Hormone Therapy:

Health Protection Lessons from the Women's Health Initiative

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In July 2002, the American researchers conducting the Women's Health Initiative (WHI) halted their large clinical trial to evaluate menopausal hormone therapy (HT). Rather than preventing diseases in ageing women, as many had claimed, the study found that a drug called Prempro (oestrogen + progestin) actually increases a woman's risk of heart disease (heart attacks, strokes and blood clots) and breast cancer—the two most common causes of death in post-menopausal women.[1]

Hormone therapy—unsafe pills being promoted as disease preventatives for women—fits a familiar pattern: from 1941 to 1971, DES (diethylstilbestrol), a cancer-causing drug, was prescribed to women in Canada and the United States to prevent miscarriage; today, raloxifene and tamoxifen are being tested as preventives for breast cancer in spite of links to blood clots and increased risk of endometrial cancer.[2] Over a period of decades, the drug regulatory system in both countries has allowed misinformation to spread and be translated into dangerous medical practice.

Prevention pills are different from those prescribed for treatment; they require a stronger health protection policy framework. The lessons of health protection that are described in this article are drawn from the Women's Health Initiative (WHI)—an exemplary clinical trial to study disease prevention in women.

Lesson One: The standard of safety for prevention interventions must be higher than for disease treatment.

The WHI illustrates the contrasting approaches of disease prevention and disease treatment. One approach targets healthy populations, the other helps suffering individuals. To explain why the WHI study was halted, one of the study's Principal Investigators said, "We have a higher standard [of safety] for prevention."[3] Many people thought that the researchers had overreacted: the increase in the risk that any one woman in the trial would develop breast cancer or heart disease because of HT appeared to be relatively small. In fact, by the safety standards of public health where many thousands of people are exposed, these risks were so high that the Principal Investigators agreed, "There's no role for HT in disease prevention."[4]

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Lesson Two: Disease prevention requires a holistic model of health.

The WHI used a holistic model of health to scientifically address the phenomenon of "disease substitution,"

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where a drug reduces the risk of one disease while increasing the risk of others. This meant that the trial would be stopped if global risks exceeded global benefits, or vice versa. By July 2002, the significantly increased risks for breast cancer (expected) and heart disease (unexpected) overwhelmed the benefits for bone loss (expected) and colorectal cancer (unexpected).

Lesson Three: Long-term clinical trial data are essential before drugs are promoted for prevention, but few drugs warrant a clinical prevention trial. Market forces should not determine which drugs are tested for prevention.

Collecting definitive clinical trial data on prevention is much more expensive than collecting comparable data for treatment: The number of volunteers needed is enormous and the trials must run for many years. Before its launch, critics opposed the WHI as "too expensive" and "unethical"—because women in the control group would be denied the presumed protection of HT against heart disease.

Post-menopausal use of hormones for disease prevention had to be tested in a clinical trial because the practice of doctors prescribing the drugs to women had already taken hold, even though long-term safety and efficacy were not established. Clearly, drugs should be tested *before* claims are made and prescriptions written.

The Principal Investigators of the WHI argue, convincingly, that further trials to test other oestrogen + progestin formulations and doses would be both unethical and a poor use of tax dollars because there is no reason to believe other HT formulations would have a different result. Similarly, there is no reason to test HT drugs for the prevention of cardiovascular disease in women 50 to 59 years old; one-third of the WHI's volunteers were in their 50s and they had the highest increased risk of stroke.[5]

Classic public health strategies—clean air and water, nutritious food, adequate housing, and safe workplaces—prevent many diseases and cause none. Very few medications meet the stringent requirements of public health: vaccinations for common childhood diseases, anticoagulants to prevent blood clots in surgery, and Pepto-Bismol for travellers' diarrhoea are exceptions to the rule.

Lesson Four: Curb the pervasive industry influence that contributes to irresponsible drug promotion and off-label prescribing.

The widespread myths about HT were based, not on science, but on marketing that subverted science. The American physician Robert Wilson planted the early seeds in 1965 with his book *Feminine Forever*. Wilson concealed the fact that he was a consultant to the manufacturer of Premarin while he flogged his popular book. In the mid-1970s, a clinical trial showed that Premarin increased the risk of endometrial cancer, and a blue-ribbon scientific panel rejected virtually all claims for oestrogen replacement therapy except for the alleviation of hot flashes and vaginal dryness.[6] When sales fell, manufacturer Wyeth-Ayerst added progestin to the oestrogen pill, creating Hormone Replacement Therapy (HRT).

The new drug countered the increased risk of endometrial cancer, but did nothing to slow the runaway claims about the preventative benefits of HRT. Articles like "Hormone Replacement Therapy for All? Universal Prescription is Desirable"[7] ran in respected medical journals, and obstetrician-gynaecologists' organisations recommended that all post-menopausal women take hormone replace-

ment therapy for disease prevention. Conflicts of interests affect medical prescribing generally; however, preventative drugs are particularly attractive candidates for the phenomenon known as the medicalisation of health.

Lesson Five: Take regulatory action to curb medicalisation of normal conditions like menopause.

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Following the announcement of the WHI study results, the U.S. Food and Drug Administration (FDA) formally adopted the term "menopausal hormone therapy" (HT) to replace the term HRT. The change signals that hormone therapy should be considered cautiously and only for short-term symptom relief during menopause.

Lesson Six: Track and curb off-label preventative drug use separately from indicated treatment uses for the same drug.

Physicians can prescribe drugs for non-indicated ("off-label") use. While this practice may be justified in exceptional individual cases, HT illustrates the danger when off-label prescribing becomes routine. Health Canada's post-approval surveillance system does not distinguish short-term use of the drug for indicated symptoms, like hot flashes, from long-term use. In the absence of such tracking, we will probably never know how many women have died from iatrogenic endometrial cancer, heart disease or breast cancer.

Lesson Seven: Support advocacy by organisations that are independent from industry and curb the influence of groups and individuals that receive funds from companies whose products they promote.

Women's health advocates and organisations have protested the unsubstantiated claims for HRT since the 1970s. Without the leadership of organisations independent of the drug industry, HT would have been used far more widely than it was. The National Women's Health Network (NWHN) in the United States successfully fought for patient package inserts for all oestrogen products, a move the American College of Obstetricians and Gynaecologists challenged in a court action.[8] The NWHN also opposed a 1990 Wyeth-Ayerst application to the FDA to have ERT approved for prevention of heart disease, and lobbied to have the WHI study funded.[9]

Independent public-interest groups in Canada and abroad are among the few voices opposing the industry-driven system of physician education and clinical research, and the exaggerated claims about the benefits of drugs in consumer ads. However, Canadian policies restrict public input into drug policy formation through tax laws that limit advocacy by non-profit groups and through maintenance of secrecy in the drug regulatory process.

Conclusion

Canada's current health policies nourish the rapid development and dissemination of preventive drugs, but provide few checks on their over-promotion. The results of the WHI challenge these biased health policies. The experience of hormone therapy is a cautionary tale to Canadians engaged in the renewal of health protection policies and our health care system.

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Footnotes

[1] Writing Group for the Women's Health Initiative Investigators. "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from The Women's Health Initiative Randomized Control Trial." Journal of the American Medical Association 288: 321-33, 2002.

[2] Fisher, B., Costantino, J.P. et al. "Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvent Breast and Bowel Project P-1 Study." Journal of the National Cancer Institute 90: 1371-88, 1998.

[3] Scientific Workshop on Menopausal Hormone Therapy, open discussion session, Bethesda, Maryland, 23 October 2002.

[4] Scientific Workshop on Menopausal Hormone Therapy, 23 October 2002.

[5] Limacher, M. "Women's Health Initiative Data: Risk of Cardiovascular Disease and Stroke." Presentation to the Scientific Workshop on Menopausal Hormone Therapy, Bethesda, 23 October 2002.

[6] Limacher, 2002.

[7] National Women's Health Network (NWHN). The Truth About Hormone Replacement Therapy. Roseville, CA: Prima, 2002, pp. 25-26.

[8] NWHN, p. 25.

[9] NWHN, p. 180.