Use of hormone therapy in Swedish women aged 80 years or older

Lotta Järvstråt, Anna-Clara Spetz, Lotta Lindh-Åstrand, Mikael Hoffmann, Mats Fredrikson and Mats Hammar

Linköping University Post Print

N.B.: When citing this work, cite the original article.

Original Publication:

Lotta Järvstråt, Anna-Clara Spetz, Lotta Lindh-Åstrand, Mikael Hoffmann, Mats Fredrikson and Mats Hammar, Use of hormone therapy in Swedish women aged 80 years or older, 2015, Menopause: The Journal of the North American Menopause, (22), 3, 275-278.

<http://dx.doi.org/10.1097/GME.0000000000000294>

Copyright: Lippincott, Williams & Wilkins

<http://www.lww.com/>

Postprint available at: Linköping University Electronic Press

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-116336>

Use of hormone therapy in Swedish women 80-years of age and older

Running title: Hormone therapy in women above 80.

Lotta Järvstråt MSc^{1,4}, Anna-Clara E. Spetz Holm, MD, PhD¹, Lotta Lindh-Åstrand RN, PhD^{1,4}, Mikael J. Hoffmann², MD, PhD, Mats G. Fredrikson, PhD^{3,4}, and Mats L. Hammar, MD, PhD¹

¹Division of Obstetrics and Gynaecology, Department of Clinical and Experimental Medicine, ²Division of Health Care Analysis, Department of Medicine and Health, ³Division of Occupational and Environmental Medicine, Department of Clinical and Experimental Medicine, ⁴Linköping Academic Research Centre, all at the Faculty of Health Sciences, Linköping University, Sweden.

Financial support: This work was supported by grants from; the County Council of Östergötland (LIO-11877, LIO-31321, LIO-79951)

Conflicts of interest/financial disclosure: Mats Hammar has received reimbursements for lectures from Novo Nordisk, Scandinavia AB

Reprint requests and correspondence; Mats Hammar, Obstetrics and Gynaecology, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University, SE-581 85 Linköping, Sweden, e-mail: mats.hammar@liu.se; Phone +46-705293125; fax +46-10-1033194

Abstract

Objective: Menopausal symptoms with hot flashes and night sweat may persist for 10 to 20 years or even longer. There is limited information about to what extent older women use Hormone Therapy. The aim of this study was to determine the use of HT in Swedish women 80 years of age or older.

Methods: The study is based on national register data on dispensed drug prescriptions (i.e. prescribed therapy that has been provided to the patient at the pharmacy) for Hormone Therapy and local low dose estrogens.

Results: Of 310,923 Swedish women who were at least 80 years old 609 (0.2 %) were new users of Hormone Therapy. Almost one percent (2,361 women; 0.8 %) were current users of Hormone Therapy. The median duration of Hormone Therapy use in the new users was 257 days (25th - 75th percentile 611 - 120 days). About one out of six women 80 years of age and older had used local vaginal estrogen therapy for at least four three-month periods. The drugs were mainly prescribed by gynecologists and general practitioners.

Conclusions: Our results show that a number of women at or above 80 years of age still use Hormone Therapy and most women who started a new treatment period had only one or two dispensations, but the median duration of treatment was more than half a year. Since at least some of the women 80 years of age and older who used Hormone Therapy probably did so due to persisting climacteric symptoms vasomotor symptoms and Hormone Therapy are still relevant issues to be discussed when counselling women around and after 80 years of age.

Key words: menopause, hot flashes, old age, hormone therapy, vaginal dryness

Introduction

Cross sectional and prospective studies show that 50-75% of women in the western world report vasomotor symptoms, such as hot flashes and night sweat, when going through the menopause (1-3). These symptoms often cause discomfort and may negatively affect daytime activities, night sleep, and quality of life. Besides hot flashes and night sweats, vaginal dryness and dyspareunia are the only symptoms that have been proven to be associated with the endocrine changes around menopause (1-4)

Hot flashes are often described as transient symptoms but actually they may persist for many years; the median time is about five years and around 20% of women still report vasomotor symptoms 10 - 20 years after menopause(1, 5). The Heart and Estrogen/Progestin Replacement Study found that, in a sample of women with a mean age of 67 years, about every sixth woman reported very frequent or frequent hot flashes at baseline (6). Also, one out of four women reported vaginal dryness at baseline. Younger women reported being troubled by hot flashes and vaginal dryness more frequently than older women. However, almost 20% of women age 70-74 years reported very frequent or frequent hot flashes (6). In one longitudinal study, pre- and postmenopausal women were followed from the 1960s to the 1990s. Approximately 9% of the 72-year old women (4/47) reported being troubled by hot flashes (7). There are few published studies about menopausal symptoms in women over the age of 80 years. We have, however, reported that 22% of 184 women being 85 years of age either used Hormone Therapy (HT) or reported hot flashes (16 %) at least several times per week (8).

The use of HT increased gradually from the 1980s but after reports about increased risk of mainly cardiovascular disease and breast cancer (9) the use of HT decreased dramatically (10-12). Most national and international recommendations were changed and in Sweden HT is recommended only for women with moderate or severe vasomotor symptoms, and with the lowest possible doses and for the shortest possible time (13). Recently it has been shown that HT initiated shortly after menopause seems to induce low cardiovascular risks and especially if no progestagen is added only a very small or no risk of breast cancer (14). On the other hand the risks of side effects and cardiovascular events seem to increase the longer the time interval after menopause before the treatment is started. At least in Sweden, HT still seems to be controversial even among early postmenopausal women, since only about six percent of

women 47-56 years old use HT in Sweden, according to data from the Swedish Prescribed Drug Registry 2010-2012. Probably the fear of HT is still present, making many women who suffer from hot flashes to be withheld from an effective treatment (12). On the other hand low dose estrogen therapy administered locally for urogenital symptoms has very few side effects and should not have been affected by the reports on HT risks.

In Sweden there is a unique long history of creating national registers providing unique data on the entire population. The personal identity number (PIN) was introduced in 1947 making it possible to maintain national records on the entire population. Since 1991 the National Tax Board has been responsible for maintaining the Swedish PIN based registry (15). The Swedish Prescribed Drug Registry at the National Board of Health and Welfare contains information on all prescribed drugs dispensed at pharmacies in Sweden (16). Thus data on the dispensed drugs actually provided by the pharmacy to the individual patient are kept in the register but not the written prescriptions (which may not in reality have been used by the patient). The register was established in 1999 and since July 2005 the full PIN has been included for every entry. The register covers the entire population in the country, and the PIN is missing for less than 0.3% of all dispensations. Demographic and socioeconomic data on the inhabitants are registered yearly at Statistics Sweden and these data can be linked by the PIN to the Prescribed Drug Registry.

Our study is a strictly descriptive, epidemiological study linking registers from the National Board of Health and Welfare and Statistics Sweden. The aim of this study was to determine the prevalence and incidence of HT users and the use of local estrogen therapy in women age 80 years or older. We also wanted to determine the duration of HT use in incident HT users 80 years or older living in Sweden over a period of five years (April 2006 – December 2011). An additional aim was to determine the clinical specialties among physicians initiating and continuing to prescribe HT for elderly women.

Methods

The study group consists of all women, nationally registered in Sweden, who were at least 40 years old on 31 December 2005. These women were followed from 1 July 2005 until 31 December 2011. Drugs for systemic HT of climacteric symptoms were defined as oral and transdermal products within ATC-groups , G03CA03 estradiol (excluding low dose products and drugs for local vaginal treatment), G03CA57 conjugated estrogens, G03CX01 tibolone,

G03FA01 norethisterone & estrogen, G03FA12 medroxyprogesterone & estrogen, G03FA15 dienogest & estrogen, G03FA17 drospirenone & estrogen, G03FB05 norethisterone & estrogen, G03FB06 medroxyprogesterone & estrogen and G03FB09 levonorgestrel & estrogen. No injectable preparations are used for HT in Sweden. Drugs for low oral or local vaginal treatment were defined as low dose estradiol in vaginal tablets or estriol in vagitories, creme or a locally applied vaginal ring or low dose oral estriol within G03CA03 estradiol and G03CA04 estriol, respectively. Data on dispensed drugs from the Swedish Prescribed Drug Register were extracted by the National Board of Health and Welfare and linked by them to demographic and socioeconomic data from Statistics Sweden. Data on education, country of birth, living arrangements, employment status, civil status, and income were studied on one occasion during the study period (2005-12-31).

The Swedish Prescribed Drug Registry contains information on the prescriber's specialties in chronological order. The latest registered specialty was used to define the main specialty of each prescriber.

Current versus new users of HT: Data from the Swedish Prescribed Drug Registry connected to PIN are available from 1 July 2005. In Sweden HT can only be dispensed for three months at a time but prescriptions can include four 3-month periods and thus include one full year. To define new (incident) users of HT, a preceding wash-out period of nine months (274 days) without any dispensation was used. This corresponds to approximately at least six months without treatment since the maximum allowed time covered by a dispensation in Sweden is three months. A new user was hence defined as a woman who had been dispensed HT at least once between 1 April 2006 and 31 December but not during the wash-out period from 1 July 2005 to 31 March 2006.

All the new users were followed over the full study period, i.e. from the time of the first dispensation on 1 April 2006 or later until 31 December 2011. The duration of treatment was calculated as the time from the first day until 120 days after the last dispensation. For women on unit-dose dispensed drugs the duration was calculated as the time until 14 days after last dispensation since unit-dose drugs are dispensed every 14 days. The longest time we allowed between dispensations without treating the situation as a discontinuation was approximately nine months (273 days).

A current (prevalent) user was defined as a woman who had been dispensed HT at least once during a period starting from 1 July 2005 to 31 March 2006, i.e. during the 274 day long wash-out period.

Statistics: All data were delivered on Excel-files from the Board of Health and Welfare. Data were exported and analyzed by SAS version 9.3 (SAS Institute, Cary, North Carolina, USA). Persistence of treatment was calculated by Kaplan–Meier survival analysis, determining the time of discontinuation for each patient. Patients were excluded from further analysis (censored) in the event of death or the end of follow up. Descriptive statistical methods were used.

Missing data for each variable were handled as lost data.

Ethics: Data from the Swedish Prescribed Drug Register and Statistics Sweden were extracted and pseudonymized by the National Board of Health and Welfare. Data protection and encoding are kept by the National Board of Health and Welfare for at least three years. The protocol for this study was approved by the Regional Ethical Review Board in Linköping, Sweden, D-nr 2012/386-31.

Results

In all 310,923 Swedish women were at least 80 years old on 31 December 2005 and constitute our cohort. Of this total, 609 (0.2 %) became new HT-users during the study period. Another 2,361 women (0.8 %) were defined as current users of HT during the first nine months of the study period. Of these, 1,703 women (0.5 %) had three or more dispensations during the study period (Table 1).

The median duration of HT use in the new users 80 years of age or older was 257 days (25th - 75th percentile 611 - 120 days) whereas new users 40 – 79 years of age had a median HT duration of 488 days (25th - 75th percentile 1226 - 177 days) as illustrated in the Kaplan-Meier diagram in Figure 1. The mean number of days of treatment was 378 for new users 80 years old or older and 539 days for women 40 to 79 years of age.

About one out of six women 80 years of age and older had been dispensed local vaginal estrogen therapy at least four three-month periods (Table 2).

The HT use was mainly initiated by gynecologists and general practitioners, but some geriatricians also prescribed use (Table 3). Repeat prescriptions tended to be issued to a somewhat higher degree by general practitioners (from 36.8% to 42.5% of the prescribers).

When new use and current use of HT were analyzed versus demographic and socioeconomic data, no specific variables (education, country of birth, place of residence – four categories -

or civil status, and income) for those analyzed correlated with use or non-use of HT, or duration of HT use.

Discussion

Although climacteric symptoms are often claimed to be symptoms of short duration (mean five years) our data from Swedish registers show that many women over the age of 80 years are still prescribed and dispensed HT. We also found that a number of women above 80 years of age were incident users, i.e. had been prescribed and dispensed HT after the previously defined “wash-out” period of at least nine months during which they neither received nor used HT. It might however be that they were not true new users since they could have been treated earlier in life before the start of the study period.

In general medical product agencies as well as specialist associations recommend that HT be used only for the more troublesome vasomotor symptoms and for the shortest time possible with the lowest possible doses. Our finding that numerous Swedish women use HT after the age of 80 years shows that doctors do not always follow these recommendations. Even a number of women above 80 years of age were new users of HT at least during the study period, i.e. they were dispensed HT after at least six months without treatment.

We can only speculate about the reasons for prescribing HT to this old age group. In a previous study on 85 year old women, 16 % of them reported hot flashes at least several times per week (8), i.e. there may still be a need for HT in a small group of older women. Furthermore, some of the women may suffer from osteoporosis and prefer HT before other treatment options. However, HT is not the first line therapy for osteoporosis in Sweden today. A French study found that after 2002, HT tends to be prescribed more often for hot flashes than for other reasons, and less than one-third of prescriptions were written for reasons not linked to hot flashes (17). Before 2002 prescriptions written for other reasons were more common (16). Although we have no data on the indication for the prescription, probably many of the women of 80 years and older who had been prescribed HT still had hot flashes which they wanted to relieve. The fact that a number of women who had been prescribed and then had been dispensed HT after at least six months without treatment suggests that these women either were true new users or had earlier used HT which they had tried to abandon. After some time without therapy they may have decided to start again, e.g. for reasons such as impaired well-being, hot flashes and/or sleep disturbances. We have previously found that

impaired psychological well-being, and not the mere number of hot flashes, was the strongest predictor for restarting therapy after trials to abandon HT (18).

It could be argued that the register data on HT included dispensation of local estrogens due to symptoms of urogenital atrophy. However the database clearly separates these low doses of oral or vaginal preparations from HT. We also analyzed these data and found that about every sixth woman above 80 years of age had been dispensed estrogens for treatment of local urogenital symptoms. This is not surprising, because such symptoms are reported to be very prevalent and occur in up to every other woman after menopause (1, 5), and treatment has to be ongoing in order to be effective.

Conclusion

In conclusion we found that a substantial number of Swedish women at or above the age of 80 years still use HT, probably at least some of them due to vasomotor symptoms, and a number of women are prescribed and dispensed HT after not having used it for at least 6 months. Thus issues on climacteric symptoms, besides symptoms of urogenital atrophy, should not be forgotten even when counseling women around and after the age of 80 years.

Conflicts of interest:

Mats Hammar has received reimbursements for lectures from Novo Nordisk, Scandinavia AB

No other author declares any conflict of interest.

Legend to figures: Hammar et al, Menopause 2014

Legend to figure 1: Kaplan-Meier diagram showing the days of HT, in Swedish women age 40-79 and at least 80 years of age, respectively who have started HT between 1 April 2006 and 31 December 2011.

References

1. Hammar M, Berg G, Fåhræus L, Larsson-Cohn U. Climacteric symptoms in an unselected sample of Swedish women. *Maturitas*. 1984 Dec;6(4):345-50. PubMed PMID: 6533438.
2. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas*. 1992 Jan;14(2):103-15. PubMed PMID: 1565019.
3. Stadberg E, Mattsson LA, Milsom I. The prevalence and severity of climacteric symptoms and the use of different treatment regimens in a Swedish population. *Acta obstetrica et gynecologica Scandinavica*. 1997 May;76(5):442-8. PubMed PMID: 9197447.
4. Iosif CS, Bekassy Z. Prevalence of genito-urinary symptoms in the late menopause. *Acta obstetrica et gynecologica Scandinavica*. 1984;63(3):257-60. PubMed PMID: 6730943.
5. Berg G, Gottwall T, Hammar M, Lindgren R. Climacteric symptoms among women aged 60-62 in Linköping, Sweden, in 1986. *Maturitas*. 1988 Oct;10(3):193-9. PubMed PMID: 3185293.
6. Barnabei VM, Grady D, Stovall DW, Cauley JA, Lin F, Stuenkel CA, et al. Menopausal symptoms in older women and the effects of treatment with hormone therapy. *Obstetrics and gynecology*. 2002 Dec;100(6):1209-18. PubMed PMID: 12468165.
7. Rödström K, Bengtsson C, Lissner L, Milsom I, Sundh V, Björkelund C. A longitudinal study of the treatment of hot flushes: the population study of women in Gothenburg during a quarter of a century. *Menopause*. 2002 May-Jun;9(3):156-61. PubMed PMID: 11973438.
8. Vikström J, Spetz Holm A, Sydsjö G, Marcusson J, Wressle E, Hammar M. Hot flashes still occur in a population of 85-year old Swedish women. *Climacteric*. 2013;16:453-69.
9. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA : the journal of the American Medical Association*. 2002 Jul 17;288(3):321-33. PubMed PMID: 12117397.
10. Buist DS, Newton KM, Miglioretti DL, Beverly K, Connelly MT, Andrade S, et al. Hormone therapy prescribing patterns in the United States. *Obstetrics and gynecology*. 2004 Nov;104(5 Pt 1):1042-50. PubMed PMID: 15516400.
11. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA : the journal of the American Medical Association*. 2004 Jan 7;291(1):47-53. PubMed PMID: 14709575.
12. Hoffmann M, Hammar M, Kjellgren KI, Lindh-Åstrand L, Brynhildsen J. Changes in women's attitudes towards and use of hormone therapy after HERS and WHI. *Maturitas*. 2005 Sep 16;52(1):11-7. PubMed PMID: 16023804.
13. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause*. 17(2):242-55.
14. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. *The Cochrane database of systematic reviews*. 2012;7:CD004143. PubMed PMID: 22786488.
15. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European journal of epidemiology*. 2009;24(11):659-67. PubMed PMID: 19504049. Pubmed Central PMCID: 2773709.
16. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research

- and experience from the first six months. *Pharmacoepidemiology and drug safety*. 2007 Jul;16(7):726-35. PubMed PMID: 16897791.
17. Fournier A, Fritel X, Panjo H, Zins M, Ringa V. Health characteristics of women beginning postmenopausal hormone therapy: have they changed since the publication of the Women's Health Initiative? *Menopause*. 2013 Dec 30. PubMed PMID: 24378763.
 18. Lindh-Åstrand L, Bixo M, Hirschberg AL, Sundström-Poromaa I, Hammar M. A randomized controlled study of taper-down or abrupt discontinuation of hormone therapy in women treated for vasomotor symptoms. *Menopause*. 2010 Jan-Feb;17(1):72-9. PubMed PMID: 19675505.

Figure 1

Table 1 Dispensed HT to women of different age groups according to age at the start date of the study period (1 July 2005 – 31 December 2011). A current user is a woman who has been dispensed HT and with possible previous HT use before the observation period (before 1 July 2005).

Age group	Number of women	Percentage of women of the age group that has received at least N number of dispensations		
		N≥1	N≥2	N≥3
40-44	310,404	5.9	4.3	3.5
45-49	287,091	14.5	11.7	10.3
50-54	285,898	18.9	16.3	15.0
55-59	313,260	17.4	15.5	14.3
60-64	284,555	13.0	11.6	10.6
65-69	214,591	7.5	6.6	6.0
70-74	184,730	3.9	3.4	3.1
75-79	176,262	2.1	1.8	1.6
≥ 80	310,923	0.8	0.6	0.5
<u>Total</u>	2,367,714	9.9	8.5	7.7

Table 2 Use of local vaginal estrogens in women 80 years of age or older (age defined at the start date of the study period; 31 December 2005) during 1 July 2005 – 31 December 2011 in Sweden (n = 310,923).

<u>Number of dispensations</u>	<u>Number of women</u>	<u>% of age group</u>
≥1	72,250	23.2%
≥ 2	62,999	20.2%
≥ 3	56,917	18.2%
≥ 4	52,335	16.8%

Table 3: Different specialities (in %) of the prescriber for the first and fifth registered dispensation of HT for new users among Swedish women of at least 80 years of age. A prescription is normally valid for 1 to 4 dispensations in Sweden.

Last issued specialist	HT 1st dispensation (%)	HT 5th dispensation (%)
Gynecologist	30.6	26.9
General practitioner	36.8	42.5
Geriatrician	11.6	13.8
Internal medicine	3.2	1.9
Surgery	2.4	1.3
Other or no specialty	15.4	13.6