The Hormone Therapy Story

Several prescription drugs are available to help relieve menopause-related symptoms and decrease long-term health risks across the menopause transition and beyond. This section focuses on hormone therapies—the prescription drugs used most often when treating menopause symptoms.

Various terms and an “alphabet soup” of acronyms are used to describe hormone therapy and they can sometimes be confusing. Here is a brief primer:

• ET means estrogen therapy. Treatment of menopause-related conditions with estrogen was once called estrogen replacement therapy (ERT). However, the term “replacement” is a misnomer because this therapy provides only a fraction of the estrogen once produced by the ovaries; estrogen supplementation is a more accurate description. The FDA now mandates use of the term estrogen therapy (ET).

• EPT means combined estrogen plus progestogen therapy. Estrogen is the hormone in this duo that provides the most symptom relief. Progestogen is added to protect the uterus from estrogen stimulation.

• HT means hormone therapy, technically encompassing both ET and EPT. The FDA, however, refers to EPT as HT.

A wide variety of ET and EPT products are government approved in the United States and Canada for the treatment of moderate to severe hot flashes and vaginal atrophy, symptoms discussed earlier in this guidebook.
Many of these products are also approved for the prevention of osteoporosis, if used long term (see more about osteoporosis on page 36). Some studies suggest that ET/EPT has beneficial effects on other physical changes sometimes observed around menopause, such as sleep disturbances and mood swings (see The Changing Body on page 7 for more). For some women, hormone therapy has a positive effect on quality of life—they report that they simply “feel good” while on hormones. ET/EPT is an option women should consider for the relief of menopause-related symptoms. If bone health is an issue, hormones can help. If particular conditions need treatment or if ET/EPT is not an option, often more targeted therapies are available, usually one drug for each condition. Like all therapies, hormone therapy is associated with risks, and these must be considered when making a decision about therapy (see ET/EPT Risks on page 54).

A number of factors should be considered when a woman, with the guidance of her healthcare provider, decides which plan is right for her. There is no “one size fits all” approach to menopause therapy or hormone therapy.

**Estrogen Therapy**

Estrogen therapy (ET) has been widely studied and used for more than 50 years by millions of women. Many kinds of estrogen therapy are available in the United States and Canada to treat menopause-related symptoms (see Chart on page 49). A variety of estrogen types, delivery systems, and dosage strengths give each woman a better chance to find which option is best for her. Less-expensive generic products are available for some estrogen types. In special cases, estrogen therapies can be custom-made by a compounding pharmacist following a healthcare provider’s prescription (see more about custom compounding on page 51). Remember, finding the right regimen may require time, patience, and trying different prescriptions.

Estrogen therapy is available in two main dosage forms—systemic and local.

- **Systemic dosage form.** When used orally (tablet), through the skin (patch, gel, or emulsion), or as an injection, estrogen circulates throughout the bloodstream and to all parts of the body, affecting many different tissues. Almost all of the systemic forms have the potential to provide the full range of benefits and risks associated with ET. The one exception is the ultralow-dose estradiol skin patch (Menostar); it is FDA approved only for osteoporosis prevention in postmenopausal women. Women with a uterus who use systemic ET typically use another hormone (progestogen) to protect the uterus from endometrial cancer.

- **Local (nonsystemic) dosage form.** Most current vaginal estrogen products (cream, ring, or tablet) are considered “local” therapy (affecting only a specific or localized area of the body). With a low-dose local form, only a very small amount of estrogen circulates through the body and the bloodstream. Therefore, these vaginal ET products do not relieve hot flashes or lower osteoporosis risk. The estradiol acetate ring (Femring), a vaginal form that is strong enough to be systemic, is an exception; it is approved in the United States for treating hot flashes as well as vaginal atrophy. It is not clear whether lower dose local ET regimens increase the risk for endometrial cancer. However, with higher doses of local ET, enough estrogen may get into the blood to possibly harm the uterus. Thus, adding progestogen is sometimes recommended.
### Estrogen Products Used for Menopause in the United States and Canada

<table>
<thead>
<tr>
<th>Estrogen Type</th>
<th>Oral Tablet</th>
<th>Skin Patch/Gel/Emulsion</th>
<th>Vaginal Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>conjugated estrogens (formerly conjugated equine estrogens)</td>
<td>Premarin</td>
<td>Not available</td>
<td>Premarin Vaginal Cream</td>
</tr>
<tr>
<td>synthetic conjugated estrogens, A</td>
<td>Cenestin*</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>synthetic conjugated estrogens, B</td>
<td>Enjuvia*</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>esterified estrogens</td>
<td>Menest*</td>
<td>Not available</td>
<td>Neo-Estrone Vaginal Cream**</td>
</tr>
<tr>
<td>estropipate (formerly piperazine estrone sulfate)</td>
<td>Ortho-Est*</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>estradiol (sometimes called 17β-estradiol)</td>
<td>Estrace</td>
<td>Alora*</td>
<td>Estring (vaginal ring)</td>
</tr>
<tr>
<td>estradiol hemihydrate</td>
<td>Not available</td>
<td>Not available</td>
<td>Vagifem (vaginal tablet)</td>
</tr>
<tr>
<td>estradiol acetate</td>
<td>Femtrace*</td>
<td>Not available</td>
<td>Femring* (vaginal ring)†</td>
</tr>
</tbody>
</table>

* Available in the United States but not Canada.
** Available in Canada but not the United States.
† Systemic dose, although vaginal administration.
Another hormone, progestogen, has sometimes been used alone during perimenopause to treat symptoms such as hot flashes, to manage abnormal uterine bleeding, or to counter “estrogen dominance” that can occur in some women as estrogen levels fluctuate to high levels during this transition. But the most common use for progestogen is to protect against uterine cancer associated with ET.

Using ET alone for 5 or more years can triple the risk of developing cancer of the uterus, but adding progestogen prevents the uterine lining (endometrium) from thickening and reduces the cancer risk to the level of using no hormones. Women who have had their uterus removed (hysterectomy) are not at risk for uterine cancer and thus have no reason to take progestogen with ET.

Combined estrogen-progestogen therapy and progestogen-alone therapy are also used as birth control pills. However, the doses used for menopause are not high enough to provide birth control, so contraceptive methods are required until a woman has had 12 months without a natural period.

**Progestogen Types**

There are various progestogen options and they allow tailoring to a woman’s unique needs (see Chart on this page). Not all are government approved for EPT, and some are legally prescribed “off-label” (see Box on page 11). These include progesterone (bioidentical to the hormone produced by the ovaries) and several different progestins (compounds synthesized to act like progesterone). As with estrogen, progestogens are available in custom-made formulations prepared by a compounding pharmacist following a healthcare provider’s prescription (see more about custom compounding on page 51). Progesterone skin creams, whether custom-made from a prescription by a compounding pharmacy or purchased without a prescription, should not be used in EPT. No studies have been done that demonstrate that these skin creams protect the uterus from estrogen stimulation.

**EPT & Uterine Bleeding**

In most women, using a progestogen with estrogen causes the endometrium to be shed from the uterus as bleeding, similar to a

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**Progestogen Products Used for EPT in the United States and Canada**

<table>
<thead>
<tr>
<th>Progestogen Type</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progestin: Oral Tablet</strong></td>
<td></td>
</tr>
<tr>
<td>medroxyprogesterone acetate (MPA)</td>
<td>Provera</td>
</tr>
<tr>
<td></td>
<td>various generics</td>
</tr>
<tr>
<td>norethindrone (formerly norethisterone)</td>
<td>Micronor</td>
</tr>
<tr>
<td></td>
<td>Nor-QD*</td>
</tr>
<tr>
<td></td>
<td>various generics</td>
</tr>
<tr>
<td>norethindrone acetate</td>
<td>Aygestin*</td>
</tr>
<tr>
<td></td>
<td>various generics</td>
</tr>
<tr>
<td>norgestrol</td>
<td>Ovrette*</td>
</tr>
<tr>
<td>megestrol acetate</td>
<td>Megace</td>
</tr>
<tr>
<td></td>
<td>various generics</td>
</tr>
<tr>
<td><strong>Progestin: Intrauterine Device (IUD)</strong></td>
<td></td>
</tr>
<tr>
<td>levonorgestrel</td>
<td>Mirena</td>
</tr>
<tr>
<td><strong>Progesterone: Oral Capsule</strong></td>
<td></td>
</tr>
<tr>
<td>progesterone</td>
<td>Prometrium</td>
</tr>
<tr>
<td>(in peanut oil)</td>
<td></td>
</tr>
<tr>
<td><strong>Progesterone: Vaginal Gel</strong></td>
<td></td>
</tr>
<tr>
<td>progesterone</td>
<td>Prochieve 4%*</td>
</tr>
</tbody>
</table>

* Available in the United States but not Canada.
menstrual period, although fertility is not restored. Some women find this progestogen-induced bleeding very bothersome, but the bleeding often decreases or stops over time.

Newer dosage schedules that combine estrogen and progestogen daily eventually result in no uterine bleeding while still protecting the lining of the uterus. However, many women, particularly those recently past menopause, do have uterine bleeding or spotting during the first 6 months or more of these regimens. A woman should report any persistent irregular bleeding to her clinician right away.

**EPT Regimens**

Various EPT dosing schedules (often called “regimens”) can be used. These regimens include taking estrogen and progestogen separately or through convenient combination EPT products (see Chart on page 52). Each woman should feel comfortable exploring different options with her clinician to determine which is best for her. The most common EPT regimens are the following:

- **Cyclic EPT** provides estrogen for 25 days each month, adding progestogen on the last 10 to 14 days, followed by 3 to 6 days of no therapy. Thus, both hormones are “cycled.” The popularity of this regimen has waned because of uterine bleeding each month when the progestogen cycle ends (called “withdrawal bleeding”) and the possibility of hot flashes returning during the estrogen-free interval.

- **Continuous-cyclic EPT** (sometimes called sequential EPT) provides estrogen every day, with progestogen added for 10 to 14 days each month. As with cyclic EPT, this regimen causes uterine bleeding in about 80% of women when the progestogen cycle ends each month. However, bleeding gradually declines and stops in many women after a year or more.

- **Continuous-combined EPT** provides both estrogen and progestogen every day. With this EPT regimen, less uterine bleeding occurs (40% of women during the first 6 months), but the timing is less predictable. After a year of therapy, uterine bleeding stops in nearly 90% of women.

- **Intermittent-combined EPT** (provided by the brand Prefest) provides estrogen every day, then adds progestogen intermittently in cycles of 3 days on, 3 days off. Bleeding and endometrial protection are similar to that with a continuous-combined regimen.

- **A few healthcare providers are now prescribing estrogen every day, adding progestogen at longer intervals to lower exposure to progestogen. This “long-cycle” regimen needs further testing to confirm that it adequately protects the uterine lining.**

**Custom-Compounded Hormones**

Recently, there has been increased interest in custom-mixed (“custom-compounded”) hormone products—recipes containing one or more of various hormones in differing amounts, depending on the individual prescriber’s order. The recipe contains not only the active hormone (or hormones), but also other ingredients that either hold everything together (in the case of a rectal suppository, an under-the-tongue tablet, or an under-the-skin pellet) or provide a vehicle for applying the product onto the skin (such as a cream or gel) or into the body (such as a liquid for a nasal spray). These custom products have the benefit of individualized doses and mixtures of products that are not available commercially. However, risks have also been identified. Although the “active ingredients” (the raw estrogen and/or
progestogen components) are government approved, the mixtures are not, because they have not been studied to confirm that they are absorbed appropriately or provide predictable levels in blood and tissue. Thus, there is little or no scientific evidence about the effects of these hormones on the body, either good or bad.

Custom hormones have been promoted as being better or safer than other hormones that are available commercially. For instance, one popular mixture called Tri-Est contains three estrogens, including estriol—a type of estrogen not available in patented products. Unsubstantiated claims have been made that Tri-Est (or estriol alone) has the benefits of patented estrogen products without increasing certain risks, such as breast and uterine cancer. Although estriol is a weak estrogen, it can still have a stimulatory effect on the breast and uterine lining. Most information promoting these products as safer is not supported by good scientific research. Until more is known, women with a uterus who use estriol-containing products in any form except a low-dose vaginal cream for atrophy should also use a progestogen to protect the uterus. Studies have not determined what effect estriol has on the risk of breast cancer or cardiovascular disease.

Although many pharmacies have a long history of providing a wide range of compounded products, the fact that preparation methods vary from one pharmacist to another, and from one pharmacy to another, means that women may not receive consistent amounts of medication. Inactive ingredients may vary and there can be batch-to-batch differences. Reliable sterility and freedom from undesired contaminants are also concerns. Expense is also an issue, as some custom-compounded preparations tend to be more expensive and are not covered by insurance plans.

The bottom line: Custom-compounded hormones may relieve menopause symptoms, but should be used only by women who cannot tolerate commercially available preparations and who accept the risks. They should not be used to prevent osteoporosis.
Bioidentical Hormones

Sometimes custom-compounded hormones are referred to as “bioidentical hormones” or “natural hormones.” These terms mean different things to different people. To scientists and healthcare providers, bioidentical hormones are those that are chemically identical to the hormones produced by women (primarily in the ovaries) during their reproductive years. A woman’s body can make various estrogens (such as 17beta-estradiol, estrone, and estriol) as well as progesterone, testosterone, and other hormones. Thus, bioidentical hormone therapy can mean a medication that provides one or more of these hormones as the active ingredient.

Bioidentical hormones have been produced commercially to be chemically exact duplicates of naturally occurring hormones. Some of these hormones are made available in well-tested, government-approved, brand-name prescription drugs. Several FDA-approved drugs contain 17beta-estradiol (see Charts on pages 50 and 52), and those that are not taken orally remain in the body as 17beta-estradiol. Oral products break down into another estrogen type that is not bioidentical. There is one government-approved bioidentical progesterone product (see Chart on page 50). It is not necessary to custom-make a hormone product to have one that is bioidentical or natural.

Contraindications

Some women have contraindications to using ET/EPT. These are reasons not to use the treatment. In a few cases, the potential benefits may outweigh the potential risks, leading women with such contraindications to accept therapy after careful consideration. Government guidelines indicate that, in general, women who have the following conditions should not use ET/EPT. The guidelines do not make a distinction between systemic and local therapy, and advise that even local vaginal hormones should not be used in these instances. However, many experts think systemic and local hormone therapies have different risk profiles.

- Known or suspected pregnancy
- History of breast cancer
- History of hormone-sensitive cancer
- Unexplained uterine bleeding
- Liver disease (this especially applies to oral ET)
- History of blood clots
- Confirmed cardiovascular disease

Cigarette smoking is not a contraindication for ET/EPT, as it is with oral contraceptive use in women over age 35, but smokers are urged to stop before treatment starts for general health reasons.

Side Effects

Potential adverse side effects of systemic estrogen therapy are listed below.

- Uterine bleeding (starting or returning)
- Breast tenderness or pain (increased density and sometimes enlargement)
- Nausea
- Abdominal bloating
- Fluid retention in extremities
- Changes in the shape of the cornea of the eye (sometimes leading to contact lens intolerance)
- Headache (sometimes migraine)
- Dizziness
- Hair loss

So-called “natural” therapies are not without risk.
Low-dose local vaginal estrogen therapy has a similar set of possible side effects, and each type (cream, tablet, or ring) differs slightly. With all, the most often reported complaints include uterine bleeding, vulvovaginal discomfort, vaginal discharge or itching, breast tenderness, and nausea—which imply that these hormones might be initially systemically absorbed or too high a dose was used. A few women may be allergic to the plastic in the ring products. Some vaginal leakage may be noticed with the cream.

Potential progestogen side effects include uterine bleeding and some effects similar to those of PMS, including fluid retention, headache, breast tenderness, and mood changes, particularly with the synthetic progestins.

Systemic ET/EPT does not cause weight gain. However, some women do experience temporary weight gain from the side effect of water retention in the hands and feet. Systemic ET can also cause abdominal bloating with gaseous bowel distension, making the waist temporarily larger.

There is one “side effect” issue that is important to keep in mind when systemic ET/EPT is to be discontinued: stopping all at once often results in hot flashes. Gradually tapering the dose may be helpful, although this has not been proven. Experts don’t agree on the best way to stop ET/EPT. Local vaginal ET may be discontinued abruptly without any adverse effects.

Dealing with ET/EPT side effects. There are various strategies that women and their clinicians often use to deal with unwanted side effects of ET or EPT (see Box on page 55). However, in general, they have not been evaluated in clinical trials. Many side effects of therapy are temporary until a woman adjusts to the hormonal changes. Unless side effects are severe, a trial of 3 months of any hormone therapy is advised to see if they resolve. One strategy is appropriate for any side effect—stop hormones to see if hormones are the cause.

Risks

Literally hundreds of clinical studies have provided evidence that systemic estrogen therapy (with or without progestogen) relieves menopause symptoms. Use of hormone therapy should always be at the lowest effective dose and for the shortest amount of time consistent with treatment goals. This is to minimize exposure to the hormones, which have been associated with some serious risks.

It has been well documented for decades that using systemic ET alone can dramatically increase the risk of developing cancer of the uterus. However, it is also well known that using another prescription hormone—progestogen—with estrogen therapy (as EPT) reduces that risk to the level of taking no hormones. Thus, all women with a uterus who use systemic ET are advised to use progestogen (as EPT) as well, even when using estrogen therapy short term.

Low-dose, local ET for vaginal atrophy is associated with very few risks, even when used long term or initiated years after menopause. However, safety data on long-term use are not available. Higher doses could result in systemic levels, requiring consideration of progestogen therapy to protect the uterus.

The real concern about hormone safety is with long-term use of systemic ET or EPT—and concern about the risk for breast cancer is at the top of the list. Current scientific evidence supports a link between an increased risk
of breast cancer and EPT, particularly after several years of use. For example, in the large Women’s Health Initiative (WHI) study, EPT use increased the risk of breast cancer by 24% after 5 years of use. In statistical terms, this risk is small, about 8 more cases annually per 10,000 women using hormones compared with those not using hormones. Breast cancer risk did not increase in the segment of the trial that evaluated women who had a hysterectomy and who were using ET alone. In fact, risk actually declined 20% (7 per 10,000). Nonetheless, all ET and EPT products should be considered contraindicated in women with known or suspected breast cancer as well as in those with a history of breast cancer. Long-term use (or more than the 5-7 years studied) is also a concern. However, shorter term use of ET or EPT during perimenopause to relieve hot flashes and other menopause-related symptoms does not appear to increase breast cancer risk.

Previously, research indicated that using systemic ET/EPT lowered the risk of heart disease. But several large studies have clarified aspects of the impact of hormone therapy on heart health. It appears that if a woman uses hormone therapy before she has significant damage to her blood vessels (such as close to the time of menopause), her risk for developing heart disease might be reduced. However, if she already has vessel damage (which tends to occur as time away from menopause increases), hormones cannot protect her from heart disease—and will probably increase her risk, particularly of stroke. Timing of hormone therapy is crucial. But no woman should consider using hormone therapy solely for heart benefits.

Another serious concern when considering starting systemic hormone therapy many years after menopause is that of its effect on memory. The WHI study found that starting systemic EPT after age 65 should not be recommended, as it may increase the risk of dementia during 5 years of use. More research is needed to know the effects of ET started at various times after menopause.

Several trials have determined that hormone therapy with ET or EPT reduces the risk of fragile bones and fracture, especially with

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### Strategies to Help Relieve ET/EPT Side Effects

In general, all ET/EPT side effects may be relieved by lowering the dose of estrogen and/or progestogen, switching to another estrogen and/or progestogen (including progesterone), or changing to a continuous dosage schedule or a skin delivery system to avoid hormone fluctuations.

Other specific strategies include the following:

- **FLUID RETENTION.** Restrict salt intake, maintain adequate water intake, exercise, try a mild diuretic (either herbal or prescription).
- **BLOATING.** Restrict salt intake, maintain adequate water intake, exercise, try a mild diuretic (either herbal or prescription).
- **BREAST TENDERNESS.** Restrict salt intake, cut down on caffeine and chocolate.
- **HEADACHES.** Restrict salt, caffeine, and alcohol intake, ensure adequate water intake.
- **MOOD CHANGES.** Restrict salt, caffeine, and alcohol intake, ensure adequate water intake, exercise regularly.
- **NAUSEA.** Take oral estrogen tablets with meals or in the evening with a snack.
- **SKIN IRRITATION UNDER PATCH.** Keep site very clean, switch to a patch with a different adhesive, apply patch to a different area, change to oral estrogen.
adequate intake of calcium and vitamin D. Long-term use is required, since bone loss resumes after stopping therapy. When menopause symptoms are controlled or cease, continued hormone therapy can still be considered for bone effects—weighing its benefits and risks with alternate therapies.

As a result of the WHI data, the FDA and Health Canada require all estrogen-containing prescription therapies to carry a “black box” warning in their prescribing information about the adverse risks of ET/EPT. Although only two ET/EPT products were studied in WHI, Premarin and Prempro, in the absence of contrary data on other hormone products, the risks of all ET/EPT products should be assumed to be similar. There is no evidence that the use of “natural” or custom-compounded estrogens results in different risks.

**Weighing Benefits & Risks of ET/EPT**

As with all therapies, a woman who is considering hormone therapy must compare its potential benefits to its potential risks. And although short-term use is safer than long-term use, there is no time period of use that’s considered “safe.” Acceptable risk depends on a woman’s individual circumstances. Her decision will be largely influenced by the severity of her menopause-related symptoms, her risk factors for diseases such as osteoporosis, heart disease, and breast cancer, and her personal health and philosophy. She may be suffering from hot flashes that affect her quality of life, making risks more acceptable (particularly since hot flashes are typically short term and risks are low). Or she may be a healthy woman considering hormone use to stay healthy, such as by trying to prevent osteoporosis, making risks less acceptable (particularly since therapy must be long term and safe, and effective nonhormonal alternatives are available). Or maybe she wants to do both.

Each woman is in a unique situation. And her confusion is fueled by changing reports over the past decades regarding the effects and risks of hormone therapy. During these years, medical professionals have changed their views about the role of hormones as more research has been conducted. Experts agree that there is much they still have to learn. Although recent studies such as the WHI have provided some clarity for large populations, they don’t necessarily address all of the issues an individual woman faces. Only she, with the counsel of her healthcare providers, can do that.

Many factors will be part of a woman’s decision to use a particular hormone product—her age, her risks, her preferences, available treatment options, and the cost of the product. Each woman must decide if her potential benefits outweigh her potential risks. Only after examining and understanding her own situation and after a thorough consultation with her healthcare provider can a woman make the best treatment choice. A woman’s decision about hormone therapy may also change as more is learned through clinical trials and as personal situations and risk factors change.

**Different Women, Different Needs**

There is no single way to ensure the best possible quality of life around menopause and beyond. Each woman is unique. It is beneficial for a woman to invest time working with her healthcare professionals to create an individual health plan and to reevaluate and make therapeutic adjustments, not only as new therapies and guidelines are available, but also as the woman’s body continues to change in its own individual way.