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EFFECTS OF MENOPAUSAL HORMONE THERAPY ON CLIMACTERIC-RELATED SYMPTOMS IN POSTMENOPAUSAL WOMEN WITH A HISTORY OF HYSTERECTOMY: A PLACEBO-CONTROLLED DOUBLE-BLIND STUDY USING THE WOMEN'S HEALTH QUESTIONNAIRE (WHQ)

Syventävien opintojen kirjallinen työ

Turun yliopisto

Lääketieteellinen tiedekunta

Kliininen laitos

Naistentaudit ja synnytykset

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TURUN YLIOPISTO

Lääketieteellinen tiedekunta

SELINA AHTI: Effects of menopausal hormone therapy on climacteric-related symptoms in postmenopausal women with a history of hysterectomy: a double-blind study using the women's health questionnaire (WHQ) (suom. Hormonikorvaushoidon vaikutus vaihdevuosioireisiin)

Syventävien opintojen kirjallinen työ

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Naistentaudit ja synnytykset

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Tutkimuksessa selvitettiin hormonikorvaushoidon vaikutusta vaihdevuosioireisiin 63 peri- tai postmenopausaalisen naisen aineistossa.

Tutkimusaineistona käytettiin aiemmin valmiiksi kerättyä aineistoa. Vaihdevuosioireet mitattiin validoidulla kyselykaavakkeella, The Women's Health Questionnaire:lla. Tutkittavat saivat vuoroin estrogeeniä ja lumetta ja toimivat siten omina verrokkeinaan. Tutkittavilta oli poistettu kohtu eri elämänvaiheissa, joten hormonikorvaushoito tapahtui pelkällä estrogeenilla. Aineisto käsiteltiin tilastotieteen keinoin. Hypoteesi oli, että hormonikorvaushoito lievittää ainakin tyypillisimpiä vaihdevuosioireita, kuumia aaltoja, yöhikoilua sekä uniongelmia. Oletimme, hormonikorvaushoidon vaikutuksen psyykkisiin oireisiin olevan vähäinen. Kirjallisuusviitteiksi haettiin artikkeleja Pubmed:istä 2017–2020.

Tulokset olivat pääosin johdonmukaisia aikaisempien tutkimustulosten kanssa. Tutkimuksen tuloksista selvisi, että osa vaihdevuosioireista kuten kuumat aallot, yöhikoilu ja uniongelmat vähenivät merkitsevästi. Uniongelmia käsittelevistä oireista väheni tosin ainoastaan nukahtamisvaikeudet. Lisäksi havaittiin positiivinen vaikutus seksuaaliseen haluttomuuteen. Sivuvaikutuksena hormonikorvaushoidon todettiin aiheuttavan rintojen arkuutta. Estrogeenin vaikutukset mielialaoireisiin, seksuaaliseen toimintakykyyn ja kognitiivisiin vaikeuksiin olivat vähäiset: epäsuorat positiiviset vaikutukset muihinkin kuin vasomotorisiin oireisiin ovat mahdollisia, kun yleinen hyvinvoinnin kokemus kohoaa. Hormonikorvaushoitoa tulisi suositella vasomotorisiin oireisiin ja uniongelmiin, muttei ensisijaisena hoitona mielialaoireisiin. Vaihdevuosien aikana esiintyvien mielialaoireiden syynä on todennäköisesti usein muitakin tekijöitä kuin vain alentuneet hormonitasot.

Asiasanat: hormonikorvaushoito, vaihdevuosioireet, menopaussi, vaihdevuodet, kuumat aallot, masennusoireet, seksuaalisuus

Syventävät opinnot on kirjoitettu englanniksi.

Abstract

Objective. To evaluate whether menopausal hormone therapy (MHT) alleviates climacteric-related symptoms among peri- or postmenopausal women with history of hysterectomy. The key interest of the study was to evaluate the effect of unopposed estradiol (E_2) without the interference of progestin supplementation.

Methods. Altogether 63 women were accepted to the research. We used both original and revised version of The Women's Health Questionnaire to measure climacteric-related symptoms, which were included both as symptom domains and as separate items. MHT use was compared to the baseline and to placebo. The research included two 3-month treatment periods (MHT and placebo) and a 1-month wash-out period with placebo to minimize carry-over effect.

Results. As symptom domains, vasomotor symptoms (VMS) ($p<0.001$), sleep problems ($p<0.001$), depressive symptoms ($p=0.019$), anxiety/fears ($p=0.003$), cognitive difficulties ($p<0.001$) and sexual functioning ($p=0.012$) decreased with MHT compared to baseline. As separate items, when the MHT use was compared to baseline, hot flushes ($p<0.001$), night sweats ($p<0.001$), difficulty in getting to sleep ($p<0.001$), difficulty in waking up early ($p=0.015$), feeling of irritability ($p<0.001$), sensations of butterflies in one's stomach ($p=0.006$), feeling of clumsiness ($p<0.001$), feeling of poor memory ($p=0.017$), losing interest in sexual activity ($p=0.015$), feeling of sick or nauseous ($p=0.023$) and abdominal cramps ($p=0.015$) decreased. MHT increased tender breast ($p<0.001$).

When the MHT was compared to placebo, as symptom domains, VMS ($p <0.001$), sleep problems ($p=0.006$) and sexual functioning ($p=0.013$) decreased . As separate items, compared to placebo, women with MHT had less hot flushes ($p <0.001$), night sweats ($p <0.001$), difficulties getting to sleep ($p <0.001$), they were less irritable ($p=0.005$) and tense ($p=0.005$) than usual and had more interest in sexual activity ($p=0.013$). There was no effect on somatic symptoms or cognitive difficulties. Compared to placebo, women reported more breast tenderness ($p <0.001$) during MHT.

Conclusions. The results of our study bolster the hypotheses of MHT decreasing VMS (hot flushes and night sweats) and sleep problems. As to other symptoms, the diverge of results in different studies indicate the complex causes behind the symptoms: estrogen and other hormonal factors might be only one of the many

reasons behind climacteric-related symptoms. Estrogen might not have that strong effect on mood symptoms, sexual functioning and cognitive difficulties, but indirect improvements are possible. MHT should be recommended for a treatment of VMS, but MHT should not be the first line treatment for other symptoms, which are likely to have various causes behind them.

Keywords: menopausal hormone therapy, quality of life, menopause, hot flush, climacteric-related symptoms

SISÄLLYS:

1 Introduction

1.1 Climacteric-related symptoms

Climacteric-related symptoms are both physical and psychological. Symptoms include vasomotor symptoms (VMS), sleep problems, depressive and various other mood symptoms, cognitive difficulties, decreased sexual functioning and menstrual and somatic symptoms. VMS are widely known to be typical symptoms among peri- or postmenopausal women. The etiology of VMS are not fully understood, but they are known to be connected to decreasing estrogen levels.[1] The prevalence of the climacteric-related symptoms varies widely but they also often co-occur and tend to induce each other.[2] Particularly, there are strong associations between VMS, sleep problems and depressive symptoms, but the cause-effect relationships are not yet thoroughly understood. Altogether, climacteric-related symptoms may notably reduce quality of life.

1.2 Measuring climacteric-related symptoms

Since the experience of the climacteric-related symptoms is a subjective one, the measuring of the symptoms can be challenging. There are various general questionnaires, like the 36-item Short Form Health Survey, the World Health Organization Quality of Life (WHOQOL) and the EuroQol (EQ-5D) to measure wide range of symptoms and health problems[3], but also more specific ones such as the Women's Health Questionnaire (WHQ), which measures particularly symptoms connected to climacteric.[4]

1.3 The Women's Health Questionnaire

We used a previously validated and widely used questionnaire, the Women's Health Questionnaire (WHQ), to evaluate climacteric-related symptoms of the participants. [4] [5] The WHQ is a climacteric specific measure of quality of life, which is commonly used instrument for measuring various

physical and emotional sensations that are related to climacteric. The WHQ is developed by Professor Myra Hunter in 1986 and it has been translated into 27 languages afterwards.[4] The original WHQ is a 36-item questionnaire, which evaluates symptoms on scale 1 to 4 and on a binary scale (0-1). The 36 items are grouped into nine symptom domains including VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, sexual functioning, menstrual symptoms, somatic symptoms and one's experienced attractiveness and a question concerning worries about growing old. There is also revised version of the WHQ, a 23-item questionnaire scaling 0 to 100. The 23-item questionnaire has shown to be as good or even better by psychometric properties than those of the original 36-item WHQ.[6] The WHQ is validated in 2017 to match a Finnish population. [6]

1.4 Menopausal hormone therapy

Commonly, menopausal hormone therapy (MHT) refers to treatment with estrogen or to treatment with both estrogen and progestin. Estrogen is used to treat climacteric-related symptoms, and progestin is combined to avoid endometrial hyperplasia.[7] In hysterectomized women, the MHT may be performed by estrogen only.[8] If the last menstruation has taken place less than a year ago, it is recommended to start the treatment with cyclic combined MHT. If the time since the last menstruation is over a year, the bleedings may be avoided by the use of continuous combined MHT.[8] Another option is continuous treatment with tibolone. Tibolone is metabolized to compounds that have both estrogenic, progestogenic and androgenic effects.[9] Alternative for above mentioned regimen of MHT use, is to use a hormone-releasing intrauterine device combined to estrogen.[8]

Estrogen can be dosed orally or transdermally by using estrogen patch, gel or spray. The type of preparation may usually be decided by patient, but sometimes one is superior to another. For example, women with high risk for a deep venous embolism, are recommended to use transdermal MHT.

MHT has both benefits and disadvantages. The biggest benefit is the decrease of the climacteric-related symptoms. Estrogen prevents osteoporosis (menopause associated) and decreases the risk of bone fracture.[10] If MHT is started early, it may also prevent cardiovascular diseases. [11] If started later, the risk of cardiovascular diseases may increase.[11] Risk to have diabetes mellitus type II[12] and colon cancer also decreases.[13] The use of MHT has been combined to increased risk of breast cancer[14] and ovarian cancer.[15] However, as to the increased risk of breast cancer, the risk might be smaller if medication includes only estrogen, compared to the combination therapy.[16] MHT increases, at least when used orally, a risk of venous thromboembolic disease. [17] Furthermore, MHT increases the risk of cholecystitis and gallstone disease.[8]

1.5 Previous findings

The effects of MHT on climacteric-related symptoms has been under active research. Previous studies have found that MHT has positive effect on VMS and sleep problems [16–19] As to other climacteric-related symptoms, the results have been less consistent. Some of the studies have found the MHT to have positive effects also on depressive symptoms, anxiety/fears, sexual functioning and somatic symptoms. [20 2,18]

1.6 Aim of the study

The aim of our study was to evaluate the effect of MHT on the climacteric-related symptoms among peri or postmenopausal women with history of hysterectomy. Based on the results of the previous studies, our hypothesis was that MHT alleviate certain climacteric-related symptoms, such as VMS and sleep problems, whereas the effect on the other symptoms would be minor.

2 Material and methods

2.1 Subjects

Our study was a part of a larger trial investigating sleep and cognition in healthy peri- and postmenopausal women. Subjects for the study were recruited through announcements in local newspapers in Turku, Finland. Main focus of the study was to study the effect of unopposed estradiol (E_2) without the interference of progestin supplementation. Thus, the previous hysterectomy for benign indication was considered as an inclusion criterion. This enabled also a double-blind study designs. Women using MHT were accepted only if they agreed to interrupt the therapy for five months before entering the study. Peri- and postmenopause was defined by serum follicle-stimulating hormone (FSH) level >30 IU/l. Two women with lower FSH levels were included because of their age, which were 56 years (FSH 28 IU/l) and 62 years (FSH 29 IU/l). The baseline serum E_2 level was <50 pmol/l in all the women except two, who were accepted because of their high serum FSH levels; their E_2 levels were 90 pmol/l and 105 pmol/l, and FSH 70 IU/l and 55 IU/l, respectively. The participants with severe neurological, severe cardiovascular, endocrinological, or mental disease, venous emboli, medicated hyperlipidaemia, and malignancies, abuse of alcohol or medications, or smoking (more than 10 cigarettes/day) were excluded. Blood haemoglobin, leucocytes, sedimentation rate, serum thyrotropin, free thyroxin, vitamin B_{12}, creatinine, glucose, and cholesterol levels were checked before the study; only women with levels within the reference ranges were accepted. The women were not allowed to use any hormonal preparations or medications affecting the central nervous system during the research.

Altogether, 71 women were accepted to the study. Though, five women discontinued. Two of them drop out the study because of intolerable climacteric-related symptoms during placebo, one because of headache on estrogen, one because of fear of MHT use and one because of personal reasons. One

woman was excluded from the final analyses because she used antidepressive medication on the second three-month period. Furthermore, two women were excluded because of incomplete data. Altogether, 63 women were accepted to the final analysis. The follow-up time included two 3-month treatment periods (MHT and placebo) and a 1-month wash-out period with placebo, to minimize carry-over effect (a possible residual of treatment affecting next observed period). Randomization codes were kept at the drug companies until the data analyses were done. Participants served as their own controls.

2.2 The Women's Health Questionnaire (instrument)

Climacteric-related symptoms were measured by the WHQ, in which the symptoms are grouped into nine symptom domains: VMS (two items), sleeping problems (three items), depressive symptoms (seven items), anxiety symptoms (four items), cognitive difficulties (three items), sexual functioning (three items), somatic symptoms (seven items), menstrual symptoms (four items) and one's experienced attractiveness (two items).[6] The domain of the one's experienced attractiveness was excluded. Because all women were peri- or postmenopausal and hysterectomized, the domain of menstrual symptoms was also excluded. However, because three of the items do not concern menstruation directly, they were included in the item by item analyses. An item "worry about growing old" was analysed separately. The scores of the WHQ were summated and divided by the number of the items in each domain to obtain major factor scale scores. The scoring was reversed for certain items, since some items in the original questionnaire were phrased positively and some were phrased negatively.[4] The original scale is from 0 to 1. However, to gain more dynamics to the results, we used a scale 1 to 4, which is preferable in a Finnish population.[6] Missing data was handled as disclosed in the user manual of the questionnaire.[4] Women were instructed to reply to the questions of sexual functioning only if they were sexually active. The item #18. was formed as *I suffer from pain in my limbs* instead of the original, *I suffer from backache or pain in my limbs*.

As mentioned earlier, also a revised 23-item version of the WHQ, in which domains are regrouped, has been developed.[4] The items of depressive symptoms, anxiety/fears and attractiveness are regrouped and renamed in the revised WHQ as "anxiety/depressed mood" and "well-being". Furthermore, six items are excluded completely: #11: *I am restless and can't keep still* (sleep problems), #1: *I am more irritable than usual* (depressive symptoms), #13: *I worry about growing old* (an independent item), #21: *I feel rather lively and excitable* (attractiveness), #30: *I often notice pins and needles in my hands and feet* (somatic symptoms), and #35*: I need to pass urine/water more frequently than usual* (somatic symptoms). The revised version of the WHQ scales 0 to 100; the value 0 match the original number 1 and the value 100 to the original 4.[4] We performed all the analyses also including only the items/domains of the revised version.

2.3 Statistical analysis

Statistical analyses were carried out using the SAS (version 9.4) system for Windows. The symptom domains of the WHQ were submitted first for descriptive statistics. The women served as their own controls. The changes between the baseline and the follow-up measurements were compared.

The analyses were started by testing whether there was any residual effect (carry-over affect) of MHT after four months. As no carry-over effect was observed, the period effect (whether the order of the treatment periods (MHT or the placebo) affects the results) was tested with analysis of variance for repeated measures. For the carry-over and period effects, p-values less than 0.05 were considered significant. Since no carry-over or period effect was observed, the answers of the two MHT periods were combined as well as the answers of the two placebo periods. Thus, there were two groups (MHT and placebo) in the study, and both included all the 63 women. To investigate the effects of MHT on climacteric related symptoms, the placebo and MHT phases were compared to each other by using two sample t-test. A parametric statistical method for a cross-over study design of two treatments and

two periods was applied. The treatment effect was considered to be significant, if the p-value was less than 0.05.

All the analyses were performed also using the revised WHQ, as well as using the separate items of the original WHQ.

3 Results

3.1 Subject characteristics

The mean age of the women was 56.5 years (range 47 to 65 years). The mean body mass index (BMI) was 27.0 kg/m^2 (standard deviation [SD]) 3.9 kg/m^2, range 20.0-39.0 kg/m^2). Seventy-five percent had previously used MHT, the mean duration of which was 48.5 months (range 1 month to 22 years). The mean time elapsed since interruption of MHT was 35.3 months (range 5 months to 19 years). Ten women had used local estrogen treatment before the study, and 53 women had never used it. At the moment of the study, none of the women used local estrogen treatment. Hysterectomy was accompanied by a unilateral oophorectomy in 14% and a bilateral oophorectomy in 27% of the women. The time elapsed since the oophorectomy ranged from 5 months to 25 years.

3.2 Symptoms at the baseline of the study

The WHQ symptom domain means and SDs at the baseline and after the treatment periods are shown in table 1. At the beginning of the study, on scale 1-4, the most prevalent symptoms were VMS and the second prevalent symptoms were cognitive difficulties. The remainder symptom domains in order from the highest means to the lowest means were sexual functioning, sleep problems, somatic

symptoms, depressive symptoms and anxiety/fears. Of the separate symptoms, the most reported symptoms were hot flushes (item #19), night sweats (item #27) and poor memory (item #36).

3.3 MHT compared to baseline

When compared to baseline, VMS decreased after the MHT use, both as a domain and as separate items, including hot flushes and night sweats (items #19 and #27). Sleep problems as a domain were also decreased by the MHT use and as separate items, women had less difficulty in getting off to sleep (item #1) and lower score in waking up early and then sleeping badly for the rest of the night (item #29). On the domain of depressive symptoms, symptoms decreased as a domain. But as separate items, women had lower scores only in the item #12 "I am more irritable than usual." As to anxiety/fears, symptoms decreased as a domain. However, as separate items, only palpitations and sensations of "butterflies" in one's stomach or chest were reduced after the treatment period (item #6). MHT was associated with decrease in cognitive difficulties both as a domain and two of the separate items were decreased: "I am more clumsy than usual" (item #20) and "My memory is poor" (item #36). MHT also had positive effect on sexual functioning as a domain, but of the separate items, the score was decreased only in one item: "I have lost interest in sexual activity" (item #24). Somatic symptoms as a domain did not change after the MHT use. However, there was positive effect in one item: women felt themselves less sick or nauseous (item #23). As to menstrual symptoms, MHT increased the feeling of tender or uncomfortable breast (item #17) and decreased abdominal cramps or discomfort (item #22).

3.4 MHT compared to placebo

When MHT was compared to placebo, the results were quite comparable to the results that were acquired when compared the treatment period and baseline, but some differences were found. When MHT use was compared to placebo, women had fewer VMS, both as a domain and as separate items.

There was no difference in sleep problems as a domain, but treatment had more beneficial effect on difficulties in getting off to sleep (item #29) than placebo. There was no difference in depressive symptoms or anxiety/fears as domains either. As separate items, women had less irritability (item #12) and the felt themselves less tense or "wound up" (item #9) when using MHT compared to placebo. In cognitive difficulties there was no difference between MHT and placebo, neither as a domain nor as separate items. Effects regarding to sexual functioning were similar to as when compared the MHT use to baseline. Compared to placebo, women had better sexual functioning and lower score in "I have lost interest in sexual activity (item # 24) when they used MHT. On the domain of somatic symptoms, there was no differences between MHT and placebo. As to the items of menstrual symptoms, women had more breast tenderness (item #17) during MHT compared to placebo.

3.5 Placebo effect

Placebo effect was also investigated. When compared to the baseline, placebo had positive effect on two items: women had less hot flushes (item #19, VMS domain) and they felt themselves less clumsy than usual (item #20, cognitive difficulties domain). Placebo had no effect on the rest of the symptom domains or separate items.

Table 1.

	Baseline Mean (SD)	After MHT Mean (SD)	After placebo Mean (SD)	Baseline vs MHT			Placebo vs Baseline			Placebo vs MHT		
				N	Mean difference (SD)	P	N	Mean difference (SD)	P	N	Mean difference (SD)	P
WHQ total score	2.19 (0.48)	1.86 (0.41)	2.10 (0.43)	63	-0.33 (0.33)	<0.001	63	-0.09 (0.33)	0.041	63	-0.24 (0.36)	<0.001
Vasomotor symptoms domain	2.91 (0.97)	1.65 (0.75)	2.73 (1.05)	63	-1.25 (0.97)	<0.001	63	-	ns	63	-1.08 (1.06)	<0.001
19. I have hot flushes	3.08 (1.05)	1.68 (0.82)	2.83 (1.12)	63	-1.40 (1.06)	<0.001	63	-0.25 (0.86)	0.023	63	-1.14 (1.08)	<0.001
27. I suffer from night sweats	2.73 (1.04)	1.62 (0.79)	2.64 (1.11)	63	-1.11 (1.08)	<0.001	63	-	ns	63	-1.02 (1.20)	<0.001

Sleep problems domain	2.25 (0.77)	1.97 (0.66)	2.18 (0.75)	63	-0.28 (0.55)	<0.001	63	-	ns	63	-0.21 (0.57)	0.006
1. I wake early and then sleep badly for the rest of the night	2.71 (1.11)	2.37 (0.97)	2.52 (1.11)	63	-0.35 (1.11)	0.015	63	-	ns	63	-	ns
11. I am restless and can't keep still	1.59 (0.85)	1.49 (0.74)	1.56 (0.76)	63	-	ns	63	-	ns	63	-	ns
29. I have difficulty in getting off to sleep	2.44 (1.18)	2.05 (0.96)	2.44 (1.15)	63	-0.40 (0.81)	<0.001	63	-	ns	63	-0.40 (0.81)	<0.001
Depressive symptoms domain	1.69 (0.54)	1.59 (0.46)	1.61 (0.51)	63	-0.10 (0.33)	0.019	63	-	ns	63	-	ns
3. I feel miserable and sad	1.57 (0.73)	1.43 (0.67)	1.57 (0.69)	63	-	ns	63	-	ns	63	-	ns
5. I have lost interest in things	1.81 (0.88)	1.70 (0.82)	1.70 (0.84)	63	-	ns	63	-	ns	63	-	ns
7. I still enjoy the things I used to [a]	1.84 (0.94)	1.84 (0.97)	1.68 (0.84)	63	-	ns	63	-	ns	63	-	ns
8. I feel life is not worth living	1.41 (0.78)	1.44 (0.84)	1.41 (0.75)	63	-	ns	63	-	ns	63	-	ns
10. I have a good appetite [a]	1.33 (0.74)	1.44 (0.89)	1.30 (0.61)	63	-	ns	63	-	ns	63	-	ns
12. I am more irritable than usual	2.00 (0.98)	1.60 (0.77)	1.92 (0.96)	63	-0.40 (0.77)	<0.001	63	-	ns	63	-0.32 (0.86)	0.005
25. I have feelings of well-being [a]	1.82 (0.80)	1.65 (0.79)	1.70 (0.71)	61	-	ns	62	-	ns	62	-	ns
Anxiety/fears domain	1.48 (0.49)	1.34 (0.41)	1.41 (0.50)	63	-0.14 (0.34)	0.003	63	-	ns	63	-	ns
2. I get very frightened or panic feelings for apparently no reason at all	1.29 (0.58)	1.21 (0.54)	1.30 (0.66)	63	-	ns	63	-	ns	63	-	ns
4. I feel anxious when I go out of the house on my own	1.29 (0.61)	1.19 (0.40)	1.21 (0.57)	63	-	ns	63	-	ns	63	-	ns
6. I get palpitations or a sensation of "butterflies" in my stomach or chest	1.89 (0.88)	1.60 (0.75)	1.75 (0.84)	63	-0.29 (0.79)	0.006	63	-	ns	63	-	ns
9. I feel tense or "wound up"	1.44 (0.67)	1.37 (0.60)	1.40 (0.69)	63	-	ns	63	-	ns	63	-0.03 (0.57)	0.005
Cognitive difficulties domain	2.57 (0.72)	2.36 (0.71)	2.42 (0.66)	62	-0.24 (0.42)	<0.001	63	-0.15 (0.46)	0.012	62	-	ns
20. I am more clumsy than usual	2.67 (0.93)	2.25 (1.06)	2.35 (0.95)	63	-0.41 (0.73)	<0.001	63	-0.32 (0.74)	0.001	63	-	ns
33. I have difficulty in concentrating	2.32 (0.95)	2.23 (0.90)	2.29 (0.85)	62	-	ns	63	-	ns	62	-	ns
36. My memory is poor	2.73 (0.81)	2.57 (0.78)	2.64 (0.79)	62	-0.18 (0.56)	0.017	63	-	ns	62	-	ns
Sexual functioning domain	2.41 (0.78)	2.12 (0.64)	2.36 (0.74)	45	-0.29 (0.74)	0.012	45	-	ns	45	-0.25 (0.65)	0.013
24. I have lost interest in sexual activity	2.60 (0.96)	2.29 (0.95)	2.55 (0.94)	62	-0.31 (0.95)	0.015	62	-	ns	62	-0.26 (0.79)	0.013
31. I am satisfied with my current sexual relationship [a]	2.17 (0.92)	1.96 (0.80)	2.18 (0.98)	45	-	ns	45	-	ns	45	-	ns
34. As a result of vaginal dryness sexual intercourse has become uncomfortable	2.53 (1.08)	2.30 (0.90)	2.41 (1.06)	44	-	ns	44	-	ns	43	-	ns

Somatic symptoms domain	2.13 (0.58)	2.07 (0.53)	2.10 (0.57)	63	-	ns	63	-	ns	63	-	ns
14. I have headaches	2.25 (0.97)	2.05 (0.92)	2.21 (1.02)	63	-	ns	63	-	ns	63	-	ns
15. I feel more tired than usual	2.29 (0.92)	2.32 (0.94)	2.14 (0.82)	62	-	ns	63	-	ns	62	-	ns
16. I have dizzy spells	1.68 (0.88)	1.64 (0.79)	1.60 (0.83)	62	-	ns	62	-	ns	63	-	ns
18. I suffer from pain in my limbs	2.63 (1.08)	2.78 (1.08)	2.71 (0.97)	62	-	ns	62	-	ns	63	-	ns
23. I feel sick or nauseous	1.46 (0.71)	1.27 (0.55)	1.41 (0.73)	63	-0.19 (0.64)	0.023	63	-	ns	63	-	ns
30. I often notice pins and needles in my hands and feet	2.19 (1.05)	2.14 (1.00)	2.25 (1.09)	63	-	ns	63	-	ns	63	-	ns
35. I need to pass urine/water more frequently than usual	2.38 (1.18)	2.30 (1.07)	2.33 (1.09)	61	-	ns	63	-	ns	61	-	ns
Menstrual symptoms domain [b]												
17. My breasts feel tender or uncomfortable	1.37 (0.70)	1.91 (1.09)	1.35 (0.60)	63	0.54 (1.18)	<0.001	63	-	ns	63	0.56 (1.10)	<0.001
22. I have abdominal cramps or discomfort	1.70 (0.84)	1.44 (0.78)	1.52 (0.78)	63	-0.25 (0.80)	0.015	63	-	ns	63	-	ns
28. My stomach feels bloated	2.29 (1.04)	2.11 (0.99)	2.25 (1.09)	62	-	ns	63	-	ns	62	-	ns

Differences of means are given with standard deviations in braces.
Only the data on statistically significant ($p<0.05$) changes are shown.
Ns=non-significant.
[a] Reversed scoring
[b] All women were postmenopausal and hysterectomized, thus no response to the item #26. *I have heavy periods*.

4 Discussion

Our results corresponded quite well with our hypotheses. As expected, VMS, both hot flushes and night sweats, decreased with MHT compared to placebo. This finding is in line with the results of the previous studies. [20] [21] [2] [18] [19] [22] [23] [24] As to other symptoms, as supposed according to inconsistent results in previous studies[2,18–20,22] , our findings were rather sporadic. It is proposed that some of the effects of MHT on other climacteric-related symptoms might be induced by the decrease of VMS. Supporting this theory, Savolainen-Peltonen et al. found that in women who had not baseline hot flushes, MHT had no effect on the other climacteric-related symptoms included in the WHQ.[2] It is also important to keep in mind that not all symptoms related to climacteric are always caused by hormonal factors.

According to previous studies [20 2 18 19 22 23 24], we hypothesized that MHT would have positive effects on sleep problems. However, compared to placebo, the only sleep problem that was decreased with the MHT was difficulty of getting off to sleep. Inability to stay asleep was reduced with the use of MHT compared to baseline; but interestingly, there was no difference in symptoms when compared placebo and MHT nor when compared baseline to placebo. This probably means that the effect of MHT on inability to stay asleep was rather weak. Also, there is always a change for type II error, in other words MHT actually helps, but the effect cannot be seen on the results for some unknown reason. In this case, maybe because of the rather small size of the population in our study. It is typical that sleep problems become more common when ageing. Thus, it is difficult to separate sleep problems related to ageing from sleep problems related to climacteric.[25 26] As waking up early and then sleeping badly for the rest of the night is one of the most common climacteric-related symptom[27], further research around this area is needed. The lack of significant results in sleep item "I am restless and can't keep still" (item #11, sleep problems domain) might be explained by the phrasing of the item as it was not asked if the symptom occurred during the sleep time.

As we assumed according to previous studies[2,18,23], the effect of MHT on mood symptoms were minor. MHT did have an effect only on feeling more irritable or tense. The lack of decrease in other mental symptoms might be explained by a low number of depressive and anxiety/fears symptoms at the baseline. The mean value was lower than 2 in all other symptom items besides in the feeling more irritable or tense. The differences between previous studies, might be caused by the different MHT preparations or by differing study populations. One confusing factor between studies might also be placebo effect, even though in our study, placebo had no effect on mental symptoms. It must also be considered that mental symptoms may be caused by various factors, which may also create disagreement between studies. Researchers cannot separate symptoms caused by climacteric hormonal changes from other symptoms, and it is unlikely that MHT would decrease symptoms that

are not caused by hormonal factors. It is also possible that depressive and anxiety symptoms related to climacteric are associated stronger to other climacteric-related symptoms than to low estrogen levels.[28,29 30 29,31] The possible lack of symptoms at the baseline of studies also makes interpretation of results more complex. As mentioned above, the participants in our study had quite low scores in mood symptoms at the baseline, which may explain why potential effect did not appear in results. This may also have been the case in some of the previous studies. Rudolph et al. (2004) investigated 129 women with a mild to moderate depressive episode in the context of a postmenopausal syndrome.[24] They measured depressive symptoms with Hamilton Depression Rating Scale (HAMD), and VMS and sleep disturbances with the WHQ. The reduction of depressive symptoms seemed to be only partially a consequence of improvement of VMS and sleep disturbances, thus some of the positive effect of MHT on mood symptoms is probably caused by pure hormonal changes. The various factors behind decreasing symptoms is important to keep in mind while deciphering different studies around this area.[24] Moreover, also pain might be a confusing factor around depressive symptoms and climacteric-related symptoms. Estrogen has an impact on pain transmitting nerves and it has been proven that sudden ending of an MHT can cause arthalgia.[32]

MHT did not alleviate cognitive difficulties compared to placebo and similar findings have been seen by other researchers. [18,20,23] Though, some have also found positive effects.[2] In our study, compared to baseline, MHT was effective on poor memory, but there was no difference between the MHT and placebo. It is unclear whether cognitive difficulties experienced by climacteric women are directly related to hormonal changes or are rather a consequence of other climacteric-related symptoms, such as night sweats or sleep problems.[33 34 35 29 30 36] In the previously mentioned study by Savolainen-Peltonen et al. (2014), MHT was effective for treating cognitive difficulties only in women who had disturbing hot flashes at baseline.[2] Cognitive difficulties go along with depressive symptoms and anxiety, which must be kept in mind when investigating the impact of MHT on cognitive difficulties.

Other confusing factors behind cognitive difficulties are chronic diseases, stress and mental load.[37] Even though, most of the studies only approve participants with no chronic diseases or with no significant mental problems.

Some studies have found that MHT has positive effects on sexual functioning.[18,20,22,23] Our study showed that women got helped with losing sexual interest, but the other sexual-related symptoms remained unchanged. It is possible that the increase of sexual interest is connected to increase of general feeling of well-being as decrease in VMS. Better sexual functioning has also been seen by other researches.[18,20,22,23]

In our study, there was no change in somatic symptoms, and similar findings have been seen before.[23] In some studies, there MHT has found to have positive effects on aching joints and muscles and other somatic symptoms.[22] [20] The differences between studies might be caused by indirect effects of MHT, as aches and experiences of pain may decrease when general well-being increases. As to the side-effects of MHT use, it is well known that MHT sometimes causes breast tenderness. [38] [39], which was also seen in our study.

More investigation is needed to determine whether MHT is useful against other climacteric-related symptoms than VMS and sleep problems, particularly when VMS and sleep problems are not principal symptoms of the participants.

5 Bias

The use of validated and widely used questionnaire, the WHQ, was a merit in our study. Furthermore, we used both original and the revised WHQ, the latter of which have shown to be the most sensitive

in Finnish population.[6] Recall biases are sometimes possible, when not using objective measurements such as laboratory tests. The experience of symptoms is, however, always a subjective experience and the use of a validated questionnaire might be the best possible way to evaluate climacteric-related symptoms in peri- and postmenopausal women. The fact that we measured serum follicle-stimulating hormone concentration, makes results more reliable, since being in peri- or postmenopause was confirmed.

The fact that women had only few depressive and anxiety/fears symptoms at the baseline, might explain the absence of significant positive effects in the results. Thus, the lack of change in these symptoms when MHT was used, does not directly mean that MHT does not affect these symptoms. Further research around this area is needed.

As our study was a randomized double-blind trial, we avoided some of the potential biases of observational studies. Moreover, because all the women in our study had gone through hysterectomy, our study population was ideal to investigate unopposed estrogens effects on climacteric-related symptoms without the possibility of progestin affecting the results. As all the participants used both MHT and placebo the selection biases were avoided. The separate comparisons (baseline vs MHT ; placebo vs baseline ; placebo vs MHT) makes the results more reliable. Furthermore, there was no carry-over effect (a possible residual of treatment affecting next observed period) affecting the results, which enabled us to use participants as their own controls. This also increases the reliability in our study. However, because of the rather small study population, the results may not be fully comparable to other populations.

6 Conclusions

In the light of previous research on this area, the results of our study strengthen the fact that MHT effectively decreases VMS, such as hot flushes and night sweats. Sleep problems were also relieved. As other symptoms, differences between studies probably indicate that unopposed estrogen does not have that strong effects on depressive symptoms, anxiety, sexual functioning and cognitive difficulties, but indirect improvements on the symptoms are still possible or even probable. Therefore, VMS and climacteric-related sleep problems should be treated effectively with MHT, but MHT should not be recommended as a first line treatment for the other climacteric symptoms, which are likely to be caused by diverge or multiply causes.

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