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ORIGINAL ARTICLE

Progesterone for hot flush and night sweat treatment – effectiveness for severe vasomotor symptoms and lack of withdrawal rebound

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A controlled trial recently showed that oral micronized progesterone (Progesterone, 300 mg at h.s. daily) was effective for vasomotor symptoms (VMS) in 133 healthy early postmenopausal women. Here, we present subgroup data in women with severe VMS (50 VMS of moderate–severe intensity/wk) and also 1-mo withdrawal study outcomes. Women with severe VMS (*n* = 46) resembled the full cohort but experienced 10 VMS/d of 3 of 4 intensity. On therapy, the progesterone VMS number (#) decreased significantly more than placebo # to 5.5/day (d) versus 8/d (ANCOVA −2.0 95% CI: −3.5 to −0.4). Just after trial midpoint, a withdrawal substudy (D/C) was added – 56 women were invited and 34 (61%) took part (progesterone 17; placebo 17). Those in the D/C cohort resembled the whole cohort. On stopping, VMS gradually increased – at D/C week 4, on progesterone, VMS daily # reached 78% and significantly less than baseline (−3.0 to −0.8) but placebo VMS # did not differ from run-in. In summary, progesterone is effective for severe VMS and does not cause a rebound increase in VMS when stopped. That progesterone may be used alone for severe VMS and unlike estrogen does not appear to cause a withdrawal rebound increases VMS treatment options.

Keywords: hot flushes, progesterone, night sweats, withdrawal syndrome, postmenopause, insomnia, cardiovascular disease, social stress

Introduction

Recently published randomized, double-blind placebo-controlled clinical trial evidence shows that oral micronized progesterone (progesterone, 300 mg at bedtime daily) is effective for hot flushes and night sweats (vasomotor symptoms, VMS) in healthy early postmenopausal women [1]. This trial was in 133 women who were 1–11 years since their final menstruation, whose mean age was 55 years, who were nonsmokers and healthy (so that the cardiovascular effects of progesterone could be accurately assessed). Progesterone caused an overall hot flush and night sweat number decrease to 59% of baseline (as monitored by a daily diary over a 4-week run-in and a 12-week experimental period). This differed significantly from the placebo-related decrease of about 20% ($p < 0.001$ [1]). There were no serious side effects, and no women randomized to progesterone withdrew for lack of efficacy. However, the published data do not provide detailed evidence that progesterone is effective for "severe VMS", defined by the Food and Drug Administration (FDA) as frequent (50 or more/week) and intense (moderate or high intensity, 2–4/4) hot flushes and night sweats [2].

In addition, it is important to know whether or not progesterone, as estrogen or hormone therapy (HT) may, causes an increase in VMS number and intensity when it is stopped [3]. Most reported data on estrogen or HT withdrawal VMS are by questionnaire [3–6]. The only study so far to show diary-based drug-withdrawal data is the escitalopram VMS trial [7]. However, all document that 25–50% of women whose VMS were estrogen- or HT-treated experienced important worsening of VMS when they stopped therapy.

Finally, there are subtle judgements clinicians need to make to confidently and appropriately treat VMS with progesterone [1], estrogen/estradiol [8,9], estradiol with progesterone [10], or with medroxyprogesterone [11]. In addition, health care providers must decide if their patients with VMS are better treated with a serotonin reuptake or serotonin-norepinephrine reuptake [7,12] inhibitor, gabapentin [13], or one of the several alternative therapies [14] or those that decrease central adrenergic tone (exercise training, relaxation, etc [15]).

Let us start with a couple of clinical situations:

- *Ms. BN is a 52-year-old kindergarten teacher* whose last flow was 13 months ago. She has had increasing hot flushes (8 or 10 times a day) and night sweats (waking her soaked with sweat twice every night) for the last year but she has resisted hormonal treatment. "The flooding and breast tenderness misery of perimenopause are gone but I can no longer cope with these hot flushes and not sleeping! The two antidepressants I tried made my sleep worse and didn't take away my night sweats".
- *Mrs. MA is a 68-year-old menopausal woman banker* for a local credit union. She has just started again having many daytime hot flushes as well as night sweats waking her multiple times. Sometimes now, when she wakes soaked at night, she also has chest pain that responds rapidly to nitroglycerin. Her final flow was at age 53. "Around menopause", she reports severe VMS that were effectively treated with continuous combined HT. "But I nearly died of the flushes and sweats when I tried to stop my estrogen!" she asserts.

These two patients are both in stressful public jobs (whose stresses may be making their VMS worse [16]) and illustrate a couple of the issues related to treatment of VMS. *Ms. BN* had high estrogen symptoms (flooding menstruation and breast tenderness) in

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perimenopause, is bothered by sleep disturbances, and was not effectively treated by escitalopram or venlafaxine. What is an appropriate treatment for her severe VMS? *Mrs. MA* has had a recurrence of past VMS – why? She had hormone withdrawal rebound increases in VMS in the past and now has coronary artery disease – she needs something effective for severe VMS that will not cause withdrawal and that is not contraindicated given her heart disease.

The purposes of this work are to present results of two additional outcomes of the recent randomized controlled trial (RCT) of progesterone for VMS [1]: (1) effectiveness of progesterone in the subset of women with severe VMS by FDA criteria [2] and (2) the outcomes of an untreated 4-week withdrawal phase in a portion of the cohort. We will also follow these two patients and their responses to treatments to fine-tune clinical judgements about progesterone therapy for hot flushes.

Methods

These data are all from the original progesterone for VMS RCT [1], but have not been reported in detail previously. All participants signed informed consent for all aspects of this RCT – the principles of Helsinki have been followed throughout. The presented data are all derived from Daily Menopause Diary [17] records that women kept daily during run-in and experimental therapy. The design, participant characteristics and statistical analyses related to each of two outcomes will be presented separately as severe VMS and progesterone withdrawal.

Severe VMS

The whole study was a community-based investigation of progesterone for postmenopausal VMS; therefore, enrolment was not restricted to those with the most frequent or problematic VMS. At the time this trial began (spring of 2003), the FDA guidance related to hormone studies of severe VMS was not yet available [2]. Nevertheless, a portion of the participants had severe VMS with ≥50 moderate–severe VMS/week [2]. The trial design for these participants was the same as the whole study [1]. Statistical analysis focuses on the 24-hour day (hot flushes plus night sweats) *number* of VMS (number) and uses the percentage change from baseline on progesterone compared with placebo across the 12-week trial – this allows comparability with other VMS trials. In addition, for comparison with the main cohort data [1], VMS Score (hot flush number [#] times intensity plus night sweat # times intensity) is also presented. Analysis of covariance (ANCOVA) is of last 4-week weekly VMS number and percentage change on progesterone and placebo referenced to baseline. All analyses use Stata (StataCorp, State College, TX) version 9.2.

Progesterone withdrawal

In 2006, an additional end point was added to the original RCT – a 4-week untreated withdrawal phase analyzed by experimental assignment without breaking the code although women may/may not have known their preceding treatment. Women were invited to continue to monitor VMS number and intensity on a daily diary [17] during 4-week after stopping experimental therapy. We do not know whether or not, before entering the withdrawal phase, women accessed the information available from the pharmacist about their experimental assignment. Statistical analysis analyzed VMS weekly number (per 24 hours) as percentage change from baseline and from the end of randomized therapy.

Results

A consort figure showing the flow of participants through the entire trial is previously reported [1]. Characteristics of the whole cohort, compared with women in the severe VMS cohort (by therapy assignment) and in the withdrawal cohort (by therapy assignment), are shown in Table I.

Severe VMS

Forty-six women met criteria for severe VMS during run-in including 29 randomized to progesterone and 17 randomized to placebo. Their baseline characteristics are shown in Table I. They did not differ within the severe VMS substudy by random assignment or in demographics from the whole cohort.

Table I. Demographic, reproductive and hot flush and night sweat (vasomotor symptoms, VMS) characteristics of the whole progesterone for VMS treatment cohort (full cohort), the severe VMS cohort (having 50 VMS of intensity 2–4/4 per week) and the progesterone discontinuation cohort.

	Full cohort		Severe VMS subgroup		Discontinuation subgroup	
	Progesterone (n = 68)	Placebo (n = 46)	Progesterone (n = 29)	Placebo (n = 17)	Progesterone (n = 17)	Placebo (n = 17)
Age	55.5 (4.2)	54.4 (4.6)	56.1 (5.1)	52.8 (4.9)	57.1 (3.6)	55.6 (4.2)
Body mass index (kg/m^2)	24.6 (2.7)	24.9 (2.9)	24.8 (2.8)	24.2 (1.9)	26.1 (2.6)	23.4 (2.1)
Years since final flow[a]	3.9 (2.3, 7.2)	2.5 (1.8, 4.6)	5.3 (2.3, 8.4)	2.2 (1.6, 4.0)	5.3 (3.1, 7.2)	3.5 (1.9, 5.3)
Years since first VMS[a]	5 (2.3, 8.7)	4 (3, 10)	6.0 (4.0, 10.0)	3.8 (2.5, 9.5)	5.0 (2.5, 11.0)	3.8 (2.8, 7.4)
White, Caucasian	60 (88%)	44 (96%)	25 (86%)	15 (88%)	15 (88%)	16 (94%)
Natural menopause	64 (94%)	45 (98%)	25 (86%)	17 (100%)	15 (88%)	16 (94%)
Daily baseline VMS data						
Baseline VMS number	7.1 (3.1)	6.3 (3.4)	9.6 (2.4)	9.7 (2.7)	8.4 (2.9)	7.1 (3.7)
Baseline VMS score[b]	18.3 (10.5)	15.1 (10.0)	27.2 (8.9)	24.3 (9.7)	23.5 (10.3)	17.4 (11.8)
Baseline VMS intensity	2.6 (0.6)	2.4 (0.6)	3.0 (0.5)	2.6 (0.5)	2.9 (0.5)	2.4 (0.6)
Daily VMS data – day/night						
Baseline VMS number – day	4.5 (2.3)	4.1 (2.6)	6.2 (2.0)	6.7 (2.0)	5.0 (2.0)	4.5 (2.9)
Baseline VMS intensity – day	2.3 (0.7)	2.1 (0.6)	2.7 (0.5)	2.4 (0.5)	2.6 (0.6)	2.1 (0.5)
Baseline VMS number – night	2.6 (1.5)	2.2 (1.2)	3.4 (1.4)	3.0 (1.3)	3.3 (1.5)	2.6 (1.1)
Baseline VMS intensity – night	2.4 (0.7)	2.2 (0.6)	2.8 (0.6)	2.3 (0.6)	2.7 (0.6)	2.2 (0.6)

Data are mean (SD) or median (quartile 1, quartile 3).
[a]Years since final flow and years since first VMS shown as median (Q1, Q3).
[b]VMS Score is number x intensity for both hot flushes (awake time) and night sweats (during sleep).

Given that a minimal clinically important difference in VMS Score is 3.0 [18], results of progesterone for treatment of severe VMS showed an important difference in VMS Score of −4.8 95% CI of −9.8 to −0.4. This was a numerically larger difference, despite the small numbers, than in the whole cohort: −4.3 95% CI of −6.6 to −1.9. Figure 1 shows the percentage change in VMS daily number per 24-hour day from run-in (mean of 4 weeks) to average daily number reported weekly over the 12 weeks of the experimental phase. There was a significant improvement in progesterone versus placebo with the final adjusted mean difference in VMS daily number of −2.0, 95% CI of −3.5 to −0.4.

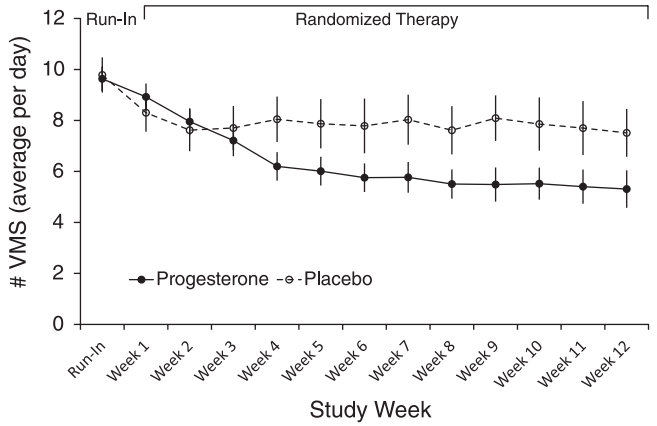

Figure 1. Daily number (#) of hot flushes and night sweats (vasomotor symptoms, VMS) during the oral micronized progesterone for menopausal VMS treatment randomized controlled trial in women meeting criteria for severe VMS (≥50 VMS/week of moderate to very severe [scoring 2–4 of 4] intensity by random assignment to progesterone ($n = 29$) or placebo ($n = 17$). Run-in shows the average number across the first 4 weeks of baseline run-in period, and the rest of the data are shown by study week on experimental therapy. Data are mean ± SE error bars.

- *Ms. BN, 52-year-old kindergarten teacher* agrees to take estradiol gel (Estragel) one pump a day with 100 mg of progesterone at bedtime daily. However, she makes an unexpected return visit after 3 weeks saying that her daytime flushes and night sweats are better but she has stopped her HT because of breast tenderness. She reports finding online information that women who get breast tenderness during HT experience a higher later risk for breast cancer [19]. She also reports that she is still not having a restful sleep.

She asks for progesterone treatment by itself – she is prescribed 300 mg at bedtime daily. On her routine follow-up in 3 months, she notes no further breast tenderness, reports that now she has only the odd mild daytime sweat ("maybe every 4 days") and no night sweats. "And, I'm sleeping better than I can ever remember", she happily asserts.

Progesterone withdrawal

Starting in 2006, 54 women were invited to participate in the untreated 40-week progesterone withdrawal substudy – 34 (61%) agreed. Of these 34 in this subset, 17 had been previously in the progesterone arm and 17 in placebo arm. Table I shows that the women were not different by previous randomization (except a trend toward a higher percentage of women assigned to progesterone experienced surgical menopause) nor did they importantly differ from women in the entire cohort.

Results of this withdrawal month showed that VMS in both groups increased gradually (Figure 2). Those women previously on progesterone had an increased weekly number of VMS from about 40% of baseline up to 78% of the run-in number. Women previously on placebo increased nonsignificantly. Using the weekly VMS number, those assigned to progesterone averaged 8.4 VMS per day during run-in, decreased to 3.4 VMS per day in the last week of progesterone therapy, and at the end of 1 month's withdrawal had increased to 6.4 VMS per day. Ninety-five percent CI of the difference between the discontinuation phase and the run-in showed that on progesterone, both VMS Score (−1.3, −9.9) and VMS daily number (−0.1 to −3.0) remained less than at baseline. By contrast, at 4 weeks of discontinuation, those assigned to placebo did not differ from baseline in VMS daily number or in VMS Score. Diary data also showed no marked increases in sleep disturbances, fatigue, or other rebound symptoms in those discontinuing from progesterone compared with those stopping placebo (data not shown).

- *Mrs. MA, a 68–year-old menopausal woman banker* is now having severe VMS since her husband died suddenly 2 weeks ago. She wakes with night sweats two to four times a night despite the sleeping pill her family doctor prescribed for 2 weeks to help her deal with grief. Given the angina that is sometimes associated with her night sweats, her age and results of the HERS trial [20], oral estrogen-progestin therapy is not preferred. Progesterone shows beneficial endothelial effects [21] and may be safe in a woman with coronary artery disease. Results of this progesterone withdrawal sub-study also suggest that she can be reassured that she will experience no rebound increase in VMS when she stops progesterone as she previously did when stopping estrogen-progestin therapy.

On progesterone, 300 mg at bedtime, the night sweats and nocturnal angina stop and mild daytime flushes occur only about twice a day. She stops progesterone after 1 year without a rebound in VMS and discovers that her night sweats are now gone, sleep problems are minimal and hot flushes are mild and only in stressful situations.

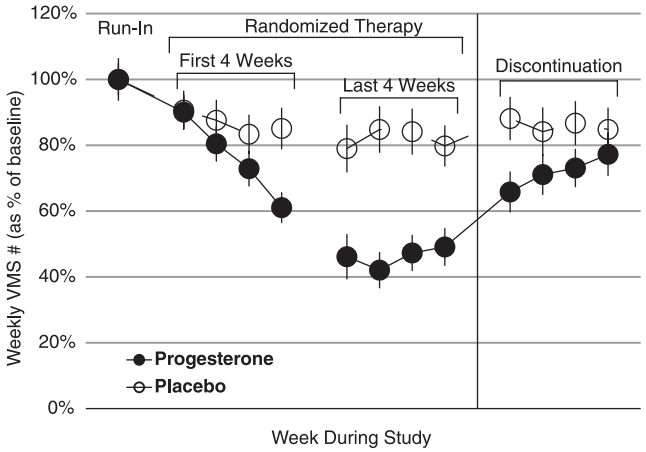

Figure 2. Number of hot flushes and night sweats (vasomotor symptoms, VMS) per week during the oral micronized progesterone for menopausal VMS treatment randomized controlled trial as a percentage (%) of pretherapy run-in, weekly VMS numbers during weeks 1–4 and final 4 weeks on experimental therapy and during each of the four posttherapy discontinuation weeks by random assignment to progesterone ($n = 17$) or placebo ($n = 17$). The discontinuation phase was open-label, and investigators were unaware but participants potentially aware of their previous experimental assignment. Data are mean ± SE error bars.

Discussion

Additional data from the placebo-controlled trial of 300 mg of oral micronized progesterone [1] show that progesterone, as well as effectively treating the entire cohort, also is effective for severe VMS. There was a significant absolute decrease of two VMS per day more than on placebo in those with ≥50 moderate to very intense VMS a week. Progesterone also does not cause a rebound increase in VMS when it is stopped. This is supported by daily diary data over an untreated month – the number and intensity have not returned to baseline for women formerly on progesterone but are not different from run-in for women previously on placebo. These two subgroup analyses of data from the entire progesterone for VMS trial [1] were likely underpowered [18], and neither outcome was initially listed as primary.

These results will likely have important clinical implications. First of all, progesterone offers an alternative to estrogen, estradiol, or HT for women with severe VMS. In addition, although there are no long-term safety data on progesterone alone, several lines of evidence suggest that it may be safer than oral estrogen in terms of risk for thromboembolism [22] and stroke [23] and that it improves endothelial function [21] and should not carry the breast cancer risks related to estrogen/estradiol therapy or HT [24]. Progesterone increases breast cell proliferation [25] but only briefly before it converts to cause differentiation and cell maturation. Recent experimental and in vitro studies suggest that micronized progesterone may have a more favorable effect on risk biomarkers for breast cancer than some other synthetic progestins [26,27]. Progesterone also counterbalances estradiol-related breast endothelial cell proliferation [28–30] and, based on these trial data, does not appear to cause breast tenderness. In addition, progesterone has the added benefit of improving disturbed sleep without negative neurocognitive effects [31] as well as preventing disturbed sleep with situations that would otherwise cause wakening [32].

The two patients presented here each uniquely benefit from evidence that progesterone is effective for VMS treatment:

Ms. BN is in very early postmenopause and has a history suggesting sensitivity to estrogen effects, perhaps because of a genetic tendency to metabolize and more slowly excrete it [33]. The standard combined, continuous HT (even with bio-identical hormones) includes full dose estradiol and one-third physiological dose progesterone – it caused breast tenderness (and fear of breast cancer) and did not improve sleep. Daily luteal phase equivalent dose progesterone (300 mg at bedtime [34]) effectively treated her VMS, sleep disturbances and did not cause breast tenderness.

Mrs. MA is 15 years postmenopausal, older than 65 and has coronary artery disease. The loss and grief related to her husband's death caused a resurgence of severe VMS. She is reluctant to take estrogen again, because she recalls her very difficult HT withdrawal about 10 years ago. Her clinicians are apprehensive about giving her oral estrogen with progestin because of RCT data showing at least short-term worsening of heart attack risk [20]. She needs progesterone or a progestogen, because she has not had a hysterectomy. Although there are no published RCT data on progesterone and cardiovascular risk factors, available data suggest that it will improve endothelial function [21], be lipid neutral, may improve blood pressure and will not increase thromboembolism – data presented here suggest no rebound VMS increase above or to baseline on progesterone withdrawal.

The strengths of these data are that they are placebo-controlled and blinded (severe VMS) and have full 4-week run-in and 12-week treatment phase durations. In addition, this progesterone trial tested, for the first time on VMS, a physiological dose [34] of progesterone, a medication that is molecularly identical hormone to women's endogenous production. The weaknesses of these data are that both the severe VMS and the progesterone withdrawal subsets were likely underpowered and were not primary outcomes. In addition, it would be ideal to perform a placebo-controlled withdrawal study although this would involve deception. These subset data of progesterone for severe VMS treatment and progesterone withdrawal need to be repeated with a larger cohort, in a multicentre trial and perhaps in a noninferiority study compared with estradiol rather than with placebo.

In summary, these subgroup analyses of data from the progesterone for VMS randomized double-blind placebo-controlled trial [1] show that progesterone effectively treats frequent and intense (severe) hot flushes and night sweats as well as showing no rapid increase in VMS symptoms with discontinuation.

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Declaration of Interest: Neither author has any financial conflicts of interest. One author experienced severe peri- and postmenopausal VMS and was effectively treated with oral micronized progesterone. Both are affiliated with the Centre for Menstrual Cycle and Ovulation Research, a not-for-profit research and knowledge translation unit associated with both the University of British Columbia and with the Vancouver Coastal Health Research Institute.

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