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Apples are not Oranges— Prevention and Treatment are Different!

The aftermath of the abrupt termination of the estrogen-progestogen (EPT) arm of the Women's Health Initiative (WHI) in July 2002, as well as the recent publication of its substudies, has produced at least one major benefit—women are having more interactive discussions with their health providers about their overall care. Unfortunately, many aspects of these discussions have been clouded by confusion. Examples include misunderstandings about the difference between relative risk and absolute risk, equating estrogen alone (ET) with EPT combination therapy, extrapolating results of studies in non-symptomatic women to symptomatic women, or extrapolating findings in older women with higher disease prevalence to younger women with lower disease prevalence.

However, the issue I intend to focus on is that prevention of potential future disease is not equivalent to treatment of an existing problem! Let me repeat that. Prevention and treatment are very different issues. This simple fact is often neglected in the design, reporting, and interpretation of major studies, including the WHI and the Heart and Estrogen/Progestin Replacement Study (HERS), and has not been recognized by us or our patients in discussions of pharmacotherapy for either prevention or treatment.^{1,2}

Let me review the background and make a clinical recommendation. A fact long recognized in clinical practice and by the FDA in their drug-approval process is that tolerance for potential minor or major drug-induced side effects is greater for a population with established disease and symptoms than for those who may, or may never, develop the condition.

Let us first consider the issue of prevention. Studies like HERS and WHI were designed with primary endpoints to determine whether hormone therapies could reduce the likelihood of developing heart disease (WHI)¹ or repeat heart attacks (HERS).² Study volunteers are screened as those most likely to remain in the study and not drop out; otherwise, statistical power could be lost. For example, in WHI, the authors stated that “women who reported moderate or severe menopausal symptoms during a washout period were discouraged from participating in the study....”³ Nonetheless, secondary endpoints, including “health-related quality of life” and “sexuality,” were later analyzed and the hormone therapy was reported to be essentially non-effective. Evaluating a treatment effect in a population pre-screened for a different purpose is a transparent non-sequitur. The study population is pre-selected to provide ability and statistical power to compare the effect of a placebo against an active drug for its impact on a clearly defined endpoint. When other endpoints are added, the pre-selected study population may no longer be the

relevant one for the additional endpoint being considered.

The most recent example of this are the data from the Women's Health Initiative Memory Study (WHIMS), published in the May 28th issue of the *Journal of the American Medical Association*.^{4,5} Data supporting a possible biological plausibility for a potential benefit of hormones on cognitive function has largely been confined to estrogen only, and usually in younger postmenopausal women. Some data suggest a potential negative effect of the progestin component of the combined therapy. There also is the possibility that an advantageous effect of hormones on cognitive function is limited to women who commence ET or EPT shortly after menopause.⁶ WHIMS, on the other hand, studied only women over age 65 (mean age, 71) who were on one form of EPT.^{4,5} It, therefore, is very difficult to extrapolate the meaning of these results for women ages 45-60, the usual symptomatic menopausal population.

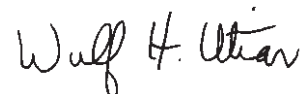
But let us move further and consider the issue of treatment of an established medical problem. The FDA has published very clear "guidances for industry" clarifying the requirements needed to achieve approved product indications during clinical development of therapeutic drug products.^{7,8} Take, for example, female sexual function. The FDA mandates use of "developed, tested and validated scales" to measure sexual response to drugs.⁸ In the WHI, "sexual functioning was reported by a single item," yet the authors had the audacity to report that "there were no significant effects of estrogen plus progestin on...sexual satisfaction."³ Simply put, the data emanating from studies like WHI and HERS on treatment outcomes like quality of life and sexuality would simply not cut the mustard with the FDA. Is it too much to ask our clinical researchers to put in place validated instruments that can really measure the endpoints they are considering? This is the least they owe us, their providers of research funds, and the population they profess to care about.

The media inevitably embellish these scientific publications or create their own meaning of the reports, rather than stating exactly what these studies do report, or at least offering a balanced perspective. Clinicians, in turn, have to deal with the aftermath of misinterpretation of poor science.

The point I am belaboring is that when we evaluate patients in our offices, it is mandatory to differentiate current problems requiring treatment from risk factors for diseases requiring potential preventive therapy. In turn, in considering whether to prescribe ongoing drug therapy, whatever the drug or drug family, the balance of risk-to-benefit will depend on whether we are prescribing to prevent or to treat. A woman

with severe, debilitating vasomotor symptoms presents a very different profile than a healthy non-symptomatic woman with reduced bone mass or elevated blood pressure. We all need to practice applied risk-benefit analysis in our efforts to assist patients in their decision-making with regard to therapeutic options.

The clinical recommendation during the patient visit, therefore, is to clearly differentiate and document the existing actual problems on the one hand and the risk factors for future disease on the other. We must explain the difference to the patient and the relative balance of risk and benefit. With a clearer understanding, women will find the issues surrounding the decision-making—about whether to take an active medication for treatment or for prevention, be it a hormone, a statin, a bisphosphonate, or other option—less confusing and less threatening.



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