Combined Estrogen and Progestin Products For Hormone Therapy

VHA Pharmacy Benefits Management Strategic Healthcare Group, the Medical Advisory Panel and Women Veterans Health Program

This report was developed using the best evidence currently available. The recommendations are dynamic and will be revised as new clinical data becomes available. They are not intended to interfere with clinical judgment; rather to assist practitioners in providing consistent, high quality care.

INTRODUCTION

Hormone therapy (HT) with estrogen is beneficial in treating the 3-5 year short-term symptoms of menopause. Women with an intact uterus are prescribed combination HT (estrogen and progestin) to provide protection from endometrial hyperplasia which is a risk factor for uterine cancer. Available oral estrogens include conjugated equine estrogens (CEE), micronized estradiol or 17β-estradiol, and ethinyl estradiol (EE). There are many oral progesterones available for HT, including medroxyprogesterone acetate (MPA), norethindrone acetate (NETA), and the newer agents norgestimate (NGM) and levonorgestrel (LNG). Lastly, estrogen/androgen combination products target the loss of libido associated with menopause, however the Food and Drug Administration (FDA) is currently reviewing their approval for hot flashes in menopausal women.

PHARMACOLOGY

The progestin's antiestrogenic properties cause a decrease in the estrogen-induced elevation of sex hormone binding globulin or SHBG which binds 17β-estradiol. The currently available progestins are classified as pregnanes and gonanes. MPA is a pregnane 17α-hydroxyprogesterone acetate derivative, and has been widely studied. The gonane class includes estrane 19-nortestosterone derivatives norethindrone (NE) and NETA (which convert to NE). NGM is a highly potent and selective gonane which is metabolized to LNG, a medium-potency gonane. Desogestrol and gestodene are not yet available for HT in the United States (US). Of the oral estrogen products, CEE has been the most widely used and studies in US trials. equivalent HT doses are EE 5 mcg = 0.625 mg CEE = 17β-estradiol 1 mg. In general, EE in HT is a 5 times lower dose than in oral contraceptives (OC's); addition of a high potency gonane progestin reduces the EE dose in OC's to 20 mcg.[1]

Clinically, EE/NETA is felt to cause less bleeding and abdominal pain than CEE/MPA; EE/NETA also attenuates the increase in TG (however it lowers HDL-C) and is associated with less breast pain and headache[2]; refer to table 1 for more information. While gonane products' low androgenicity offer a good choice for hormone related acne, their bioavailability can be influenced by changes in plasma SHBG such as obesity, hyperinsulinemia, genetic decreases in SHBG, and thyroid hormone (increases SHBG 5-10 times normal).[3]

[1] Rowlands S. Newer progestins. J of Family Planning and Reprod Health Care 2003;29(1):13-16.
[2] Mattox JH, Shulman LP. Combined oral hormone replacement therapy formulations. Am J Obstet Gynecol 2001;185:s38-46.
[3] Hammond GL , Rabe T, Wagner JD. Preclinical profiles of progestins used in formulations of oral contraceptives and hormone replacement therapy. Am J Obstet Gynecol 2001;185:s24-31.

CLINICAL DATA

Evidence continues to emerge on the benefits and risks of postmenopausal HT. In brief, as of July 2002 a component of the Women's Health Initiative (WHI) trial was stopped by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH), 3 years short of its expected duration. The WHI trial enrolled 16,608 women 50-79 years of age with an intact uterus at 40 sites from 1993-1998. The objective was to examine combination HT's preventative effect on heart disease and hip fractures, and its association with the risk of breast and colon cancer. The Data and Safety Monitoring Board reviewed evidence May 31, 2002 that showed a 26% increase in cases of invasive breast cancer in this estrogen plus progestin group. There was also an associated increase in the risk of stroke, heart attack, venous thromboembolism, and total cardiovascular disease, which outweighed the reduction in fractures and colon cancer. On July 9, 2002 the Journal of the American Medical Association published an early release article on the findings of this trial. Refer to Appendix 1 for further detail on the WHI trial findings, as well as patient information of the benefits and risks of therapy. Additional information for patients is available on the NIH-NHLBI's web site on Postmenopausal HT at http://www.nih.gov/PHTindex.htm

INDICATIONS AND USAGE

A summary of the available HT products for vasomotor symptoms of menopause and their usage in the VHA are included in Tables 1& 2. Over 60% of our use is in estrogen only products, reflecting the high incidence of hysterectomy in women veterans. The number of unique veteran patients using estrogen HT has declined from over 35K prior to the WHI ending in June of 2002, to 27K in the 2nd quarter of FY03, comprising less than 1% of our total unique patients. CEE has the highest utilization of VHA's HT products; however practitioners may now choose another estrogen or progestin combination in light of the adverse events reported with this agent in the WHI trials. Worldwide, estradiol is the most commonly used estrogen for HT and is available in both oral and transdermal preparations.

RECOMMENDATIONS

A combination HT product would improve delivery and potentially compliance for our women veterans. As more combination products are available, they offer alternatives for women experiencing adverse effects such as lipoprotein abnormalities and pain. VHA's PBM-MAP and Women Veterans Health Program recommend our formulary include CEE/MPA combination products as well as EE/NETA combination products in addition to the CEE, estradiol, and MPA individual products currently on the formulary. After the FDA review on the effectiveness of estrogen/methyltestosterone products for HT is completed, their significant use in the VHA system will need to be addressed.

Chris Chandler, Pharm D, VHA PBM

Table 1.[a,b]

HT COMBINATION PRODUCTS	LIPID/ ADVERSE EVENTS*	BRAND NAME	30D Equiv rx's 10 mo. 10/02-7/03	30D	MANUFACTURER
Micronized estradiol (**17β-estradiol**)1mg/ 0.5mg **norethindrone acetate (NETA**)	<HDL-C, <TG <LDL-C ++breast pain +headache +back pain	Activella	308 (1.0%)	$16.14	Novo-Nordisk $75.34/140(5x28s)
Estradiol (**17β-estradiol**) 0.05 mg /0.14 mg **NETA**/24 hours Estradiol (micronized **17β-estradiol**)0.05 mg /0.25 mg **NETA**/24 hours Matrix delivery system surface area 16 cm^2	N/A	Combipatch Applied twice weekly	358 (1.2%)	$21.29 28-day	Novogyne (Novartis/Noven) $63.87/24s $65.40/24s
Micronized estradiol (**17β-estradiol**) 1mg/ 0.09mg **norgestimate (NGM**)	>HDL-C, >TG <LDL-C, <Lp(a) +breast pain ++headache ++back pain	(Ortho-Prefest) NOW Prefest	112 (0.4%)	$8.61	Monarch $51.68/180(6x30s)
Ethinyl estradiol (EE) 0.005mg/1mg **NETA**	<HDL-C <LDL-C +headache +abdominal pain	Femhrt	1,972 (6.8%)	$11.66	Warner Chilcott/ Galen $54.44/140s $34.99/90s
Conjugated equine estrogens (CEE) 0.625mg /5mg **medroxyprogesterone acetate (MPA)** cyclic combo	>HDL-C, >TG <LDL-C +++breast pain +++headache +++abdominal pain	Premphase	838 (2.9%)	$8.70	Wyeth $24.37/84s
CEE 0.625mg/2.5mg **MPA** **CEE** 0.625mg/5mg **MPA** **CEE** 0.45mg/1.5mg **MPA**		Prempro	15,307 (52.5%)	$9.90	Wyeth $27.46/84s
Esterified estrogens (EE) 0.625mg/ 1.25mg **methyltestosterone** **EE** 1.25mg/2.5mg **methyltestosterone**	UNDER FDA REVISION	Estratest H.S. Estratest	10,281 (35.2%)	$21.13 $26.29	Solvay $70.43/100s H.S. $87.64/100s

[a] Adapted from Mattox J. Combined oral hormone replacement therapy formulations. Am J Obstet Gynecol Aug 2002 S38-46.

[b] HDL-C=high lipoprotein density cholesterol; LDL-C=low lipoprotein density cholesterol; TC= total cholesterol; TG=triglycerides

Table 2.

HT SINGLE INGREDIENT PRODUCTS	DOSE	30D Equiv rx's 10 mo. 10/02-7/03	30D Supply 28-day patches	BRAND NAME	MANUFACTURER
Estradiol (17-beta estradiol), micronized oral	0.5 mg 1.0 mg 2.0 mg	22,261	$1.87	generic ?Estrace	Duramed $3.69/100s $6.23/100s Watson $2.73/100s
Estradiol (17-beta estradiol), patches	0.05 mg 0.075 mg 0.1 mg	755	$11.40/4s once weekly	generic	Mylan
	0.25 mg 0.05 mg 0.075 mg 0.1 mg	233	$8.72-$19.13/8s twice weekly	Alora	Watson
	0.25 mg 0.05 mg 0.075 mg 0.1 mg	6,221	$7.74-$18.45/4s once weekly	Climara	Berlex
	0.25, 0.375, 0.05, 0.075 mg 0.1 mg	11	$14.87/8s twice weekly	Esclim	Women First Healthcare ***March 03- DoD Formulary agent BPA $0.65/patch**
	0.05 mg 0.1 mg	8,062	$17.05 twice weekly	Estraderm	Novartis $93.83-$102.32/ 48s
	0.25,0.375 , 0.05, 0.075, 0.1	3,384	$19.04/8s twice weekly	Vivelle	Novartis
	0.25 mg 0.375 mg 0.05 mg 0.075 mg 0.1 mg		$16.29-$18.66 twice weekly	Vivelle-Dot	Novartis $48.88-55.98/24s
Estrogens, conjugated equine, oral	0.3, 0.45, 0.625, 0.9, 1.25, 2.5mg tabs	179,889	$7.66	Premarin	Wyeth $25.55/100s 0.625 mg
Medroxyprogesterone acetate (MPA), oral	2.5,5,10 mg tab	39,530	$1.39-$11.81	generic, Provera	Greenstone$4.66/100 Pharmacia& Upjohn
NON FORMULARY AGENTS					
Estrogens, synthetic conjugated, oral	0.3, 0.625, 0.9, 1.25 mg	51	$8.80	Cenestin	Duramed$29.32/100s
Estrogens, esterified, oral	0.3 mg 0.625 mg 2.5 mg	1,201	$6.00 $2.96	?generic, Estratab, Menest	Monarch $20.13/100s $9.98/100s 0.625 mg
Estropipate, oral	0.625 mg 0.75 mg 1.25 mg 1.5 mg 2.5 mg 3 mg	1,088	$3.32 $6.17	generic Ogen 1.25mg= estropipate 1.5mg	Duramed/WmnsFirst $11.08/100s 1.5 mg Pharmacia (Ogen brand)

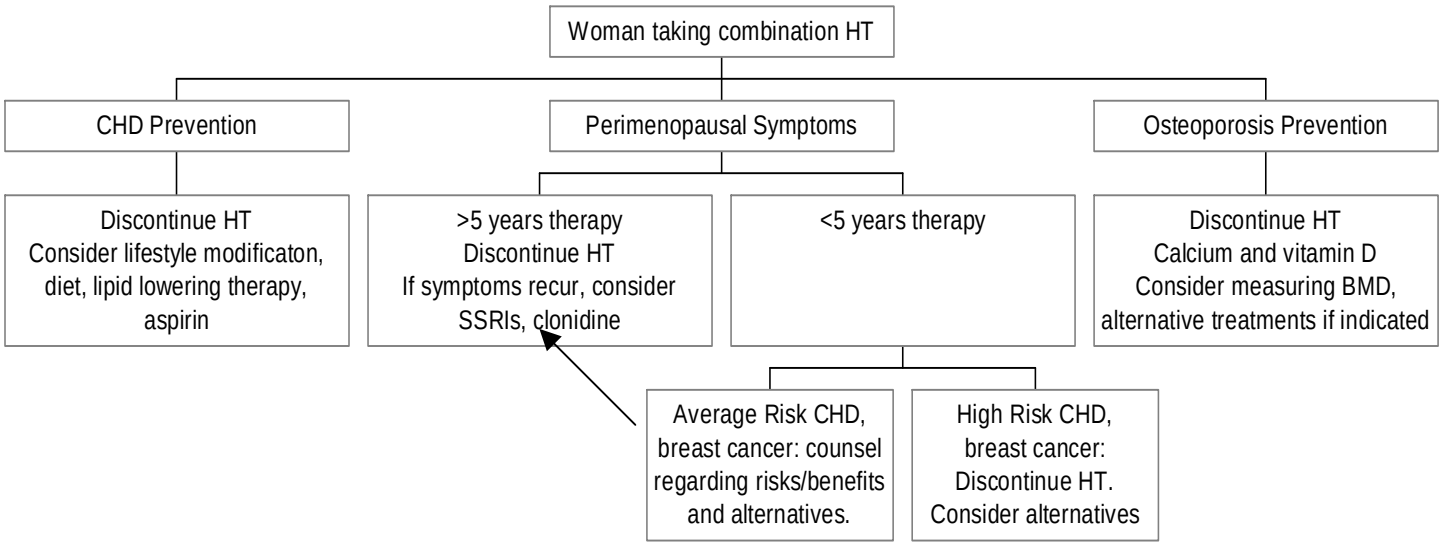
Appendix 1.

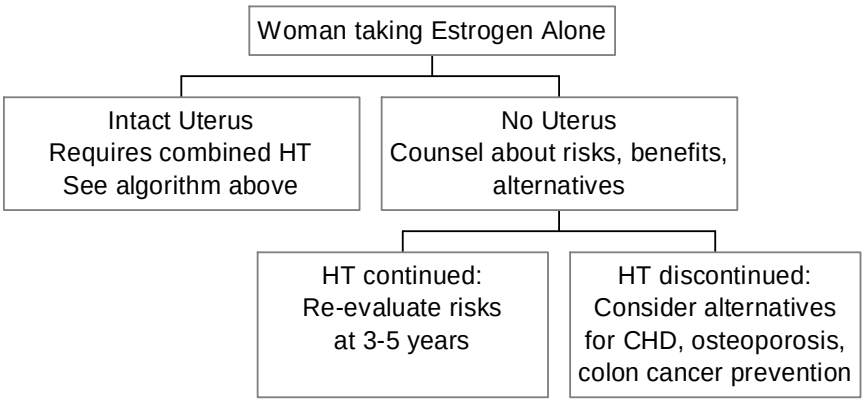
In light of data from the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) revealing excess morbidity in women receiving combination hormone therapy (HT), the following were developed to assist clinicians in managing women currently taking or contemplating HT. The following key points were considered in the development of these guidelines.

- In the WHI, combined estrogen/progesterone used for primary prevention for 5.2 years conferred a small but significant change in clinical events including:
    a) 7 excess coronary heart disease events/10,000 women-years
    b) 8 excess strokes/10,000 women-years
    c) 8 excess pulmonary emboli/10,000 women-years
    d) 8 excess invasive breast cancers/10,000 women-years
    e) 6 fewer colorectal cancers/10,000 women-years
    f) 5 fewer hip fractures/10,000 women-years
- In the HERS trial, combination HT was ineffective for secondary coronary heart disease prevention over more than 6 years of follow-up, and was associated with increased CHD risk in the first year of therapy.
- Risks for individual patients are small, but may increase with continued use (e.g. breast cancer).
- HT has established benefit in reducing peri-menopausal symptoms, including improved quality of life for women with hot flashes. Combination therapy with a progestin is needed for women with a uterus to reduce the risk of uterine cancer.
- Effective alternatives for primary and secondary fracture prevention are available including calcium/vitamin D, bisphosphonates, raloxifene, and calcitonin.
- Excess morbidity from estrogen replacement alone has not been clearly established. Randomized controlled trials of HT are ongoing.

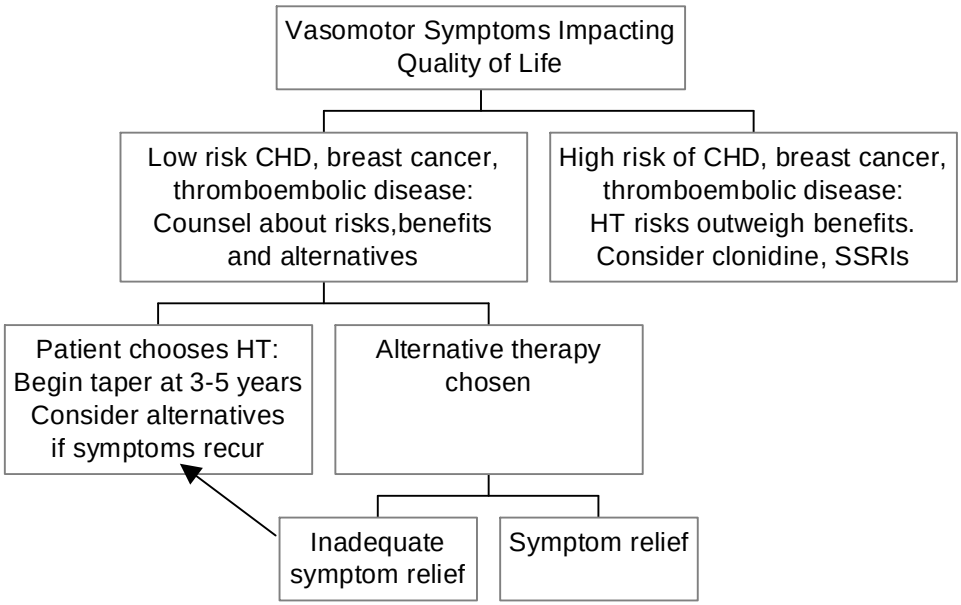
Clinical Scenarios

1. Established HT use.





2. Woman contemplating HT therapy.



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2. Hulley S, Grady D, Bush T et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280(7):605-613.
3. Hlatky MA, Boothroyd D, Vittinghoff E et al. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy. JAMA 2002;287(5):591-597.

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09/03

HORMONE THERAPY: QUESTIONS AND ANSWERS

Many women have questions about recent studies of female hormones (estrogen and progesterone). This handout was put together by physicians to tell you about the risks and benefits of hormone replacement as we understand them today.

What are the benefits of hormone therapy?

1. Hormone therapy prevents osteoporosis, preventing 5 hip fractures in 10,000 women in a year.
2. Hormone therapy reduces risk of colon cancer, preventing 6 cancers in 10,000 women in a year.
3. Hormone therapy helps with symptoms at the menopause, especially hot flashes.

What are the risks of combination hormone therapy? Combination hormone therapy contains both estrogen and progesterone. Women who still have their uterus (have not had a hysterectomy) need to take combination therapy.

1. Combination hormone therapy increases the risk of heart disease, causing 7 extra heart attacks in 10,000 women in a year.
2. Combination hormone therapy increases the risk of stroke, causing 8 extra stokes in 10,000 women in a year.
3. Combination hormone therapy increases breast cancer, causing 8 extra cases in 10,000 women in a year.
4. Combination hormone therapy increases the risk of blood clots, causing 8 extra clots to the lungs in 10,000 women in a year.

What are the risks of estrogen therapy alone? Women who have had a hysterectomy can take estrogen alone. Less is known about the risks and benefits, and studies are still going on.

What should you do? The risk to most woman taking hormones for a short time is small. However, safe and effective alternatives to hormones exist. Most doctors agree that hormones are not the best choice for preventing heart disease, osteoporosis, or colon cancer. Talk with your doctor to learn what options are right for you.

If you choose to take hormones to treat hot flashes, plan on using them for a short time. Hot flashes decrease in most women after 3-5 years, so talk to your doctor about stopping the medicine at that time.

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