

2008 UPDATE on the WHI & The Critical Therapeutic Window

Based on data presented by the author at PRIMARY CARE TODAY May 9, 2008

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NANCY'S DILEMMA :

“To take postmenopausal hormones or not to take postmenopausal hormones” – that is the question.

54-yo married teacher, G2P2 (both unremarkable) 4 years postmenopausal, presents with recurrence of troublesome menopausal symptoms after discontinuing HT 1 year ago

She took CEE (0.625 mg) + MPA (2.5 mg) for 4 years without problems and felt well, but stopped HT after reading about the WHI . She has tried naturopathic preparations and OTC's with little effect.

“I thought menopause was going to be a breeze, and then I stopped my HT”

Now: 6 to 8 hot flushes a day
1 to 2 soaking night sweats a week
Insomnia resulting in increased fatigue
Dyspareunia and decreased libido

Past health unremarkable

No medications/drugs, no allergies
Non smoker; 1-2 glasses wine/week

Family History:

Mother: died after stroke at age 85 yo
Father: died of colon ca 79 yo
Brother HT – on Rx
Maternal grandmother: fractured hip at age 81
Paternal aunt: diagnosed with breast cancer at age 70

Physical Examination :

BMI 29
BP 124/80
Breasts fibrocystic
Pelvic exam: pale, atrophic-looking vagina & cervix
Otherwise NAD

Investigations:

Mammogram: breasts heterogeneously dense, otherwise negative
TSH 3.0
Pap smear: “changes consistent with mild atrophy”
Lipids : TC 6.3
HDL 0.94
LDL 3.40
TG 50
Bone density: LS -1.8
Total Hip -1.1

THE MENOPAUSAL PATIENT'S HISTORY SHOULD INCLUDE --

AGE: How old is the patient?

When was her LMP?

CURRENT SYMPTOMS:

**Why is she considering ET/HT? : Vasomotor symptoms/
sleep disorders**

Vaginal Dryness

Sexual Function

Urinary issues

Cognitive decline/Alzheimer's

HEALTH HISTORY: Current & Past Illnesses

Surgeries(?hysterectomy)

Medications (including previous ET/EPT use)

SIGNIFICANT FAMILY HISTORY: e.g Cancer – Breast/Ovarian/Endometrial/Colon

Osteoporosis / Hip Fractures

Cardiovascular Diseases incl HT, CVA

Thrombophilia /Hx Thromboembolism

Diabetes

LIFESTYLE ISSUES: Smoking

Alcohol

Exercise

Sexual Partner?

FAQ's : FREQUENTLY ASKED QUESTIONS

1. PROGESTERONE/ PROGESTINS

Some of my patients want to treat their menopausal symptoms with progesterone alone, or ask me to prescribe progesterone cream. Is that appropriate?

2. DURATION OF ET/EPT THERAPY

I have taken over a practice in which some patients have been taking menopausal hormones now for more than a decade; there are no medical issues and they say they feel great. Should I insist that they stop?

3. DISCONTINUING HORMONE TREATMENT

What is the “best” way to stop hormones: Tapering or stopping abruptly?

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BACKGROUND

A decade ago prevailing opinion, based on a vast body of evidence from large observational studies, epidemiological studies, randomized controlled trials with surrogate end points, and from the laboratory, held that postmenopausal hormone therapy reduced coronary heart disease (CAD) by 30-50%. However, the Women's Health Initiative (WHI), which intended to show definitively that in healthy menopausal women, hormone therapy was both safe and protective of the cardiovascular system, failed to produce the hoped-for results.

In 2002, the combined EPT treatment arm of the WHI which had enrolled >16,000 postmenopausal women aged 50 – 79 yo was stopped after only 5.6 years of treatment . The first reports to reach not only the public, but also the medical world came from the press which boldly announced that the results of the WHI categorically proved that : based that HRT caused

↑CHD	29%
↑ <i>Breast Cancer</i>	26 %
↑Stroke	41%
↑PE	113 %

These conclusions were based on the raw unadjudicated data. ¹

No mention was made in the press of a highly significant 40% reduction in all fractures, including hip fractures (absolute reduction of 4-5/ fewer fractures/1000 treated women/year) than in the placebo group.

Following adjudication, the corrected results were released and indicated that the increase in CHD was not statistically significant, that the increase in breast cancer was barely significant and that overall the absolute occurrence of any of these events was rare i.e. < 1/1000/year. Nonetheless, the message of HARM stuck. The results of the ***E+P Arm of the WHI*** ² reported in 2002 have deterred both patients and prescribers from using hormone therapy to treat menopausal women . The medical world was stunned by the announcement;; clinicians and investigators were perplexed; women stopped taking hormones and sought alternative treatments for their symptoms; scientists and investigators returned to their laboratories and their desks to seek explanations, and once again the quest for “the truth” began.

Few women and not all prescribers even heard the 2004 announcement of the results of the ***estrogen only arm of the WHI study*** ³ which was stopped after 8.2 years and showed very different effects : NO increase in breast cancer (in fact a non statistically significant reduction in breast cancer), NO increase of CHD.

Even today, hormonal therapy with estrogen + progestin or, in hysterectomized women, estrogen alone, remains the most effective currently available therapy for menopausal symptoms. The question that remains is :

Is treatment with menopausal hormones safe?

CARDIOVASCULAR EFFECTS

In contrast to the initially reported results from the WHI, findings from early small RCT's and approximately 20 clinical observational studies, including the Nurses' Health Study (NHS), which began in 1975 by enrolling 121,00 female nurses, 20-50 yrs of age, were consistent in showing a reduction in CAD and deaths in postmenopausal women treated with hormones. In a 2006 the NHS investigators published an update paper on the NHS, reporting, on 220,368 women years (wy) of estrogen+progestin therapy (EPT), 124,391 wy of estrogen only therapy (ET), and 313,661 wy of information on women who had never taken hormones, their results continue to show a 30-40% overall reduction in CHD in the ET/EPT treatment group. ⁴

It is now evident that the women studied in *earlier observational trials* generally were *younger and closer* to menopause. A reanalysis of the WHI recruits by age (by decades) and by years since menopause (<10 years, 10 – 20years, >20 years) were quite consistent with the results of the observational studies. Notably, there was

- a) no increased CV risk when HT/ET treatment was started within 10 years of menopause,
- b) (borderline p for trend 0.06) for reduction in mortality in the treated 50-59 yo age group and
- c) a trend for increasing risk of CHD with increasing time since menopause.

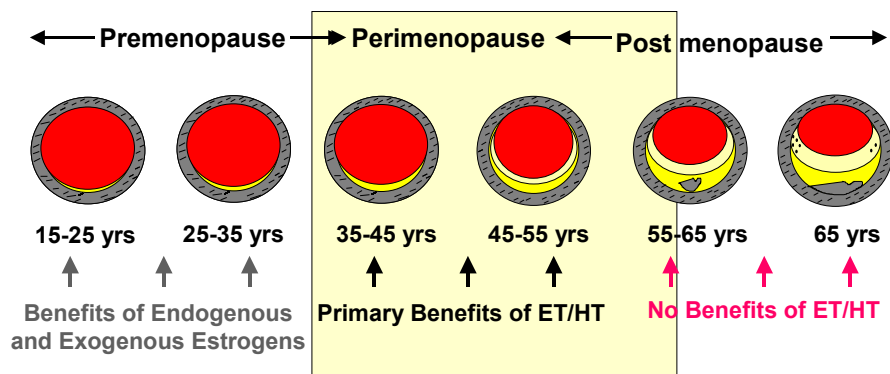
In the older age groups, the higher risks for CHD appear to be concentrated in a group of women with moderate or severe vasomotor symptoms indicating that this might be a particularly at risk population. The reason is as yet unknown.

In summary, the WHI, shows that ET/HT prescribed to younger women 50-59 yo, or begun within 10 years of menopause are cardioprotective, as shown in the observational trials, in which the majority of study patients also began HT/ET treatment at a younger age and soon after menopause. The thesis proposed by Dr. Thomas Clarkson that

Reproductive stage is a major determinant of the effect of estrogens on atherosclerosis progression, complications and plaque vulnerability⁵

had strong biological support from his laboratory and his studies in monkeys and is summarized in the figure below¹⁸:

There is Increasing Evidence that ET/HT Initiated During the Perimenopausal/Early Postmenopausal Period, BUT NOT Late Menopause, Inhibits the Progression of Atherosclerosis



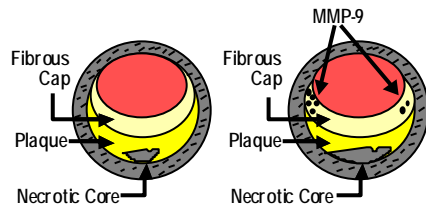
Normal Estrogen-----→ Decreasing Estrogen -----→ Estrogen Deficiency

Mikkola TS, Clarkson TB, Notelovitz M. Ann Med. 2004;36(6):402-13⁶

Exactly how atherosclerosis impedes the beneficial action of estrogens on the arteries is unclear. Two of the proposed mechanisms :

- 1) 27 Hydroxy cholesterol, a cholesterol metabolite which is increased in hypercholesterolemia and is also present in atherosclerotic plaques, has been shown to competitively inhibit estrogen-dependent production of nitric oxide and to interfere both with arterial function and re-endothelialization.⁷
- 2) Exposure of established atherosclerotic plaques to estrogen releases *matrix metalloproteinases* (MMP's) without a concomitant release of their balancing inhibitors, *tissue inhibitors of metalloproteinases* (TIMP's) as occurs in healthy vessels. This can result in plaque degradation, destabilization and rupture, as shown below. Statins which are known to inhibit MMP's, when used concomitantly with estrogens reduce clinically evident plaque ruptures.⁸

Effects of Initiating Estrogen Treatment at the Complicated Plaque Stage of Atherosclerosis



• Estrogen Effects on Complicated Plaques

↑ Inflammation ⇒	↑ PQ instability
	↑ lesion progression
↑ MMP expression ⇒	↑ PQ instability/rupture

• Loss of Estrogen Benefits

- ↓ Expression of estrogen receptors
- ↓ Vascular responsiveness

Potentially adverse effects of estrogen on atherosclerosis/CHD

*** (Ref -- Dr. Thomas B. Clarkson, Winston-Salem, NC in Derzko CM. *Menopause, Hormones and the Critical Therapeutic Window. (Endocrinology Rounds 2007;7(1):1-6 (available @ www.endocrinologyrounds.ca)*⁸

STROKE & VTE'S :

Although, in the WHI, the overall risk for stroke was increased by 32% and did not vary by age or time since menopause, when compared to placebo, there was no increased stroke risk in women ages 50-59 years.

In the WHI, the increase in VTE's in women 50-59 is categorized as rare : with 4 event per 10,000 women per year of use in the **ET group** and 7/10,000/year with **EPT**.

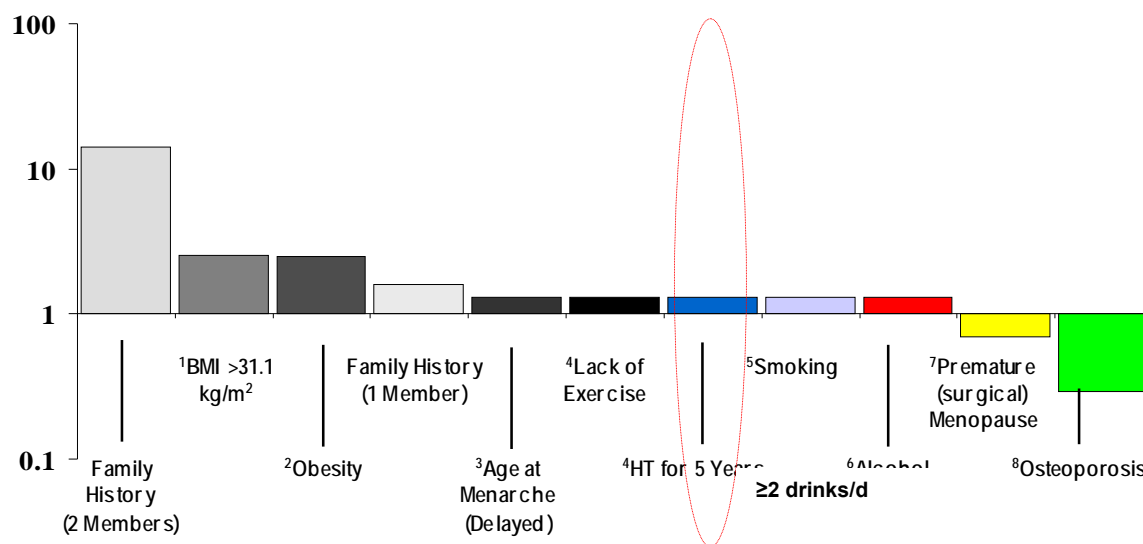
Based on the results of the WHI and other recent studies, the **August 2008 updated NAMS HT POSITION STATEMENT**⁹ concludes, that ,

“Pending additional data, HT is currently not recommended as a sole or primary indication for coronary protection in women of any age” but that ...”There is emerging evidence that initiation of HT in early postmenopause may reduce CHD risk.”

WHAT ABOUT THE INCREASED RISK OF BREAST CANCER REPORTED IN THE WHI?

There is definitely good news here too. Firstly, it is important to recognize what we have long known : i.e that postmenopausal hormone therapy is not a major factor in the increase in breast cancer risk. In fact there are a number of risk factors over which we women do have control and which we need to address, most notably obesity prevention/weight control, moderation in alcohol intake, a need to exercise and smoking cessation.

Magnitude of Various Risk Factors for Breast Cancer



RR of 1 = no risk; RR >1 = risk; RR <1 = benefit; Not head-to-head comparisons.

¹Morimoto LM, et al. *Cancer Causes Control*. 2002;13:741-51; ²Huang Z, et al. *JAMA*. 1997;278: 1407-11; ³Thune I, et al. *N Engl J Med*. 1997;336: 1269-75; ⁴McTiernan A, et al. *JAMA*. 2003;290:1331-6; ⁵Reynolds P, et al. *J Natl Cancer Inst*. 2004;96:29-37; ⁶Li CI et al. *Cancer Epidemiol Biomark Prev*. 2003;12:1061-6; ⁷Society of Obstetricians and Gynaecologists of Canada. Available at: <http://sogc.medical.org/>; ⁸Kuller LH, et al. *Environ Health Perspect*. 1997;105(Suppl 3):593-9.

Derzko CM. Menopause, Hormones and the Critical Therapeutic Window. *Endocrinology Rounds* 2007;7(1):1-6 (available @ www.endocrinologyrounds.ca)

At the 7.1 year completion of the **ET arm**⁸ of the WHI, in all age groups there was a non significant reduction in breast cancer (i.e. 6 fewer cases of breast cancer/10,000 women/year of use). The reason for the reduction in breast cancer remains unclear and still needs to be explained.

In the **EPT arm**⁹, there was no increase in breast cancer for the first five years of use, with an increase of 4-6 additional invasive cancers/10,000 women/year reported after 5 years of EPT use,-- still placing it in the “rare” category i.e. <1/1000/year).

Two additional factors need to be remembered : 1) There was no increase in breast cancer in EPT users in the 50 – 59 yo age group. 2) The increase in risk of invasive breast cancer in the EPT arm was limited to those who had used HT prior to entry into the study.

Prior HT Use	% of Study Population	HR (95% CI)
No prior use	74%	1.09 (0.86–1.39)
<5 years of prior use	14.8%	1.70 (0.99–2.91)
≥ 5 years of prior use	11.2%	2.27 (1.00–5.15)

Chlebowski RT, et al. *JAMA*. 2003;289:3243-53¹⁰

OTHER BENEFITS OF ET/EPT USE

OSTEOPOROSIS

Prevention of osteoporosis and osteoporotic fractures is an important consideration for all postmenopausal women. Unquestionably calcium and vitamin D are important. In a 2007 meta-analysis of 17 clinical trial with >52,000 people of whom >92% were women average age 68 years, using 1200 mg or more of calcium and 800 IU or more of vitamin D, significantly reduced fractures by 24% (p=0.0001). The importance of vitamin D has moved to the forefront with the recognition that the prevalence of Vitamin D deficiency and insufficiency is quite high, particularly in northern climates including Canada, given our limited availability of and exposure to sunshine. The importance of Vitamin D was emphasized by the publication of results from a pooled analysis of 12 RCT's showing a significant reduction in hip fractures in individuals taking a supplement of 700-800 IU of Vitamin D.¹¹ Clearly, patients should be encouraged to supplement their diet as needed to ensure that their daily intake of calcium and vitamin D is adequate.

With respect to hormonal therapies, it has long been known that estrogen and estrogen+ progestin therapy even at low doses, increases BMD. The impressive result from the WHI is that in a non osteoporotic population and indeed in a "not at risk for osteoporosis" population (based on BMI, history, all ages) there was a 35-40% reduction in fractures across all ages (i.e. absolute fracture reduction : 44-56 fewer fractures/10,000 women/year and 5-6 fewer hip fractures/10,000 women/year).^{7,8} Osteoporosis prevention is an indication for hormone therapy, particularly in symptomatic women and has been recommended as an osteoporosis treatment for those who do not tolerate other therapies e.g. bisphosphonates.

TYPE II DIABETES MELLITUS

Adult onset (Type II) diabetes mellitus increases with age and is associated with an increase in morbidity and mortality, notably from cardiovascular disease. The prevalence of diabetes in women 50 years of age and older is increasing as obesity rates increase and currently is approaching 20% in US women and approximately 17-18% in Canadian women*. An unexpected and frequently unappreciated benefit of postmenopausal hormone therapy has been the significant reduction in incident diabetes mellitus with both estrogen and estrogen/progestin therapy.

In the WHI, when compared to placebo, the EPT arm showed a 21% reduction in new onset type II diabetes mellitus (HR=0.79, 95% CI: 0.67-0.93)¹² and in the ET group there was a 12% reduction (HR=0.88,, 95% CI:0.77-1.01)¹³. The reduction in Type II diabetes mellitus seen in both arms of the WHI study was also reported in other large RCT's. While the precise mechanism has not been determined, meta-analysis data suggest a reduction in insulin resistance is a major factor, but another possibility that has been suggested is a reduction in centripetal weight gain. Furthermore, use of ET appears to reduce the dose of medications required to achieve glycemic control.⁹

COLORECTAL CANCER

In women, colorectal cancer is the third most common cancer and the third most common cause of cancer death.

In the in the **WHI ET alone arm of the trial**, there was no significant difference in the rate of colorectal cancer between the ET-treated women and those in the placebo group. (HR 1.08; 95% nCI 0.75–1.55)¹⁴

**(Personal communication – Dr. G. Booth)*

However, in the combined **(EPT) arm** of the WHI, women on EPT had a significantly lower incidence of invasive colorectal cancers (HR, 0.56; 95% nCI, 0.38–0.81; 95% aCI, 0.33–0.94)¹⁵. As the effect was seen as early as the first year of treatment, the WHI investigators postulated that this could represent an effect on existing/established cancers as well. Disappointingly, in a follow-up study of WHI participants done three years after discontinuation of treatment, the significant reduction in invasive colorectal cancer in the EPT treated group did not persist.**Heiss G, Wallace R, Anderson GL, et al Health Risks and Benefits 3 years after stopping Randomized Treatment with Estrogen and Progestin. JAMA 2008;299:1036-1045

WHAT ABOUT NANCY'S CONCERNS?

Nancy stopped her HT because she feared the results of the WHI :

WHAT RELEVANT INFORMATION FROM THE WHI CAN WE PASS ALONG TO HER?

2007 WHI Analyses of Younger Women (aged 50-59 yo)¹⁶

- **7% decrease in CHD with ET or EPT** (↓ 2/10,000/yr of use)
- **24% increase** in breast cancer with EPT** (↑ 9/10,000/yr of use)**
- **20% decrease in breast cancer with ET** (↓ 7/10,000/yr of use)
- **30% decrease in total mortality with ET or EPT** (↓ 10/10,000/yr of use)

***NO increase in breast cancer for 5 years in women who had not taken HT prior to entering the study*

WHI Summary (ages 50-59 years)¹⁶

Effects per 10,000 women/year of ET use

- 10 fewer deaths
- 10 fewer CHD events
- 4 more VTE's
- 2 fewer strokes

Effects per 10,000 women/year of EPT use

- 9 fewer deaths
- 5 more CHD events
- 5 more strokes
- 11 more VTE's

NANCYS DILEMMA :

Information for Nancy to consider as she decides whether or not to take HT

54-yo : AGE APPROPRIATE /WITHIN 4 YEARS OF LMP
DEMONSTRATED PREVIOUS RESPONSE & NO PROBLEMS WITH HT
SYMPTOMATIC -6 to 8 hot flushes a day) All these should
1 to 2 soaking night sweats) respond to
Sleeps poorly) HT

Sex: dyspareunia / ↓ libido) Vaginal dryness may respond
to systemic Rx
--additional local vaginal E Rx
vaginal estrogen treatment
may be required

** Additional sexual counseling may be needed.

Family History:

Mother: died after stroke at age 85 yo) – continue to monitor bp
Father : died of colon ca 79 yo) – encourage colonoscopy
Brother HT – on Rx) –
Maternal grandmother: fractured hip at age 81) -- HT will ↑BMD, ↓hip # risk
Paternal aunt: diagnosed with breast cancer at age 70) – Postmenopausal breast ca:
Not a major factor here

Physical Examination :

BMI 29 <----- encourage wt loss/exercise
BP 124/80
Breasts fibrocystic<----- continue mammograms
Pelvic exam : pale, atrophic-looking vagina & cervix ←HT will Rx
Otherwise NAD

Investigations:

Mammogram : breasts heterogeneously dense, otherwise negative : *Continue to monitor*

TSH 3.0 N

Pap smear : “changes consistent with mild atrophy”

Lipids : TC 6.3

HDL 0.94 <----- ↑ with exercise and oral E

LDL 3.40 ←----- ↓ “ “

TG 50 ←----- watch effect of ET :(oral ET ↑TG

(transdermal ET- no change in TG

Bone density: LS -1.8) HT will ↑BMD, ↓ # risk

Total Hip -1.1)

*LIPIDS : N Encourage increased exercise and attention to weight
Exercise & Oral estrogen treatment will increase HDL
Oral estrogen, alcohol, adiposity will increase TG*

General Lifestyle Advice :

1. *Ensure adequate calcium (from diet + supplement as needed) to 1200 – 1500 mg/d*
2. *Recommended Vitamin D dose : 1000 – 2000 units /day (especially in Canada)*
3. *Daily exercise 30 minutes / day is ideal – at least 3-4 times/week*
4. *Watch weight / avoid obesity*
5. *Continue regular mammogram*
6. *Repeat BMD in 2- 3 years as indicated*
7. *Moderate alcohol intake (Do not smoke)*

What about hormones? :

SHE IS AN EXCELLENT CANDIDATE FOR EPT

FAQ's : FREQUENTLY ASKED QUESTIONS

1. PROGESTAGENS (PROGESTERONE/ PROGESTINS)

Some of my patients want to take only progesterone or ask me to prescribe progesterone cream for their symptoms. Is that appropriate?

Adding a progestin may enhance the efficacy of low dose estrogen therapy in treating vasomotor symptoms. However, the major indication for progestogen use is to endometrial protection from unopposed stimulation by exogenous systemic estrogen or excess endogenous (unopposed) estrogen (e.g. in the obese or PCO hyperestrogenic woman). When low dose vaginal estrogen products are used for local therapy, it is generally agreed that progestagens are not required. There is no indication to use progesterone in a woman without a uterus. There is a lack of scientific evidence, either positive or negative, supporting the efficacy or the safety of progesterone creams for menopausal therapy.

2 DURATION OF ET/EPT THERAPY

*How long can ET/EPT be continued? When should HT be stopped?
The answer is : "We don't know."*

The data are quite conflicting as to whether taking postmenopausal hormone treatment, particularly low dose hormone treatment, for an extended time, (beyond 5-8 years) improves or worsens the benefit : risk ratio. Nonetheless, the known *risks and benefits* need to be assessed with each patient at least annually, and when, in the opinion of both the patient and her physician this ratio is favorable, continuation of low dose treatment, under continued clinical supervision may be appropriate

e.g. -- recurrence of intolerable vasomotor or other menopausal symptoms when ET/EPT is discontinued

--prevention of osteoporosis in symptomatic women

-- osteoporosis prevention or treatment when other available osteoporosis

There are no data to inform the question of long term use of ET/EPT . The decision to continue their long term hormone treatment, particularly "low dose therapy" (e.g. in women who began HT before the WHI and have continued it, without problems, for a decade or more) may be quite appropriate, when these women, who, having reviewed the known risks and benefits with their physician, elect to do so.

As the WHI studied only women 50-80 yo, the results are not applicable and should not be extrapolated to younger (<50 yo) menopausal women, in whom the risks of early estrogen deficiency are associated with a significant increase in osteoporosis and cardiovascular risks and a lower risk of breast cancer. In women with POF (premature ovarian failure) or with a surgical or early menopause ET/EPT. Higher hormone doses may be required.

3. WHAT IS THE “BEST” WAY TO STOP Rx?

There is a 50% chance that vasomotor symptoms will recur when hormone therapy is stopped, regardless of the patient's age or duration of hormone therapy. Neither *tapering the dose* nor *abruptly discontinuing treatment* alters this rate.

If symptoms recur and there are no contraindications, hormone therapy may be restarted, if the patient chooses to do so.

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