Impact of recent evidence on the use of hormone therapy in the South African private sector (2001-2005)

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Abstract

Background: The release of the results of the oestrogen plus progesterone therapy (EPT) arm of the Women's Health Initiative (WHI) in July 2002 started a worldwide process of reconsideration of the rationale behind hormone therapy (HT). This process was accelerated after the release of the results from the oestrogen-only (ET) arm of the same study. The results of the WHI reinforced the indications of HT to alleviate vasomotor symptoms and to prevent bone loss associated with early menopause, but refuted the possibility of cardioprotective effects and raised uncertainty around the risk of breast cancer for long-term users. In response, new guidelines and position statements were developed to aid healthcare practitioners and patients in various countries, including South Africa. The dissemination and penetration of all this information has been assessed in a number of countries, but the extent of its effect on the South African market is as yet unknown. Accordingly, the aim of this study was to assess the use of HT in the South African private sector from 2001 to 2005.

Methods: Monthly HT sales data for January 2001 to October 2005 were obtained from IMS Health (SA). Three successive periods were compared: (1) January 2001 to June 2002 (discontinuation of the WHI oestrogen plus progestogen arm), (2) July 2002 to February 2004 (termination of the WHI oestrogen only arm) and (3) March 2004 to October 2005.

Results: Overall, sales of HT fell 6.9% between periods 1 and 2 and 14.6% between periods 2 and 3. The total sales of ET predominated; they were more than double those of EPT. For ET, the sale of conjugated equine oestrogen (CEE) preparations exceeded those of non-CEE ET preparations, while for EPT preparations the reverse was true. The decline in ET sales was mostly accounted for by the fall in sales of CEE, by 9.8% and 20.6% for the two periods respectively. There was an increase in sales of both low-dose CEE and non-CEE, although the magnitude of increase in the case of the latter was much greater. Throughout the entire study period, CEE 0.625 mg tablets were found to account for the greatest sales volumes. Private sector sales represented 74.4% of total national HT sales over this period.

Conclusion: The release of the WHI findings resulted in a modest decrease in HT sales in South Africa, although it was less dramatic than sales reported elsewhere. The change in prescribing cannot be attributed to any single factor. Factors such as publicity, adherence to new guidelines, and pharmaceutical marketing may all have contributed. Guidelines need to be updated as the results of new research continue to be published. There is also a need to periodically review prescribing trends, and to assess compliance with evidence-based guidelines, in order to improve the quality of medicines use. The majority of prescriptions for HT in South Africa are written by general practitioners, rather than by specialists. It is thus imperative that guidelines be appropriately framed for this market, as well as interpreted and applied.

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Background

Globally, the release of results from the oestrogen plus progesterone therapy (EPT) arm of the Women's Health Initiative (WHI) in July 2002 marked the start of a process of reconsideration of the rationale behind hormone therapy (HT).[1,2] This process was accelerated after the release of the results from the oestrogen-only (ET) arm of the same study.[3] The results of the WHI reinforced the indications of HT to alleviate vasomotor symptoms and to prevent bone loss associated with early menopause, but refuted the possibility of cardioprotective effects and raised uncertainty around the risk of breast cancer for long-term users. In response, new guidelines and position statements were developed to aid healthcare practitioners and patients in various countries, including South Africa.[4]

The extent of the reaction to this new evidence, from a large randomised controlled trial rather than observational studies, can be gauged by the speed with which guidelines were produced. The South African Menopause Society guidelines were published only five months after the release of the results from the WHI ET arm.

The WHI results received wide publicity in both the lay press and medical literature. Any changes in sales of HT products, which are obtainable only by prescription, would thus result from a combination of changes in patient demand, prescriber attitudes, adherence to published guidelines, and also ongoing marketing efforts by pharmaceutical manufacturers. The dissemination and penetration of all this information has been assessed in a number of countries, but the extent of its effect on the South African market is as yet unknown. Accordingly, the aim of this study was to assess the use of HT in the South African private sector from 2001 to 2005.

Methods

This study was approved by the Research Ethics Committee, Nelson R Mandela School of Medicine, Durban, South Africa (Ref: E201/05). Data were obtained from the IMS Health (SA) pharmaceutical market measurements database. IMS Health (SA) is an independent company that collects monthly data as electronic downloads of pharmaceutical sales to retail pharmacies, dispensing medical practitioners and private hospitals. Total private sector monthly sales of ET, EPT and progestogen-only preparations (PT) products for the management of menopause were collected for the period January 2001 to October 2005. Data were individually presented for each formulation, strength and pack size. Sales of oral solid dosage forms were thus expressed as the total number of dosage units ("pills"), while those of other formulations, such as creams and patches, were recorded as sales units.

Data were presented graphically as total sales per quarter. Sales in three successive periods were compared: (1) January 2001 to June 2002 (corresponding with the discontinuation of the WHI EPT arm); (2) July 2002 to February 2004 (corresponding with the early termination of the WHI ET arm); and (3) March 2004 to October 2005. Within each period, data were presented as mean monthly sales per period. Mean monthly sales for each period were calculated using the total sales and the number of months in that particular period. The mean monthly sales in each period were compared by expressing the difference in sales, as a percentage of the mean of sales in the preceding period. As total national sales figures for the private sector were used, not merely a sample thereof, no confidence intervals or other measures of variability were computed.

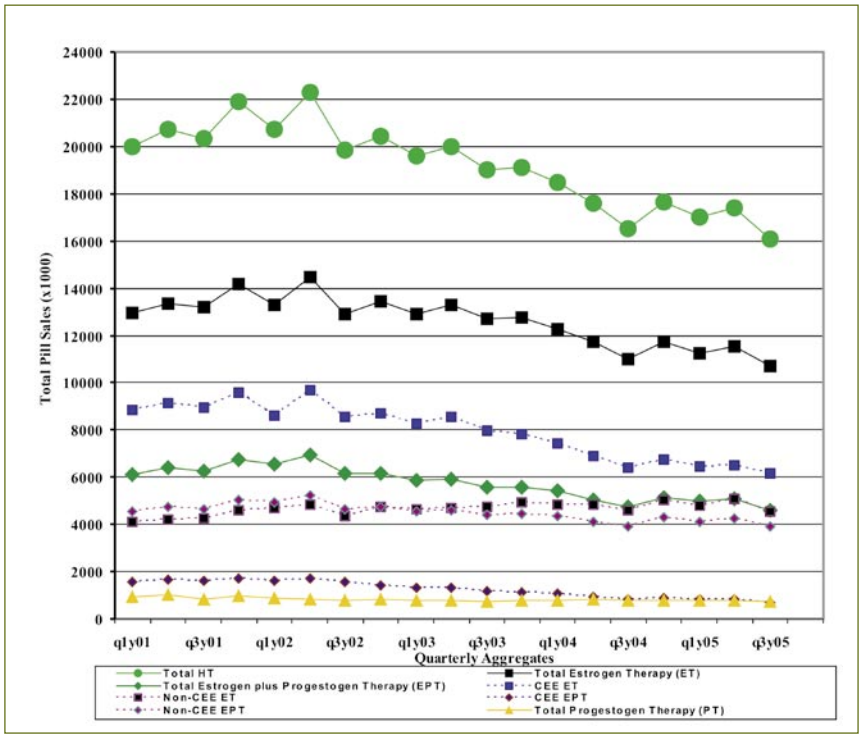
Results

Private sector sales of the oral solid dosage forms for the entire study period are shown in Figure 1. The total sales of ET predominated; they were more than double those of EPT. For ET, the sale of conjugated equine oestrogen (CEE) preparations exceeded those of non-CEE ET preparations, while for EPT preparations the reverse was true.

Overall sales of HT fell by 6.9% between periods 1 and 2 and 14.6% between periods 2 and 3. Over the entire study period, all sales declined except those of non-CEE ET preparations.

Sales of ET fell by 4.7% and 12.3% between periods 1 and 2 and periods 2 and 3, respectively. The decline in ET sales was accounted for by the decrease in CEE ET preparations (9.8% and 20.6%, respectively). In fact, sales of non-CEE ET preparations actually rose by 5.6% and 2.2% for the two periods, respectively.

Figure I: Total Sales per Quarter of Oral Hormone Therapy in the South African Private Sector, 2001-2005



Sales of EPT declined by 10.3% and 15.5% between periods 1 and 2 and periods 2 and 3, respectively. The decline in sales of CEE EPT preparations was greater than the decline in sales of non-CEE EPT preparations. For period 1 to 2, sales of CEE EPT preparations fell by 21.9% compared to only 6.3% for non-CEE EPT preparations. The decreases from period 2 to 3 were 35.8% and 9.7%, respectively.

While falling gradually during the study period, sales of PT remained consistently low.

Table I shows the mean sales in each of the three periods for the dominant form of oral HT,

disaggregated by the type of oestrogen (CEE and 17β oestradiol) and strength, together with sales of vaginal and transdermal formulations.

Table I: Mean of monthly sales of selected strengths and formulations of oestrogen therapy (ET) for the periods 1, 2 and 3

	PERIOD 1	PERIOD 2	PERIOD 3
Oral Oestrogen	**Pills (x1000)**	**Pills (x1000)**	**Pills (x1000)**
Conjugated equine oestrogens			
0.3 mg	189	208	268
0.625 mg	1871	1699	1351
1.25 mg	933	837	559
2.5 mg	48	0	0
Micronised 17β oestradiol			
1 mg	12	153	345
2 mg	613	589	492
4 mg	239	230	203
Other Oestrogen Formulations	**Units (x1000)**	**Units (x1000)**	**Units (x1000)**
Vaginal preparations	8	8	9
Transdermal patches	29	26	23

Throughout the entire study period, CEE 0.625 mg tablets were found to account for the greatest sales volumes. The highest strength CEE formulation (2.5 mg) was removed from the market in April 2002. The sales of CEE 1.25 mg, though declining,, remained relatively high. However, they declined more than those of the equipotent 17β oestradiol strength (4 mg); they declined by 10.3%, compared to 3.8% for period 1 to 2, and by 33.2%, compared to 11.7% for period 2 to 3. Similarly, sales of CEE 0.625 mg declined more than those of the equipotent 17β oestradiol strength (2 mg). Between periods 1 and 2 the declines were 9.2% and 3.9% respectively, while for periods 2 to 3 they were 20.5% and 16.4%, respectively. In contrast, there was an increase in sales of both low-dose CEE (0.3 mg) and 17β oestradiol (1 mg). Of particular interest is the magnitude of the increase in sales of low-dose 17β oestradiol. While sales of CEE 0.3 mg increased by 9.8 and 29% from periods 1 to 2 and periods 2 to 3, respectively, the corresponding increases in sales of 17β oestradiol 1 mg were 1211.6% and 125.3%.

Sales of vaginal preparations were small, and increased only slightly (12.2% from period 2 to 3, and 13.4% overall), while sales of oestrogen-only transdermal preparations declined gradually.

Discussion

South Africa's private health sector predominantly serves a highly urbanised and relatively affluent sub-population, which enjoys easy access to various media. The sales figures captured by IMS Health would therefore represent, in the main, prescriptions issued to peri- and post-menopausal women from the almost 7 million insured population (about 15% of the total population).[5] HT use in this highly selected sub-population is expected to be high. Private sector sales represented 74.4% of total national HT sales over this period. A survey among a sample of 398 post-menopausal women seen at a single specialist private practice in Cape Town, South Africa, showed that, as at July 2003, 78.6% were using HT.[6] A similar survey by the same group in 2004 showed that 78.5% of the women were using HT.[7] Other developing and middle-income countries have similar elite populations, served by the private healthcare sector. Data from Chile showed that, after the release of the first WHI report, 67.3% of a sample of women aged 40 to 64 years, living in an exclusive residential area and receiving private health care, were using HT and 47.3% were aware of the WHI study.[8]

Reaction to the WHI results in other countries has been marked, if variable. Comparisons of findings between different countries are not straightforward. Some studies are population based while others are drawn from selected sub-populations. The time periods surveyed also vary. We found a modest reduction (6.9%) in total private sector HT sales after the release of results from the EPT arm of the WHI, and a further decline (14.6%) after the release of results from the ET arm. The reaction in both the United States of America (USA) and United Kingdom (UK) was far more marked, showing reductions of 38% and 20.7% when the EPT arm was discontinued.[9,10] The UK response was, however, characterised by the authors as "limited", in comparison to that seen in the USA. Based on a random national sample, another USA survey showed that use of HT had decreased 57% from the first half of 2002 to the first half of 2004; from 28% of the sample to 12%.[11] This survey would however not have captured the full impact of the WHI ET results. The extent of exposure to the WHI results, after the discontinuation of the EPT arm, has been assessed in a USA setting.[12] Of a sample of HT users, 93% reported knowing about the WHI and 56% had reported attempting to discontinue HT in the 6 to 8 months after July 2002. In Australia, where in 2004 the ever use of HT in women aged 50 years and older was reported to be 46.5% (with a mean duration of use of 7.46 years),[13] current use dropped from 28% in 2000 to 10.2% in 2002 (a fall of 64%), but returned to 18.8% in 2003.[14] The media was shown to have had the main influence on women's decision making. It was also noted that half of those who restarted therapy changed to another type of HT.[14] In the Netherlands, by contrast, a more marked decline in use of EPT was seen after the publication of the observational Million Women Study[15] than after the release of the WHI EPT arm results.[16] A follow-up study in the Netherlands showed a 66% reduction in EPT use among women aged 47–74 years between 2001 and 2004.[17] Prevalence of HT use in this age group was, however, markedly lower than in other countries, at 5.64% and 2.39% in 2001 and 2004, respectively. According to Townsend and Nanchahal, even after taking into account the 21% reduction in HT use seen in the UK after 2001 (from an estimated baseline prevalence of 36% of postmenopausal women), HT would be still be "unprecedented as a drug in widespread use by a predominantly well population".[10]

Differences in the relative use of EPT and ET are also striking. In both our study and in the US, use of unopposed oestrogen products dominated. The same has been shown in Hong Kong.[18] The reverse was true in the UK and the Netherlands. The appropriateness of unopposed HT use needs to be carefully reviewed by all healthcare practitioners at every opportunity.

Differences in the use of CEE and non-CEE HT preparations also point to how the results of the WHI study (and the Million Women study) have been interpreted and applied. Although the Hong Kong data showed a 43.5% decline in CEE EPT public sector prescriptions from the first to the second half of 2002, the usage trend was already negative. Prescriptions for CEE ET preparations in Hong Kong fell by 22.4% over the same period. Overall, HT use stabilised in Hong Kong in 2003. In the USA, CEE preparations accounted for most of the ET and EPT sales, while the opposite was true in the UK. In our study, sales of CEE ET preparations exceeded those of other products, while for EPT preparations the reverse was the case. Despite the fact that the initial WHI report involved EPT only, our study showed that ET sales also fell by 4.7% after the EPT arm was stopped. This trend was also observed in the USA, although there the decline was much larger. These declines, in both countries, may have been partly due to the fact that some women were getting their opposed HT in the form of two

medicines rather than a combination formulation. This possibility is, to some extent, supported by the reduction observed in the sales of PT. On the other hand it is possible that women taking ET only, and their healthcare practitioners, were extrapolating the findings from the EPT arm of the study, to a possibility of harm with ET. Indeed, in January 2003 the FDA ordered black box warnings to be placed on the labels of all drugs for menopausal symptoms containing oestrogen or oestrogen and progestogen. Not unexpectedly, we observed a larger fall in ET sales once the ET arm of the WHI was stopped (12.3%).

That the greater decline in sales was seen with CEE preparations is also consistent with findings in the UK and USA, and is probably related to the fact that the WHI study involved the use of these products specifically, and therefore, they were perceived as most directly linked with the evidence of harm. In addition, changes in marketing activity may be responsible for some of the changes seen. In the quarter before the release of the WHI EPT results, promotional spending on HT in the USA was shown to be $71 million, or $350 per USA physician.[19] This decreased by 37% after the release of the WHI EPT results. The greatest decline in promotional spending was associated with the 0.625 mg CEE EPT product. A 100% decrease in direct-to-consumer advertising spending was seen. Importantly, this study also showed a "resurgence" in promotional spending on low-dose EPT and a modest increase in prescriptions for this type of HT towards the end of 2003. USA data also showed that sales of 0.3 mg CEE grew by 6% in the second half of 2002. While we have no access to data that show even a temporal association with promotional spending in South Africa, the marked increases in sales of low-dose HT products, especially non-CEE preparations, are noteworthy. This may partly be explained by the inclusion in local and international guidelines of recommendations that lower than standard dose products should be used if effective.[4,20] In the Hong Kong study, the use of low dose ET doubled between the first half of 2002 and the second half of 2004.[18]

The slight changes in the low sales of vaginal preparations over the entire study period in South Africa are not markedly different from those seen elsewhere. In the Netherlands, for example, the prevalence of the use of low-potency vaginal oestrogens did not change between 2001 and 2004.[17] The slow decline in sales of transdermal preparations seen in our study also mirrors that seen in the US, but is less than that seen in the Netherlands. Although new evidence has raised the possibility that transdermal administration may not be associated with increased risk of venous thromboembolism, it has shown that the use of 17β oestradiol products is associated with increased risk.[21]

Data from the ESTHER study have raised the possibility that the type of HT (particularly the type of progestogen) and the route of administration may influence the risk benefit profile.[21] Acknowledging the new data, in relation to venous thromboembolism risk, Rexrode and Manson[22] nonetheless highlighted the need for further research on this issue.

Increased use of low-dose HT products would seem to be in line with published guidelines. However, although sales of the higher doses of ET in South AFrica decreased over the study period, the reduction was considerably smaller than that seen in other countries. While direct-to-consumer advertising is not allowed in South Africa, this cannot account for the differences seen, as Europe and Australia also prohibit such practices. While no data exist to show how well the lay press covered the WHI study, a clear guideline from the South African Menopause Society was quickly published in a local medical journal. That a modest change is seen in prescribing behaviour, even after the release of important new data, has been shown before, in relation to alpha-blocker use after the publication of the ALLHAT study.[23] The dissemination of written material only is recognised as a poor way to improve the rationality of medicines use.[24] Naylor has attempted to analyse the differences in response in the USA to the WHI and ALLHAT results, and has identified pharmaceutical marketing as one of the more powerful forces at work.[25]

The present study was subject to various limitations. Although responsible for the majority of national HT sales, the private healthcare sector serves a highly selected sub-population. In addition, sales data lack information related to the patient, such as age, presence or absence of a uterus, and co-morbidities. No information can be obtained about the number of repeat prescriptions, duration of use, switching between dosages and formulations, or reasons for discontinuing therapy.

Conclusions

The release of the WHI findings in 2002 resulted in a decline in HT sales in South Africa, but it has been much less dramatic than reported elsewhere. More recent secondary analyses of the WHI data have raised the possibility that women who started HT closer to menopause tended to have a reduced risk of coronary heart disease compared with women who started HT later.[26] This appears to confirm the results of previous meta-analyses.[27,28] Nonetheless, Grady and Barrett-Connor provided a succinct bottom line based on available data: "treat bothersome menopausal symptoms with the lowest effective dose of HT for the shortest time possible and do not use it to prevent disease ".[29] Attributing the observed changes in prescribing behaviour to any one factor is not possible in view of the complexities involved. Although publicity, both in the lay and professional press may have had some effect, a certain degree of adherence to new guidelines and awareness of labelling changes made in other countries, notably the USA, may also have impacted on either prescriber or patient behaviour. In addition, the impact of marketing by pharmaceutical manufacturers cannot be discounted. Guidelines need to be updated as the results of new research become available. There is also a need to periodically review prescribing trends, and to assess compliance with evidence-based guidelines, in order to improve the quality of medicines use. Finally there is some evidence from IMS Health SA (Personal communication: IMS Health SA, based on the National Disease and Therapeutic Index stratified sample of health practitioners in South Africa.) that the majority of prescriptions for HT in South Africa are written by general practitioners rather than by specialists. It is thus imperative that guidelines be appropriately framed for this market, as well as adequately interpreted and applied.

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Declarations

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