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REVIEW

Progesterone for treatment of symptomatic menopausal women

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ABSTRACT

This review's purpose is to highlight evidence that oral micronized progesterone (progesterone) is effective for hot flushes and night sweats (vasomotor symptoms, VMS), improves sleep and is likely safe in menopausal women (who are more than 1 year since last menstruation). Methods include randomized controlled clinical trials (RCT) supplemented with basic science, population and observational data as needed. The barrier to use of progesterone is lack of awareness that safety concerns with estrogen-including 'menopausal hormone therapy' (MHT) are *not applicable to progesterone*. In a single 3-month RCT, progesterone (300 mg at bedtime) was effective treatment of VMS in 133 healthy menopausal women. It caused an overall 55% VMS decrease, no withdrawal-related VMS rebound and a greater VMS decrease in 46 women with ≥50 moderate-intense VMS/week. Progesterone is equally or more effective than estradiol in improving cardiovascular endothelial function and caused no cardiovascular safety concerns in a 3-month RCT. An 8-year prospective cohort study (E3N) in more than 80 000 menopausal women showed progesterone prevented breast cancer in estrogen-treated women. Multiple RCTs confirm that progesterone (300 mg daily at bedtime) does not cause depression and improves deep sleep. In conclusion, progesterone effectively treats VMS, improves sleep and may be the only therapy that symptomatic women, who are menopausal at a normal age and without osteoporosis, need.

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Introduction

Menopausal women (1+ years past last menstruation) today may be highly symptomatic with disturbing hot flushes/flashes and night sweats (vasomotor symptoms, VMS) yet reluctant to seek treatment. Why? They believe that 'hormone replacement therapy', an inappropriate estrogen marketing term[1], better called menopausal hormone therapy (MHT), is harmful. This is due to widely publicized results from the Women's Health Initiative hormone therapy (WHI-HT) randomized control trials (RCTs) showing that both estrogen with progestin (EPT)[2] and estrogen-only (ET)[3] therapy caused more health risks than benefits. Few remember that the WHI-HT trials enrolled largely *asymptomatic* menopausal women. The purposes of the WHI-HT trials were to document whether or not MHT protected against heart attacks and osteoporosis or caused breast cancer or blood clots. MHT (which means both ET *and* EPT) traditionally contains *oral* estrogen and may include progestins that are synthetic 'knock offs' of women's endogenous hormone, progesterone. Potentially safer MHT options are now available in transdermal estradiol (tE2) and oral micronized progesterone (oP4)[4]; however, this newer therapy did not prevent age-related cardiovascular marker increases in a 4-year RCT in women early and late in menopause[5].

Thus today, although doctors may/may not reassure symptomatic menopausal women that MHT is recommended for problematic VMS and is the most effective therapy[6,7], women are still often wary of MHT[8]. And any woman with a hormone-sensitive cancer diagnosis (breast, endometrium), uncontrolled hypertension, high cardiovascular risk, severe liver disease or increased risks for venous thromboembolism is usually counseled to avoid MHT.

The purpose of this review is to provide the available scientific evidence related to whether or not progesterone, the ovarian steroid produced in high doses during the luteal phase of ovulatory menstrual cycles and pregnancy, is effective treatment for menopausal VMS, improves sleep and is safe related to coagulation, mood, cardiovascular, breast or endometrial cancer risks. This topic is controversial. Most of us think of 'Estrogen (as) what makes a girl, a girl'[9] and therefore progesterone is either forgotten[10] or blamed[11]. Historically, progesterone (P4) was discovered after estradiol (E2) and was inactive by mouth[12]. Later it was micronized, delivered in oil and became available in the 1980s in France[13], but not until the 1990s or later in North America and other countries. Synthetic progestins were created in the 1940s; to be so classified, they only needed to show P4-like transformation of a proliferative-secretory endometrium and preservation of pregnancy. However, progestin's actions are too diverse to be a hormonal 'class' effect[14]. Thus P4, an original ovarian hormone that can be used as therapy, and is

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(A)

Daily Menopause Diary

Name: _____ Month: _____ Year: _____

Calendar Day	1	2	3	4	5	6	7

Record 0 = none, 1 = minimal, 2 = moderate, 3 = moderately intense, 4 = very intense

Flush intensity – day							
# Hot flushes – day							
Flush intensity – night							
# Hot flushes – night							

(B)

Daily Menopause Diary

Name: _____ Month: _____ Year: _____

Calendar Day	1	2	3	4	5	6	7

Record 0 = none, 1 = minimal, 2 = moderate, 3 = moderately intense, 4 = very intense

Flush intensity – day	2	3	1	2	4	3	3
# Hot flushes – day	3	5	2	6	5	8	7
Flush intensity – night	4	2	0	2	3	2	1
# Hot flushes – night	1	3	0	1	2	4	1

Figure 1. The four lines on the Daily Menopause Diary© used to describe day and night vasomotor symptoms (A) and a typical symptomatic woman's record over a week (B). The data from B can be used to create a VMS Score of 107 = daytime # × intensity = 80 + nighttime # × intensity = 27; the number of moderate-intense VMS #/week = 45 (falling short of criteria for 'severe VMS'; Night wakening with VMS = 11/week.

E2's endogenous partner, has been wrongly equated with progestins or forgotten[9].

Physiology and effects of hot flushes and night sweats

VMS are the abrupt onset of physiological changes and experiences that last a few minutes, are preceded by a small core temperature increase and characterized by a heat dissipation response (vasodilatation, fingertip warming, sweating)[15]. They are related to a massive discharge of every known measured neurohormone[16]. Although men on androgen-ablation therapy for prostate cancer may also experience VMS, they are primarily a problem for perimenopausal and menopausal women. According to a population-based survey of more than 4000 women aged 40–65 years in the USA, 79% of perimenopausal and 65% of menopausal women experience VMS[17]. Severe VMS (≥50 moderate-to-intense episodes/week) occurred for 9% of perimenopausal and 7% of menopausal women[17]. VMS were less prevalent in women of East Asian racial origin (20–25%) in the USA's Study of Women Across the Nation[18] and in an international survey[19]. Swedish population-based prospective studies showed that VMS increased between 1992 and 1998 as body mass index and physical activity increased but smoking decreased[20].

But what *causes* VMS? They were originally thought due to 'estrogen deficiency'. However, that makes no sense since children whose E2 levels are low do not experience VMS. The current concept is that E2 exposure followed by withdrawal is a key VMS etiology since E2-treated VMS often rebound on therapy withdrawal[21,22]. That 'estrogen withdrawal' notion of VMS fits with the fact that VMS may begin in menstruating women early in perimenopause[23]. It is now known that perimenopausal E2 levels are not only significantly higher than in similar-aged non-perimenopausal women but also are erratic with many peaks and troughs[24].

More than 15 years ago, using data from the Daily Perimenopause Diary© (DPD, free on www.cemcor.ca for individuals) we showed night sweats in regularly cycling midlife women[25] but few daytime VMS[25]. (Data from an RCT of P4 for perimenopausal VMS, *completed but not yet published,* confirm that observation; personal communication, J. C. Prior, January 2018.) Furthermore, VMS at night and breast tenderness were both *cyclic* around menstruation[25]. That may be explained by the 'luteal out of phase' atypical 2° high E2 peak before and during menstrual flow in some perimenopausal cycles[26]. Those who are more likely to experience VMS are smokers[27], obese[28] and under personally perceived economic[29] or psychosocial stress[30] and less likely if of East Asian racial origin[15,18,19] and residing in rural regions and cooler climates[18,19].

VMS are primarily an individual person's *experience* and thus, by definition, are subjective, although they are also associated with clear physiological markers, e.g. increased galvanic skin response, elevated finger temperature and sweat rate[31]. RCTs and prospective studies documenting VMS may use intermittent questionnaires (ideally as direct VMS questions rather than as part of some broad scale, e.g. Kupperman Index[32], Greene Climacteric Scale[33]). However, most VMS RCTs today are required to use continuous or intermittent daily records[34]. CeMCOR has created two daily diary tools (Daily Perimenopause Diary[25] and Daily Menopause Diary©[35,36] (free for individuals at www.cemcor.ca) for documenting women's positive and negative experiences. They both allow separate records for daytime VMS (hot flushes) and night sweats, document the actual number plus the intensity of daily VMS on an ordinal 0–4 scale (where 1 is mild and without sweating and 2–4 are moderate to intense sweating) and are similar to the validated tool used by the Mayo Clinic group[34]. Figure 1 illustrates the Daily Menopause Diary VMS recording and shows a typical symptomatic woman's experience. For night sweats, an intensity score of ≥2 means that they caused wakening, although a VMS score of 1 would not disturb sleep.

Brain norepinephrine in animals caused narrowing of the core temperature's 'thermoneutral zone' (range of comfortable basal temperatures – no sweating/shivering) that characterizes all with VMS. Research says that E2 withdrawal from an E2-treated animal causes release of brain norepinephrine[15]. This is followed by narrowing of the thermoneutral

zone to nearly zero, a heat dissipation response[15] and rapidly increased galvanic skin response. VMS episodes are associated with massive release of neuroendocrine, cytokine and stress hormones[31] and thus may have a clinical 'aura' of weakness, dizziness or nausea, especially in perimenopausal women. Recent evidence suggests that the hypothalamic control processes involved in the pulsatility of gonadotropin releasing hormone may relate to VMS. A receptor blocker of neurokinin 3 that slows luteinizing hormone pulsatility appears to act rapidly and with sustained response to decrease VMS[37].

How are VMS typically treated? Almost everything imaginable has been tried, from sleeping on a metal-threaded cloth to all manner of herbs[38,39] and diets[40] (especially since low blood sugar, perhaps through a brain stress pathway[41], is associated with VMS). Drugs include anti-anxiety medications to antidepressants[42] and other neuroactive interventions such as gabapentin, acupuncture[43], clinical hypnosis[44] and stellate ganglion blockade[45]. The standard approach is estrogen-based therapy[6] – a Cochrane meta-analysis of trials showed that there was a significant reduction in VMS with ET or EPT versus placebo; EPT was significantly more effective than ET[46]. A poorly recognized fact is that multiple different progestins were effective for VMS (as reviewed[47]). In fact, a 1-year comparative RCT in women immediately following premenopausal ovariectomy/hysterectomy showed medroxyprogesterone acetate (10 mg/day) was as effective as oral equine estrogen (0.6 mg/day)[36].

Progesterone for hot flushes and night sweats

Before oral micronized progesterone became available, progesterone cream, typically in a 20-mg/day dose, became popular.

Transdermal (cream) progesterone

The first RCT of transdermal progesterone (tP4; 20 mg/day) for VMS was in 102 (90 completed) menopausal women in urban New York; all were ≤5 years since last menstrual period and 69 initially reported VMS[48]. This was a 1-year RCT (1 : 1) of tP4 vs. placebo. VMS (presumably only daytime) were recorded weekly by questionnaire as 'increased, remained the same, improved, or stopped'[48]. Results showed that VMS improved or disappeared in 25 of 30 (83%) of the tP4 group and in five of 26 (19%) of the placebo group[48] ($p < 0.001$)[48]. No consort table or detailed data on initial demographics and VMS or the number, intensity and changes across the trial were reported.

The second tP4 study (32 mg/day) vs. placebo (1 : 1) was a 12-week RCT in 80 urban Australian women ≤3 years into menopause that significantly increased serum P4 levels but below the luteal-phase range[49]. VMS were assessed using the Greene Climacteric Scale[33] and Menopause Quality of Life Questionnaire (MENQOL)[50] – again baseline VMS and demographic details and consort figure were absent. Seventy-two completed the trial with 33 women on tP4 and 38 on placebo. There was a nearly significant difference in the decrease in VMS by assignment ($p = 0.07$) but a non-significant difference by MENQOL[49].

The third RCT of tP4 was a five-arm, double-blind, dose-ranging trial of placebo to 5, 20, 40 and 60 mg/day; 223 women were enrolled and were analyzed by intent-to-treat[51]. It was a well-conducted study with a consort table, minimal drop-out, good adherence and analysis[51]. Again, the Greene Climacteric Scale was used and only recorded daytime VMS; there was a trend toward greater VMS improvement the higher the dose and a nearly significant improvement from baseline vs. placebo on the 60 mg/day dose (−8.0, 95% confidence interval (CI) −16.8 to 0.7; $p = 0.07$)[51]. The 20 mg/day tP4 dose improved physical and emotional components on the generic quality-of-life SF-36 scale[51]. Serum progesterone significantly increased versus on placebo in each of the dose groups[51]. A fourth cross-over, 1-month RCT of tP4 in 30 symptomatic menopausal women did not detail VMS changes separately from the total changes in Greene Climacteric Scale and was focused on inflammatory and thrombotic markers[52]. Thus, there is minimal evidence that low-dose tP4 is effective for menopausal VMS.

Oral micronized progesterone

The notion that progesterone might be effective for VMS was initially based on the evidence that progestins are effective[47] and that progesterone counterbalances estradiol's actions at tissue levels[53]. However, recent data that antagonism of receptors for neurokinin 3 improves VMS[37] and slows pulsatility of luteinizing hormone (as progesterone also does[54]) suggest an additional potential mechanism.

A systematic review using Google scholar revealed only one RCT of oral micronized progesterone (oP4) for menopausal VMS[55]. It was donor-funded by the Centre for Menstrual Cycle and Ovulation Research; the design was a 4-week baseline followed by 12 weeks randomized 1 : 1 to oP4 (300 mg at bedtime daily – a dose that keeps the progesterone blood level in the luteal phase for 24 h[56]) vs. placebo therapy. Altogether 133 healthy, nonsmoking women aged 44–62 years who were 1–11 years since menopause onset (1 year post last menstrual period) participated[55]. Its consort table showed a 14% discontinuation rate; analysis of covariance (baseline VMS Score as covariate) used last observation carried forward and had good adherence (>83% of participants took ≥80% of medication for ≥60 days). The overall assessment of VMS was as the VMS score (day VMS number × intensity plus night VMS number × intensity)[34] (Figure 2). The primary outcome was the 24-h VMS score in the last 4 weeks of the 12-week trial[55].

Results at baseline were balanced by arm except that the VMS score was slightly higher on oP4 (18.3; 95% CI 15.8–20.8) than placebo (15.1; 95% CI 12.1–18.0) (non-significant); VMS intensity (0–4 scale) was statistically higher on oP4 vs. placebo ($p < 0.05$). Results showed that, in the last 4 weeks, the VMS score had significantly ($p = 0.001$) decreased by 10.0 on oP4 and by 4.4 on placebo with a clinically[34] and statistically significant difference of −4.3 (95% CI −6.6 to

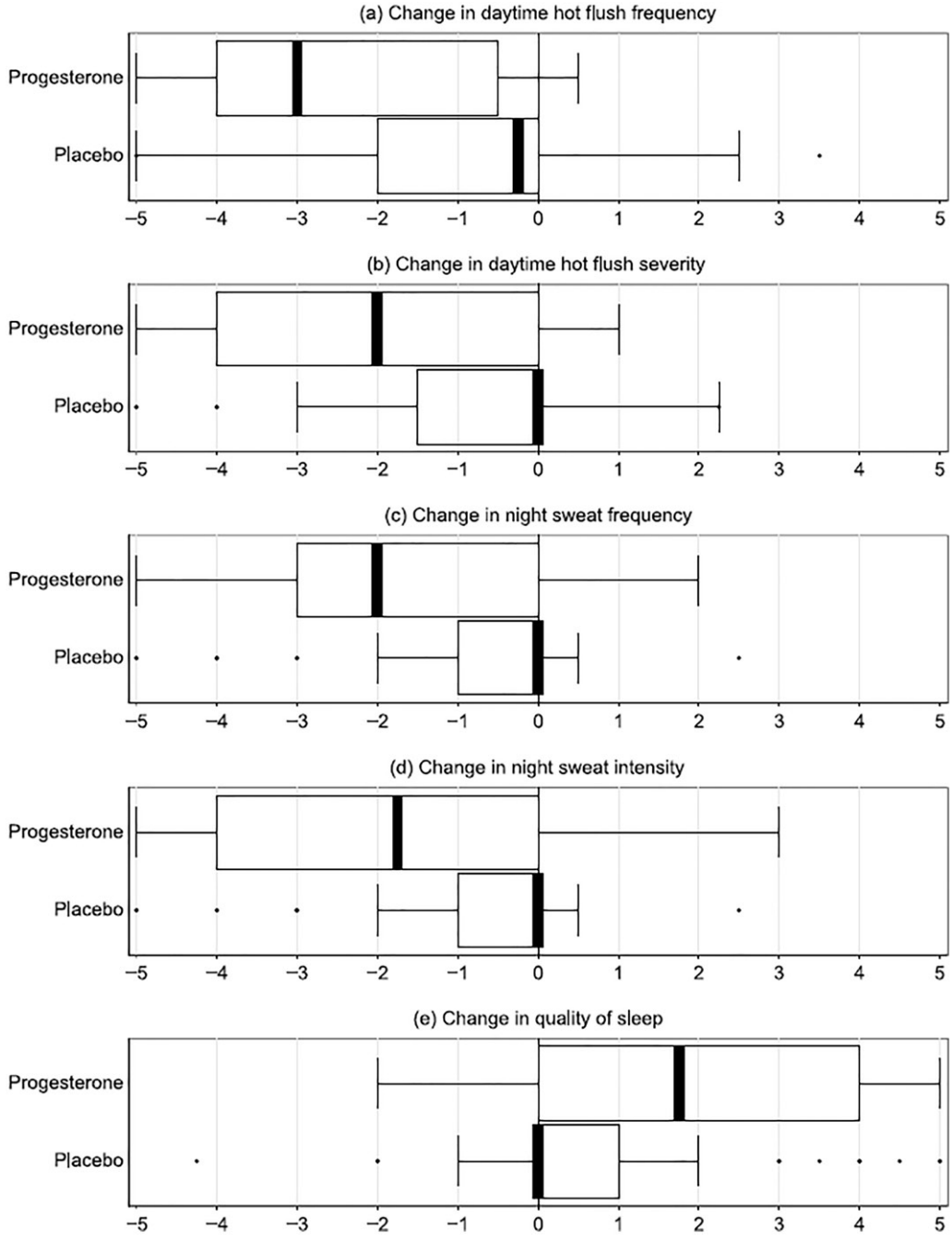

Figure 2. Data from randomized clinical trial on oral micronized progesterone (Progesterone) or placebo at the end of the study reported their change (from −5 to +5) by therapy assignment, shown here in box-and-whiskers plots of ratings for (a) changes in daytime hot flush number, (b) changes in daytime hot flush intensity (severity), (c) changes in night sweat frequency, (d) changes in night sweat intensity, and (e) changes in sleep quality. All differences are significant by Mann–Whitney *U*-test in favor of progesterone ($p = 0.001$ to 0.013). (Reprinted with permission from *Menopause*[55]).

−1.9) between treatment arms. This translates into an overall 55% decrease in VMS Score on oP4 and a 29% decrease on placebo[55]. The number of daytime VMS episodes decreased on oP4 therapy from 4.5 on average to 3.6/day ($p < 0.05$) and of night sweats from 2.6 to 1.6/night ($p < 0.05$). Hot flush/night sweat intensity also significantly decreased ($p < 0.05$). Recent evidence, presented only in abstract, suggests that oP4 is also effective for *perimenopausal* VMS[57].

Since we enrolled all women seeking treatment for VMS, only a proportion (∼40%) met the 'severe VMS' criterion. However, in this small group of 29 women randomized to oP4 and 17 to placebo ($n = 46$), there was even greater improvement on oP4 over placebo with an adjusted mean VMS Score difference of −4.8 (95% CI −9.3 to −0.4; $p < 0.001$)[58].

We asked women in their final visit to record change (on a plus or minus five-point scale from baseline) in the number of daytime VMS and their intensity, the same for night sweats and also for changes in sleep quality. Results of that analysis are shown in Figure 3. Women assigned to oP4 perceived a significantly greater decrease in both day and night VMS number and intensity than did women on placebo.

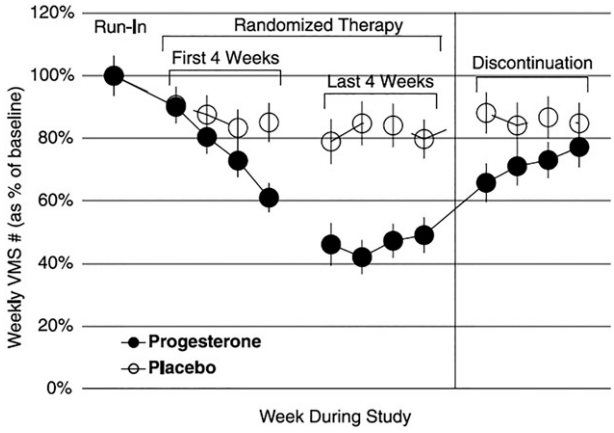

Figure 3. The percentage change from baseline (run-in) in the number of day and night hot flushes per week in the first and third of 4 weeks of 12-week treatment on oral micronized progesterone (Progesterone) and 4 weeks after stopping (dark circles) or placebo (open circles) therapy with SEM error bars. Ninety-five percent confidence intervals 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 their baseline. By contrast, at 4 weeks of discontinuation, those assigned to placebo did not differ from their baseline in VMS daily number or in VMS Score. With permission from *Gynecological Endocrinology*[58].

They also perceived a significantly greater improvement in sleep; all women's perceived differences were statistically significant, with results ranging in p values from 0.001 to 0.013[55].

Oral micronized progesterone discontinuation sub-study

A clinically important portion of women treated for VMS with estrogen-based therapy will experience a withdrawal-related VMS rebound to become worse than before starting therapy[21]; the same will also occur for some stopping selective serotonin reuptake inhibitors[59] and serotonin-norepinephrine reuptake inhibitors[60]. Therefore, it was important to know whether or not stopping oP4 would cause withdrawal-related increased VMS. From approximately mid-RCT, we invited participants in the previously described trial (without investigator knowledge of random assignment) to continue to record Daily Menopause Diary data for a further month after the end of the study[58]. Of 54 women invited, 34 agreed (17 oP4, 17 on placebo) and provided data. These women could have known their therapy assignment[58] since, at the end of this trial (because it spanned 6 years), we arranged for the research pharmacy to reveal individual therapy to each woman. The 61% of invited women agreeing to participate in this sub-study were similar to women in the whole trial[58]. Over the first 4 weeks off experimental therapy, women on placebo developed VMS scores similar to their own baselines; VMS scores for those who had been on oP4 increased (from 3.4 to 6.4) but not yet to their baseline of 8.4 (Figure 3). These results suggest that there was no progesterone-related withdrawal rebound increase in VMS.

Oral micronized progesterone adverse events and safety

There were no serious adverse events over 3 months of progesterone therapy during this randomized, double-blind, placebo-controlled RCT[55]. Withdrawal from oP4 occurred for 15% of women and was for mild/moderate but not drug-related adverse events (e.g. nausea, rash, headache, sleep problems and chest pain investigation, with one for emergency pancreatic surgery) and 19% on placebo in whom two of 11 were for VMS ineffectiveness.

Progesterone and safety in treatment of symptomatic menopause

The physiology of P4 compared to E2 suggests greater safety – estradiol stimulates cell growth and proliferation; progesterone counterbalances proliferation and causes cell maturation[53]. These data are supported by numerous studies but most are of short duration and none are, in themselves, definitive. I will briefly review available data here.

Cardiovascular safety

The control of blood flow by nitric oxide release in the endothelium is a fundamental indicator of cardiovascular health. Endothelial function by venous occlusion plethysmography in a random-ordered study in 24 healthy menopausal women of intra-arterial E2, P4, E2 + P4 and vehicle documented that P4 was equivalent or superior to E2 in increasing endothelium-dependent blood flow[61]. In the same VMS RCT as described above, women were prescreened to be free of clinical, laboratory (including electrocardiogram) cardiovascular disease; oP4 effects were compared with placebo on 12-week changes in weight, waist circumference, blood pressure, fasting glucose, lipids, C-reactive protein and D-dimer[62]. Progesterone caused no changes in any of these variables or in the Framingham General Cardiovascular Risk Profile. Furthermore, there is sufficient evidence to hypothesize that it is normal premenopausal E2 and P4 levels, not just sufficient estrogen alone (in normal-length but ovulatory disturbed cycles[63]), that protects women vs. men against early heart attacks[64].

Breast cancer risk

Breast cancers primarily occur in women, are commonly hormone receptor-positive and the risk for breast cancer is complexly related to women's reproduction. In two RCTs in women with breast biopsies for benign masses, they were randomized to apply transdermal estradiol (tE2), tP4, tE2 + tP4 or vehicle to the affected breast for 11 days before surgical removal of the lump and a biopsy of uninvolved tissue[65,66]. Results showed an increased proliferation rate on tE2 and a decreased rate on tP4[65,66]. That is consistent with the epidemiological data from the E3N French study in more than 80 000 menopausal women followed for over 8 years showing that women receiving E2 versus untreated women had an increased breast cancer risk by 1.29; E2 plus progestin increased it by 1.69 and E2 plus P4 gave a breast cancer risk of 1.00 (95% CI 0.83–1.22) and not different than in untreated women[67]. These results have seen been confirmed by a population-based study in fewer French women[68] and in a

meta-analysis of estrogen–progesterone vs. estrogen–progestin studies[69]. These results suggest, but no RCT has proven, that progesterone given in a near physiological dose-equivalent to estradiol (as in the premenopausal menstrual cycle[70]) would prevent breast cancer during estradiol therapy.

Venous and arterial adverse clotting

A recent international clinical guideline recommended that progesterone be used in women with increased risk for thromboembolism[6] because it is without any signal of increased clot risk[47,71].

Depression

Although depression is often said to be a side-effect of progestins, some infer that this also means that oP4 may cause it. However, the Daily Menopause Diary data in the VMS RCT described above showed no hint of an increase in self-reported depressed feelings vs. placebo (unpublished data, J. C. Prior). In addition, in a cross-over RCT of women with premenstrual symptoms, oP4 in a dose of 300 mg at bedtime for 2 weeks/cycle over two cycles caused no increased depressive scores and a significant improvement in anxiety[72]. Finally, in a Cochrane review of RCTs of progesterone for premenstrual symptoms, there was no hint of increased depression[73].

In summary, if women are concerned about adverse effects of MHT on their heart, breast or moods, the available evidence suggests that they should *worry less about progesterone*.

Summary of clinical perspectives on progesterone for symptomatic menopause

Menopausal women with sleep-disturbing VMS need to correct VMS-increasing factors like life stressors[30], cigarette use, sedentary behavior and obesity[40]. If making these lifestyle changes does not improve VMS sufficiently so they wake a fewer number of times than twice a week, I suggest that they need therapy. My recommendation is oP4 (300 mg at bedtime daily) based on effectiveness, no rebound on stopping, its sleep-enhancing benefits and its apparent cardiovascular and breast cancer safety. A woman can take oP4 as long as she needs it; discontinuing oP4 once a year will allow discovery about whether nighttime VMS have stopped.

RCT-proven sleep improvements[55,74,75] are a further benefit for a woman choosing oP4.

However, if a woman became menopausal at younger than 40, or at age $\leq$45 years with a strong family history of fragility fracture[76] or has an increased personal fracture risk[77], I would recommend progesterone (300 mg at bedtime daily) be combined with moderate dose tE2[78] since she likely has increased bone resorption that P4 alone (based on a study of medroxyprogesterone acetate) is ineffective to decrease[79]. However, evidence suggests[80] that P4 increases bone formation and adds significantly to estrogen-related improvements in bone mineral density[81]. This balanced tE2–oP4 therapy should be continued until the population average age of menopause. At that point, I recommend to avoid rebound VMS increases (based only on extensive clinical experience), that tE2 be decreased gradually (10% decrease every 2 weeks) over 6 months, while full-dose oP4 is continued as long as needed for VMS.

If a menopausal woman is symptomatic only with vaginal dryness and vaginal lubricants are not sufficient, estriol 0.5 mg/vagina weekly is safe and effective.

I continue to believe, as I summarized in a recent review of progesterone or progestins as part of MHT for symptomatic women[47], that progesterone alone is often or usually sufficient.

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