Trends in the incidence, prevalence and sales volume of menopausal hormone therapy in Sweden from 2000 to 2021

Micaela Sundell\textsuperscript{a,b,}\textsuperscript{*}, Jan Brynhildsen\textsuperscript{a,c,d}, Anna-Clara Spetz Holm\textsuperscript{a,e}, Mats Fredrikson\textsuperscript{a}, Mikael Hoffmann\textsuperscript{f,g}

\textsuperscript{a}Department of Biomedical and Clinical Sciences, Linköping University, 581 83 Linköping, Sweden
\textsuperscript{b}Department of Obstetrics and Gynaecology, Kalmar County Hospital, 391 85 Kalmar, Sweden
\textsuperscript{c}School of Medical Sciences, Faculty of Medicine and Health, Örebro University, 701 83 Örebro, Sweden
\textsuperscript{d}Department of Obstetrics and Gynaecology, Linköping University Hospital, 581 85 Linköping, Sweden
\textsuperscript{e}Department of Health, Medicine and Caring Sciences, Linköping University Hospital, 581 83 Linköping, Sweden
\textsuperscript{f}The NEPI Foundation, 111 81 Stockholm, Sweden

\textbf{ARTICLE INFO}

\textbf{Keywords:}
Menopausal hormone therapy
Hormone replacement therapy
Climacteric
Pharmacoepidemiology
Incidence
Run-in period

\textbf{ABSTRACT}

\textbf{Objectives:} To describe the trends in the prevalence of use menopausal hormone therapy (MHT) in Sweden over the period 2000–2021 and to analyse the impact of different lengths of run-in on the calculated incident use.

\textbf{Study design:} Individual-level data on MHT dispensations for 2.5 million women aged 45–69 years for the period 2006–2021 were analysed. Aggregated sales volumes in defined daily dose (DDD) were available for the whole study period (2000–2021).

\textbf{Main outcome measures:} One-year prevalence and one-year incidence (18-month run-in) per 1000 women and DDD per 1000 women per day of MHT were the main outcome measures. The predictive values for incidence representing first-ever use of MHT were calculated for different run-in periods, which is a defined period without dispensations.

\textbf{Results:} Both the DDD, from 2000, and the prevalence, from 2006, decreased by over 80 \% in women aged 50–54 years, until 2010, when the use of MHT stabilised. The predictive value for incident users to be first-ever users was 88 \% in women aged 50–54 years, with a run-in of 18 months, in 2021. The incidence was stable between 2007 and 2016. From 2017 the incidence increased, being most pronounced for women close to menopause.

\textbf{Conclusions:} MHT use decreased significantly after the turn of the century, but has increased since 2017. A run-in period of 18 months was found suitable and reliable for defining incident users of MHT in the age intervals closest to menopause. Incidence seems to be a more sensitive measure than prevalence or DDD for the early detection of changes in trends in prescriptions of MHT.

\textbf{1. Introduction}

\textbf{1.1. Menopausal hormone therapy}

Vasomotor symptoms, such as hot flushes and nocturnal sweats, are experienced by 60–80 \% of all European women at some point during the menopausal transition [1]. The most effective treatment to reduce vasomotor symptoms is menopausal hormone therapy (MHT) [2], also referred to as hormone replacement therapy (HRT).

The number of women in Sweden and other Western countries having MHT prescribed has declined dramatically in the last few decades [3–5]. The prescription of MHT peaked around the turn of the millennium [3–5], at the time the results from the Women’s Health Initiative (WHI) [6], Heart and Estrogen/Progestin Replacement Study (HERS) [7] and the Million Women Study [8] were published. In contrast to previous observational studies [9], these studies showed increased risks of cardiovascular events and cancer among postmenopausal women using MHT [6–8]. Consequently, the prescription of all types of MHT rapidly decreased worldwide [3,10–16].

Later, the generalizability of the HERS and WHI studies’ results was
challenged [17], especially since women treated nowadays are significantly younger and therefore have a lower baseline risk for cardiovascular disease. After 18 years of follow-up of WHI, no increased risk of all-cause, cardiovascular or total cancer mortality was confirmed among MHT users [18]. Current guidelines state that MHT should be initiated within ten years of menopause and not after the age of 60 [19,20]. Because many women will experience bothersome symptoms for many years, long-duration hormone therapy use may be needed, and an arbitrary age-based stopping rule is no longer considered clinically appropriate [20]. Thus, several changes in the MHT recommendations have been issued during the last few years. However, it is unclear if these changes have affected clinical practice in Sweden.

1.2. Definitions of drug use

Population-based drug utilisation studies have traditionally examined treatment practices by studying sale volumes, often by the Defined Daily Dose (DDD) linked to the substance and route of administration and defined by the World Health Organisation [21]. The DDD is defined as “the assumed average maintenance dose per day for a drug used for its main indication in adults” and is an internationally standardized unit of measurement. The actual prescribed daily dose may deviate from the DDD depending on patient groups treated and if the drug is used in different dosage intervals.

Data on the dispensations of drugs to individuals instead of aggregate sale volumes have created new possibilities to analyse drug utilisation and link personal data from different registers [22]. Use of individual-level dispensation data from 1st of July 2005 in Sweden has made it possible to separate data on new users (incident users) from data on users with ongoing use (prevalent users).

A new case of drug treatment is of particular interest since it directly correlates to a prescribing physician’s operational decision to initiate treatment and thus might be more sensitive to reflecting changes in prescribing decisions following updated guidelines. Also, beneficial effects and adverse reactions might differ between new and ongoing treatment. From a hormone treatment perspective, it is essential to clearly define a first-time user as the risk of thromboembolic events might be higher, and the proportion of episodes of drug treatment recurrence correspondingly lower [25].

A new case of drug treatment can be identified by a dispensation at a pharmacy after a defined period without dispensations - a run-in period [25]. Each identified new case might represent the first-ever use in an individual or an episode of treatment recurrence [25].

With an increased run-in period, the proportion of true first-ever use will be higher, and the proportion of episodes of drug treatment recurrence correspondingly lower [25]. However, there is no clearly defined, recommended run-in period for defining a new case or a first-ever use of MHT.

1.3. Rationale for this study

The use of MHT has changed substantially the last decades. The availability of large, national, validated registers in Sweden, with individual-level data from 1st of July 2005, offer unique opportunities to study the dispensations of MHT in the total female population, stratified by age-groups. The dispensations from pharmacies can be used as a proxy for drug use in register-based studies, like this study. To facilitate the interpretations and comparisons between different studies, uniform definitions of drug use is required.

1.4. Aim

The primary aim was to describe the dynamics of incidence, prevalence and dispensed amount measured in defined daily doses of menopausal hormone therapy in Sweden from 2000 to 2021 and relate this to new knowledge and guidelines during the interval.

The secondary aims were to analyse the impact of different run-in periods on the incidence and to apply the most suitable run-in period for describing the incidence of MHT use.

2. Methods

2.1. Data collection

The available systemic MHT used in Sweden is presented in Table 1. The DDD definitions and classification of drugs according to the Anatomical Therapeutic Chemical system (ATC) for 2021 were used [26]. The DDD of combined preparations of oestrogens and progestins are based on peri/postmenopausal hormone therapy used in cycles of 28 days. Since there for MHT in most cases exists only one strength equalling the recommended dose, the measure DDD for MHT in almost all cases is equal to the actual prescribed daily dose.

Aggregated data on dispensed amounts of MHT in DDD per 1000 women per day and number of dispensions per 1000 women were collected from official national drug consumption statistics at the Swedish eHealth Agency [27].

2.2. Study population

Dispensation data were extracted from the Swedish Prescribed Drug Register, maintained by the National Board of Health and Welfare. Population data were extracted from Statistics Sweden by the National Board of Health and Welfare and included by the authority in the data file delivered to the researchers. Data on DDD per 1000 women per day were accessible from the eHealth Agency of Sweden from calendar year 2000 through 2021. Number of dispersions per 1000 women and year were available from 2006, also with the use of population data from Statistics Sweden.

The calculation of prevalence and incidence included data on 2,438,307 women aged 45–69 years, who were residents of Sweden in at least one calendar year during 2006–2021. For the validation of different run-in periods, data on all women ≥30 years during the same time period were used (n = 4,210,827).

The calculations were made by the National Board of Health and Welfare, using SAS version 8.3, according to the instructions from the authors. The syntax is available in the supporting information. The results were exported as aggregated patient-level data for one-year prevalence proportion and one-year incidence proportion, fully anonymised and thus classified as statistics by the national authority [28]. The data were not censored for immigration.

2.3. Incidence, run-in period and predictive value

Individual level data are included in the Swedish Prescribed Drug

<table>
<thead>
<tr>
<th>Table 1 Anatomical Therapeutic Chemical (ATC) -codes of available systemic menopausal hormone therapy in Sweden 2000–2021.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>G03CA03</td>
</tr>
<tr>
<td>G03CA57</td>
</tr>
<tr>
<td>G03CX01</td>
</tr>
<tr>
<td>G03FA01</td>
</tr>
<tr>
<td>G03FA12</td>
</tr>
<tr>
<td>G03FA14</td>
</tr>
<tr>
<td>G03FA15</td>
</tr>
<tr>
<td>G03FA17</td>
</tr>
<tr>
<td>G03FB05</td>
</tr>
<tr>
<td>G03FB06</td>
</tr>
<tr>
<td>G03FB08</td>
</tr>
<tr>
<td>G03FB09</td>
</tr>
</tbody>
</table>

<sup>a</sup> CEE = conjugated equine oestrogens.
<sup>b</sup> Oestradiol = oestradiol.
<sup>c</sup> MPA = medroxyprogesterone acetate.
Register since the 1st of July 2005 [28]. The one-year prevalence could thus be estimated from the calendar year 2006. From when the incidence can be estimated depends on the run-in period, since it implicates an observational period before the incidence can occur.

Each dispensation of MHT was identified, including the number of days preceding without a dispensation of MHT. For each calendar year, the one-year incidence was calculated using different lengths of run-in (12, 18, 36, 60 and 120 months) as specified by the authors before export.

The predictive values [29] for incidence representing first-ever use were calculated as the percentage of new cases defined by a pragmatically selected run-in of 120 months as the numerator and the new cases defined by a chosen run-in as the denominator [25]. They thus represent the proportion of reported incidence for a specific run-in that represents true first-ever use (defined as no treatment in the preceding 120 months).

2.4. Ethics statements

Data were delivered from the Swedish Prescribed Drug Register by the National Board of Health and Welfare and from the eHealth Agency of Sweden as aggregated data classified as official statistics. The data delivery did not include individual-level data and is regulated by Swedish law.

3. Results

3.1. DDD/1000 women per day

The estimated use of MHT in Sweden changed significantly from 2000 to 2021 measured in DDD per 1000 women per day (Fig. 1 for age 50–54 years and supplementary Table 1 for all age intervals). From 2000 it decreased by over 80% in women aged 50–54 years, from 282 DDD per 1000 women per day to a plateau of approximately 50 during 2010–2017. It then increased to 82 DDD per 1000 women per day in 2021. The similar trends were observed in women aged 40–49 and 55–59 years, whereas the increase from 2017 did not appear in older women (supplementary Table 1).

3.2. The prevalence of MHT use

The one-year prevalence could be studied in the material from 2006 and closely followed the trend of DDD per 1000 women per day (Fig. 1). The prevalence of MHT was highest in the age interval 50–59 years 2021. In 2017 the prevalence increased slightly and there was a more significant increase the following years in all women below 65 years of age (Fig. 2 and supplementary Table 2).

3.3. Run-in period and incidence of MHT use

The one-year incidence proportion and the predictive value for

---

**Fig. 1.** Menopausal hormone therapy in Sweden, women aged 50–54 years. Volume in Defined Daily Doses (DDD)/1000 women per day, one-year prevalence and incidence (with an 18-month run-in) per 1000 women and year.

---
identifying first-ever users were studied for different lengths of run-in and for different age intervals in 2021 (Table 2). The predictive value represents the proportion of reported incidence for a specific run-in that represents first-ever use defined as no dispensation in the preceding 120 months.

Using women aged 50–54 years as an example, the estimated incidence changed from 36.5/1000 women to 30.9/1000 women when increasing the run-in period from 12 to 60 months. Meanwhile, the predictive value increased from 83 to 98% (Table 2). A run-in period of 18 months had a predictive value of 88% in the age group 50–54 years.

This run-in period made it possible to study the incidence of MHT use from 2007, since dispensation data in individual level are available from the 1st of July 2005. A run-in period of 18 months was thereafter applied for the estimation of incidence proportion from 2007 to 2021.

The incidence was at a plateau for all age groups between 2007 and 2016. From 2016 to 2017 an increase in the incidence by 10% was first identified among women aged 50–54 years, but not among other age groups. Between 2017 and 2018 a further increase with 33% was seen in the same age group and also an increase for 45–49 and 55–64 years (Fig. 3 and supplementary Table 3). In 2020, the first year of the covid-19 pandemic, the incidence decreased for all studied age intervals. At the same time, the amount in DDD (Fig. 1 and supplementary Table 1) and the prevalence (Fig. 2 and supplementary Table 2) continued to increase, although at a somewhat slower rate than in the preceding two years.

4. Discussion

The use of MHT in Sweden decreased rapidly after the publication of several pivotal studies in 2002–2003 [6–8]. During 2010–2016 the use stabilised irrespective of measurement used. The same pattern, with a rapid decrease and following stabilization, has been described in Korea [12], Spain [13], Australia [15] and New Zealand [16]. These studies mainly estimated the use of MHT based on prescriptions or dispensation of DDD’s of MHT. A Swedish study from 2014 has previously described the DDD/1000 women and day and one-year prevalence in women aged 47–56 years from 2000 to 2012 [11]. The present study contributes to the discussion with a broader age range, the inclusion of an incidence proportion with a clearly defined run-in period, and a longer time frame.

From 2017 the use of MHT has increased. The new Swedish guidelines from 2019, updated in 2021 [19], state that treatment should be initiated within ten years of menopause and not after 60 years of age. These guidelines were based on new knowledge about the benefits and risks of MHT [18], and the proposal was disseminated and discussed among gynaecologists and general practitioners in the years prior to the update of the guidelines. It thus might have affected the prescribing patterns well before the actual implementation.

For MHT the administrative unit of measurement DDD is very close to the actual prescribed daily dose in all treated age groups, i.e. the dose women usually take daily. Therefore, the DDD per 1000 women per day is a good proxy for the estimation of the proportion of women actually using MHT.

A major strength of the study is that it is based on national mandatory health registers providing a total population perspective. The data represents actual dispensations of MHT from the pharmacy, and not only issued prescriptions. It is considered a strength of the study since it makes it more probable that individuals have used the drug, compared with prescription data. The Swedish Prescribed Drug Register covers all prescribed drugs dispensed by Swedish pharmacies during the study period, irrespective of reimbursement status. Thus, there are no missing data that could bias the results. However, register-based research is associated with limitations. In this study migration or death were not adjusted for. The prevalence and incidence of MHT use were based on the total female population registered as residents of Sweden the 31st of
December the previous year. Women who emigrated during the year were not adjusted for, and immigrant women were not included until the next year.

The one-year prevalence proportion could be studied from 2006 and as expected followed the trend of DDD per 1000 women per day. The change in the prevalence was most pronounced for the 50–54 years age group when menopause typically occurs. The one-year prevalence will overestimate the number of women treated since some women will only have one or a few dispensations during a calendar year, i.e. not being treated during the full year.

The incidence is highly sensitive to how a new case of drug treatment is defined through the length of the run-in. In this study the focus is on first-ever use of MHT which motivates a long run-in. However, a long run-in period would limit the years possible to analyse. A run-in of 18 months with a predictive value of 88 % means that 88 % of women 50–54 years classified as incident users were considered first-ever users, i.e. only 12 % of the incident cases with no dispensation within 18 months had had MHT dispensed between 18 and 120 months. This was accepted for the main analysis covering this age interval when MHT was most commonly initiated. For women 55 years or older, the predictive value of a run-in of 18 months were lower but they constituted only a smaller part of the incident cases and thus did not contribute significantly to a misclassification for the total number of women studied.

The incidence is highly sensitive to how a new case of drug treatment is defined through the length of the run-in. In this study the focus is on first-ever use of MHT which motivates a long run-in. However, a long run-in period would limit the years possible to analyse. A run-in of 18 months with a predictive value of 88 % means that 88 % of women 50–54 years classified as incident users were considered first-ever users, i.e. only 12 % of the incident cases with no dispensation within 18 months had had MHT dispensed between 18 and 120 months. This was accepted for the main analysis covering this age interval when MHT was most commonly initiated. For women 55 years or older, the predictive value of a run-in of 18 months were lower but they constituted only a smaller part of the incident cases and thus did not contribute significantly to a misclassification for the total number of women studied. Thus, we consider a run-in period of 18 months to be a pragmatic and useful definition for defining incident users in the age interval where use of MHT is most common. For studying older women, a longer run-in period should be considered.

The incidence is highly sensitive to how a new case of drug treatment is defined through the length of the run-in. In this study the focus is on first-ever use of MHT which motivates a long run-in. However, a long run-in period would limit the years possible to analyse. A run-in of 18 months with a predictive value of 88 % means that 88 % of women 50–54 years classified as incident users were considered first-ever users, i.e. only 12 % of the incident cases with no dispensation within 18 months had had MHT dispensed between 18 and 120 months. This was accepted for the main analysis covering this age interval when MHT was most commonly initiated. For women 55 years or older, the predictive value of a run-in of 18 months were lower but they constituted only a smaller part of the incident cases and thus did not contribute significantly to a misclassification for the total number of women studied.

The increase in the use of MHT in Sweden measured in incidence was more pronounced and could be detected earlier than the prevalence or the amount of DDD. This finding supports the use of incidence as a more sensitive measurement of prescription changes and trends in drug use.

A pandemic effect on the amount dispensed was reported for several different drugs [30] in 2020, when healthcare was under heavy pressure. The incidence proportion of MHT decreased significantly in 2020, the first year of the Covid-19 pandemic. It is likely that first-time prescriptions of MHT, which required a physical appointment, were affected more considerably by the pandemic than repeat dispensations of already issued prescriptions and prescription renewals. This decrease could not be demonstrated using DDD or one-year prevalence and is probably a reflection of longer duration of MHT use. This also seems to be an adaption to the new guidelines issued in 2019 and again stresses the importance of separating prevalence and incidence figures to show variations in patterns of use.

5. Conclusion

The use of MHT decreased significantly after the turn of the century. It has increased since 2017, mainly in the age groups close to menopause, and more pronounced after the publication of the new Swedish clinical guidelines in 2019. A run-in period of 18 months was found suitable and reliable for defining incident users of MHT in the age intervals closest to menopause. Incidence seems to be a more sensitive measure than prevalence or DDD for detecting early changes in prescription trends of MHT.

Contributors

Micaela Sundell participated in study design, data analysis and...
Preparation of the manuscript.

Jan Brynhildsen participated in study design and preparation of the manuscript.

Anna-Clara Spetz Holm participated in study design and preparation of the manuscript.

Mats Fredrikson participated in study design and data analysis.

Mikael Hoffmann participated in study design, data analysis and preparation of the manuscript.

All authors saw and approved the final version of the manuscript.

Funding

The study was funded by The Medical Research Council of Southeast Sweden (FORSS-646401 and FORSS-746391) and the NEPI Foundation – the Swedish Network for Pharmacoepidemiology, Stockholm, Sweden. The funding sources were not involved in the study design or the data collection, analysis and interpretation.

Ethical approval

The dispensed amount in DDD is available as public statistics and was downloaded from the Swedish eHealth Agency. Data on incidence and prevalence were calculated from individual-level data from the national mandatory Swedish Prescribed Drug Register by the National Board of Health and Welfare and delivered as aggregated data classified as official statistics by the authority. The data delivery did not include individual-level data and is regulated by Swedish law.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of competing interest

The authors declare that they have no competing interest.

Acknowledgements

We thank David Berglund, statistician at the National Board of Health and Welfare, for help with data retrieval and analysis. We also thank Professor emeritus Mats Hammar, Department of Biomedical and Clinical Sciences, Division of Children’s and Women’s Health, Linköping University, Linköping for valuable input on the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2023.107787.

References
