COMMENTARY

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# The Women's Health Initiative and hormone therapy, 5 years later

AS I WRITE THIS ESSAY, it has been almost 5 years to the day since I attended the meeting of Women's Health Initiative (WHI) investigators at which the astounding results of the estrogen and progestin study were revealed for the first time. Although I knew then that we were all in for a big change, I could not have anticipated the total impact.

In a commentary on those findings,[1] published here in September 2002, I recommended that clinicians believe the results and stop prescribing combined hormone therapy for prevention of cardiovascular disease and osteoporosis. I also suggested that these results should not be overgeneralized: women who needed therapy for vasomotor symptoms, or who were taking estrogen therapy only, could continue to use hormones, and women under 50 years of age could continue with whatever they were taking. I concluded by asking readers to "stay tuned" for the complete WHI results, as well as results of other large randomized trials that were in progress.

It's time for that update.

**5 years after the WHI results were announced, it's time for an update**

## SPIN-OFFS OF THE RESULTS

Before I get to the clinical picture, I'll briefly mention a few of the scientific spin-offs of the WHI results.

- For the first time in history, hot flashes are being taken seriously by a large number of scientists. Epidemiologic studies (looking at risk factors, natural history, and impact) and basic etiology studies are currently under way that will (we hope) lead to the discovery of effective, safe prevention and treatment strategies for these symptoms.
- The value of the randomized trial as the arbiter of effective therapy was reinforced. Decades of making practice decisions based on belief, anecdote, and small studies of surrogate end points ended in 1 day with the publication of the first WHI paper. Well-designed, appropriately powered clinical trials cannot answer every question, but they generally do answer the question they set out to answer.
- The search for safe and effective treatments for menopausal symptoms and osteoporosis has intensified and become more sophisticated. We now know, for example, that low-dose estrogen does have benefits; before the WHI there was little motivation to examine this question.
- The question of whether the timing of estrogen therapy matters with respect to cardiovascular disease prevention or risk is still open—and is being actively investigated. In support of this effort, a recent reanalysis of the WHI data, combining both arms of the study, found that participants between 50 and 60 years of age did not experience increased heart disease events during the trials.[2]

In addition, the WHI investigators have just published the results of a substudy in which about 1,000 participants who were 50 to 59 years old at study entry had coronary artery calcium scores measured almost 9 years after randomization to receive either hormones or placebo. Consistent with the results of the statistical reanalysis, the group assigned to hormone therapy had lower coronary calcium scores.[3]

However, even this result does not provide a final answer as to whether estrogen prevents heart disease in younger women. The effects of estrogen are complex, and coronary calcium is an intermediate end point only. Also, this study did not include women over

60, so we don't know if the result would have been different or the same.[4]

## SOME CONFUSION PERSISTS

Some clinicians and women are still confused about what to do, in part because of difficulty in understanding how to interpret the results of the WHI or because of continued disbelief in the findings, and in part because of questions that were raised by the results but that have not yet been answered.

What is not in doubt is that the number of women who choose to take hormone therapy for any reason has dramatically decreased.

## MY VIEW

The "big" conclusions of the WHI hormone therapy studies still hold. Older women should generally not be started on long-term, standard-dose, combined estrogen-progestin or estrogen-only therapy for the purpose of preventing chronic disease.

**The 'big' conclusions of the WHI still hold**

Estrogen is still the most effective therapy for hot flashes, however, and is appropriate for healthy women who choose it for that purpose. Healthy women younger than 50 have such a low baseline risk of stroke, myocardial infarction, and thromboembolic events that estrogen or estrogen-progestin therapy is relatively safe and can be given long-term up to around the age of natural menopause.

## SEARCHING FOR NEW TREATMENTS

Although estrogen is still the most effective treatment for menopausal vasomotor symptoms, the intensified effort to find new therapies for menopausal symptoms has yielded some new approaches and has cast doubt on some old standbys.[5] The effective options for hot flashes include the serotonin reuptake inhibitors—especially venlafaxine (Effexor) and paroxetine (Paxil)—and gabapentin (Neurontin) but not clonidine (Catapres). Well-designed studies also cast doubt on the usefulness of complementary and alternative medicine options such as soy-based therapies and black cohosh.

The reduction in use of systemic hormone therapy has led to an increased problem with symptomatic atrophic vaginitis. Women who would benefit from therapy (largely to improve sexual functioning and satisfaction) should be encouraged to consider local estrogen therapy. Low-dose estrogen cream (0.5 g or less), the low-dose vaginal ring (Estring), and the vaginal estrogen tablet (Vagifem) are highly effective for this condition. Each of these products is associated with some systemic absorption, but the amount absorbed is quite small. While long-term safety cannot be assured, any risks are likely to be much less that with systemic therapy.

## REASONABLE RECOMMENDATIONS ARE AVAILABLE

The North American Menopause Society recently published a consensus statement[6] delineating the areas the panel deemed settled, and those that are not. I encourage readers to go to this organization's Web site and take advantage of all its position statements, including this one, which are available for free.[7]

While the "true" story of hormone therapy may not yet be complete, clinicians have enough information now to make reasonable evidence-based recommendations for most of their patients. But continue to stay tuned . . . and see you in 5 more years!

## REFERENCES


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