

Are Antidepressants Effective in the Treatment of Postpartum Depression? A Systematic Review

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ABSTRACT

Objective: In spite of the paucity of randomized controlled trials of antidepressants in postpartum depression, these drugs are the most commonly used agents in the pharmacologic treatment of postpartum depression. This article reviews the literature on the efficacy of antidepressants in randomized controlled trials of postpartum depression.

Data Sources: Four electronic databases, MEDLINE/PubMed (1966–2013), PsycINFO (1806–2013), EMBASE (1980–2013), and the Cochrane Database of Systematic Reviews, were searched using a combination of the keywords *antidepressive agents/therapeutic use, antidepressant drugs, antidepressant agent/drug therapy, depression, postpartum/drug therapy, postpartum depression, and puerperal depression/drug therapy*.

Study Selection: The reference lists of articles identified were also searched. All relevant articles published in English were included. A total of 124 articles were identified. The efficacy of antidepressants has been studied in 6 randomized controlled trials, of which 3 were placebo-controlled studies.

Results: Placebo-controlled randomized data do not support the notion that antidepressants are efficacious in postpartum depression. However, the methodological flaws of studies have to be kept in mind while interpreting the results of these studies.

Conclusions: Due to the paucity of controlled data and methodological limitations of studies, the question about the efficacy of antidepressants in postpartum depression cannot be answered unequivocally.

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Approximately 6.5% to 12.9% of women have a major or minor episode of depression in the first year after giving birth.¹ The disruption in the early mother-infant relationship contributes to short-term and long-term adverse child outcomes. The negative effects of maternal depression on children include an increased risk of impaired mental and motor development, difficult temperament, and behavior problems.² Given the deleterious consequences of untreated postpartum depression for the mother, her infant, and her family, it is important that women with postpartum depression be diagnosed and treated appropriately. The term *postpartum depression* is commonly used to denote an episode of unipolar depression occurring within 4 weeks postpartum, but, according to the *DSM-5*, the specifier “with peripartum onset” can be applied to a major depressive episode in women with bipolar I disorder or bipolar II disorder.³ In a recent study,⁴ nearly 23% of women who had a score ≥ 10 on the Edinburgh Postnatal Depression Screen (EPDS)⁵ actually met the *DSM-IV-TR* criteria for bipolar disorder. In another study, more than half of women referred for postpartum depression to a perinatal clinic had bipolar disorder.^{6,7} Similarly, 15% to 50% of women who experience first onset of depression after giving birth were found to have bipolar disorder.⁸

Postpartum depression is a heterogeneous entity. The majority (60%) of women with postpartum depression have onset of the index episode during, or prior to, pregnancy rather than in the postpartum period.⁴ There is emerging evidence that depression beginning prior to pregnancy may be distinct from depression that begins after childbirth.⁹ Moreover, depression with onset in the postpartum period may not be a homogenous entity. This difference is illustrated in a recent report by Munk-Olsen et al,¹⁰ who found that onset of symptoms 0 to 14 days after delivery predicted subsequent conversion to bipolar disorder (relative risk = 4.26, 95% CI, 3.11–5.85). Cooper and Murray⁹ found different recurrence patterns for depression arising de novo in the postpartum period and the depression that recurs after childbirth. Specifically, women with de novo depression in the postpartum period were at increased risk of further postpartum episodes, while women for whom the index episode was a recurrence of depression were at increased risk of further nonpuerperal episodes.⁹ It has also been found that women with postpartum depression are usually comorbid with an Axis I disorder including generalized anxiety disorder and obsessive-compulsive disorder.^{4,7} Compared to women with nonpuerperal depression, women with postpartum depression are more likely to have anxious features, take longer to respond to antidepressants, and require more antidepressants.¹¹ Other sources of heterogeneity in postpartum depression are related to the duration and severity of depressive episodes. Postpartum episodes can be brief and remit spontaneously without treatment,¹² but increased vulnerability to psychopathology may persist for a year or more.¹³ Due to the sometimes mild nature of postpartum depressive symptoms, some women do not seek any professional help, while others are at an increased risk of first-time psychiatric admission to the hospital from delivery up to 6 months postpartum.¹⁴

Pharmacotherapy as adjunct to or in place of psychotherapy has been studied in the treatment of postpartum depression. The data on the

- Postpartum depression is a heterogeneous entity.
- Women should be evaluated to clarify the nature and severity of depression prior to antidepressant treatment.
- There is a paucity of randomized controlled data in the pharmacologic treatment of postpartum depression.

pharmacologic treatment of postpartum depression include studies with antidepressants and hormonal supplements. Selective serotonin reuptake inhibitors (SSRIs) are the most-studied antidepressants in postpartum depression and are increasingly used in the postpartum period; interestingly, an opposite trend has been observed in their use during pregnancy.¹⁵ Antidepressants are generally recommended for moderate-to-severe postpartum depression or for women not responding to (or declining) psychological interventions.^{16–19} While the data to support the use of antidepressants for postpartum depression are limited, one review described the literature on pharmacologic interventions for postpartum depression as unimpressive but acknowledged the therapeutic role of antidepressants.²⁰ Results of a meta-analysis provide evidence for the efficacy of a range of interventions including pharmacotherapy for perinatal depression.²¹

The goals of this review are to (1) examine the data from existing randomized trials of antidepressants in postpartum depression and (2) offer suggestions for designing antidepressant trials in postpartum depression.

METHOD

Data Sources

On March 26, 2013, 4 electronic databases, MEDLINE/PubMed (1966–2013), PsycINFO (1806–2013), EMBASE (1980–2013), and The Cochrane Database of Systematic Reviews, were searched in order to systematically examine the efficacy of antidepressants in the treatment of postpartum depression. Combinations of the keywords *antidepressive agents/therapeutic use*, *antidepressant drugs*, *antidepressant agent/drug therapy*, *depression*, *postpartum/drug therapy*, *postpartum depression*, and *puerperal depression/drug therapy* were used. The reference lists of articles identified were also searched to select relevant publications. All relevant articles published in English were included. Although all individual case reports and case series are referred to, only randomized controlled trials of antidepressants are discussed in detail.

Data Extraction

As shown in Figure 1, a total of 124 articles were identified, of which 6 were randomized controlled trials (total of 589 participants)^{22–27} including 3 placebo-controlled studies (total of 191 participants).^{22,25,27} The following data were extracted: author name, country, study design, sample size, duration of the trial, details of treatment intervention,

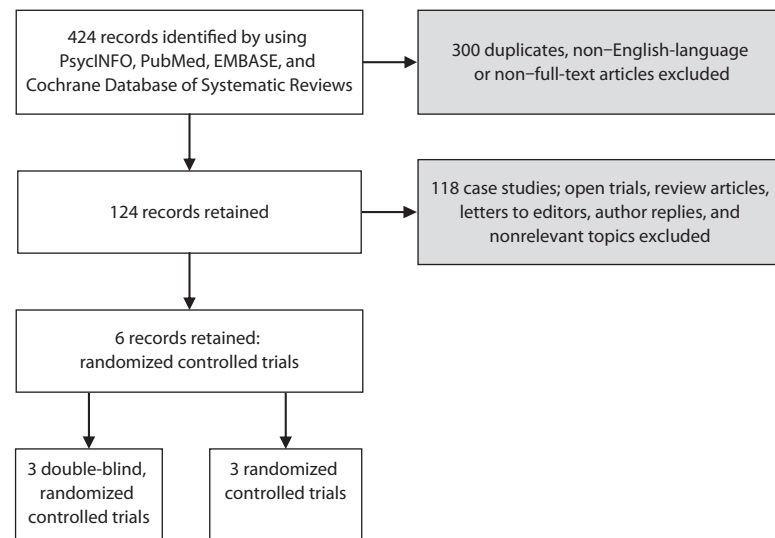
remission rate, and antidepressant dose. Two trials were carried out in the United States,^{24,25} 1 in Canada,²³ 2 in United Kingdom,^{22,26} and 1 in Israel.²⁷ Summary details of the trials are presented in Table 1. The role of concomitant psychotherapy was investigated in 3 studies: Appleby et al²² compared fluoxetine or placebo with 1 or 6 sessions of cognitive-behavioral therapy (CBT), Misri et al²³ compared paroxetine monotherapy with paroxetine plus CBT, and, finally, Bloch et al²⁷ assessed the effect of sertraline addition in women receiving brief dynamic psychotherapy for postpartum depression.

RESULTS

A review of the eligibility criteria across the trials demonstrated ample heterogeneity in the studies' populations including the type, severity, and duration of depression; current Axis I comorbidity; and onset of index episode in relation to childbirth. Participants were diagnosed with major depressive disorder using the *DSM-IV* criteria in 4 studies,^{23–25,27} with minor or major depression according to the Research Diagnostic Criteria in 1 study,²² and with major depression using the *ICD-10* in another study.²⁶ The major depressive episode diagnostic criteria differ as follows: the *DSM-IV* requires sad mood or loss of interest plus 4 symptoms of depression for at least 2 weeks, the *ICD-10* requires the presence of at least 4 symptoms of depression for a minimum of 1 month, and the Research Diagnostic Criteria requires 3 to 5 depressive symptoms. Two studies included participants who had chronic depression defined as episode onset prior to the index pregnancy²² and depression lasting up to 2 years.²⁴ Four studies allowed current diagnosis of an anxiety disorder,^{23–25,27} and, in 3 studies,^{22,23,26} it was unclear whether individuals with a diagnosis of bipolar disorder were excluded.^{22,23,26} Further, only 2 studies ruled out medical conditions with laboratory tests.^{24,25} Lastly, only 1 study reported the use of rescue medications,²⁷ and adherence to study medication/placebo was recorded in only 1 study.²⁵

Appleby et al²² studied the efficacy of fluoxetine and CBT in 87 women with a diagnosis of major or minor depression. Women with a score ≥ 10 on the EPDS 6 to 8 weeks after childbirth were interviewed using the revised Clinical Interview Schedule. Those who had a score > 12 (the threshold for significant psychiatric morbidity) and met the Research Diagnostic Criteria for minor or major depression were considered eligible to participate in the study. The exclusion criteria included chronic (> 2 years' duration) or treatment-resistant depression. Participants were allocated to 1 of 4 treatment groups: fluoxetine plus 1 session of CBT, fluoxetine plus 6 sessions of CBT, placebo plus 1 session of CBT, or placebo plus 6 sessions of CBT. Of the 87 women entering the trial, 26 (30%) women dropped out of the study before week 4 assessment. The majority of the dropouts (17/26 [65%]) occurred before the week 1 assessment.²² The mean Hamilton Depression Rating Scale (HDRS) total scores (95% CIs) in the fluoxetine group and in the placebo group were 13.3 (12.2–14.5) and 14 (12.5–15.7), respectively. All groups showed a significant improvement after 12 weeks. Fluoxetine

Figure 1. Systematic Review Flowchart



was superior to placebo (effect size = 2.4), and improvement after 6 sessions was significantly greater than after 1 session. The difference between fluoxetine and placebo was 37.1% at 4 weeks (95% CI, 5.7%–58.0%) and 40.7% at 12 weeks (95% CI, 10.9%–60.6%). However, interaction between CBT and fluoxetine was not statistically significant.²²

Yonkers et al²⁵ studied the efficacy of paroxetine in a double-blind, placebo-controlled study. Participants met *DSM-IV* criteria for major depressive disorder with onset of the depressive episode in the first 3 months after birth, were within 9 months of delivery at intake, and had a score > 16 on the 17-item HDRS. Women with onset of depression prior to delivery or with a diagnosis of bipolar disorder were excluded. Over half of the participants had a concurrent psychiatric disorder. The mean \pm SD baseline HDRS score in the paroxetine group was 23.6 ± 4.7 and in the placebo group was 24.7 ± 5.0 . Both groups improved over time but did not differ significantly on the HDRS or Inventory of Depressive Symptomatology–Self-Report at follow-up. The improvement on the Clinical Global Impressions–Severity of Illness scale was significantly better for the paroxetine group compared with the control group (mean \pm SD scores of 1.8 ± 1.4 and 3.1 ± 1.4 , respectively, $P = .05$). The paroxetine group also had a significantly higher rate of remission compared to the placebo group (37% vs 15%, odds ratio = 3.5, 95% CI, 1.1–11.5). Participants with a lifetime comorbid diagnosis were less likely to respond than those with no lifetime comorbidity. Other predictors of remission included being non-Hispanic white versus Hispanic or black and having a comorbid psychiatric disorder. The attrition rate was high: only 31 of 70 participants (17 in the paroxetine group and 14 in the placebo group) completed the study. Interestingly, 5 participants in the treatment group and 2 in the placebo group felt an improvement in their symptoms and no longer wished to participate in the study.²⁵

Bloch et al²⁷ assessed the possible advantage of sertraline as add-on treatment in 42 women with mild-moderate postpartum depression who were concurrently receiving sessions of focused brief dynamic psychotherapy (a total of 12 sessions). Participants were assessed by the Structured Clinical Interview for *DSM-IV* Axis I disorders. Inclusion criteria were onset of the depressive episode within 2 months of birth and a Montgomery-Asberg Depression Rating Scale (MADRS) score < 30. Exclusion criteria included a diagnosis of bipolar disorder and > 6-month duration of the depressive episode. The mean \pm SD baseline MADRS score was 19.8 ± 4.64 in the placebo arm and 19.8 ± 4.98 in the sertraline group. Both groups improved significantly, with no significant difference between groups. The mean \pm SD sertraline dose was 65.0 ± 23.5 at 4 weeks and 67.5 ± 24.5 at 8 weeks. Two of 20 women (10%) taking paroxetine had a hypomanic episode despite the fact that women with bipolar disorder were excluded.²⁷

Misri et al²³ conducted a 12-week comparison of paroxetine monotherapy with paroxetine plus CBT for postpartum depression with comorbid anxiety. Women who met the *DSM-IV-TR* diagnosis of major depressive disorder and anxiety disorder(s) within 6 months of giving birth and who had scores ≥ 18 on the 21-item HDRS, ≥ 20 on the Hamilton Anxiety Rating Scale, and > 12 on the EPDS were recruited. Over 60% of women had comorbid obsessions and/or obsessive-compulsive disorder. Fifteen of 16 participants in the paroxetine group and all participants ($n = 19$) in the combination group had comorbid anxiety disorders. Paroxetine was started at 10 mg daily, titrating up to a maximum dose of 50 mg daily. The mean dose in the paroxetine group was 36.25 mg compared with 32.50 mg in the combination group.²³ The baseline mean \pm SD HDRS score in the paroxetine group was 22.06 ± 3.38 and in the combination group was 21.16 ± 2.03 . Both groups

Table 1. Summary of Randomized Controlled Trials of Postpartum Antidepressant Use

| Study (year) | Study Design | Sample Size (N) | Duration | Intervention | Remission Rate | Antidepressant Dose | Comments |
|------------------------------------|---|-----------------|---------------------------|---|--|---|---|
| Appleby et al (1997) ²² | Double-blind, randomized controlled trial | 87 | 12 wk | Fluoxetine plus 1 or 6 sessions of CBT vs placebo plus 1 or 6 sessions of CBT | Not reported | 20 mg/d | After 1 session of counseling, additional benefit results from further counseling or fluoxetine, but there is no advantage to combining both |
| Misri et al (2004) ²³ | Randomized controlled trial | 35 | 12 wk | Paroxetine vs paroxetine plus CBT | Paroxetine: 87.5% vs paroxetine plus CBT: 78.9% | 10–50 mg/d Paroxetine group mean dose: 36.25 mg/d Paroxetine plus CBT group mean dose: 32.50 mg | Both groups had highly significant improvement ($P < .01$) in mood and anxiety symptoms |
| Wisner et al (2006) ²⁴ | Randomized controlled trial | 109 | 8 wk plus 16-wk follow-up | Sertraline vs nortriptyline | Sertraline: 46% vs nortriptyline: 56% | Starting dose 25 mg/d up to a maximum of 200 mg/d Starting dose 10 mg/d up to a maximum of 150 mg/d | Response rates and remission rates did not differ between the groups at 4, 8, and 24 wk |
| Yonkers et al (2008) ²⁵ | Double-blind, randomized controlled trial | 60 | 8 wk | Paroxetine vs placebo | Paroxetine: 43% vs placebo: 32% on CGI-S | Starting dose 10 mg/d for 2 wk, increased to 20 mg/d for wk 3–4, increased further to 30 to 40 mg/d depending on clinical status; mean \pm SD dose was 21.1 ± 10.7 mg/d | No statistically significant differences were found for the IDS-SR, CGI-S, or HDRS-17 |
| Sharp et al (2010) ²⁶ | Randomized controlled trial | 254 | 18 wk | Antidepressants vs nondirective counseling | Antidepressants: 45% vs nondirective counseling: 20% at 4 wk | Not provided | Antidepressants were significantly superior to general supportive care at 4 wk, but there was no significant difference between the groups at 18 wk |
| Bloch et al (2012) ²⁷ | Double-blind, randomized controlled trial | 44 | 8 wk | Sertraline plus BDP vs placebo plus BDP | Sertraline plus BDP: 65% vs placebo plus BDP: 50% | 50–100 mg Mean \pm SD dose for the sertraline group was 67.5 ± 24.5 mg/d and for the combination group was 62.5 ± 21.5 mg/d | No significant benefit for sertraline over placebo as an add-on to brief dynamic psychotherapy |

Abbreviations: BDP = brief dynamic psychotherapy; CBT = cognitive-behavioral therapy; CGI-S = Clinical Global Impressions—Severity of Illness scale; HDRS-17 = 17-item Hamilton Depression Rating Scale; IDS-SR = Inventory of Depressive Symptomatology—Self-Report.

showed significant improvement ($P < .01$) in depressive and anxiety symptoms (response rates of 87.5% in the paroxetine group and 78.9% in the combination therapy group) without significant differences between groups. Due to the absence of a placebo arm in the study, it is difficult to determine the specific effect of either intervention. Notably, the response rate in this study was higher than in the paroxetine study that included a placebo control.²³

Wisner et al²⁴ compared the efficacy of sertraline and nortriptyline in an 8-week trial with a 16-week continuation phase. Women with a *DSM-IV* diagnosis of major depressive disorder with postpartum onset (within 4 weeks of birth) and a 17-item HDRS score ≥ 18 who were within 3 months of delivery were included. Women with chronic depression (defined as an episode of depression that began before the index pregnancy) or a comorbid anxiety disorder were also included. Of the 109 women who were recruited in the study, 95 provided data for the 4-week outcomes and 83 for the 8-week outcomes. Only 49 women chose to continue the study past 8 weeks, and 29 women completed at least 20 weeks of the study. There was a high dropout rate, especially in the first 8 weeks of the study. Significantly more women who were taking sertraline versus nortriptyline (23/52 [42%] vs 13/54 [24%], respectively, Wilcoxon $P = .02$) dropped out of the study.²⁴ Occurrence of hypomania and clinical deterioration were the reasons for study withdrawal for some participants, but it is not clear exactly how many women had these particular side effects. The proportion of women who responded and remitted did not differ between the drugs at 4, 8, or 24 weeks. Similarly, there was no difference in the time to response and remission in the 2 groups, and both groups showed similar improvement in psychosocial functioning.²⁴

Sharp et al²⁶ compared antidepressants with a community-based psychological intervention among women assessed in general practice settings. Women with a score ≥ 11 on the initial screening by the EPDS or who were referred and had fulfilled the *ICD-10* criteria for major depression in the first 6 months postpartum were included in the trial. Approximately 23% of participants had mild depression and 55% had moderate depression. The mean \pm SD baseline EPDS scores in the antidepressant and psychological intervention groups were 17.3 ± 3.3 and 17.7 ± 3.5 , respectively. About half of the participants in the antidepressant group had never tried antidepressants.²⁶ Adherence to medication was checked with self-report and prescription data. Participants were randomized to an antidepressant (usually an SSRI) or general supportive care for the first 4 weeks. After 4 weeks, participants receiving general supportive care had nondirective counseling sessions for an additional 14 weeks. Participants were allowed to receive the alternative intervention if they were not responding or if they wished to change interventions or have the other intervention added. Women receiving antidepressants experienced significantly more improvement than those receiving general supportive care. Of the 106 women allocated to receive antidepressants, 48 (45%) had improved (defined as an EPDS score < 13)

compared with 22 (20%) of 112 women allocated to receive general supportive care. At 18 weeks, there was no clear difference between the 2 groups (62% vs 51%; OR = 1.5; 95% CI, 0.8 to 2.6; $P = .19$). Approximately one-third (31% at 4 weeks and 36% at 18 weeks) of participants reported missing many doses.²⁶

CONCLUSION

Given that postpartum depression is a major public health problem, it is surprising that the controlled data consist of only 6 randomized trials including 3 placebo-controlled studies. The antidepressant was superior to placebo in only one study but showed no significant benefit when combined with psychotherapy versus psychotherapy alone,²² and this study used an active control, as the participants in the placebo arm also received one to 6 sessions of counseling. In another placebo-controlled trial,²⁵ the remission rate was significantly higher among participants taking an antidepressant, but the drug was not superior to placebo on the primary efficacy variable. Four studies on the effect of antidepressant add-on including 2 placebo-controlled trials failed to show that the addition of the antidepressant was significantly more effective than psychotherapy alone.^{22,23,26,27} The lack of a placebo arm in the comparative trial makes it difficult to determine the effect of antidepressants.²⁴ The results of the randomized controlled trials are in sharp contrast to the open-label studies carried out using sertraline,²⁸ venlafaxine,²⁹ fluvoxamine,³⁰ bupropion,³¹ and nefazodone³² that have reported positive results. Because depression normally improves over time even without treatment, it is difficult to know whether the improvement in depressive symptoms seen in these studies can be attributed to antidepressant drugs.

There are some caveats to keep in mind when considering the effect of antidepressants in postpartum depression. Some of the antidepressant studies in postpartum depression included women with mainly mild-to-moderate depression.^{22,26,27} The symptoms of mild depression are difficult to distinguish from the normative postpartum symptoms in the first few weeks after delivery. Moreover, mild symptoms are more likely to remit spontaneously compared with symptoms of more severe depression. A meta-analysis of the benefits of antidepressants showed that efficacy over placebo increases when severity of depression crosses the threshold defined by the National Institute for Clinical Excellence¹⁷ for a clinically significant difference at a baseline HDRS score of 25. Among patients with HDRS scores < 23 , Cohen d effect sizes for the difference between medication and placebo were estimated to be < 0.20 (a standard definition of a small effect).³³ To assess the effect of baseline depression severity on response to antidepressant (sertraline), Bloch et al²⁷ performed a post hoc analysis but did not find any between-group difference.

Due to the paucity of controlled data and methodological limitations of studies including small sample sizes, heterogeneity of the study populations, high attrition rates, and inadequacy of antidepressant doses, the question about the efficacy of antidepressants in postpartum depression cannot be answered unequivocally. The attrition rates were

higher in these studies than those reported in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.³⁴

The general lack of efficacy of antidepressants in placebo-controlled trials could be due to several reasons. Some studies included participants with comorbid anxiety disorders. There is some evidence that patients with major depressive disorder and comorbid anxiety have a poorer response to antidepressants than patients with major depressive disorder alone. In the STAR*D study, patients with anxious depression had lower response rates, took longer time to improve, and had greater side effect burden.³⁴ Another potential reason for the poor response to antidepressants could have been the subtherapeutic doses of antidepressants. The doses of antidepressants were in the low to medium range³⁵ in all of the studies except one.²⁴ Nonadherence to medication could have been another factor. Undetected bipolarity is another important consideration because antidepressants are not as effective in bipolar depression as in unipolar depression.⁷ Depressive mixed states defined as the occurrence of 2 or 3 manic features during a major depressive episode are present in approximately 8% of individuals with depression occurring outside of the postpartum period,³⁶ but depressive mixed states may be particularly common among women with postpartum depression. Another possible explanation for the lack of significant drug effect may be the unique milieu of the postpartum period. Women may respond poorly to antidepressants due to the low levels of estrogen in the postpartum period.²⁷

The use of placebo in women with postpartum depression poses an ethical dilemma due to the potentially serious consequences of untreated disorder for the woman and her family. Yet placebo-controlled trials are needed to determine whether antidepressants are efficacious in postpartum depression. Due to the difficulty of recruiting and retaining women in placebo-controlled trials, future studies may need to consider alternative designs including the use of active controls as employed by Appleby et al.²² and Bloch et al.²⁷ Combining a psychotherapeutic intervention with placebo may make it easier for women to consider participation in placebo-controlled trials.

The broad conceptualization of postpartum depression in contemporary clinical practice appears to include a mixture of depressions with different etiologies, different clinical profiles, different comorbid patterns, and different responses to treatments. It is possible that antidepressants are effective in a subgroup of patients with narrowly defined unipolar postpartum depression with onset in the postpartum period. A better characterization of the postpartum depressive episode might help to clarify the "profile" of an antidepressant responsive episode. Researchers should specify the time of onset of the index episode so as to determine whether it began in the postpartum, during pregnancy, or prior to pregnancy. A postpartum episode should be specified as first occurrence or recurrence of a depressive episode within 4 to 24 weeks of delivery. The postpartum onset should be further characterized as early onset (within 4 weeks after birth) or

late onset (between 4 to 24 weeks after birth). Symptomatic composition of the episode including the number of concomitant manic symptoms, current and lifetime Axis I comorbidity, and duration of the index episode should be specified. Women with bipolar disorder should be excluded from trials of traditional antidepressants. Manic symptoms at baseline and during the course of the study should be quantified with a rating scale such as the Young Mania Rating Scale.³⁷ Laboratory tests such as thyroid-stimulating hormone and complete blood count should be done prior to randomization of participants to the study. Hypothyroidism can mimic symptoms of postpartum depression and also affect the clinical response to antidepressants.^{27,32} A recent study observed a strong association between low serum ferritin and postpartum depression.²⁶ Prior use of antidepressants should be noted because the long-term use of antidepressants in some patients may attenuate the response to these drugs.^{38,39} Reasons for withdrawal from the study including clinical deterioration and induction of (hypo)mania should be provided. Whether or not rescue medications are allowed in the study, and the extent of their use, should be reported.

As sleep loss is common after birth and may precipitate or perpetuate depression, the role of drugs such as quetiapine should be explored in postpartum depression.⁴⁰ Studies are also needed in the long-term treatment of postpartum depression to assess the durability of acute antidepressant response. Another important area of neglected inquiry is the drug treatment of bipolar postpartum depression. It is rather surprising that there are no studies on the pharmacologic treatment of bipolar postpartum depression in spite of its prevalent nature including the increased risk of harm to self and the newborn.^{5,41} Lastly, there are also no data to guide clinicians in the management of postpartum depression that has failed to respond adequately to antidepressant therapy; thus, this area should also be explored.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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