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Effect of medroxyprogesterone on depressive symptoms in depressed and non-depressed perimenopausal and postmenopausal women following discontinuation of transdermal estradiol therapy

Maria Pia Rogines-Velo, MD, PhD, Amy E Heberle, AB, and Hadine Joffe, MD, MSc

Center for Women's Mental Health, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School

Abstract

Objectives—Concern about adverse effects of progestins on mood has influenced the use of medroxyprogesterone (MPA) and other progestins. In this brief report, we examined whether administration of MPA leads to depressive symptoms in two groups of peri- and postmenopausal women randomly assigned to treatment with estrogen: one currently experiencing clinical depression and another without depression.

Methods—Open-label MPA 10-mg/day was administered for 14 days for endometrial protection after completion of double-blinded treatment with 17- β -estradiol 0.1-mg/day for 8–12 weeks in 40–60-year-old peri/postmenopausal women enrolled in two separate randomized placebo-controlled trials for treatment of cognitive problems (“non-depressed group”) or clinical depression (“depressed group”). Non-parametric tests were used to compare changes in depressive symptoms on the Beck Depression Inventory (BDI) within each group and between groups during MPA therapy.

Results—Of 24 non-depressed (median BDI at baseline 5.5, interquartile range [IQR] 2.5, 8.5) and 14 depressed (median BDI at baseline, 17, IQR 15, 21) women treated with MPA, BDI scores did not change during MPA treatment in either group (median change 0, IQR –2, 0.5, and median 0, IQR –0.5, 1.5, $p=0.28$ and $p=0.50$, respectively). Changes in BDI scores during treatment with MPA did not differ between groups ($p=0.25$).

Conclusions—Among women receiving MPA for two weeks following discontinuation of estradiol, depressive symptoms did not emerge on MPA. These findings were consistent for both depressed and non-depressed women, suggesting that, even among women who are currently experiencing depression, brief treatment with MPA is unlikely to disrupt mood.

Keywords

medroxyprogesterone; depression; perimenopause; menopause; women; estradiol

Address for correspondence/reprint requests: Hadine Joffe, MD MSc, Center for Women's Mental Health, Massachusetts General Hospital, Simches Research Building, 185 Cambridge Street, Suite 2000, Boston MA 02114, (T) 617-724-1849, (F) 617-643-3080, hjoffe@partners.org.

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Introduction

More than half of all women initiating treatment with hormone therapy (HT) will stop within the first year of treatment, primarily because of side effects.^{1–3} While estrogen given alone,^{4, 5} and in combination with a progestin,⁶ has been shown to improve mood in peri- and early postmenopausal women, mood disturbance secondary to HT is also an adverse effect that results in treatment discontinuation.²

Previous studies have suggested that the progestin in the combined HT preparation is responsible for these negative mood effects.^{7–12} However, several randomized controlled trials have shown no negative effect of progestin treatment on mood when administered in combination with estrogen therapy (ET),^{13–17} or alone.¹⁸

The lack of consistency in these data raise the question of whether progestin therapy is likely to result in negative effects on mood, and whether adverse mood side effects should be taken into account when discussing the short-term risks of HT. This consideration is particularly important for women with depression, in whom there is heightened concern about the potential for mood destabilization with HT use. However, little is known about the effect of progestins on mood in women who are currently experiencing depression because they have been excluded from previous studies investigating the effects of progestin on mood. Because depression commonly co-occurs with vasomotor symptoms, the primary indication for HT use,^{19–21} and women are at greater risk for experiencing a clinical depression during the menopause transition,^{20, 22, 23} the question of whether women with depression are especially susceptible to mood deterioration when treated with progestins is particularly relevant.

In this brief report, we examine whether administration of medroxyprogesterone (MPA), the most commonly prescribed progestin, leads to depressive symptoms in peri- and postmenopausal women who were treated with 17- β -estradiol in two randomized placebo-controlled trials. This analysis was conducted in two groups of women: one that was currently experiencing clinical depression as part of the indication for ET,²⁴ and another that was not depressed but sought treatment with ET because of cognitive difficulties.²⁵ We hypothesized that depressed, but not non-depressed, women would be susceptible to negative effects of MPA on their mood.

Methods

Study participants and design

This analysis examines the effect of medroxyprogesterone (MPA) 10-mg/day on mood in 40–60-year-old peri- and postmenopausal women with menopause-related symptoms in two double-blind randomized placebo-controlled trials of ET.^{24, 25} Both trials enrolled women from the community who were perimenopausal (early or late menopause transition stage),²⁶ postmenopausal (natural or surgical), or hysterectomized without bilateral oophorectomy if serum follicle-stimulating hormone (FSH) levels were >25 IU/L. Both trials involved randomized assignment to unopposed transdermal 17 β -estradiol 0.05-mg/day or placebo. At the end of the trial, treatment assignment was revealed and all women who had uterus and received ET, were treated with open-label MPA 10-mg for 14 days. The Partners Healthcare Systems Institutional Review Board approved both study protocols, and written informed consent was obtained from all participants. Further details describing these two trials have been reported elsewhere.^{24, 25}

The two trials differed primarily on the symptom profile required for eligibility. The first trial was restricted to healthy **non-depressed** women (n=52) who perceived cognitive

problems they attributed to the menopause transition.²⁵ The goal of the trial was to determine if ET alters specific cognitive processes involved in verbal and visual learning and memory and frontal executive function. Women with depression and any other psychiatric illness were excluded using the standardized clinician-rated Structured Clinical Interview for DSM-IV Disorders (SCID).²⁷ Women with hot flashes and sleep disturbance were not excluded and the majority of women experienced these symptoms. The randomization involved double-blinded assignment to ET or placebo for 12 weeks, such that 26 women were assigned to treatment with ET.

The second trial was restricted to women with a clinical **depression** (n=72) who were concurrently experiencing hot flashes and sleep disturbance attributed to nocturnal hot flashes.²⁴ Using the SCID, women currently experiencing clinical depression (71% major depression, 29% dysthymia or minor depression) and who had a score on the Montgomery-Åsberg Depression Rating Scale (MADRS)²⁸ of 15–31 were enrolled. Participants were randomly assigned to one of three treatments (ET, zolpidem 10-mg/day, or placebo) in a 2-to-2-to-1 ratio for 8 weeks such that 27 women received ET. The goal of the trial was to determine if depression would improve in women treated with ET more than in those receiving a specific treatment for sleep disruption (zolpidem).

In both trials, depression symptoms were assessed at study entry, at the end of the double-blinded ET treatment, and at the end of 14 days of MPA using the Beck Depression Inventory (BDI), a widely used 21-item self-report scale that records the severity of depression symptoms over the previous week (range 0–63, higher score indicates greater symptom burden).²⁹ BDI scores range from minimal (scores 0–9), mild (10–16), moderate (17–29), and severe (30–63) depressive symptoms, with a score 18 typically used to indicate clinically relevant depression symptoms.³⁰ Only women treated with MPA underwent the additional follow-up assessment of mood after completion of each trial. This analysis reports on changes in BDI scores for women discontinuing ET who then received treatment with MPA.

Analysis

The analysis was conducted using non-parametric tests because of small sample size. Within-group comparisons were made using Wilcoxon signed-ranks tests, and between group comparisons using the Wilcoxon rank-sum test. To adjust for characteristics that differed between groups (i.e., education status, hot flashes or night sweats on MPA), the change in BDI scores on MPA was Box-Cox transformed because of non-normal distribution and linear regression analysis was conducted on the transformed dependent measure. All analyses were conducted using STATA (College Station, Texas) with an alpha=0.05.

Results

Participants

Of 26 non-depressed women randomly assigned to ET, 24 (92.3%) received a 14-day course of MPA after completing the 12-week course of ET. Two women did not receive MPA because they had previously undergone a hysterectomy. In the trial for depressed women, 21 (77.8%) of 27 women assigned to ET completed the 8-week course of treatment, and 14 (66.7%) of the 21 received a 14-day course of MPA. Seven women who completed the course of ET did not receive MPA because they had undergone a hysterectomy and 2 were lost-to-follow-up during the MPA phase of the study.

Within each trial, there were no differences between the ET and other treatment groups in demographic characteristics, menopause status, or baseline levels of FSH, sleep quality, BMI or depressive symptoms. Detailed descriptions of study population characteristics are available elsewhere.^{24, 25} When the subgroup of women treated with MPA in each trial was compared, the only characteristics that differed between the depressed and non-depressed study populations were that the non-depressed group was more likely to have graduated college and less likely to experience hot flashes at study entry and on MPA (Table 1). Briefly, both groups included predominately perimenopausal women with a mean overall age for both groups together of 50.6 (± 3.4) years. No participant in either group discontinued MPA due to side effects.

Depressive symptoms on estradiol and medroxyprogesterone (Table 1, Figure 1)

Consistent with eligibility criteria for each study, the depressed group had higher BDI scores at study entry (median 17, IQR 15, 21, vs. median, 5.5, IQR 2.5, 8.5, $p < 0.001$), and they continued to have higher BDI scores on ET (median 9, IQR 5, 15, vs. median 2, IQR 0, 4.5, $p < 0.001$), and on MPA (median 9, IQR 6, 16, vs. median 1, IQR 0, 4, $p < 0.001$). However, depressive symptoms improved on ET in both the depressed (median decrease of 9, IQR 3, 12, $p = 0.004$) and non-depressed (median decrease of 3, IQR 1, 5, $p = 0.007$) groups, with greater mood improvement on ET in the depressed group ($p = 0.02$).

BDI scores did not change significantly on MPA in either the non-depressed group (median change 0, IQR -2, 0.5, $p = 0.28$) or the depressed group (median 0, IQR -0.5, 1.5, $p = 0.50$). Despite the higher BDI scores on E2 in the depressed group prior to MPA therapy, the extent to which depressive symptoms changed on MPA did not differ between groups ($p = 0.25$). Adjusting for education status and hot flashes/night sweats on MPA did not alter these findings ($p = 0.96$).

Discussion

Results of this brief report indicate that MPA does not increase depressive symptoms in peri- and postmenopausal women treated sequentially with estradiol and then MPA, even among women receiving ET for treatment of depression. We found that improvements in mood on ET among women who were and were not experiencing clinical depression were not lost when ET was discontinued and MPA was started, even when hot flashes and night sweats recurred. To our knowledge, this is the first study to investigate the effects of MPA on mood specifically in a depressed population. Our findings suggest that MPA can be used safely in depressed, as well as non-depressed women, and that progestins should not be withheld from depressed women because of an expectation that the progestin will make them more depressed.

Our results are consistent with previous data in non-depressed women showing that administration of progestins does not detract from the positive mood effects of estrogen therapy.^{13–18} These studies include a variety of different progestin and estrogen preparations and doses, making direct comparison challenging. Studies using MPA specifically have shown that mood does not worsen on MPA, when co-administered with 17 β -estradiol 50–100-mcg/day,^{14, 16} conjugated equine estrogens (CEE) 0.625-mg/day,¹⁷ or no estrogen.¹⁸ In contrast, studies finding an adverse effect of MPA on mood have observed that the effect varies by dose of the estrogen preparation, with mood worsening occurring when MPA was administered together with only the highest (3-mg/day, but not 2-mg/day) doses of 17 β -estradiol,³¹ and lower (0.625-mg/day) but not higher (1.25-mg/day) doses of CEE,¹² suggesting that the nature of the mood response may vary with the dose and preparation of the co-administered ET.

This study is limited by its sample size, although the size of our study population is within the same range as that studied in most other investigations of the effect of progestins on mood.^{7-9, 11-15, 17, 18} The only large intervention study that has specifically investigated the mood effects of progestins found no effect of a variety of progestin preparations on mood in a sample of non-depressed women.¹⁶ It is also notable that our depressed study population had BDI scores within the mild-to-moderate range of depressive symptoms at baseline, which were subsequently reduced to minimal-to-mild levels on ET and then remained minimal-to-mild on MPA. It is therefore unknown whether our findings are generalizable to women with more severe depression episodes or those who have previously demonstrated susceptibility of their mood to fluctuations in reproductive hormones, such as postpartum depression, premenstrual dysphoric disorder, or onset of depression in the perimenopause. The generalizability of our findings to women using MPA concurrent with ET, rather than sequentially, with ET, is also unknown. However, while concurrent withdrawal of ET may have confounded our results, ET discontinuation would be expected to worsen, rather than improve, mood. This study addresses the mood effects related to the specific dose and preparation of progestin that was administered for only a brief period of time. Further randomized trials, with different types of progestins used for longer periods of time, are warranted to address the generalizability of our findings to other progestins and the effects of chronic progestin therapy on mood.

Conclusions

In summary, results of our study indicate that MPA administered for 2 weeks following discontinuation of 17 β -estradiol does not have adverse effects on depressive symptoms in peri- and postmenopausal women who are currently experiencing clinical depression, as well as those without depression, even in the context of persistent hot flashes and night sweats. These findings support the use of MPA for endometrial protection as part of an HT regimen in all women, regardless of depression status.

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Figure 1.

Depressive symptoms, as measured by the Beck Depression Inventory (BDI) for women treated with medroxyprogesterone at (a) baseline, prior to randomization to estradiol; (b) the end of the estradiol treatment period; and (c) the end of the 14-day treatment with medroxyprogesterone, according to depression status at study entry.

Data are presented as box plots with the box representing the interquartile range bisected by the median value, and the error bars representing the extreme values.

Table 1

Demographic, menopause, and psychiatric characteristics of study participants by depression group status at study entry

	Non-depressed (n=24)	Depressed (n=14)
<i><u>Demographic Characteristics</u></i>		
Age (yrs)	51.0 ± 3.4	49.9 ± 3.9
Caucasian	20 (83%)	9 (64%)
College graduate [@]	19 (79%)	5 (36%)
Marital Status		
Married	13 (54%)	3 (21%)
Separated/divorced/widowed	9 (38%)	9 (64%)
Never married	2 (8%)	2 (14%)
Employed	22 (92%)	10 (71%)
Menopause Status		
Perimenopausal	17 (71%)	8 (57%)
Postmenopausal	7 (29%)	6 (43%)
Serum estradiol, pg/mL	57.4 ± 86.6 ^a	54.6 ± 45.2
Follicle stimulating hormone, IU/L	87.9 ± 47.4 ^a	78.5 ± 70.0
<i><u>BMI categories^c</u></i>		
Category 1 (normal: <25 kg/m ²)	7 (30%)	4 (28.6%)
Category 2 (overweight: 25–29.9 kg/m ²)	8 (34.8%)	5 (35.7%)
Category 3 (obese: ≥30 kg/m ²)	8 (34.8%)	5 (35.7%)
<i><u>Hot flashes/night sweats</u></i>		
Baseline [†]	14 (58.33%)	14 (100%)
On medroxyprogesterone ^{d†}	10 (41.67%)	12 (100%)
<i><u>Psychiatric Characteristics</u></i>		
Current Depressive Disorder		
Major depressive disorder	N/A	10 (71%)
Dysthymia or minor depression	N/A	4 (29%)
<i><u>Beck Depression Inventory (BDI) Scores</u></i>	Median (interquartile range)	Median (interquartile range)
Baseline [†]	5.5 (2.5, 8.5)	17 (15, 21)
On estradiol [†]	2 (0, 4.5)	9 (5, 15)
Change in BDI on estradiol ^{†#}	−3 (−1, −5)	−9 (−3, −12)
On medroxyprogesterone ^{b†}	1 (0, 4)	9 (6, 16)
Change in BDI on medroxyprogesterone	0 (−2, 0.5)	0 (−0.5, 1.5)

Continuous data are presented as mean ± standard deviation and categorical data are presented as N (%). For continuous data, p-values represent between-group differences using the Wilcoxon signed-rank test and the Wilcoxon rank-sum test for within-group differences; Fisher's exact tests were used for categorical data.

Data missing for:

^a 7 non-depressed participants;

^b 2 depressed participants who were treated with medroxyprogesterone but did not complete mood assessments on medroxyprogesterone;

^c one non-depressed participant;

^d 2 depressed participants.

[@] p=0.01;

[†] p<0.006 for between-group analyses;

^{*} p 0.007 for within-group analyses for both groups;

[#] p=0.02 for within-group analysis for the depressed group only.