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***A randomized controlled study of taper down or abrupt discontinuation of hormone therapy in women treated for vasomotor symptoms.***

**Running title:** Discontinuation of hormone therapy

**Authors:** Lotta Lindh-Åstrand, RN<sup>1</sup>, Marie Bixo, MD, PhD<sup>2</sup>, Angelica Lindén Hirschberg, MD, PhD<sup>3</sup>, Inger Sundström-Poromaa, MD, PhD<sup>4</sup>, Mats Hammar, MD, PhD<sup>1</sup>

**Affiliations:** From the <sup>1</sup>Division of Obstetrics and Gynecology, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping, <sup>2</sup>Department of Clinical Science, Obstetrics and Gynecology, Umeå University, <sup>3</sup>Department of Woman and Child Health, Division of Obstetrics and Gynecology, Karolinska Institutet, Stockholm, Sweden <sup>4</sup>Department of Women's and Children's Health, Uppsala University, Uppsala,

**Corresponding author:**

Lotta Lindh-Åstrand,  
Division of Obstetrics and Gynecology,  
Faculty of Health Sciences,  
University Hospital,  
S-581 85 Linköping,  
Sweden  
Tel +46-13-22 31 72  
Fax +46-13-22 31 94  
E-mail Lotta.lind.astrand@lio.se

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## **Abstract**

**Objective:** To investigate if tapering down of combined estrogen plus progestogen therapy (EPT) reduced recurrence of hot flashes and resumption of therapy compared with abrupt discontinuation. A secondary aim was to evaluate if Health-related Quality of life (HRQoL) was affected following discontinuation and to investigate possible factors predicting resumption of EPT.

**Design:** Eighty-one postmenopausal women with EPT due to hot flashes were randomized to tapering down or abrupt discontinuation of EPT. Vasomotor symptoms were recorded in self-registered diaries and resumption of hormone therapy (HT) was asked for at every follow-up. HRQoL was assessed with the Psychological General Well-being Index (PGWB).

**Results:** Neither the number nor the severity of hot flashes or HRQoL or frequency of resumption of HT differed between the two modes of discontinuation of EPT during up to 12 months of follow-up. About every other woman had resumed HT within one year. Women who resumed HT after four or twelve months reported more deteriorated HRQoL and more severe hot flashes following discontinuation of therapy than women who did not reuptake HT.

**Conclusion:** Women who initiate EPT due to hot flashes may experience recurrence of vasomotor symptoms and impaired health related quality of life after discontinuation of EPT regardless of abrupt or taper down discontinuation. Since in addition to severity of flashes decreased wellbeing was the main predictor of the risk to resume HT it seems important to also discuss quality of life in parallel with efforts to discontinue HT.

**Keywords:** Menopause, hormone therapy, discontinuation of therapy, vasomotor symptoms, Health-related Quality of life (HRQoL)

**Introduction:** As many as 50 to 70 % of women in the Western world experience menopause-related symptoms such as hot flashes and sweating<sup>1-4</sup> during the menopausal transition. Sleep disturbances and vaginal discomfort are other common symptoms associated with the menopausal transition<sup>3,4</sup>. These symptoms may affect health-related quality of life (HRQoL)<sup>5,6</sup>. Previous observational<sup>7-9</sup> and randomized controlled studies (RCT) investigating secondary endpoints<sup>10,11</sup> reported benefits of long-term use of hormone therapy (HT). The results from the Women's Health Initiative (WHI)<sup>12</sup> and Heart Estrogen/Progestin Replacement Study (HERS)<sup>13</sup> dramatically changed treatment recommendations of HT in both the USA and Europe and led to updated guidelines from national and international menopause societies. According to the current guidelines, HT is the most effective and safe therapy for symptomatic women in early postmenopause with moderate to severe vasomotor symptoms, but should be used in the lowest effective dose and for the shortest possible duration. It is necessary to stop HT to evaluate whether the symptoms persist or have been resolved. An individual risk profile should be considered for every woman before initiation and after a failed attempt to discontinue HT<sup>14,15</sup>.

There is a lack of evidenced-based recommendations on how best to discontinue HT. Different types of gradual discontinuations are suggested either by "dose taper" i.e. decreasing the every-day dose or "day taper" i.e. by decreasing the number of days per week that HT is used<sup>16</sup>. Neither retrospective<sup>17-20</sup> nor prospective RCTs<sup>21,22</sup> have shown significant differences in the recurrence of vasomotor symptoms or resumption of HT between gradual or abrupt discontinuation of HT. In these studies both women with and without hot flashes as indications for therapy have been included and changes in HRQoL have usually not been studied. Since a history of vasomotor symptoms before HT was initiated and recurrence of symptoms after discontinuation seem to be important factors for resuming HT<sup>17,23</sup> it would be of interest to specifically study symptom recurrence and the impact of discontinuation of HT on HRQoL in women who initiated HT due to vasomotor symptoms.

The hypotheses of the study were that tapering down continuous combined estrogen/progestogens therapy (EPT) would reduce the recurrence of hot flashes and resumption of HT compared with abrupt discontinuation.

The aim of this randomized, prospective, open, controlled multicenter study was to compare effects of two different methods to discontinue continuous EPT, i.e. tapering down or abrupt discontinuation, on the recurrence of hot flashes, resumption of therapy and on HRQoL in women with vasomotor symptom before initiating EPT. We also investigated possible predictors for resumption of HT.

## Methods

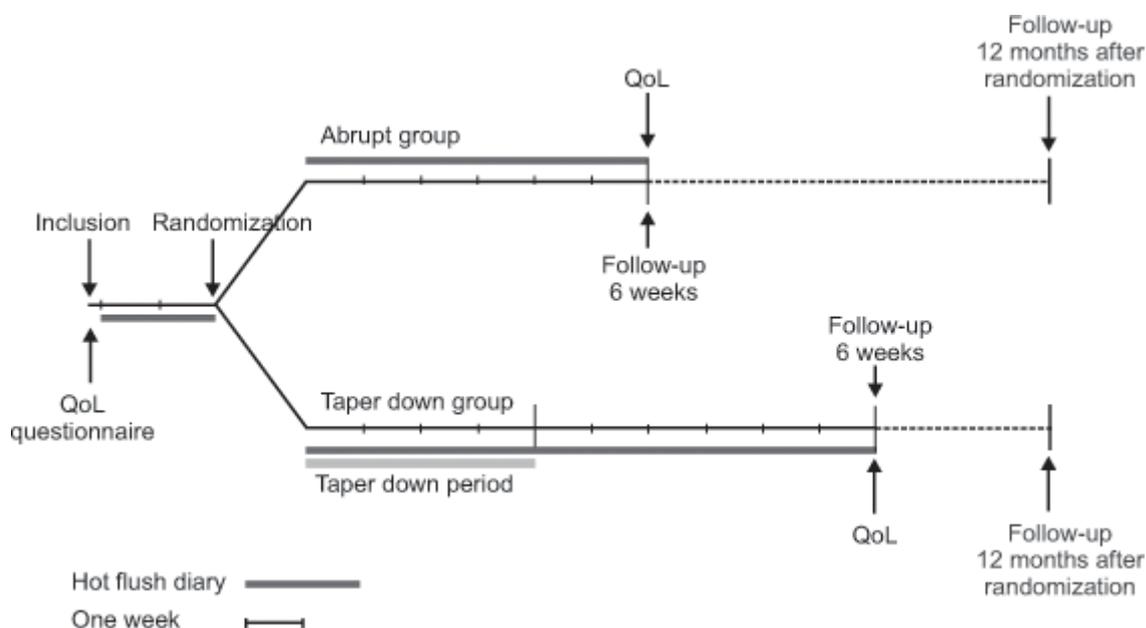
### Participants

Postmenopausal women were consecutively invited to participate in the study by advertisement in local press or at visits to their gynecologist. Enrollment took place at 12 gynecological out-patient university based or private clinics in Sweden between March 2005 and December 2007. Women were eligible if they had used HT between 3-11 years, used continuous EPT or tibolone at least during the last year, had originally started HT due to vasomotor symptoms, and were suitable to try to discontinue EPT according to the gynecologist's and her own judgment. The exclusion criteria were; unstable thyroid or other metabolic disease, indication to stop EPT rapidly (e.g. breast cancer), recently started or changed medication for any psychiatric disorder, other treatments for vasomotor symptoms, more than one hot flash/24 hours according to the two-week screening diary, unsuccessful discontinuation of EPT during the last year, or EPT due to premenopausal hypogonadism.

The trial was conducted in accordance with Good Clinical Practice and The Declaration of Helsinki. Approval from the regional ethics board at Linköping University was received before study start. Written informed consent was obtained from all study participants before inclusion. An independent monitoring was performed to assure quality control during the study.

### Intervention

Eligible women were planned to be equally randomized to either tapering down (taper group) or abrupt (abrupt group) discontinuation of EPT. The taper group was instructed to take their usual EPT dose every other day during four weeks, i.e. "day-taper", before total discontinuation and the abrupt group discontinued EPT immediately after randomization. A follow-up telephone interview was performed six weeks after discontinuation of EPT and four and twelve months after randomization (Figure 1).



*Figure 1 Design of the study.*

An independent statistician prepared a computer-generated separate randomization list for each centre and the randomization was carried out with blocks of four patients. The randomization process and block lengths were unknown to the investigators and nurses participating in the study.

If the inclusion- and exclusion criteria were met after the two-week screening period the study nurse allocated the next available number from the randomization list for the specific centre and instructed the woman about how to discontinue the EPT.

### *Outcomes*

The primary study variables were the median number and severity of hot flashes/24 hours in self-registered diaries during the 6<sup>th</sup> week following discontinuation of EPT. The secondary variables were the proportion of women who had resumed HT at the follow-up and the total score of HRQoL measured with the Psychological General Well-Being Index (PGWB). Adverse events were documented using open questions at each contact.

### *Measurements of study variables*

*Hot flashes:* To assess vasomotor symptoms we used a manual hot flash diary during the two weeks screening period, four weeks tapering period (tapering group) and six weeks after discontinuation of EPT (both groups). The woman registered number and severity of hot flashes daily after waking up and before bedtime. The severity was subjectively rated with a scale ranging from 0 (not bothersome at all) to 10 (extremely bothersome) and consisted of a summative rating of all hot flashes experienced. The baseline average number and severity of flashes/24 hours was calculated from the two-week screening period and the six-week figure was calculated as an average of the seven days of the 6<sup>th</sup> week. In nine women (five in the taper and four in the abrupt group) who resumed HT during the six-week follow-up, the median number of days before reuptake was 26 days (range 7-38). We did not analyze the diary registrations after reuptake of HT, but instead the mean value of frequency and severity from the last seven days for the specific woman, before she resumed HT, was carried forward to constitute the 6<sup>th</sup> week data. With this procedure about 5 % of diary recordings were replaced. Additionally, 22 women did not complete every recording during the 6<sup>th</sup> week and a similar carry forward procedure was used, making us complete another 1.4 % of missing values in incomplete diaries.

*Health-related Quality of life:* HRQoL was assessed by using the PGWB form at baseline and six weeks after discontinuation of EPT. This self-administered instrument is validated and used to assess general psychological well-being<sup>24</sup> and has been validated in Swedish<sup>25</sup>. The PGWB contains 22 items referring to anxiety, depressed mood, well-being, self-control, general health, and vitality. Each item is graded between 0-5 with a total score between 0-110. The value 0 is the most negative option and 5 the most positive option. In total 4 out of 162 questionnaires were missing (2.5 %), one baseline registration and three from the 6 week follow-up and were replaced by group means for the visit concerned.

At the follow-up telephone interviews the women were asked to grade their general health as “unchanged”, “improved” or “worsened”.

*Resumption of EPT:* According to the protocol the study nurse asked if the woman had resumed treatment for menopause-related symptoms at every contact, i.e. at six weeks after discontinuation of EPT, four and twelve months after randomization and at every unplanned contact.

Open-ended questions if any adverse events had occurred since the last contact were registered at all follow-up contacts.

### *Statistical methods*

The assumption was that tapering down of EPT would lead to a mean recurrence of two hot flashes/24 hours and abrupt discontinuation of EPT would cause 20 % more hot flashes/24 hours, i.e. 2.4 flushes/24 hours, six weeks after discontinuation. Standard deviation was estimated to be one hot flash/24 hours. To obtain a power of 80 % we would need 100 women per group to detect a significant difference between groups ( $p < 0.05$ , two-sided test). An alternative power calculation was based on the assumption that 33 % of women in the tapering group had resumed HT after four months and 66 % in the abrupt group. To obtain a power of 80 % we would need 35 women per group to detect a significant difference between groups ( $p < 0.05$ , two-sided test).

Due to a slow recruitment rate, probably due to the substantial decline in HT use in Sweden, and the fact that many women had tried to discontinue HT by themselves, the study was prematurely discontinued in December 2007 and the intended sample size of 200 women was not reached.

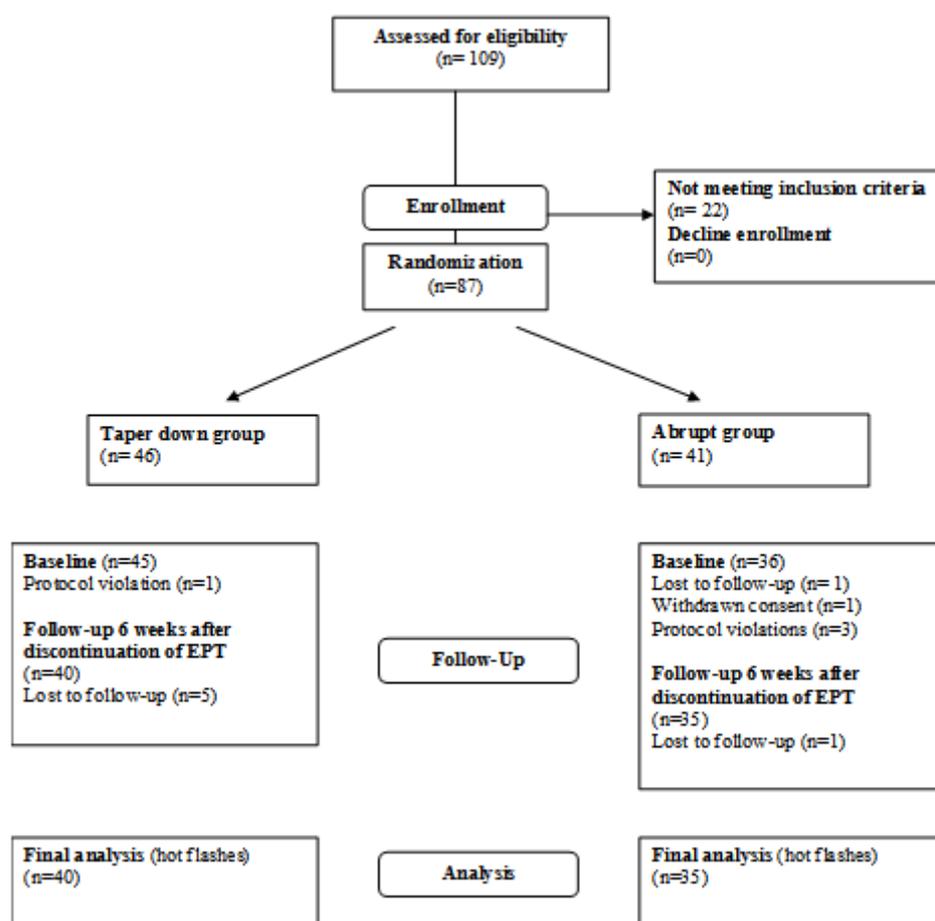
Data were analyzed according to “intention to treat”, i.e. including all women who fulfilled the inclusion criteria (except HT >11 years), had no exclusion criteria, had initiated their change in EPT use according to randomization at least one day, and who had any available measurements after randomization. In addition we made analyzes “per protocol” for primary and secondary outcomes, including only women who had completely followed the protocol.

Baseline and demographic data were described by using median and 25<sup>th</sup> – 75<sup>th</sup> percentiles (IQR). To compare differences between groups Mann-Whitney U-test was used for continuous variables. Proportions were compared by the use of Pearson chi-square test or Fisher’s exact test when appropriate. Analysis of variance (ANOVA) with repeated measures was used to compare hot flashes/24 hours between the two groups from baseline to six weeks follow up. Logistic regression analyses were used to establish which factors predicted the risk of resuming HT, both by entering all variables at the same time and with stepwise procedure. The p-value was set at <0.05 (two-sided) to be considered significant. Data analyses were performed by SPSS for Windows 14.0.0 standard version.

## Results

### Study population

Of the 109 women screened for eligibility 87 women were randomized to either taper-down (n=46) or abrupt (n=41) discontinuation of EPT (Figure 2). Four women were withdrawn from analyses due to protocol violations, i.e. did not meet inclusion or exclusion criteria. One woman withdrew her consent and one was lost to follow up. Thus baseline data include the remaining 81 women. Fourteen of these women (nine in the taper-down group and five in the abrupt group) had used HT for more than 11 years (12-21 years) but were kept in the analyses. The distribution of these women between the two groups was equal ( $p = 0.47$ ). All analyses of primary and secondary outcomes were performed with and without these 14 women, and it appeared that the results were not affected if they were included. In the analyses of resumption of EPT the PGWB scores of all 81 women were included, whereas in the analyses of hot flashes another six women were omitted because they had not filled in the diaries after baseline.



*Figure 2: Consort figure showing the recruitment and patient flow regarding the patient included in the hot flash analyses (primary end point) of the study*

The women were 50 to 72 years old (median 59.0, 25<sup>th</sup> – 75<sup>th</sup> percentiles 55-61). No differences in baseline and clinical characteristics were found between the two groups except that more women in the abrupt group smoked (Table 1). In total more than one third of the women used estradiol (E2) 1 mg + norethisterone acetate (NETA) 0.5 mg, about 25 % used E2 + medroxyprogesterone acetate (MPA) and approximately 10 % used tibolone or E2 2 mg

+ NETA 1 mg. It was no differences between the groups regarding type of EPT use, medical history and health status at screening (data not shown).

**Table 1. Baseline demographic and clinical characteristics for participating women**

	<b>Taper down group</b> (n=45)	<b>Abrupt group</b> (n=36)	<b>P-value*</b>
<b>Age at inclusion</b>	58.0 (54.0-61.0)	59.0 (57.0-61.0)	0.40
<b>Age at menopause<sup>1</sup></b>	50.0 (48.0-52.0)	49.5 (48.0-51.8)	0.95
<b>HT duration (year)</b>	9.0 (5.3-10.0)	9.5 (6.0-10.9)	0.44
<b>Number of children</b>	2.0 (2.0-2.5)	2.0 (1.0-2.0)	0.45
<b>Number of hot flashes/24 h</b>	0.0 (0-0.07)	0.0 (0-0.18)	0.79
<b>Education (numbers; %)</b>			0.11
- nine-year compulsory school	17 (38)	14 (39)	
- high school	16 (36)	6 (17)	
- university degree	12 (27)	16 (44)	
<b>Smoking in numbers n/y (%)</b>	40/5 (89/11)	25/11 (69/31)	0.03
<b>Marital status numbers (%)</b>			0.91
- married/cohabiting	33 (73)	26 (72)	
- other	12 (27)	10 (28)	
<b>Reason HT was stopped<sup>2</sup></b> <b>(number, %)</b>			0.93
- fear of side effects	14 (31)	10 (28)	
- patients decision	23 (52)	20 (56)	
- doctors advice	7 (16)	6 (17)	

Data are presented with median and 25<sup>th</sup> - 75<sup>th</sup> percentiles

\* Mann-Whitney U-test or  $\chi^2$

<sup>1</sup> Taper down group n=31, abrupt group n=28 (women with known menopause)

<sup>2</sup> One missing case in the taper down group

### *Hot flashes*

The two groups did not differ regarding frequency or severity of hot flashes/24 hours at baseline or at the 6<sup>th</sup> week after discontinuation of EPT (Table 2), neither with intention to treat nor with per protocol analysis. Analyses of frequency of hot flashes at day- or night time in separate yielded no further information. The repeated measures ANOVA indicated that flashes per day, per night and per 24 hours increased significantly in both groups but the change over time did not differ between the groups ( $p = 0.85$ ).

The hot flash frequency/24 hours at the 6<sup>th</sup> week did not differ between the groups of women who had or had not resumed HT at six weeks, or at four months. In contrast, women who had resumed HT after one year had significantly more hot flashes at the 6<sup>th</sup> week than women who still abstained from HT. Women who had resumed HT at four or 12 months reported significantly more severe hot flashes at the 6<sup>th</sup> week than women who had not resumed therapy (Table 3).

In women in the abrupt group, who had recurrence of hot flashes and who had no flashes at all during the screening period, flashes appeared already 8.3 days (mean) after the last intake of HT, versus 7.6 days (mean) in the taper down group. Only three women in total did not have any recurrence of hot flashes at all during the six weeks diary period, two women in the gradual group and one in the abrupt group.

**Table 2.** Hot flash frequency (numbers of flashes), severity (0-10) per 24 h and Psychological General Wellbeing total score range 0-110 (PGWB) between the taper down group (TG) and abrupt group (AG)

	<b>Taper down group</b>	<b>Abrupt group</b>	<b>P-value*</b>
<b>Hot flash frequency/24 h</b>			
Baseline (n = TG 45, AG 36)	0.0 (0.0-0.1)	0.0 (0.0-0.2)	0.79
6 <sup>th</sup> week (n = TG 40, AG 35)	3.4 (1.3-6.4)	4.0 (1.4-6.1)	0.50
<b>Hot flash severity/24 h</b>			
Baseline (n = TG 45, AG 36)	0.0 (0.0-0.0)	0.0 (0.0-0.5)	0.54
6 <sup>th</sup> week (n = TG 39, AG 34)	3.1 (0.7-7.4)	4.1 (1.0-7.0)	0.75
<b>PGWB score</b>			
Baseline (n = TG 45, AG 36)	95 (78-100)	91 (82-96)	0.25
6 <sup>th</sup> week (n = TG 45, AG 36)	86 (70-96)	85 (75-92)	0.50
Reduction from baseline to 6 <sup>th</sup> week	4 (2-10)	4 (1-15)	0.64

Data are presented as median and 25<sup>th</sup> -75<sup>th</sup> percentiles

\* Mann-Whitney U-test

**Table 3.** Hot flash frequency (numbers of flashes), severity (0-10) per 24 h and Psychological General Wellbeing total score range 0-110 (PGWB) in women who resumed hormone therapy at the 6<sup>th</sup> week, or at 4 and 12 months.

	Resumption 6 w		P-value	Resumption 4 m		P-value	Resumption 12 m		P-value
	Yes (n= 8)	No (n=67)		Yes (n=24)	No (n=51)		Yes (n=34)	No (n=40)	
<b>Hot flash frequency/24 h</b>									
Baseline	0.1 (0.0-0.5)	0.0 (0.0-0.1)	0.20	0.0 (0.0-0.4)	0.0 (0.0-0.7)	0.27	0.0 (0.0-0.2)	0.0 (0.0-0.1)	0.67
6 <sup>th</sup> week	4.0 (2.7-6.9)	3.6 (1.3-6.1)	0.68	4.4 (2.7-8.8)	3.3 (0.6-5.3)	0.06	5.1 (3.4-9.1)	2.5 (0.4-4.0)	<0.001
<b>Hot flash severity/ 24 h</b>									
Baseline	0.0 (0.0-0.5)	0.0 (0.0-0.0)	0.26	0.0 (0.0-0.2)	0.0 (0.0-0.0)	0.40	0.0 (0.0-0.1)	0.0 (0.0-0.0)	0.63
6 <sup>th</sup> week	7.1 (2.3-9.2)	3.4 (0.7-6.4)	0.16	6.6 (2.7-9.3)	2.9 (0.6-5.9)	0.05	7.0 (4.6-9.9)	1.8 (0.4-4.0)	<0.001
<b>PGWB score</b>	<b>Yes (n= 11)</b>	<b>No (n=70)</b>		<b>Yes (n=28)</b>	<b>No (n=53)</b>		<b>Yes (n=38)</b>	<b>No (n=42)</b>	
Baseline	96 (73-102)	92 (82-97)	0.48	93 (73-100)	92 (86-97)	0.94	93 (77-99)	92 (84-97)	0.83
6 <sup>th</sup> week	80 (53-85)	87 (76-94)	0.055	80 (53-92)	87 (80-96)	0.005	81 (66-92)	87 (81-96)	0.013
Reduction from baseline to 6 <sup>th</sup> week	15 (3-30)	3 (2-8)	0.005	11 (3-28)	1 (3-7)	<0.001	8 (3-24)	1 (3-6)	<0.001

Data are presented as median and 25<sup>th</sup> -75<sup>th</sup> percentiles

\* Mann-Whitney U-test

### *Resumption*

No significant differences were found between the two groups regarding resumption of HT at six weeks (6/45, 13.3 % in the taper down group and 5/36, 13.9 % in the abrupt group;  $p = 0.94$ ), at four months (16/45, 35.6 % in the taper down group and 12/36, 33.3 % in the abrupt group;  $p = 0.83$ ), or at 12 months (24/44, 55.0 % in the taper down group and 14/36, 39.0 % in the abrupt group;  $p = 0.12$ ) after discontinuation of EPT. Analyses of the data “per protocol” yielded similar results.

### *Health-related Quality of life*

Total PGWB score did not differ at baseline ( $p = 0.25$ ) or at the 6<sup>th</sup> week ( $p = 0.5$ ) after discontinuation of EPT between the two randomization groups (Table 2). On the other hand, women who had resumed EPT at the six-week follow-up ( $p = 0.005$ ) and at the four- and 12 month follow-ups ( $p < 0.001$ ) had a significantly more pronounced decrease in PGWB total score at the 6<sup>th</sup> week compared to women who had not resumed HT at that time, whereas PGWB did not differ at baseline between these groups (Table 3). All the sub-scores of PGWB referring to anxiety, depressed mood, well-being, self-control, general health and vitality decreased significantly between baseline and six weeks in women who had resumed HT within four months.

More women who had resumed HT at four months after randomization reported, at the six week telephone follow-up, that their general health had deteriorated compared to the women who had not resumed HT at four months (54 vs. 26 %;  $p = 0.04$ ).

A logistic regression analysis including number and severity of hot flashes at six weeks, number of years with EPT, education, smoking habits, and change in PGWB between baseline and six weeks, showed that these factors together had a  $R^2$  value (Nagelkerke) of 0.56 in explaining reuptake of HT after 12 months. The most important single predictor seemed to be the severity of hot flashes at six weeks with a  $R^2$  value (Nagelkerke) = 0.37 ( $p < 0.001$ ). Also the reduction in PGWB from baseline to six weeks was an important factor and together with the severity they had a  $R^2$  value (Nagelkerke) = 0.46 ( $p = 0.016$ ) ( $p = 0.002$ ). The odds ratio for the factor “severity of hot flashes at six weeks” was 1.42 (95 % CI 1.19-1.69) with the stepwise method, thus similar to the result with all variables included (Table 4). We interpreted the results as indicating that the other variables did not confound this single variable. In addition smoking habits predicted resumption of HT but with borderline significance.

### *Adverse events*

The proportion of women experiencing adverse events during the study was slightly, albeit not statistically, higher in the taper down group, 39 women (54 %) compared to 29 women (48 %) in the abrupt group. The most common adverse event in the total group was vaginal dryness (15 %), joint pain (12 %), depressed mood (11 %), infections (7.5 %) and sleep disturbances (6 %). One woman in the abrupt group had a breast cancer diagnosed during the study and another woman in the taper-down group had a deep vein thrombosis.

**Table 4** Logistic regression analysis of variables predicting reuptake of HT after 12 months in 71 postmenopausal women

<b>Variable</b>	<b>P-value</b>	<b>Odds ratio</b>	<b>95 % confidence interval</b>	
<i>Hot flash frequency the 6<sup>th</sup> week</i>	0.21	1.19	0.91	1.56
<i>Hot flash severity the 6<sup>th</sup> week</i>	0.007	1.45	1.11	1.90
<i>HT duration</i>	0.22	1.13	0.93	1.36
<i>Change in PGWB from baseline to the 6<sup>th</sup> week</i>	0.009	1.08	1.02	1.14
<i>Smoking habits</i>	0.049	0.13	0.02	0.995
<i>Education</i>	0.31			
- nine-year compulsory school		1.00		
- high school	0.19	3.40	0.56	20.72
- university degree	0.18	3.24	0.57	17.92

HT, hormone therapy

PGWB, Psychological General Well-Being Index

## **Discussion:**

This study failed to show any significant difference between women who tapered down EPT over four weeks and women who stopped abruptly regarding recurrence of vasomotor symptoms or resumption of HT. Four months after randomization more than a third of the women had resumed HT and after one year almost 50 % had resumed treatment, independently of randomization group. However, due to the premature discontinuation of the study the statistical power is low leading to a risk not to find a significant difference between the two ways to discontinue EPT although it may really exist.

On the other hand, the women who resumed HT estimated the severity of flashes to be more pronounced and reported a greater impairment in HRQoL than the women who did not resume HT. Our design, which has not been previously reported from other studies on the issue, with baseline PGWB measurements and another measurement 6 weeks after stopping EPT enabled us to state that women who resumed HT had a high PGWB-index during HT but deteriorated after stopping HT. Thus our data suggest that deteriorated well-being and the severity of hot flashes contributed to the women's decision to resume HT, which was confirmed in the logistic regression analysis. Several studies<sup>26-29</sup> have stated that HT has a positive impact on HRQoL, most evident in women with vasomotor symptoms and sleep disturbances. Whether severe flashes negatively affect HRQoL or if a generally negative quality of life makes women report more severe hot flashes cannot be analysed with the present design. In addition smoking decreased the risk to resume HT, which may be a result of women's belief that possible risks with HT may be increased by smoking.

The high rate of recurrence of flashes in our study may be related to the fact that all women had flashes before they once started HT and were long-term HT-users (median nine years). It could be argued that the number of hot flashes was rather low but evidently the flashes were experienced severe enough to make the women resume HT. Factors such as hot flashes as an indication for starting HT, troublesome withdrawal symptoms after discontinuation of HT, hysterectomy and long-term HT use have been reported as predictors for difficulty to stop HT successfully<sup>17, 20, 23</sup>. Haimov-Kochman reported a more than two-fold risk and Grady and co-workers reported a sevenfold increased likelihood for resuming HT with the first two abovementioned factors. Long-term users also have experience of the benefits of HT use and may therefore be more prone to take up HT. Haimov-Kochman and co-workers<sup>23</sup> found that the maximum severity score was equal in women who resumed HT and those who successfully quit HT, whereas in the latter group symptoms declined more rapidly. They concluded that return to HT is expected in women intolerant to prolonged climacteric symptoms. This is in line with our findings that the proportion of women who had resumed HT increased from six weeks, to four and 12 months.

Neither retrospective observational studies<sup>17, 18</sup> nor small, randomized controlled trials<sup>21, 22</sup> performed after the WHI study show any difference between gradual and abrupt discontinuation of HT. Haskell and colleagues suggested that women who chose the tapering method differ from those who chose the "cold turkey" method (Haskell 2009) by being younger, more likely to use HT due to menopausal symptoms, long-term users and more prone to use alternative treatments. They found, however, that tapering was associated with lesser recurrence of menopausal symptoms but increased resumption of HT.

It has been reported that vasomotor symptoms will usually improve between a few months to a few years after onset<sup>4, 30</sup> whereas 10-15 % of the women still have symptoms many years after onset<sup>31, 32</sup>. Our population, with women on average 58 to 59 years of age and with long-time EPT use, still reported troublesome hot flashes after discontinuation of EPT. Possibly our sample consisted of a subgroup of women who had prolonged vasomotor symptoms. The

results are in line with data from a large, cross-sectional study showing that more than half of the women, between 50 to 60 years of age, with a history of moderate to severe hot flashes before initiating HT reported such symptoms after discontinuation<sup>20</sup>. The women included in the present study thus resemble those who today are well suited for HT according to current guidelines. Ness and colleagues<sup>19</sup> reported similar results indicating that 40 % of the women below 65 years of age experienced vasomotor symptoms after discontinuation of HT. In a cross-sectional population-based study performed in Linköping, Sweden, 87 % of women age 53 - 54 who initiated HT due to vasomotor symptoms experienced such symptoms when they discontinued HT, although more than half experienced less distressing symptoms than before they had started HT<sup>33</sup>.

Grady and co-workers<sup>17</sup> reported, in a cross-sectional study, that 30 % of the women, who stopped HT experienced troublesome vasomotor symptoms that began about 1 week after discontinuation HT in line with our results with recurrence after 7-8 days.

Haimov-Kochman and colleagues<sup>23</sup> suggested a time frame up to three months after discontinuation of HT when the risk of resuming HT was highest. Others found that 25-50 % of the women who stopped HT returned to HT mainly due to vasomotor symptoms within six months<sup>17, 34</sup>. In line with this we found that more than a third of the women had resumed HT after four months.

In this study the primary study variable was a subjective estimation of number and severity of hot flashes. This method has been used in several studies and is considered to be a valid and reliable method<sup>35, 36</sup>. However, studies comparing subjectively and objectively registered vasomotor symptoms, suggested a falsely low subjective reporting of hot flashes with between 43 to 60 %<sup>37, 38</sup>. Thus, with objectively measured vasomotor symptoms the frequency of flashes probably would have been higher but it is unlikely that this would have affected the results.

A number of women did not complete every recording during the six weeks and missing data were added by means of the carry forward method. Of course this is a weakness, but the proportion of missing data was below the limit of 5 % which is even recommended to be ignored<sup>39</sup>. We therefore do not consider that the missing data in our study may jeopardize the results.

We decided to follow the number and severity of flashes during the first six weeks after complete discontinuation of EPT. It would have been advantageous to have followed flashes with diaries for the first four months and to have measured PGWB again after resumption of HT. For practical reasons, however, we decided to limit the diaries to the first six weeks, and could therefore relate reuptake of HT only to data obtained during the first six weeks.

In this study a four-weeks dosing-interval taper technique was used. Although it is possible that a longer taper down period would have been better prior studies have not indicated that the length of the tapering down period affects the outcome<sup>22</sup>. We suggest that more gradual tapering and longer duration of tapering should be tested prospectively.

It could be argued that the risk of symptom recurrence would differ in women with a high body mass index (BMI), in smokers, in women with regular exercise, or in women with certain EPT preparations. We did not measure BMI and exercise. The randomization should minimize the risk that these factors were not evenly distributed between our groups. It appeared that smokers were more common in the group of women who were randomized to abrupt discontinuation but if anything, this would increase their risk to have recurrence of flashes, which the study could not confirm. Use of different EPT preparations was similar between the randomization groups and therefore we do not consider that this potential confounding factor jeopardizes our results. However, a study on a population using one

specific regimen out of those used in the present study might have yielded other results which have been concealed with our design.

### **Conclusion**

Our results indicate that women who initiate HT due to current guidelines (hot flashes) may experience recurrence of vasomotor symptoms and impaired health related quality of life after discontinuation of HT regardless of abrupt or taper down discontinuation. Since in addition to severity of flashes decreased wellbeing was the main predictor of the risk to resume HT it seems important to also discuss quality of life in parallel with efforts to discontinue HT.

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Text to the Table of contents:

This randomized controlled study between tapering and abrupt discontinuation of hormone therapy failed to show any difference in number or severity of hot flashes, quality of life or resumption of HT during up to 12 months follow-up. About every other woman, regardless of randomization group, had resumed HT within one year, and those who resumed HT reported more deteriorated quality of life and more severe hot flashes following discontinuation of therapy.