Delfini Group ™, LLC

Evidence-based Solutions

Clinical Improvement Consults, Medical Education Training & Tools

Patient & Clinical Decision Aid – Menopause
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The information provided here is to assist patients and health care professionals understand about what the best available scientific evidence tells us about menopause.

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Our Mission –

To assist medical leaders, clinicians and other health care professionals by ~

- Bringing science into medical practice in an **easy-to-understand** way.
- Using **simplified methods** to help navigate the complexities of such areas as evidence-based medicine and other topics.
- Building **competencies** and **confidence** in improving medical care through our well received consultations, educational programs and tools.
- Providing inspiration to others to **improve** medical care and help bring about needed change.

Did you know?

1. Nearly **half** of all women experiencing menopause **do not** have significant menopausal symptoms such as hot flashes or vaginal dryness, which are thought to be caused by a drop in estrogen blood levels that happens naturally as we age.

Nearly 50% of all women have an easy menopause.

2. Although estrogen can be effective in treating symptoms of menopause, **estrogen replacement with progestin has risks** as shown by a major, high quality research study – the ***Women's Health Initiative***.

3. There are **less risky, but less effective alternatives** to estrogen replacement therapy for women.

4. You will need to make the choice **that *you* feel is best for you** because there is such a variety in many factors –

   - The number and severity of symptoms and how frequently you experience them.
   - Personal situations (e.g., whether or not you have a family history of breast cancer or bone fractures).
   - Individual preferences.
   - People **react differently to the same medication** – a medication that works well for someone else might not be the best choice for you – and vice versa.
   - Many choices can be used **in combination**.

We have put together the following information to help you understand your **options** and to make a treatment decision:

I. **Quick Reference Summary –** Quick information by treatment options.
II. **Detailed Reference Summary on Options –** Detailed information by symptom.
III. **Benefits, Risks and Uncertainties of Estrogen and Progestin –** Visual aids.
IV. **Scientific Information –** How we analyzed this information for you.

I. Quick Reference Summary

● Indicates **strong** scientific evidence is behind the recommendation, based on high quality research.

⊙ Indicates the strength of the scientific evidence is **moderate**.

○ Indicates the **opinion** of medical experts or others, but scientific evidence is **absent or weak**.

Reminder ►

Benefit: What works for someone else, might not work for you – and vice versa.

Risks: With any product, **long term risks may be unknown.**

Treatment	Symptoms & Strength of Evidence							
Options for Menopause	**Relieving Hot Flashes & Night Sweats**	**Relieving Vaginal Dryness & Discomfort**	**Relieving Mood Symptoms**	**Protection against Fracture**	**Protection against Colon Cancer**	**Increased Chance of Heart Attack, Stroke, Blood Clots in Leg or Lung, urinary incontinence**	**Increased Chance of Invasive Breast Cancer**	**Increased Chance of Endometrial Hyperplasia**
Lifestyle (e.g., smoking, weight, exercise)	○			○				
OTC Products		○						
Calcium and Vitamin D				⊙				
Soy and Other Phyto-estrogen Products	○							
Black Cohosh	○							
Evening Primrose Oil	○							
Dong quai	○							
Anti-depressants & blood pressure meds	⊙		**Anti-depressants may be helpful**					
Biphosphonate meds (e.g., Fosamax)				●				
Estrogen	●	○	○	●	○	●	○	●
Estrogen & progestin	●	○	○	●	●	●	●	

II. Information to Help Women Facing Decisions at Menopause

Treating Hot Flashes	Information About Options	Scientific Evidence
Lifestyle Changes	▪ Removable layers of clothing ▪ Exercise ▪ Zero to moderate use of alcohol, caffeine and spicy foods ▪ Quitting smoking ▪ Fluid intake (cool liquids may be helpful)	○ **Weak** Consensus of medical experts and weak scientific evidence.
Soy and Other Phytoestrogen Products	▪ **Soy foods** seem to have estrogen-like effects because of their plant-based estrogens (phytoestrogens). ▪ **Soy extracts and supplements** (e.g., isoflavones formulated into powder or pills) should be use with some caution because, in order to relieve hot flashes, the amount of supplement required might possibly be as risky as estrogen replacement pills. We do not know. ▪ Flaxseeds, oats, lentils, almonds also contain phytoestrogens and may be added to the diet. There is no evidence showing that these items are effective or harmful.	○ **Weak** There are limited studies of soy products which are of short duration and which show contradictory results (e.g., placebo may be as effective as soy)
Herbal Remedies **Black Cohosh**	▪ Available in teas, powders, liquid extracts, e.g., Remifemin. ▪ Usually taken twice daily	○ **Weak** There are limited studies which are of short duration and show contradictory results (e.g., placebo may be as effective as black cohosh).
Herbal Remedies **Evening Primrose Oil**	▪ Evening primrose oil is a source of gamolenic acid, which is believed by some to suppress hot flashes. ▪ Optimal dosage is unknown. The one study available in the published medical literature (showing no benefit) utilized 500mg capsules taken twice daily.	○ **Weak** Very little evidence is available and that evidence is weak.
Herbal Remedies **Dong Quai**	▪ Dong quai is produced from the crushed root of Angelica sinensis and is available over the counter. ▪ Optimal dosage is unknown.	○ **Weak** Very little evidence is available and that evidence is weak.

Treating Hot Flashes	Information About Options	Scientific Evidence
Other Prescription Drugs **Antidepressants and/or Blood pressure medications**	▪ You should discuss the use of antidepressant medications or blood pressure medications for hot flashes with your doctor.	⊙ **Moderate** There are several small clinical trials demonstrating relief from hot flashes.
Estrogen (without prosgestin)	▪ Estrogen alone (also known as conjugated estrogen) is available generically and in other forms, such as the brand name, Premarin. ▪ A large study (the ***Women's Health Initiative***) evaluated the risk of invasive breast cancer, heart attack, stroke and blood clots in women taking estrogen alone (without progestin) after having had a hysterectomy. The risk of stroke was increased by 12 strokes per 10,000 persons over a time period of 6.8 years. The risk of hip fracture was decreased by 2 fractures per 10,000 persons over 6.8 years. A later Women's Health Initiative study (Feb, 2005) reported that the risk of urinary incontinence with conjugated estrogen was increased by 10 cases of incontinence per 100 women over 1 year. ▪ Taking estrogen alone should be discussed with your doctor. ▪ See below on **Progestin** which is used to reduce the risk of endometrial hyperplasia.	• **Strong** Strong evidence of **benefit** for hot flashes and reduced risk of fractures of the hip and spine. Strong evidence of **harms** (increased risk of endometrial hyperplasia, stroke and urinary incontinence). ⊙ Moderate -Moderate evidence of increased risk of blood clots in the legs (7 clots per 10,000 persons over a time period of 6.8 years). - Moderate evidence of no increased or decreased risk of breast cancer, colon cancer, death, heart disease, or blood clots in the lungs. ○ **Weak** Weak evidence of **benefit** for vaginal symptoms, mood symptoms or colon cancer.

Treating Hot Flashes	Information About Options	Scientific Evidence
Estrogen plus Progestin Combination (oral)	▪ Available as a combination or as separate prescriptions. Progestin is used to reduce the risk of endometrial hyperplasia. ▪ Prempro (used in Women's Health Initiative study), Femhrt, Activella, Premarin with a progestin (given in two different pills) ▪ The table below on **How the Risks and Benefits of Estrogen and Progestin Stack Up** shows you the data from the ***Women's Health Initiative*** regarding the benefits and increased risk of using these medications. The women in the first published report took Prempro (estrogen and progestin) for about 5 years, and the numbers below are the risks and benefits you might have over 5 years of time. There is less risk if you take estrogen for a shorter length of time. ▪ You may wish to discuss a reduced dosage of estrogen and progestin with your doctor. It is possible, **but unproven**, that taking a lower dose will reduce risks of invasive breast cancer, blood clots, etc.	● **Strong** Strong evidence of **benefit** for hot flashes, reduced risk of fractures and colon cancer. Strong evidence of **harms** (e.g., increased risk of dementia, heart attack, stroke, blood clots in leg and lung, urinary incontinence and invasive breast cancer). ○ **Weak** Weak evidence of benefit for vaginal symptoms or mood symptoms.

Treating Vaginal Dryness & Discomfort	Information About Options	Scientific Evidence
Over-The-Counter Products	▪ K-Y Jelly, Replens and other preparations may relieve vaginal dryness, itching and pain	○ **Weak** Consensus of medical experts
Estrogen preparations used vaginally	▪ Estrogen preparations for use vaginally have been shown to improve vaginal dryness, but the risks of estrogen pills may be as great as with oral medications	○ **Weak** Consensus of medical experts
Estrogen	▪ See the table for estrogen and progestin above in the section, **Treating Hot Flashes**.	○ **Weak** Very little evidence is available and that evidence is weak.
Estrogen and Progestin	▪ See the table for estrogen and progestin above in the section, **Treating Hot Flashes**.	○ **Weak** Very little evidence is available and that evidence is weak.

Relieving Mood Symptoms	Information About Options	Scientific Evidence
Estrogen or Estrogen and Progestin (Oral)	▪ See the table for estrogen and progestin above in the section, **Treating Hot Flashes**.	○ **Weak** Very little evidence is available and that evidence is weak.
Anti-depressants	▪ No studies have been done specific to menopausal moods swings; however, there is **strong evidence** anti-depressants can help depression and other mood symptoms.	

Protecting Bone from Fracture	Information About Options	Scientific Evidence
Lifestyle Changes.	▪ Weight bearing exercise ▪ Zero to moderate use of alcohol; smoking cessation ▪ Attention to slippery rugs, shoes. In high risk patients, hip protectors may prevent fracture	○ **Weak** Consensus of medical experts and weak evidence.
Calcium & Vitamin D	▪ The National Osteoporosis Foundation recommends postmenopausal women and men > 50 years old maintain adequate calcium intake (at least 1,200 mg/day) and vitamin D intake (800-1,000 units/day).	⊙ **Moderate** Recent meta-analyses (studies that incorporate multiple previous studies) report that a combination of calcium and vitiamin D reduces hip and non-spine fracture but vitamin D alone does not. To complexify this further, there is weak and inconclusive evidence from several studies suggesting that calcium plus vitamin D supplements increase stroke and heart attack risk. Further studies are needed to clarify this issue.
Biphosphonates (e.g., alendronate - brand name, Fosamax)	▪ Fosamax or Actonel (can be taken daily or weekly). ▪ In women at high risk for fractures (e.g., taking seizure medications, steroids such as prednisone, or if you have severe arm and leg weakness and are very thin) you may benefit from Fosamax or Actonel (alendronate). If 25 women at high risk are treated for 3 years with biphosphonates, one will benefit by not having a hip fracture. There are also benefits in the prevention of other fractures. ▪ Biphosphonates can cause serious reactions such as esophageal and stomach irritation and ulceration	● **Strong** Strong evidence of **benefit** by increasing bone density and preventing of fractures in **high risk** women Strong evidence of **harms** – side effects (stomach irritation) are fairly common.
Estrogen preparations	▪ See the table for estrogen and progestin above in the section, **Treating Hot Flashes**.	● **Strong** Strong scientific evidence of benefit.

Protection Against Colon Cancer	Information About Options	Scientific Evidence
Estrogen	▪ See the table for estrogen and progestin above in the section, **Treating Hot Flashes**.	○ **Weak** Very little evidence is available and that evidence is weak.
Estrogen and Progestin	▪ See the table for estrogen and progestin above in the section, **Treating Hot Flashes**.	

Protection from Heart Attack & Stroke	Information About Options	Scientific Evidence
Lifestyle Changes	▪ Quitting smoking, healthy diet, avoiding obesity, regular exercise and maintaining normal blood pressure.	○ **Weak** to ⊙ **Moderate** For some risk factors, such as quitting smoking, there is moderate scientific evidence of benefit. For others, such as obesity, the evidence is weaker.
Aspirin	▪ Discuss benefits/risks with your doctor. If your risk is high, aspirin may be recommended. ▪ If a woman has had a heart attack, aspirin is likely to be beneficial: For every 10 women with a history of a heart attack who takes aspirin for 5 years, 1 woman will be prevented from having another heart attack or dying from a heart attack.	● **Strong** There is strong evidence that aspirin is effective in decreasing cardiac risk. Potential side effects (stomach irritation, bleeding) exist.
Treatment for other cardiovascular risk factors.	▪ Your doctor may advise that you should treat your cholesterol or blood pressure, but the decision is made after knowing what your BASELINE risk is. To do this, your doctor must calculate your risk of a cardiovascular event (heart attack, stroke) when he or she knows your gender, age, blood pressure, cholesterol levels (total cholesterol and HDL), smoking and diabetic status.	● **Strong** There is strong evidence that treating elevated blood pressure and high cholesterol reduces risk of heart attack and stroke in patients at increased risk.

III. Benefits, Risks and Uncertainties of Estrogen and Progestin

Uncertainties

There are many uncertainties involved. For example –

- What about the risks of estrogen without progesterone **for women who have had a hysterectomy**? A large study (the ***Women's Health Initiative***) evaluated the risk of invasive breast cancer, heart attack, stroke and blood clots in women taking estrogen alone (without progestin) after having had a hysterectomy over a time period of about 6.8 years. The risk of stroke was increased (statistically significant increase) by 12 strokes per 10,000 persons. The risk of blood clots in the legs was significantly increased by 7events per 10,000 persons. The risk of hip and spine fracture was significantly decreased by 6 fractures per 10,000 persons. There was no statistically significant increase in the risk of breast cancer, colon cancer, or death.

- Are the risks **decreased by using estrogen patches instead of pills**? Since blood levels of estrogen are lower with patches, the risks may be lower, but again we are uncertain.

- Does **progestin alone** (without estrogen) relieve hot flashes? Are the risks lower? There is evidence that progestins decrease hot flashes in studies comparing progestins to placebo, but the studies are of short duration and the long term risks are unknown.

Risk & Benefit Information

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Hormone Replacement Therapy

The best evidence indicates there are benefits (+) and risks (–) of taking estrogen and progestin. Compared to placebo, within the treatment period below, out of **400 women** the following is expected:

+ Benefit or – Risk	Number of Women	Treatment Years	Outcome
+	133	3	will avoid hot flashes
+	1	5	will be prevented from having a hip fracture
+	~9	5	will be prevented from having any fracture
+	1	5	will be prevented from having colon cancer
–	~1-2*	5	will have a heart attack
–	~1-2*	5	will have a stroke
–	~1-2*^	5	will have invasive breast cancer
–	~1-2	5	will have a pulmonary embolism
–	~1-2	5	will have a deep venous thrombosis in the leg
–	3-4	4	will develop dementia
–	~36	1	Will develop urinary incontinence

*Note: Some risks may be lower in younger postmenopausal women. Important mortality data was obtained by pooling data from the 2 large Women's Health Initiative (WHI) trials [4]. The two trials included 8,832 women aged 50 to 59 years. There were some methodological limitations (grade B-U evidence) but the evidence is suggestive that women < 60 years of age who use HRT for the first time in early menopause for ≤ 10 years may *not* be at increased risk for breast cancer, heart attack, or stroke. According to this data for women with no history of cardiovascular disease approximately 1 death per 1,000 women per year would be prevented by taking HRT

^Note: Based on a follow-up WHI study published in 2011 women with prior hysterectomy taking conjugated equine estrogens may not be at increased risk for CHD and may even be at lower risk for breast cancer than women not taking HRT. However, the breast cancer risk data is conflicting and because of chance or bias the difference in risk for developing breast cancer in HRT users and non-users in this population is inconclusive.

Dosing Information:

Before prescribing any medication, review full prescribing information such as from the Physicians Desk Reference, DrugStore.Com or other source.

Evidence (See References for full citations)

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IV. Scientific Information

We used a process called **Evidence-based Medicine** to tell you the best information we have about these different choices.

About Evidence-based Medicine ►

Evidence-based medicine (EBM) a relatively ***new*** and ***improved*** way of using science to help doctors understand the best way to practice medicine. In medical publications, there are good research studies and not-so-good research studies. This can be confusing even to the best of doctors. EBM helps make science easier to understand for both doctors and patients.

In EBM, research studies are evaluated by experts to find the "best available" evidence. This helps doctors and patients more accurately predict the health benefits and health risks that patients might expect from using specific drugs or undergoing certain procedures.

About Medications

People react differently to the same medication – a medication that works well for someone else might not be the best choice for you. Often there is no way to know ahead of time which drug will work best for a specific person. Frequently, the best that science can tell us are the chances of benefit or risk by examining health results in a group of people who may be similar to you or different from you in important ways.

This is similar to what happens in a lottery. Each person has so many chances to win or lose, based on estimates of the odds of winning or losing.

Many drugs are so similar that they are considered to be in the same family or "drug class." Drugs in the same class are often substituted for each other even if research has not been done for each of the specific drugs.

◄ About Drug Families

If one type of medication has not worked for you, there may be another drug in the same medication "family" or "drug class" which may work very well. You do not always have to change to a newer, more expensive drug to find a solution. However, sometimes this may be the best solution for you.

About New Drugs ►

Many of us become hopeful when we learn about a new drug on the market. But **new** does not always mean ***improved***. We need good science, through evidence-based medicine, to learn if a new drug really ***is*** better – or even as good as – the older drug. And sometimes this takes time before we know.

Many patients begin treatment with **lifestyle changes** and **older drugs** that are frequently **"over-the-counter."** Many of these patients do well without ever needing the newer and usually more expensive medications.

There are some **definite advantages** to taking this more conservative approach:

Safety	™ **Older medications are frequently safer.** Newer medications are sometimes found after a year or more to have unsuspected side effects or health risks. Most long-term risks of newly-approved medications are not known until physicians discover unsuspected side effects in their patients over time. (For example, it took several years before it was discovered that certain drugs used by millions of people to treat heart attacks actually ***increased*** heart problems.)
Effectiveness	™ **Many newer medications provide little improvement for patients.** Even when effective advertising and marketing make it appear that the newer medications are "breakthroughs," often they are not.
Cost	™ **Cost is a real issu**e. Older drugs are frequently less expensive than newer medications.

However, ***many*** **new drugs** ***are*** **significant advances in health care**. You need to make a decision on what you feel may **be most right for you**.

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