Hormone replacement and quality of life: 2 experts comment on the latest WHI findings

Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med*. Posted March 17, 2003. Because of its potential therapeutic implications, this article was published early at: www.nejm.org. It appears in the May 8th issue.

OBJECTIVE In this latest offering from the Women's Health Initiative (WHI), researchers investigate whether estrogen plus progestin increases quality of life in postmenopausal women.

METHODS AND RESULTS This study consisted of 16,608 postmenopausal women ranging in age from 50 to 79 (mean, 63) with an intact uterus. Participants received either a combination of 0.625 mg of conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate (Prempro) or placebo. Quality-of-life measures were collected at baseline and 1 year, and again at 3 years in a subgroup of 1,511 women.

Estrogen and progestin resulted in no significant effects on general health, vitality, mental health, depressive symptoms or sexual satisfaction. After 1 year there was a statistically significant "but small and not clinically meaningful" benefit in terms of sleep disturbance, physical functioning, and bodily pain. At 3 years there were no significant benefits in terms of any quality-of-life outcomes.

WHO MAY BE AFFECTED BY THESE FINDINGS? Older, asymptomatic postmenopausal women on or considering hormone replacement therapy (HRT).

A study with 4 inescapable limitations

—ALAN M. ALTMAN, MD

EXPERT COMMENTARY Four key problems limit the effectiveness of this study.

1. Inappropriate population

Seventy percent of the women in this study were between the ages of 60 and 79 with a mean age of 63. This fact disqualified the WHI's first report as a primary prevention study of cardiovascular disease, and it has a major nullifying impact on this study as well.

Only a small percentage of older postmenopausal women have vasomotor symptoms; in this study just 12% noted them as "moderate to severe." Women with severe vasomotor symptoms were dissuaded from joining the study due to inability to take placebo. In her editorial, D. Grady comments that, "Among the 12% of women who did report moderate-to-severe vasomotor symptoms at baseline, the symptoms were unlikely to be very bothersome, since the women were willing to be randomly assigned to placebo."[1] Hence, this is not an appropriate population from which to draw conclusions about quality of life issues.

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2. Discontinuation rate was 42%

This was an intent-to-treat study and almost half of those in the study group discontinued therapy. This is certainly not unexpected when women are arbitrarily placed on a single estrogen-progestin combination therapy without regard to individualizing treatment—especially when you consider that 88% were without vasomotor symptoms at baseline. The breast tenderness, bloating, bleeding, headaches, and mood changes from a 1-size-fits-all regimen would be enough to make most women discontinue treatment if their clinicians were unable to adjust their therapy.

Subjects who stopped therapy remained in the treatment arm for determination of quality of life results. The authors admit that "it is possible that differences were not significant at 3 years because of … poorer adherence to assigned therapy."

3. The conjugated equine estrogen/ medroxyprogesterone acetate combination in this study does not represent all HRT formulations

The definition of what constitutes HRT is vastly different today than it was a mere 20 years ago. Thus, it is impossible and misleading to extrapolate the WHI results to the many different options of estrogens, progestogens and delivery systems presently available in the US.

Numerous studies have shown estrogen-associated increases in quality of life. Progestogens, especially medroxyprogesterone acetate—the most potent synthetic progestin we have—can attenuate these estrogen benefits by down-regulation of the estrogen receptor. This is a process we seek in the endometrium, but want to avoid in brain, bone, vascular tree, genitalia, and skin. Better progestogen choices now available, such as micronized progesterone, norethindrone acetate, and norgestimate, are less potent and far better tolerated in combination with the many estrogen options.

4. Quality of evaluation tools

This study attempts to evaluate quality of life using various medical scales—each designed to assess a specific function, but none developed to actually measure quality of life. The most primitive scale, utilized to evaluate "sexual satisfaction," consisted of just 1 question with 4 choices: very unsatisfied, a little unsatisfied, somewhat satisfied, or very satisfied. Other researchers have utilized vehicles with 40 questions on a 10-point scale in studies of sexuality, and the academic sexual societies are constantly trying to evolve more sophisticated tools to evaluate this complex concept. One question simply cannot assess sexual satisfaction.

BOTTOM LINE Individualization of therapy has been, and should continue to be, the guiding principle in helping patients decide whether or not to begin HRT, and ultimately which combination best fits their needs. This unsatisfying study uses the wrong population, continuation, combination, and evaluation and fails to consider the variations in genetic complement of estrogen receptors. No single therapy is appropriate for all women.

REFERENCE

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Women's Health Initiative: An inherently flawed design

—GLORIA BACHMANN, MD

BACKGROUND Since July 2002, the major news dominating headlines in medical publications dealing with women's health has been the data from the WHI. Alarmingly, there is little consensus among both experts and practicing clinicians alike on how best to interpret the WHI results in this cohort of older women who were given estrogen-plus-progestin therapy. The general assumption of the lay press has been that randomized clinical trials are without study-design or interpretation flaws

and therefore are the cornerstone of clinical practice. This unfortunate assumption fails to recognize the specific limitations of clinical trials—the very limitations that hinder this study.

As clinicians we are keenly aware of the WHI's shortcomings. For instance, there have been concerns regarding the cohort studied. The WHI subjects were older than the typical menopausal patient, and generally without symptoms related to loss of estrogen. The cohort also represented a wide range of ages (from 50 to 70 years), and many patients with a markedly increased body mass index. Add to this some of the obvious idiosyncrasies of the data itself—for instance, the low rate of adverse events tracked in the placebo group for year-5 data—and the findings generate many questions for practicing clinicians and their patients.

EXPERT COMMENTARY Questions about this newly released data focus on the same issues raised by the original article, as well as a few new ones. The most obvious concern is a practical one that usually stirs no debate: How can a clinical trial study the effects of pharmacologic interventions on quality of life in a group of women who were not recruited because of poor lifestyle or dissatisfaction with their everyday living? In fact, women were excluded from this study if they reported symptoms related to the menopause.

Studying asymptomatic menopausal women is akin to prescribing antifungal or placebo vaginal preparation in a blinded manner to subjects without a yeast vaginitis, and then collecting data to evaluate which group is most satisfied after intervention.

Prior studies using hormonal therapy in women with symptoms related to hypoestrogenism have shown improvement in vasomotor symptoms and quality of life.[1,2] Women without symptoms related to estrogen loss cannot be expected to show an improvement in well-being with the use of hormone therapy.

My other concern is that these data may spur an increased use of unproven alternative therapies. For example, most nonhormonal interventions, such as herbal and dietary supplements, have either scant or nonexistent data supporting their role in improving patient well-being.

The question for clinicians is obvious: Is there a place for hormonal therapy in improving quality of life? To practice the best-quality medicine, we must use the data generated by randomized clinical trials, observational trials, retrospective reviews, and clinical judgement.

Each has a role in forming opinion: A randomized controlled trial recruits women willing to accept placebo intervention, randomization to different treatments, and a certain degree of the unknown.

Data from observational trials complement randomized controlled trial data because they more accurately reflect standards of medical care and either refute or support existing management protocols.

Retrospective reviews offer useful information about trends and prove helpful as pilot data to construct prospective trials.

Lastly, clinician acumen and the doctor-patient relationship take into account the individual needs of women. The best clinical practice does not rely on 1 set of data derived from a single data set.

BOTTOM LINE The data from this article should be shared with women, but should not overshadow other data on hormone therapy or the individual needs of an informed patient. Rather, it should be a piece of the pie—i.e., the aggregation of all objective data on HRT—and assist the woman and her physician in deciding whether the benefits outweigh the risks for her specific situation. ■

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