THE IMPACT OF THE WOMEN'S HEALTH INITIATIVE STUDY ON INCIDENT CLONIDINE USE IN ONTARIO, CANADA

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ABSTRACT

Background
Following publication of the Women's Health Initiative (WHI) study, many women discontinued use of estrogen replacement therapy. There is some evidence that the antihypertensive agent clonidine can reduce the frequency of hot flashes associated with menopause.

Objectives
To determine the impact of the WHI study on incident use of clonidine in elderly women in Ontario, Canada.

Methods
Retrospective, population-based administrative database design. Data on all residents of Ontario over the age of 65 years were included. Time series methods were used to analyze change in incident clonidine use following publication of the WHI study.

Results
Following publication of the WHI study, incident use of clonidine increased substantially among elderly women in Ontario, Canada. Similar trends were not observed for incident use of other antihypertensive medications.

Conclusion
During a period of time in which a large proportion of women discontinued estrogen replacement therapy, incident use of clonidine increased. There is some evidence that a small number of women may have sought alternative relief from menopausal symptoms using other pharmacological therapies.

Key Words: clonidine, menopause, estrogen replacement therapy, health services research, pharmacoepidemiology

Estrogen Replacement Therapy (ERT) has long been used for treatment of menopausal symptoms. The Women's Health Initiative (WHI) trial, published on July 17, 2002, concluded that overall health risks exceeded benefits from use of combined estrogen plus progestin among healthy postmenopausal women.[1] A recent study demonstrated that subsequent to the publication of these results, the proportion of elderly women in Ontario who used estrogen declined significantly.[2] Furthermore, a survey reported that 44% of women using ERT discontinued therapy in the year following the study's publication.[3]

Conflicting evidence exists as to the effectiveness of the antihypertensive agent clonidine for the relief of hot flashes associated with menopause.[4-10] Two reviews suggest that clonidine should be considered as an alternative to

ERT for the management of hot flashes associated with menopause,[11-12] however one cautions about possible adverse effects.[12] A third review cautions against the use of clonidine due to limited efficacy and adverse effects[13] (the most common side effects are dry mouth, sedation, and hypotension[14]).

Thus, some evidence suggests that clonidine may be perceived as one of the limited alternatives to ERT for the relief of hot flashes associated with menopause. The purpose of this study is to examine trends in incident use of clonidine following publication of the WHI trial.

METHODS

We studied incident claims for clonidine to Ontario's universal Drug Benefit program for seniors (ODB), which tracks medication use by all 1.3 million residents of Ontario 65 years of age and older. We studied claims submitted between January 1, 1992 and June 30, 2003.

For each quarter of each year, we determined the number of prescriptions filled by women who had not filled a prescription for clonidine in the previous 365 days to determine the number of incident clonidine users in each quarter. As a control analysis, we examined incident clonidine use by elderly males during the same time period in Ontario.

Time series analysis using exponential smoothing models was used to model quarterly data from the first quarter of 1993 to the second quarter of 2002. In order to determine the impact of the publication of the WHI trial on the use of clonidine, projections and 95% confidence intervals were obtained for the last two quarters of 2002 and for the first two quarters of 2003. The magnitude of the impact of the WHI study on incident use of clonidine in Ontario was assessed by comparing the predicted number of incident users had the WHI not been published, with the observed number of incident users in the four quarters following the publication of the study.

As a sensitivity analysis, we examined the impact of the publication of the WHI study on trends in incident use of other antihypertensive agents (thiazide-type diuretics, beta-blockers, ACE inhibitors, and calcium channel blockers). This was done separately for males and females.

RESULTS

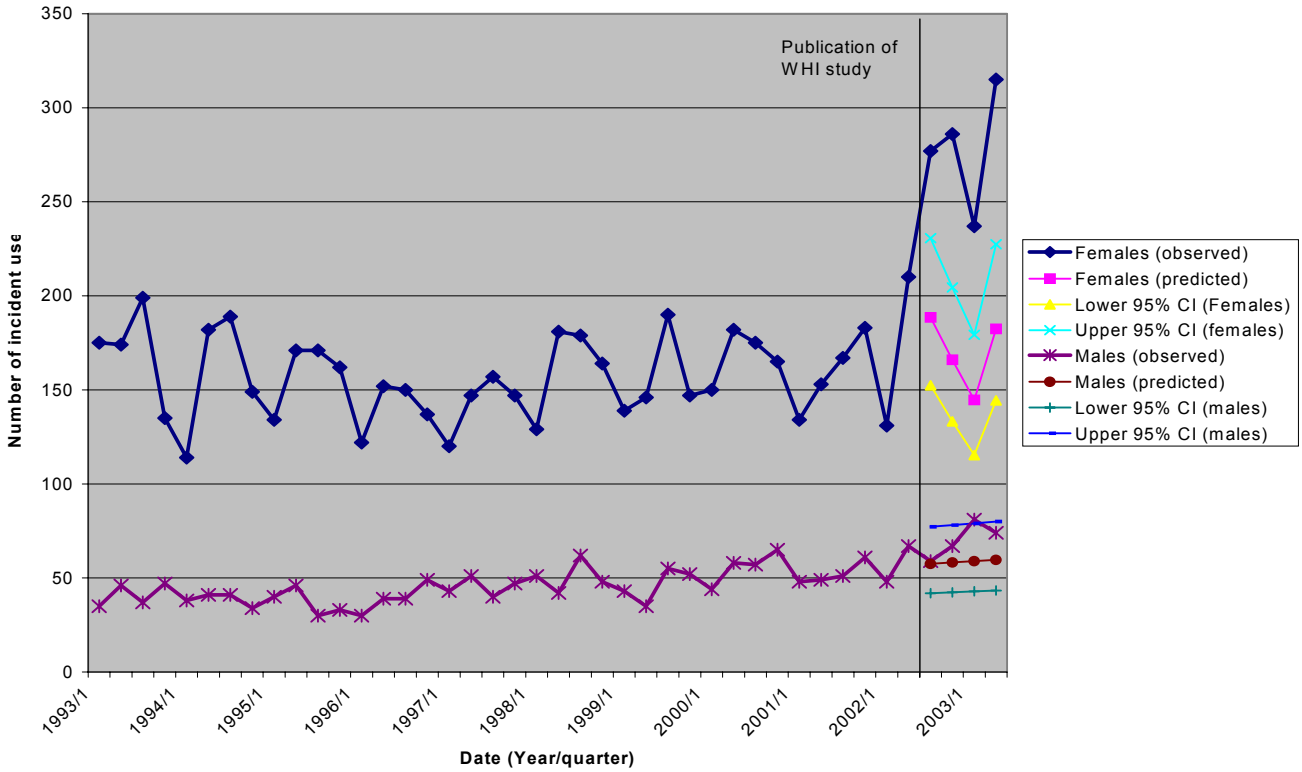
The number of incident female users of clonidine is described in Figure 1. The number of new female users of clonidine decreased slightly from 1993 until 1996, after which the number of incident female users increased slightly until the second quarter of 2002. However, following the publication of the WHI study, the number of new female users increased significantly beyond that predicted by the model ($P < 0.0001$ for each of the four quarters following publication of the WHI study). According to the time series model, the predicted number of new female users, had the WHI study not been published, was 682, whereas the observed number of new users was 1,115. Thus, the observed number of incident female users was 63% higher than predicted by historical trends.

The number of incident male users of clonidine is also described in Figure 1. Incident use of clonidine was substantially lower in males than in females. However, prior to the publication of the WHI study, the trend in incident clonidine use by males mirrored that observed for females.

Initially, there was a modest decrease from 1993 until 1996, after which the number of incident male users increased slightly until the publication of the WHI study. Only in the third quarter following the publication of the WHI study was the number of incident male users of clonidine significantly higher than that predicted by the time series model ($P = 0.0158$). In the remaining three quarters, the number of incident male users was not significantly different than that predicted by the model ($P = 0.4417$, 0.1935, and 0.0836 for the remaining three quarters). According to the time series model, the predicted number of new male users, had the WHI study not been published, was 234, whereas the observed number of new users, which was 281. Thus, the observed number of incident male users was 20% higher than predicted by historical trends.

The publication of the WHI study did not result in an increased incident use of other antihypertensive medications (thiazide-type diuretics, beta-blockers, ACE inhibitors, and calcium channel blockers) in either men or women. Indeed, in two of the four quarters following the publication of the WHI study,

Figure 1: Incident use of Clonidine in Ontario



incident use among women of other antihypertensive medications was statistically significantly lower than predicted by historical trends. Furthermore, in the first quarter following the publication of the WHI study, incident use among men of other antihypertensive medication was significantly lower than predicted by historical trends.

DISCUSSION

In the four quarters following the publication of the WHI study, we demonstrated a substantial and statistically significant increase in incident use of clonidine amongst elderly women in Ontario, Canada. This increase in incident use was not mirrored in elderly men. Furthermore, such a trend was not observed for incident use of other antihypertensive agents.

Earlier studies demonstrated that the proportion of elderly women using ERT decreased substantially following publication of the WHI study.[2, 3] There is controversy in the medical literature as to the appropriateness of the use of clonidine for relief of menopausal symptoms.[4-13] We have presented preliminary evidence that one of the unintended consequences of the WHI study may have been the initiation of therapies with inconclusive evidence. As women abandoned ERT, some may have initiated treatment with medications such as clonidine, for the treatment of menopausal hot flashes.

There are limitations of our study. First, we were unable to determine the exact reason for initiating clonidine. Although clonidine is classified as an antihypertensive medication, it is not commonly used for hypertension. Second, our data were limited to those over the age of 65 years, and thus are not representative of all post-menopausal women. However, this is balanced by the fact that the data are population-based, providing coverage for all elderly women in Ontario, Canada's largest province.

Our study demonstrated a significant increase in incident clonidine use exceeding secular trends among elderly postmenopausal women. The clinical implications of such an unintended event require exploration.

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