# Effects of Open-Label, Adjunctive Ganaxolone on Persistent Depression Despite Adequate Antidepressant Treatment in Postmenopausal Women:
## A Pilot Study

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**ABSTRACT**

***Objective:*** The neuroactive steroid metabolite of progesterone, allopregnanolone, is a positive allosteric modulator of γ-aminobutyric acid–A ($GABA_A$) receptors and a putative treatment for mood disorders. This pilot study was performed to determine whether an oral allopregnanolone analog (ganaxolone) may be effective adjunctive therapy for persistent depression despite adequate antidepressant treatment in postmenopausal women.

***Method:*** Ten postmenopausal women (mean ± SD age: 62.8 ± 6.3 years; range, 53–69 years) with persistent depression despite adequate antidepressant treatment (current *DSM-IV-TR* major depressive episode per the Structured Clinical Interview for *DSM-IV-TR*, Montgomery-Asberg Depression Rating Scale [MADRS] score ≥ 16, and treated with an adequately dosed antidepressant for ≥ 6 weeks) were studied from December 2016 to April 2018. Open-label ganaxolone (225 mg twice daily, increased to 450 mg twice daily if tolerated) was administered for 8 weeks, followed by a 2-week taper.

***Results:*** Mean ± SEM total MADRS score (primary endpoint) decreased by 8 weeks (24.4 ± 1.6 to 12.8 ± 2.9, $P = .015$), and the decrease persisted over the 2-week taper ($P = .019$); of the 9 subjects who completed the full 8-week treatment period, 44% (4/9) experienced response (MADRS score decrease ≥ 50%) and remission (final MADRS score < 10), which persisted in 100% and 50% of subjects at 10 weeks, respectively. Secondary endpoints showed significant improvement, including Inventory of Depressive Symptomatology–Self-Report score ($P = .003$), MADRS reduced sleep subscale score ($P < .001$), total Symptoms of Depression Questionnaire (SDQ) score ($P = .012$), and scores on SDQ subscales for disruptions in sleep quality ($P = .003$) and changes in appetite and weight ($P = .009$) over 8 weeks. No significant effects were observed on quality of life or sexual function. All subjects experienced sleepiness and fatigue; 60% experienced dizziness.

***Conclusions:*** In this open-label, uncontrolled pilot study, adjunctive ganaxolone appears to exert antidepressant effects but produces sedation with twice-daily dosing. Ganaxolone may also improve sleep, which may be useful in patients with depression and insomnia.

***Trial Registration:*** ClinicalTrials.gov identifier: NCT02900092

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Resistance to selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) treatment occurs in about 50%–70% of patients with major depressive disorder (MDD), a condition associated with significant morbidity[1] and affecting women at higher rates than men.[2] Few well-tolerated, effective augmentation therapies are available for such patients.[3] Therefore, new therapeutic strategies for persistent depression despite adequate antidepressant treatment are needed.

Ganaxolone (Marinus Pharmaceuticals; Radnor, Pennsylvania), an allopregnanolone analog with similar biological activity,[4] is a candidate for such a therapy. Allopregnanolone is a neuroactive steroid metabolite of progesterone and positive allosteric modulator of γ-aminobutyric acid–A ($GABA_A$)–inhibitory brain receptors, acting with 10 times the potency of benzodiazepines at these receptors.[5–7] Progesterone is converted to allopregnanolone by the enzymes 5α-reductase and 3α-hydroxysteroid dehydrogenase (3α-HSD). The addition of a methyl group in the 3β position of ganaxolone prevents back conversion to progesterone and extends its effect. Additionally, ganaxolone can be administered orally in the outpatient setting, while allopregnanolone itself must be administered by continuous intravenous (IV) infusion.

The rationale for studying the effects of a neuroactive steroid analog in women with persistent depression despite adequate antidepressant treatment has its basis in cross-sectional and observational studies. Our group[8] has demonstrated that serum levels of allopregnanolone, but not its precursor progesterone, are inversely associated with depression symptom severity in a group of female volunteers with a wide range of weight (from anorexia nervosa to obesity) without MDD. Other groups[9–11] have demonstrated inverse associations between allopregnanolone cerebrospinal fluid (CSF) and serum levels and severity of depression symptoms in patients with MDD, as well as lower allopregnanolone levels in depressed subjects

**Clinical Points**

- The neuroactive steroid allopregnanolone is a positive modulator of γ-aminobutyric acid–A ($GABA_A$) receptors and a putative treatment for mood disorders. However, it has not been studied as augmentation therapy in postmenopausal women with persistent depression despite adequate antidepressant treatment.
- Oral ganaxolone, an allopregnanolone analog, as augmentation therapy to traditional antidepressants led to improvement in mood in this open-label pilot study of postmenopausal women with persistent depression despite adequate antidepressant treatment.
- Additional randomized, double-blind, placebo-controlled studies are warranted to assess the antidepressant effects of oral ganaxolone augmentation therapy in this population.

compared with nondepressed controls. Observational prospective studies also support a role for allopregnanolone in depression, and, in particular, the data suggest that an increase in allopregnanolone levels (both CSF and serum) occurs in patients after administration of SSRIs and other antidepressants.[9,11–13] The rationale for studying the effects of ganaxolone specifically in postmenopausal women is that progesterone, the precursor of allopregnanolone, is very low in this demographic; thus, postmenopausal women are likely in a state of relative deficiency of this neuroactive steroid.

Finally, recent data demonstrating the positive effects of allopregnanolone administration in postpartum depression provide further evidence of the antidepressant potential of allopregnanolone.[14,15] In a double-blind, randomized, placebo-controlled trial[14] of 21 women with severe postpartum depression, those who received IV brexanolone experienced a very substantial reduction in depression symptom severity compared to the placebo group. This finding was subsequently confirmed by two larger phase 3 randomized, double-blinded trials[16] of the same formulation of allopregnanolone. Short-term studies[17,18] of SAGE-217, an oral positive allosteric modulator of $GABA_A$ receptors and a neuroactive steroid as well, suggest potential efficacy in the treatment of moderate-to-severe major depressive disorder.

We hypothesized that oral ganaxolone would be an effective augmentation therapy for postmenopausal women with persistent depression, and we report here the results of a pilot study investigating this hypothesis. We also investigated the effects of ganaxolone on symptoms associated with depression and/or its treatment, including sexual function, fatigue, and sleep disturbance. Finally, we hypothesized that subjects with lower allopregnanolone levels at baseline would demonstrate greater improvement with ganaxolone treatment.

## METHODS

### Participants

The protocol was approved by the Partners Human Research Committee and conducted from December 2016 to April 2018 (ClinicalTrials.gov identifier: NCT02900092). Written informed consent was obtained from all participants prior to any procedures being performed. Inclusion criteria were female sex; age 50–75 years; postmenopausal status; diagnosis of MDD with a current major depressive episode per *DSM-IV-TR* criteria by the Structured Clinical Interview for *DSM-IV-TR*, Patient Edition (SCID-I/P)[19]; Montgomery-Asberg Depression Rating Scale (MADRS)[20] score ≥ 16; and current treatment with an antidepressant taken at an adequate dose for at least 6 weeks. The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ)[21,22] was used to confirm source documentation of adequate antidepressant treatment dose and duration to fulfill trial inclusion criteria.[21] Exclusion criteria were serious suicide or homicide risk, current or history of psychotic features, or substance abuse disorder active within the last 6 months.

### Design

The study schema is presented in Table 1. In this open-label pilot study, 10 postmenopausal women with persistent depression despite adequate antidepressant treatment were administered ganaxolone over an 8-week treatment period followed by a 2-week taper. Psychiatric measures (clinician-administered and self-rated questionnaires) were assessed at baseline; at weeks 2, 4, 6, and 8 of ganaxolone treatment; and immediately after the drug taper at 10 weeks. Self-rated questionnaires were also administered remotely at 22 weeks, which was 3 months after discontinuation of the study drug.

### Psychiatric Measures

The primary study endpoint was the change in total MADRS score over the 8-week treatment period.[23,24] Secondary measures of depression symptom severity were the Inventory of Depressive Symptomatology–Self-Report (IDS-SR)[25–27] and the Clinical Global Impressions–Severity of Illness scale (CGI-S).[28] The Symptoms of Depression Questionnaire (SDQ)[29] was designed to more fully capture the heterogeneity of symptom presentations of depressive disorders and includes 5 factors focusing on the following dimensions: (1) lassitude, mood, and cognitive functioning; (2) anxiety, agitation, irritability, and anger; (3) suicidal ideation; (4) disruptions in sleep quality; and (5) changes in appetite and weight. Quality of life was measured using the 36-item Short Form Health Survey (SF-36),[30] a self-administered, validated, and widely used quality-of-life questionnaire. Effects of drug on fatigue severity were measured using the Brief Fatigue Inventory (BFI)[31] and Fatigue Severity Scale (FSS),[32] and sleepiness was measured using the Epworth Sleepiness Scale (ESS).[33] Sexual function was assessed with the Derogatis Interview for Sexual Function–Female Version (DISF).[34–36] The Cognitive and Physical Functioning Questionnaire (CPFQ),[37] designed to assess cognitive function in mood and anxiety disorders with a focus on executive dysfunction, was also administered. The presence of suicidal thoughts was assessed using the Concise Health Risk Tracking scale (CHRT).[38]

**Table 1. Ganaxolone Dosing Plan and Schedule of Assessments**

| Assessment | Baseline: Start 225 mg Twice Daily | Week 1: Dose Increase 450 mg Twice Daily | Weeks 2, 4, and 6: Continue 450 mg Twice Daily | Weeks 8 and 10: Drug Taper | Week 22: 3 Months Posttreatment[a] |
|---|---|---|---|---|---|
| Depression symptom severity | | | | | |
| MADRS (primary endpoint) | x | | x | x | |
| CGI-S | x | | x | x | |
| IDS-SR | x | | x | x | x |
| SDQ | x | | x | x | x |
| Fatigue/sleepiness | | | | | |
| BFI | x | | x | x | x |
| FSS | x | | x | x | |
| ESS | x | | x | x | |
| Quality of life (SF-36) | x | | x | x | |
| Sexual function (DISF) | x | | x | x | |
| Cognitive function (CPFQ) | x | | x | x | |
| Suicidality (CHRT) | x | x | x | x | |

[a]Visit occurred remotely; only self-administered questionnaires were completed.
Abbreviations: BFI = Brief Fatigue Inventory, CGI-S = Clinical Global Impressions–Severity of Illness scale, CHRT = Concise Health Risk Tracking scale, CPFQ = Cognitive and Physical Functioning Questionnaire, DISF = Derogatis Interview for Sexual Function, ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, IDS-SR = Inventory of Depressive Symptomatology–Self-Report, MADRS = Montgomery-Asberg Depression Rating Scale, SDQ = Symptoms of Depression Questionnaire, SF-36 = 36-Item Short Form Health Survey.

**Table 2. Depression Symptom Severity Over Time[a]**

| Assessment | Treatment Period: Baseline | Treatment Period: Week 8 | Drug Taper Week 10[b] | 3 Months Posttreatment Week 22[b,c] | Baseline vs Week 8 *P* Value |
|---|---|---|---|---|---|
| Clinician-Administered Questionnaires | | | | | |
| Total MADRS score | 24.4 ± 1.6 | 12.8 ± 2.9* | 14.4 ± 2.5* | | .015 |
| Apparent sadness | 2.4 ± 0.2 | 1.7 ± 0.4 | 1.4 ± 0.3 | | .11 |
| Reported sadness | 2.9 ± 0.2 | 2.2 ± 0.5 | 1.8 ± 0.3 | | .35 |
| Inner tension | 3.0 ± 0.4 | 1.9 ± 0.6 | 1.9 ± 0.5 | | .11 |
| Reduced sleep | 3.1 ± 0.3 | 0.7 ± 0.4* | 1.3 ± 0.4* | | < .001 |
| Reduced appetite | 0.7 ± 0.4 | 0.1 ± 0.1 | 0.1 ± 0.1 | | .17 |
| Concentration difficulties | 3.0 ± 0.4 | 1.9 ± 0.6† | 2.2 ± 0.6 | | .067 |
| Lassitude | 3.0 ± 0.4 | 1.3 ± 0.4* | 2.0 ± 0.4† | | .024 |
| Inability to feel | 2.9 ± 0.5 | 0.9 ± 0.3* | 1.7 ± 0.3 | | .028 |
| Pessimistic thoughts | 2.6 ± 0.3 | 1.9 ± 0.5 | 1.6 ± 0.5 | | .30 |
| Suicidal thoughts | 0.8 ± 0.3 | 0.2 ± 0.2 | 0.4 ± 0.3 | | .31 |
| CGI-S score | 3.8 ± 0.1 | 2.4 ± 0.4* | 2.9 ± 0.4† | | .004 |
| Self-Rated Questionnaires | | | | | |
| IDS-SR Score | 29.7 ± 2.1 | 17.1 ± 2.9* | 19.5 ± 2.2* | 15.7 ± 3.1* | .003 |
| Total SDQ Score | 136.4 ± 5.8 | 108.5 ± 8.0* | 109.5 ± 7.4* | 104.7 ± 6.8* | .012 |
| Factor 1 (lassitude, mood, and cognitive functioning) | 55.4 ± 3.3 | 44.6 ± 4.3† | 44.6 ± 4.6 | 38.7 ± 4.6 | .064 |
| Factor 2 (anxiety, agitation, irritability, and anger) | 41.2 ± 1.3 | 31.1 ± 3.0* | 31.0 ± 1.9* | 32.0 ± 1.8* | .012 |
| Factor 3 (suicidal ideation) | 16.1 ± 0.8 | 13.0 ± 1.1* | 13.0 ± 1.0* | 12.3 ± 1.1* | .041 |
| Factor 4 (disruptions in sleep quality) | 9.5 ± 0.9 | 5.1 ± 0.6* | 6.7 ± 0.6* | 6.7 ± 0.7† | .003 |
| Factor 5 (changes in appetite and weight) | 9.5 ± 0.4 | 8.3 ± 0.2* | 8.7 ± 0.2 | 9.0 ± 0.5 | .009 |

[a]For all questionnaires, higher values indicate worse symptom severity. Data are reported as mean ± SEM.
[b]Paired *t* tests were performed between baseline and the 10- and 22-week follow-up time points only if a significant difference was found during the treatment period (baseline and 8 weeks).
[c]Clinician-administered questionnaires were not completed at week 22.
*Indicates $P < .05$ for change from baseline.
†Indicates trend ($.05 < P < .1$) for change from baseline.
Abbreviations: CGI-S = Clinical Global Impressions–Severity of Illness scale, IDS-SR = Inventory of Depressive Symptomatology–Self-Report, MADRS = Montgomery-Asberg Depression Rating Scale, SDQ = Symptoms of Depression Questionnaire.

### Laboratory Measures

Allopregnanolone, allopregnanolone sulfate, pregnenolone, and pregnenolone sulfate were quantified at baseline and 8 weeks in human K2EDTA plasma using Turbo Ionspray LC-MS/MS (Keystone Bioanalytical Inc; North Wales, Pennsylvania) with the respective deuterated neurosteroids as internal standards. The lower limit of quantification was 25 pg/mL for allopregnanolone and pregnenolone, 2.5 ng/mL for pregnenolone sulfate, and 250 pg/mL for allopregnanolone sulfate.

### Statistical Analysis

Paired *t* tests were performed between baseline (pretreatment) and 8-week time points for all endpoints, as prespecified, and 2-tailed *P* values are reported. If the 2-tailed *P* value was < .05, then paired *t* tests were also performed between baseline and 10 weeks and between baseline and 3 months to assess whether the treatment effects were durable during the 2-week taper (8–10 weeks) and at the 3-month follow-up assessment (week 22), respectively. Neuroactive steroid variables were

log-transformed prior to analysis, and Pearson correlation coefficients are reported.

## RESULTS

### Pretreatment Clinical Characteristics

The mean ± SD age of the participants was 62.8 ± 6.3 years (range, 53–69 years), and the mean ± SD body mass index was 26.2 ± 4.0 kg/m$^2$ (range, 21.6–33.8 kg/m$^2$). The mean ± SD time since menopause was 12.4 ± 7.5 years (range, 3–30 years). Three participants (30%) reported hot flashes over the past month, only 1 of whom reported hot flashes that interfered with sleep. Two participants reported intermittent use of vaginal estrogen, but no participant was taking systemic estrogen. Six participants (60%) were on treatment with an SSRI only, 3 (30%) were on treatment with an SNRI only, and 1 (10%) was on treatment with an SSRI and bupropion. Duration of antidepressant use was 7 weeks for 2 participants and at least 10 weeks for 8 participants, with 4 of the latter group reporting a stable dose for 1 year or longer. The mean ± SD total MADRS score was 24.4 ± 5.1 (range, 18–34), indicating moderate depression.[39]

### Psychiatric Measures

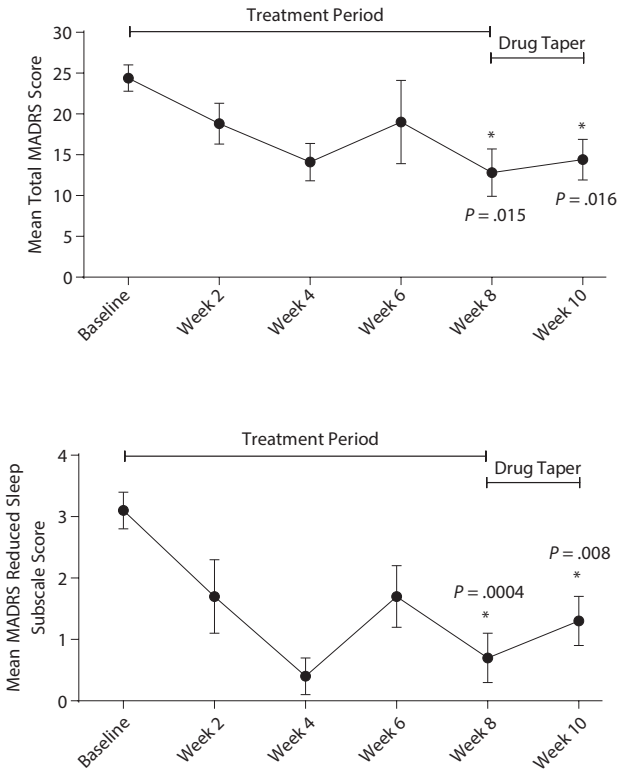
All psychiatric measures are reported in Table 2.

***Primary endpoint.*** The primary endpoint was change in total MADRS score over the 8-week main-study period. Nine of 10 subjects completed the full 8-week treatment period. Forty-four percent of these subjects (4/9) experienced both response to treatment (> 50% reduction from baseline in total MADRS score) and remission (final MADRS score of < 10). Thus, every subject who responded also achieved remission. Responders and remitters did not differ with respect to use of SSRIs versus SNRIs, menopausal stage, presence of hot flashes, or current use of vaginal estrogen. The mean ± SEM total MADRS score (primary endpoint) decreased significantly between pretreatment (week 0) and 8 weeks (from 24.4 ± 1.6 to 12.8 ± 2.9, $P = .015$) (Figure 1A). MADRS subscales demonstrating significant reductions between pretreatment and 8 weeks were reduced sleep ($P < .001$) (Figure 1B), lassitude ($P = .024$), and inability to feel ($P = .028$). There was no significant worsening in scores on any subscales.

***Secondary endpoints.*** There was no significant worsening in scores on any secondary endpoint scale or subscale.

Depression symptom severity. There were significant improvements in IDS-SR (Supplementary Figure 1), CGI-S, and total SDQ (Figure 2A) scores. There were also significant improvements in scores on 4 of the 5 SDQ subscales: Factor 2 (anxiety, agitation, irritability, and anger), Factor 3 (suicidal ideation), Factor 4 (disruptions in sleep quality), and Factor 5 (changes in appetite and weight) (Figures 2C–2F). There was a trend toward a significant improvement in Factor 1 (lassitude, mood, and cognitive and social functioning) (Figure 2B).

**Figure 1. (A) Total MADRS Scores[a] and (B) MADRS Reduced Sleep Scores[b] From Baseline Through the 2-Week Taper[c]**




[a]There was a reduction in depression symptom severity, as measured by mean total MADRS score, that remained through the 2-week taper period.
[b]There was an improvement in sleep quality, as demonstrated by a reduction in the mean MADRS reduced sleep subscale score, that remained through the 2-week taper period.
[c]Error bars indicate SEM.
*Indicates significant change ($P < .05$) compared to baseline with $P$ values noted.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Quality of life. There was a trend toward improvement with ganaxolone therapy over 8 weeks in score on the SF-36 Mental Health Component Summary Scale, with no notable improvement in the Physical Component Summary Scale score.

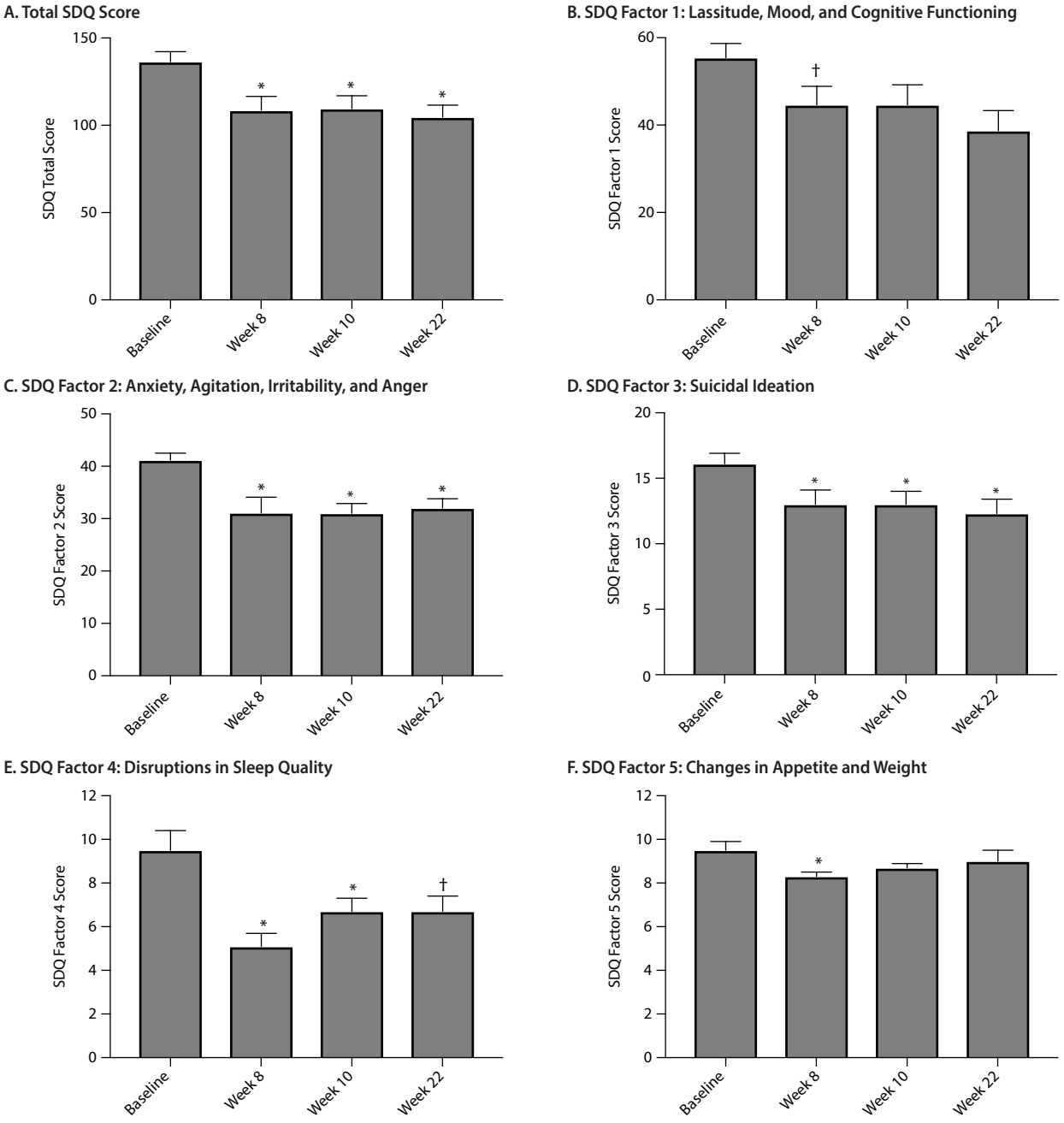
Fatigue, sexual function, and cognitive function. There were no significant changes in any measures of fatigue (ESS, FSS and the BFI), sexual function (DISF), or self-reported cognitive function (CPFQ).

***Posttreatment data.*** The effect of ganaxolone on depression symptom severity, as measured by the total MADRS score (primary endpoint), was retained at 10 weeks, after a 2-week drug taper (Figure 1A). All subjects who experienced a response at 8 weeks had retention of that response through 10 weeks. Half of subjects with remission at 8 weeks had retention of that remission at 10 weeks.

Significant improvement in the MADRS reduced sleep subscale was durable through the 2-week taper (Figure 2B). The significant positive effect on the MADRS lassitude subscale was maintained as a trend through the 2-week taper.

The significant effect on depression symptom severity as measured by the secondary endpoint measure, IDS-SR, was

**Figure 2. Total SDQ Score and Scores on Multiple SDQ Factors During the Treatment Period, After 2-Week Drug Taper, and 3 Months After the End of Drug Treatment[a]**




[a]There were improvements in SDQ total score and all factor scores shown from baseline to week 8; some improvements remained after the 2-week drug taper (week 10) and at 3 months off of drug treatment (week 22).
*Indicates significant difference ($P < .05$) and †indicates trend in difference ($.05 < P < .1$) compared to baseline value. Error bars indicate SEM.
Abbreviation: SDQ = Symptoms of Depression Questionnaire.

also maintained after the 2-week drug taper (Supplementary Figure 1). The response persisted 3 months after study drug discontinuation. The significant positive effects on the total SDQ, SDQ Factor 2 (anxiety, agitation, irritability and anger), SDQ Factor 3 (suicidal ideation), and SDQ Factor 4 (disruptions in sleep quality) scores were also maintained off drug at 10 weeks (Figures 2A and 2C–2E). Of these, the total SDQ, SDQ Factor 2, and SDQ Factor 3 scores continued to showed improvement 3 months after drug discontinuation with a trend toward continued improvement in SDQ Factor 4 scores (Figure 2A, 2C–E).

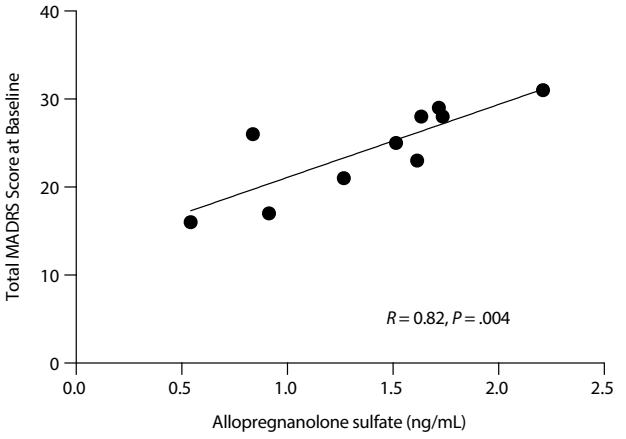
### Neuroactive Steroid Levels

Baseline allopregnanolone levels were below the limit of quantification (< 25 pg/mL) in the majority of subjects (6/10). Allopregnanolone sulfate, pregnenolone, and

pregnenolone sulfate were quantifiable in all subjects (10/10). Allopregnanolone sulfate levels ($R = 0.82$, $P = .004$) (Figure 3) were positively associated with greater depression severity by total MADRS score at baseline. Pregnenolone and pregnenolone sulfate levels were not associated with baseline total MADRS scores.

Neither baseline levels nor change in levels of allopregnanolone sulfate, pregnenolone, or pregnenolone sulfate over the 8-week treatment period predicted response to ganaxolone treatment. There were no differences in mean baseline neuroactive steroid levels between the responders and remitters (n = 4) versus those with no response or remission of depressive symptoms. Allopregnanolone levels were undetectable in equal frequency across groups regardless of response (undetectable in 3 of 4 responder/remitters and 3 of 5 nonresponder/nonremitters).

**Figure 3. Association of Allopregnanolone Sulfate Levels With Baseline Total MADRS Scores[a]**




[a]Plasma allopregnanolone sulfate levels were positively associated with depression severity, as indicated by baseline total MADRS scores.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

### Dropouts and Adverse Events

Nine of 10 study subjects completed the 10-week protocol. All 10 reported adverse events that were possibly or probably treatment-related adverse events, as follows. All subjects experienced sleepiness and fatigue, and 6 of 10 subjects experienced dizziness. One subject was discontinued by the investigators after experiencing somnolence and dizziness after 1 dose of ganaxolone (225 mg). Four of the 10 participants were able to tolerate dose increases (450 twice daily), 3 subjects tolerated the initial dose (225 mg twice daily) but were unable to tolerate attempted dose increases (450 twice daily), and 2 subjects did not tolerate the initial 225-mg twice daily dose well enough to have their doses increased. There was no change in score on the CHRT, an assessment of suicidal thoughts and behaviors. Mean levels of transaminases (aspartate aminotransferase and alanine transaminase) did not increase over the 8-week study.

## DISCUSSION

This pilot study is the first to explore the effects of oral ganaxolone, an allopregnanolone analog and neuroactive steroid, for persistent depression despite adequate antidepressant treatment in postmenopausal women. Our data suggest that ganaxolone exerts antidepressant effects in a subset of such patients. Although all participants reported daytime sleepiness at the current dosing schedule, we also observed significant improvements in sleep during the treatment period, which were most likely related to ganaxolone. In addition, our data suggest possible positive effects on anxiety, agitation, irritability and anger, and suicidal ideation with ganaxolone treatment, as well as persistence of treatment effects beyond the period of drug administration.

Our remission rate of 44% (4 of 9 subjects) appears greater than that of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) augmentation trial[40] that demonstrated a remission rate of approximately 30% (by Hamilton Depression Rating Scale [HDRS] score < 7) in citalopram-treated subjects whose treatment was augmented using sustained-release bupropion or buspirone. There are sparse data on the treatment of persistent depression despite adequate antidepressant treatment specifically in postmenopausal women. Previous studies in peri- and postmenopausal women with untreated depression report wide-ranging remission rates of 38%–88% with conventional antidepressants.[41–43] However, we have not identified any other studies of augmentation therapy in postmenopausal women with depression resistant to standard therapies. Therefore, it is not possible to determine how our remission rate compares with that of other adjuvant therapies specifically in postmenopausal women.

The results of 2 recent studies[17,18] of SAGE-217, another positive $GABA_A$ allosteric oral synthetic neurosteroid, have recently been reported in the treatment of patients with major depressive disorder. In a randomized, placebo-controlled trial[17] of 89 men and women with moderate-to-severe depression (MADRS score > 32 and HDRS score > 22), administration of SAGE-217 for 14 days led to improvement in depression symptom severity. A second, larger study (n = 323) of SAGE-217[18] did not demonstrate a greater reduction in depression symptom severity compared to placebo at 15 days. However, these results, which were negatively affected by a high placebo response, became significant in post hoc analyses when subjects in the SAGE-217 group with no measurable drug concentrations were excluded or when only patients with higher depression symptom severity at baseline were included. These studies differed from ours in that they tested a different medication—though one with a similar mechanism of action—and they did not specifically target our study population of postmenopausal women with moderately severe persistent depression (MADRS score ≥ 16) despite adequate antidepressant treatment. Nevertheless, these studies highlight the importance of nonspecific, placebo-like effects in interpreting depression study results, particularly in patients experiencing less severe depression severity, who may be more susceptible to these

effects.[44,45] Placebo-controlled studies of ganaxolone are therefore warranted to confirm the findings we report here.

The signal detected that ganaxolone may improve sleep is particularly important, given that 75% of patients with depression struggle with insomnia.[46] The durability of antidepressant effects over the 2-week taper period suggests that administering the entire dose before bedtime might provide assistance with sleep, followed by sustained daytime antidepressant effects without the significant somnolence observed with morning dosing. Thus, our study suggests that perhaps lower doses with fewer side effects or evening dosing may be particularly efficacious, taking advantage of these moderately sedating effects for improved sleep, though further studies would be necessary to determine if this is the case. This finding is consistent with the results from the Amaryllis study,[47] which compared oral ganaxolone at a low dose (675 mg at dinner) and a high dose (initiated at 675 mg at dinner and bedtime for 2 days followed by a transition to 1,125 mg once daily at dinner) in women with postpartum depression. The higher-dose regimen was well tolerated and showed a reduction in 17-item HDRS scores that was greater than that with the low-dose regimen. Thus, these data support use of the once-daily 1,125-mg oral evening dose in future clinical studies.[47]

Our findings also suggested that improvements in depression, anxiety, agitation, irritability and anger, suicidal ideation, sleep quality, and overall disease severity may be sustainable with drug taper and even 3 months after drug discontinuation. Part 1 of the Magnolia study[47] (Marinus Pharmaceuticals) showed a similar durable response at 1 month after IV ganaxolone treatment (48-hour infusion followed by 12-hour taper) in women with postpartum depression. Part 2 of the Magnolia study[47] showed an immediate response to combined IV and oral ganaxolone treatment (6-hour infusion followed by 1 oral dose) in the same population but failed to demonstrate a durable response at 1-month posttreatment. Thus, these data raise the possibility of sustained antidepressant effects with ganaxolone administration, but further studies are needed to confirm this finding and determine the mechanism of response durability.

Our data demonstrate that postmenopausal women with persistent depression despite adequate antidepressant treatment have largely undetectable to low levels of allopregnanolone, consistent with our original rationale for investigating allopregnanolone analog administration in such women. However, we also found that allopregnanolone sulfate, which was detectable in all subjects, was positively associated with depression severity as indicated by MADRS score prior to ganaxolone treatment. The precise relationship of allopregnanolone sulfate to allopregnanolone levels is not entirely understood, and we are limited in drawing conclusions regarding this relationship between allopregnanolone and allopregnanolone sulfate because of the number of undetectable allopregnanolone levels in our cohort. Of note, these data should be interpreted in the context of the fact that all study participants were receiving antidepressant medications upon entry to the study, and prior data[9,11,12] suggest that antidepressants may increase allopregnanolone levels. Despite these limitations, these data provide a plausible mechanistic role for the direct association between allopregnanolone sulfate levels and depression severity in this cohort and further raise the scientific question of whether neuroactive steroid dysregulation could be a mechanism underlying persistent depression despite adequate antidepressant treatment.

Limitations of the current study include its uncontrolled design. As such, the signal observed in this study provides preliminary data for future, more definitive studies in this area. In addition, we were unable to assess neuroactive steroid levels in nondepressed controls, nor were we able to reliably measure additional neuroactive steroids in the pathway to help identify possible enzymatic regulatory steps. Finally, we do not have data regarding prior history of hormone-related depression, which may be useful in this population. Further studies are warranted to determine whether neuroactive steroids play a direct role in the pathophysiology of persistent depression despite adequate antidepressant treatment.

In summary, our pilot data suggest that oral ganaxolone, an analog of allopregnanolone, may be a promising pharmacotherapy for postmenopausal women with persistent depression despite adequate antidepressant treatment and raise the question of whether neuroactive steroid dysregulation may contribute to depressive symptoms in this population. Furthermore, definitive studies in these areas are warranted, and the observed positive effects on sleep and the potential for sustained treatment effects also merit further study. Randomized, placebo-controlled studies are necessary to rule out placebo effects for both mood and sleep. Given the sedation experienced by a majority of participants and the promising durability of antidepressant effects over the 2-week period, bedtime dosing only should be considered for future studies. Finally, should rigorous studies confirm an antidepressant effect, it will be important to identify subsets of women who respond—for example, women with neuroactive steroid dysregulation—and to identify specific mechanisms of action, including regional brain targets.

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***Disclaimer:*** Dr Shapero is currently employed by the National Institutes of Health. The opinions expressed in this article are the authors' own and do not

reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

***Supplementary material:*** Available at PSYCHIATRIST.COM.

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*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.



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# Supplementary Material

**Article Title:** Effects of Open-Label, Adjunctive Ganaxolone on Persistent Depression Despite Adequate Antidepressant Treatment in Postmenopausal Women: A Pilot Study

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## List of Supplementary Material for the article



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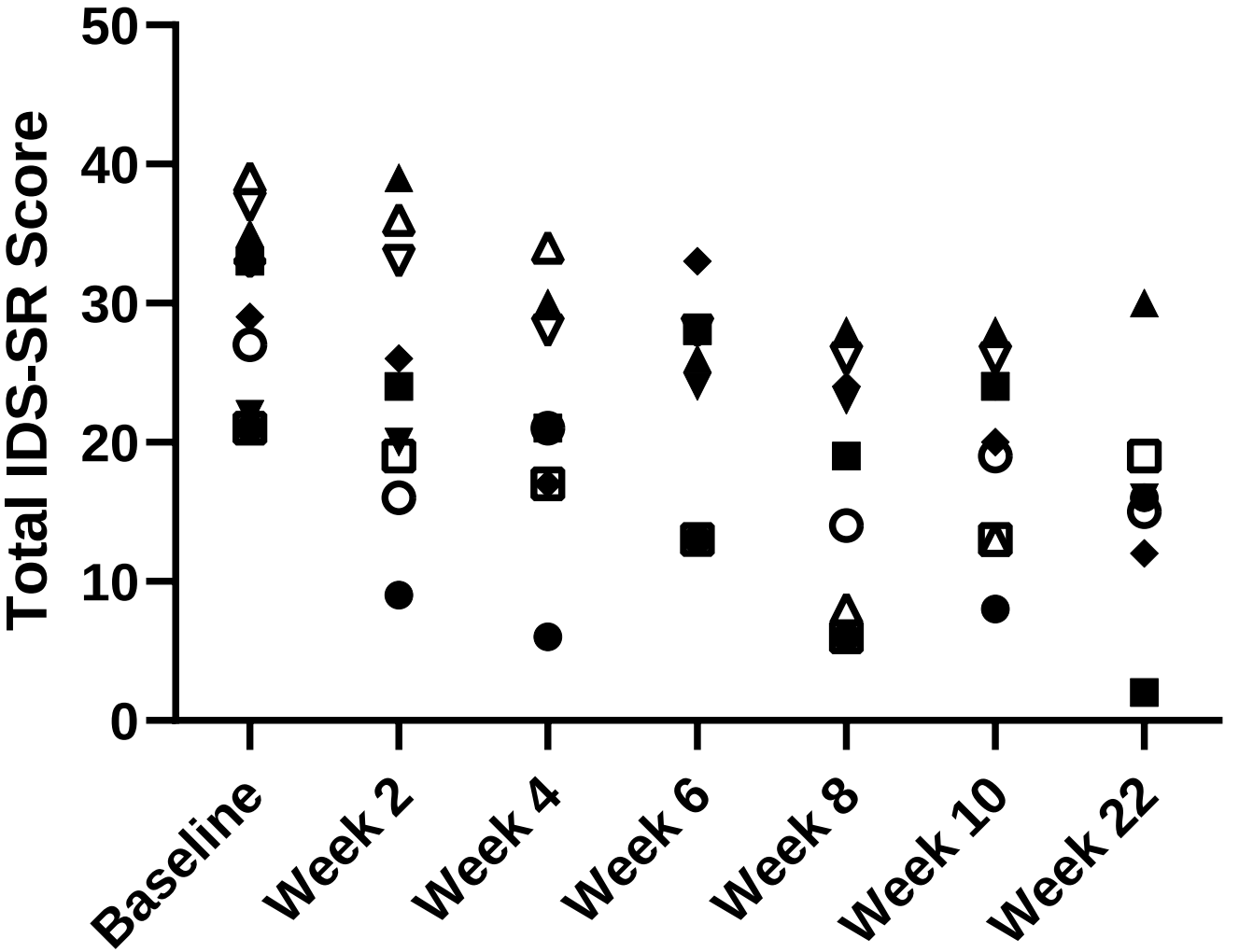
**Supplementary Figure 1. Total IDS-SR score for all subjects at each time point[a]**




[a]Each unique symbol represents a single subject.