausal Hormone Therapy*, National Institutes of Health, Pub No 05-5200. Revised June 2005.

1. Based on Women's Health Initiative Study, 2002. Study enrolled healthy women so risk may be greater if other risk factors are present.

2. "Not certain" means studies don't allow conclusive statement of risk: studies are ongoing. Some increased risk may exist. "No difference" means neither increased nor decreased risk was found. Based on results of Women's Health Initiative.

3. Not statistically significant.

Choosing Hormone Treatment — Our *Best Buy* Picks

All the hormone products are effective at reducing the symptoms of menopause. And studies have found low-dose formulations just as effective. That's significant because they may carry lower risks than the doses used in the past. Studies to date have mostly focused on hot flashes and night sweats. They have consistently found that 70% to 90% of women who have hot flashes and night sweats experience an average 75% reduction in these symptoms. Studies have also found that all the hormone pills, patches and creams reduce vaginal dryness. (*Remember, the creams are primarily used to treat vaginal dryness.*)

The existing scientific evidence does not indicate that any one form of estrogen or estrogen plus progestin is more effective than any other in reducing the discomforts of menopause. In general, the patches produce results similar to pills. Hormone-containing creams and gels were similarly effective at relieving vaginal dryness, but are usually not as effective in reducing hot flashes, night sweats, or sleep problems.

Although all the FDA-approved estrogen preparations have been shown effective at reducing bone loss, one to two years of treatment usually does not produce any significant impact. Typically, a lowered incidence of bone fractures is only seen after many years of hormone use. None of the hormone products has been shown any more effective at reducing bone loss than any other. Importantly, studies comparing prescription drugs specifically developed to reduce bone loss show that they do so more effectively than hormone treatment and with less risk.

Should your doctor and you decide that hormone treatment is appropriate and needed, your choice of a product and its dose will be based mainly on your symptoms and circumstances, your medical history, past treatment of your symptoms, your preference for pill or a patch, and others medicines you are taking. Be sure to tell your doctor about all the other medicines you are using, including nonprescription medicines. Some medicines interact adversely with hormones and that could well affect his or her choice of a hormone treatment.

There is emerging evidence that esterified estrogen pills—for example, Estratab and Menest—may carry a lower risk of blood clots and strokes than conjugated

equine estrogen. While this evidence is not yet conclusive, we factor it into our *Best Buy* selections below.

Taking effectiveness, safety, the choice for mode of delivery, and cost into account, we have chosen the following as *Consumer Reports Best Buy Drugs* for the treatment of menopausal symptoms:

- *Generic estradiol pills*
- *Gynodiol pills (estradiol)*
- *Estratab or Menest pills (esterified estrogen)*
- *Generic medroxyprogesterone pills (when a progestin pill is needed)*
- *Generic estradiol patch*
- *Alora patch*
- *Vivelle or Vivelle Dot patch*
- *Premarin Cream (conjugated equine estrogen)*
- *Ogen Cream (estriopipate)*
- *FemRing (estradiol)*
- *Estring (estradiol)*

All these are as effective as the other hormone medicines, but less expensive. (See Table 3 on the next page.) In particular, the two estradiol pills could save you \$300 to \$450 a year out of pocket compared to brand name Premarin, one of the largest selling and most-promoted products in this class. Similarly, if you choose an estrogen patch, our *Best Buys* could save you up to \$400 a year over the higher-priced products.

We were unable to choose a *Best Buy* in the categories of estrogen plus progesterone pills or skin patches. Studies do not indicate that any of the medicines in these two categories is any better than any of the others and their prices are in the same ballpark. Among vaginal creams, Premarin is the least expensive on average and among the most widely prescribed. Because of the relative similarity in pricing, we chose Ogen as another *Best Buy* option.

Among the progesterone-only pills, generic medroxyprogesterone at both low and high doses is the *Best Buy* over competitor medicines.

Table 3. Hormones Cost Comparison

Generic Name	Brand Name(s) ¹	Dose Ranges	Frequency of Use ²	Average Monthly Cost ³
Estrogen-only pills				
Estradiol	Estrace	0.5-2.0mg	1 daily	\$32-\$45
CR BEST BUY Estradiol	Generic	0.5-2.0mg	1 daily	\$6-\$14
CR BEST BUY Estradiol	Gynodiol	0.5-2.0mg	1 daily	\$8-\$16
Conjugated equine estrogen	Premarin	0.3-2.5mg	1 daily	\$34-\$52
Synthetic conjugated estrogen	Cenestin	0.3-1.25mg	1 daily	\$33-\$39
CR BEST BUY Esterified estrogens	Estratab, Menest	0.3-2.5mg	1 daily	\$14-\$61
Estropipate	Ogen, Ortho-Est	0.625-2.5mg	1 daily	\$27-\$69
Estropipate	Generic	0.625-3.0mg	1 daily	\$9-\$23
Estrogen-only skin patches				
Estradiol	Climara	0.025-0.1mg per 24 hours	1 weekly	\$48-\$54
Estradiol	Estroderm	0.05-0.1mg per 24 hours	2 weekly	\$52-\$56
Estradiol	Esclim	0.025-0.1mg per 24 hours	2 weekly	\$46-\$51
Estradiol	Menostar	0.014mg per 24 hours	1 weekly	\$62
CR BEST BUY Estradiol	Vivelle, Vivelle Dot	0.025-0.1mg per 24 hours	2 weekly	\$32-\$59
CR BEST BUY Estradiol	Alora	0.025-0.1mg per 24 hours	2 weekly	\$31-\$53
CR BEST BUY Estradiol	Generic	0.05-1.0mg per 24 hours	1 weekly	\$29-\$37
Estrogen-only skin creams				
Estradiol	Estrogel	1.25 grams	once daily	\$40-\$49
Estradiol	Estrasorb	3.5 grams	once daily	\$47-\$62
Estrogen plus progestin pills				
Conjugated equine estrogen/medroxyprogesterone	Prempro, Premphase	0.3-0.625mg/1.5-5mg	1 daily	\$50-\$52
Estradiol plus norgestimate	Ortho-Prefest	1mg/0.09mg	1 daily	\$41-\$46

Table 3. Hormones Cost Comparison

Generic Name	Brand Name(s) ¹	Dose Ranges	Frequency of Use ²	Average Monthly Cost ³
Estrogen plus progestin pills (continued)				
Estradiol plus norethindrone	Activella	1mg/0.5mg	1 daily	\$47
Ethinylestradiol plus norethindrone	FemHRT	0.5mg/1mg	1 daily	\$49
Estrogen plus progestin skin patches				
Estradiol plus levonorgestrel	Climara Pro	0.045mg/0.015mg per 24 hours	1 weekly	\$53
Estradiol plus norethindrone	CombiPatch	0.05mg/0.14mg per 24 hours	2 weekly	\$51-53
Estrogen-only vaginal creams, tablets or rings				
 Conjugated equine estrogen	Premarin Cream	0.625mg/gram	1/2 to 1 gram a day	\$20-\$39 ⁴
 Estropipate	Ogen Cream	1.5mg/gram	1 to 2 grams a day	\$27-\$54 ⁴
Estradiol	Estrace Cream	1.5mg/gram	1 to 2 grams a day	\$41-\$81 ⁴
Estradiol tablet	VagiFem	0.025mg	1 per day for 2 weeks then 10 a month	\$34-\$50
 Estradiol	FemRing	0.05-0.1mg per 24 hours	1 every 3 months	\$42-\$48
 Estradiol	Estring	0.0075mg per 24 hours	1 every 3 months	\$42
Progestin pills				
Medroxyprogesterone	Cycrin, Provera	2.5mg	1 daily	\$27
Medroxyprogesterone	Cycrin, Provera	5mg to 10mg	1 per day part of month ⁵	\$20-\$25
 Medroxyprogesterone	Generic	2.5mg	1 daily	\$10
 Medroxyprogesterone	Generic	5mg to 10mg	1 per day part of month ⁵	\$15-\$21
Norethindrone	Aygestin	5mg	1 per day part of month ⁵	\$77
Progesterone	Prometrium	100mg, 200mg	Usually part of the month	\$48-\$89

1. Generic means that this line quotes the average price of available generics.

2. As typically prescribed. May vary and that will affect the cost. Prices for creams are calculated for common dose ranges.

3. Reflects nationwide average retail price in July 2005, rounded to nearest dollar. Monthly cost ranges reflect varying price of different doses. Lower doses are less expensive, higher doses more expensive. Principle data source: NDCHealth, a health-care information company. Additional pricing data from other sources.

4. Price range for these creams depends on how much is applied. Use is generally for 21 days of each month and price is calculated on that basis.

5. May also be used 1 per day for a full month. If so, price would be greater than listed.

The Evidence

This section presents more information on the effectiveness and safety of hormone treatment for menopausal symptoms.

This report is based primarily on a systematic analysis of the scientific evidence on hormone therapy for menopause. This analysis was conducted by the Drug Effectiveness Review Project (see page 20). Overall, close to 2,000 scientific papers were screened. In addition, pharmaceutical companies submitted 58 papers or data sets. The analysis focused on 42 controlled clinical trials which evaluated hormones as a treatment for hot flashes and night sweats. An additional 62 trials were evaluated which focused on hormones as a treatment for low bone density or to prevent bone fractures. We also consulted an analysis conducted by RegenceRx, a group affiliated with the Regence Group, a company that owns Blue Cross and Blue Shield plans in four states in the Pacific Northwest. That analysis, dated February 2005, systematically probed the findings of dozens of studies on hormone treatment conducted between January 1999 and January 2005.

How Effective Are Hormones?

Hormones have been conclusively shown to reduce the frequency and severity of hot flashes more successfully than other prescription or nonprescription medicines. The studies show a fair amount of consistency in their findings. Most have evaluated two forms of estrogen: conjugated equine estrogen and estradiol. But research has found that all the estrogen-containing pills and patches reduce hot flashes, night sweats, sleeping problems, and vaginal dryness.

Most studies measured the affect of hormone treatment on hot flashes and night sweats. Fewer assess the affect on vaginal dryness or atrophy (the thinning of tissues in the vagina). But generally, creams, gels and hormone-containing vaginal rings appear to work as well as hormone pills or patches in short term treatment of vaginal dryness and atrophy. That may be important for women whose main symptom or complaint is vaginal dryness and pain on intercourse.

The gels and creams also can reduce hot flashes and night sweats since the hormones they contain are absorbed into the body. But they may not be as

effective as pills and patches in reducing these symptoms. Few studies have compared these different routes of drug administration.

Likewise, there's no evidence that patches are any better than pills or vice versa. Both appear to work equally well in reducing symptoms. Thus, you could try one or the other based solely on your personal preference. However, be mindful that individuals differ and you may respond better to pills than patches or vice versa. The patches come in twice-weekly and once-weekly forms.

Some studies include sleep disturbance as a measure of a hormone drug's effect. No studies indicate that any one type of hormone treatment is better than another at helping you get a good night's rest. For the most part, sleep is improved when night sweats are reduced. But here, doctors often emphasize that keeping your room cool – especially in the summer – and not drinking caffeinated beverages at night can help a lot.

Four of the estrogen preparations (all except synthetic conjugated estrogen and estropipate) have been shown to be similarly effective at reducing the natural loss of bone that occurs in women after menopause. Additionally, conjugated equine estrogen and estradiol have been proven to reduce fractures associated with low bone density in women.

Studies show that other prescription drugs – including risedronate (Actonel), ibandronate (Boniva) and alendronate (Fosomax) – are usually superior to hormone treatment in preventing or treating low bone density or preventing bone fractures.

Women with intact uteruses face a higher risk of endometrial cancer if they use estrogen-only drugs. That is why many women who take hormones take one containing both an estrogen and a progesterone. Fortunately, studies convincingly show that adding progestin to their hormone regimen can help prevent the heightened risk of endometrial or uterine cancer. In addition, studies show that relatively low doses of progestin (either alone or in estrogen-progesterone combinations) are just as effective at lowering that risk.

How Safe Are Hormones?

This report has discussed at some length the potential adverse effects and long-term consequences of taking hormones. This section will elaborate a bit more on the side effects of hormones.

The most common side effects are heavier or lighter vaginal bleeding, thickening of the uterine lining, nausea and vomiting, breast tenderness, headache, weight change, and dizziness. Vaginal bleeding and breast tenderness are consistently reported by women and tend to be the most bothersome. But the precise rates of these effects differ in the studies done to date. In one analysis, for example, the number of women experiencing breast tenderness ranged from 10% to 19%. The number of women experiencing heavy vaginal bleeding ranged from 22% to 37%.

You may face a tough decision if hormone side effects become intolerable. In studies, the treatment “drop out” rates vary but generally between one in four and one in five women stop taking hormones because of the side effects. In general, women who took higher doses had more, or more severe, side effects and were more likely to stop taking their medicines. Thus, the practice in recent years of prescribing lower doses may reduced your risk of suffering side effects.

Studies do not show that any one type of hormone treatment – or means of taking hormones, patches versus pills, for example – is an better than any other when it comes to the frequency of side effects. However, if you do have side effects that compel you to want to stop treatment, your doctor may try you on another medicine. He or she may also lower the dose of hormones you are taking if you are not already taking the lowest dose possible.

Some studies have found that conjugated equine estrogen, either alone or with progestin, can increase the risk of urinary incontinence and worsen it in women who were already experiencing it. If you have this side effect, you may want to talk with doctor about trying something else.

Estrogens can interact with other medicines to increase the risk of problems. For example, women taking the blood thinner warfarin (coumadin) are already at high risk for blood clots and thus should not take

hormones. Other medications can limit blood levels of estrogen, such as antibiotics, antacids, and fiber aids such as Metamucil and Citracel.

Race and Ethnic Factors

Women of differing ethnic backgrounds experience menopause differently. For example, Asian women appear to experience fewer hot flashes than Hispanic, African American, or Caucasian women in the United States. Asian women living in Asia also have more osteoporosis, but fewer hip fractures than Caucasian women.

Unfortunately, almost all the research to date on the relief of menopausal symptoms has been conducted primarily on Caucasian women. In addition, study results have not been separated out by race or ethnic factors. Thus, while it’s known that the experience of menopause and rates of osteoporosis and fracture differ by race and culture, we do not know how estrogen’s effectiveness and safety vary in these subpopulations.



Talking with Your Doctor

It's important for you to know that the information we present here is not meant to substitute for a doctor's judgment. But we hope it will help your doctor and you arrive at a decision about which hormone drug is best for you, and which gives you the most value for your health care dollar.

Bear in mind that many people are reluctant to discuss the cost of medicines with their doctors and that studies show doctors do not routinely take price into account when prescribing medicines. Unless you bring it up, your doctors may assume that cost is not a factor for you.

Many people (including physicians) also believe that newer drugs are always or almost always better. While that's a natural assumption to make, the fact is that it's not true. Studies consistently show that many older medicines are as good as, and in some cases better than, newer medicines. Think of them as "tried and true," particularly when it comes to their safety record. Newer drugs have not yet met the test of time, and unexpected problems can and do crop up once they hit the market.

Of course, some newer prescription drugs are indeed more effective and safer. Talk with your doctor about the pluses and minuses of newer versus older medicines, including generic drugs.

Prescription medicines go "generic" when a company's patents on a drug lapse, usually after about 12 to 15 years. At that point, other companies can make and sell the drug.

Generics are almost always much less expensive than newer brand name medicines, but they are not lesser quality drugs. Indeed, most generics remain useful medicines even many years after first being marketed. That is why today about 47% of all prescriptions in the U.S. are for generics.

Another important issue to talk with your doctor about is keeping a record of the drugs you are taking. There are several reasons for this:

- First, if you see several doctors, each may not be aware of medicines the others have prescribed.
- Second, since people differ in their response to medications, it is very common for doctors to prescribe several medicines before finding one that works well or best.
- Third, many people take several prescription medications, non-prescription drugs and dietary supplements at the same time. These can interact in ways that can either reduce the benefit you get from the drug, or be dangerous.
- And fourth, the names of prescription drugs — both generic and brand — are often hard to pronounce and remember.

For all these reasons, it's important to keep a written list of all the drugs and supplements you are taking, and to periodically review this list with your doctors.

Always be sure, too, that you understand the dose of the medicine being prescribed for you and how many pills you are expected to take each day. Your doctor should tell you this information. When you fill a prescription at the pharmacy, or if you get it by mail, you may want to check to see that the dose and the number of pills per day on the pill bottle match the amounts that your doctor told you.

How We Picked the *Best Buy* Drugs for Menopausal Symptoms

Our evaluation is based on an independent scientific review of the evidence on estrogen-containing hormone drugs in the treatment of menopausal symptoms and bone loss. A team of physicians and researchers at Oregon Health & Science University Evidence-based Practice Center conducted the analysis as part of the Drug Effectiveness Review Project, or DERP. DERP is a first-of-its-kind 15-state initiative to evaluate the comparative effectiveness and safety of hundreds of prescription drugs.

A synopsis of DERP's analysis forms the primary basis for this report. A consultant to *Consumer Reports Best Buy Drugs* is also a member of the Oregon-based research team, which has no financial interest in any pharmaceutical company or product. The full DERP review of estrogen-containing drugs is available at <http://www.ohsu.edu/drugeffectiveness/reports/final.cfm>. (This is a long and technical document written for physicians.)

The Oregon-based research team also conducted a review of studies on other methods of treating menopausal symptoms. This was done for the National Institutes of Health and used in May 2005 by an expert panel to make recommendations on hormone treatment for menopausal symptoms. We used some of the materials from this review and the NIH recommendations as resources for this report. The NIH recommendations can be found at http://consensus.nih.gov/ta/025/menopause_final_052505.htm

We also used as a resource an analysis of hormone drugs conducted by The Regence Group – a company

that operates Blue Cross and Blue Shield insurance plans in Oregon, Utah, Idaho and Washington. In addition, we adapted material from *Consumer Reports Medical Guide*, an online subscription Web site recently launched by Consumers Union and *Consumer Reports*. (Go to www.ConsumerReportsMedicalGuide.org.)

The drug costs we cite were obtained from a health-care information company which tracks the sales of prescription drugs in the U.S. Prices for a drug can vary quite widely, even within a single city or town. All the prices in this report are national averages based on sales of prescription drugs in retail outlets. They reflect the cash price paid for a month's supply of each drug in July 2005.

Consumers Union and *Consumer Reports* selected the *Best Buy Drugs* using the following criteria. The drugs (and doses) had to:

- Be as or more effective than others to treat menopausal symptoms
- Have a safety record equal to or better than other drugs used to treat menopausal symptoms
- Have an average price for a 30-day supply that is lower than the most costly prescription drug meeting the first two criteria.

The *Consumers Reports Best Buy Drugs* methodology is described in more detail in the Methods section at www.CRBestBuyDrugs.org.

About Us

Consumers Union, publisher of *Consumer Reports* magazine, is an independent and nonprofit organization whose mission since 1936 has been to provide consumers with unbiased information on goods and services and to create a fair marketplace. It is solely responsible for the content of this report. Its main Web sites are www.consumersunion.org and www.consumerreports.org.

Consumer Reports Best Buy Drugs is a public education project administered by Consumers Union. Two outside sources of generous funding made the project possible. They are a major grant from the Engelberg Foundation, a private philanthropy, and a supporting grant from the National Library of Medicine, part of the National Institutes of Health. A more detailed explanation of the project is available at www.CRBestBuyDrugs.org.

We followed a rigorous editorial process to ensure that the information in this report and on the *Consumer Reports Best Buy Drugs* website is accurate and describes generally accepted clinical practices. If we find, or are alerted to, an error, we will correct this as quickly as possible. However, *Consumer Reports* and its authors, editors, publishers, licensors and any suppliers cannot be responsible for medical errors or omissions, or any consequences from the use of the information on this site. Please refer to our user agreement at www.CRBESTBUYDRUGS.org for further information.

Consumer Reports Best Buy Drugs should not be viewed as a substitute for a consultation with a medical or health professional. This report and the information on www.CRBESTBUYDRUGS.org are provided to enhance your communication with your doctor, rather than to replace it.

Sharing this Report

This copyrighted report can be freely downloaded, reprinted and disseminated for individual noncommercial use without permission from Consumers Union or *Consumer Reports*® magazine as long as it clearly attributed to *Consumer Reports Best Buy Drugs*™. We encourage its wide dissemination as well, for the purpose of informing consumers. However, Consumers Union does not authorize the use of its name or materials for commercial, marketing or promotional purposes. Any organization interested in broader distribution of this report should contact Wendy Wintman at wintwe@consumer.org. *Consumer Reports Best Buy Drugs*™ is a trademarked property of Consumers Union. All quotes from the material should site *Consumer Reports Best Buy Drugs*™ as the source.

©Consumers Union 2005

References

1. Landau, Carol and Cyr, Michele G., *The New Truth About Menopause*, 2003, St. Martins Griffin Press, New York.
2. Love, Susan M., *Dr. Susan Love's Menopause and Hormone Book*, Revised and Updated Edition, 2003, Three Rivers Press, New York.
3. National Institutes of Health State-of-the-Science Conference on Management of Menopause-Related Symptoms, Conference final statement (March 23, 2005). Available at http://consensus.nih.gov/ta/025/menopause_final_052505.htm.
4. *Facts About Menopausal Hormone Therapy*, National Institutes of Health, U.S. Department of Health and Human Services, NIH Publication Number 05-5200. (Revised Edition, June 2005)
5. *Menopausal Hormone Use and Cancer: Questions and Answers*, National Cancer Institute (Updated July 18, 2005). Available at http://cis.nci.nih.gov/fact/3_76.htm.
6. *Hormone Replacement Therapy Therapeutic Class Review*, a report by RegenceRx, Portland, Oregon. (February 2005).
7. Petitti, D.B., "Some surprises, some answers, and more questions about hormone therapy," *JAMA* (July 13, 2005) Vol. 294, No 2:245-246.
8. Petitti, D.B. "Hormone replacement therapy for prevention: more evidence, more pessimism," *JAMA* (July 3, 2004) Vol. 288, No 1:99-101.
9. Ockene, J.K. et al., "Symptom experience after discontinuing use of estrogen plus progestin," *JAMA* (July 13, 2005) Vol. 294, No 2:183-193.
10. Col, N.F. et al., "Short-term menopausal hormone therapy for symptom relief: an updated decision model," *Arch. Intern. Med.* (August 9/23, 2005) Vol. 164:1634-1640.
11. Col, N.F., "The impact of risk status, pre-existing morbidity, and polypharmacy on treatment decisions concerning menopausal symptoms," In press, November 2005.
12. Smith, N.L., "Esterified estrogens and conjugated equine estrogens and the risk of venous thrombosis," *JAMA* (October 6, 2004) Vol. 292, No 13:1581-1587.
13. Krieger, N. et al, "Hormone replacement therapy, cancer, controversies, and women's health: historical, epidemiological, biological, clinical, and advocacy," *J. Epidem Community Health* (2005) Vol. 59:740-748.
14. Nedrow, A., Systematic Review of Alternatives to Estrogen in the Management of Menopausal Symptoms, slide packet, undated. (Center for Women's Health, Oregon Health & Science University).
15. Boodman, S.G., "Hormones Weather 'the Change,'" *The Washington Post* (September 20, 2005): F1.
16. Gorman, C. and Park, A., "About Hormones" *TIME* magazine (July 22, 2002):33-40
17. Cowley, G and Springen, K. "The End of the Age of Hormones," *Newsweek* magazine (July 22, 2002): 38-45.
18. Al-Azzawi, F. and Buckler, H.M.. "Comparison of a novel vaginal ring delivering estradiol acetate versus oral estradiol for relief of vasomotor menopausal symptoms." *Climacteric*, 2003;6(2):118-127.
19. Anderson G.L. et al., "Effects of Estrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures: The Women's Health Initiative Randomized Trial." *JAMA* 2003;290:1739-1748.
20. Archer D.R. et al., "Estrace vs. Premarin for treatment of menopausal symptoms: dosage comparison study." *Advances in Therapy*. 1992;9(1):21-31.
21. Buckler H.A., et al., "The effect of a novel vaginal ring delivering oestradiol acetate on climacteric symptoms in postmenopausal women." *BJOG: International Journal of Obstetrics & Gynaecology*. 2003;110(8):753-759.
22. Cauley J.A. et al., "Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial." *JAMA*. 2003;290(13):1729-1738.
23. Chlebowski R. et al., "Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women: the Women's Health Initiative Randomized Trial." *JAMA* 2003;289:3243-3253.
24. Curb J.D., et al., "Outcomes Ascertainment and Adjudication Methods in the Women's Health Initiative." *Ann Epidemiol* 2003;13:S122-S128.
25. Cushman M. et al., "Estrogen Plus Progestin and Risk of Venous Thrombosis." *JAMA* 2004;292(13):1573-1580.
26. Gordon S.F. et al. "Efficacy and safety of a seven-day transdermal estradiol drug-delivery system: comparison with conjugated estrogens and placebo." *Int J Fertil Menopausal Stud*. 1995;40(3):126-134.
27. MacLennan A.H. et al., "Oral estrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes." *Cochrane Database Syst Rev*. 2004.
28. Miller, J. et al. Postmenopausal Estrogen Replacement and Risk for Venous Thromboembolism: A Systematic Review and Meta-Analysis for the U.S. Preventive Services Task Force." *Ann Intern Med*, May 2002; 136: 680.
29. Nelson H.D. et al, *Drug Class Review on Estrogens*. Final Report: [http://www.ohsu.edu/drug-effectiveness/reports/documents/Estrogens Final Report u2.pdf](http://www.ohsu.edu/drug-effectiveness/reports/documents/Estrogens%20Final%20Report%20u2.pdf)
30. Nelson H.D. et al., "Management of Menopause-Related Symptoms. Summary, Evidence Report/Technology Assessment No. 120." Prepared by the Oregon Evidence-based Practice Center, under Contract No. 290-02-0024. AHRQ Publication No. 05-E016-1. Rockville, MD: Agency for Healthcare Research and Quality. (March 2005).
31. Nelson H.D. "Commonly Used Types of Postmenopausal Estrogen for Treatment of Hot Flashes: Scientific Review." *JAMA*, April 2004; 291: 1610 - 1620. .
32. Nelson H.D., et al., "Postmenopausal Hormone Replacement Therapy: Scientific Review." *JAMA*, Aug 2002; 288: 872.
33. Rossouw J.E. et al., "Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial." *JAMA* (July 17, 2002) Vol. 288(3): 321-333.
34. Saure A. et al., "A double-blind, randomized, comparative study evaluating clinical effects of two sequential estradiol-progestogen combinations containing either desogestrel or medroxyprogesterone acetate in climacteric women." *Maturitas*. 2000;34(2):133-142.
35. Studd J.W. et al., "Efficacy and tolerance of Menorest compared to Premarin in the treatment of postmenopausal women." *Maturitas*. 1995;22(2):105-114.