

## CLINICAL PRACTICE

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## Postpartum Depression

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

**A 28-year-old single mother of a 3-month-old son reports severe fatigue, general loss of interest, irritability, poor concentration, insomnia, low energy, and tearfulness that have lasted for 2 months. She had similar symptoms for several weeks when she was 18 years of age and again in mid-pregnancy, but her symptoms resolved spontaneously on those occasions. She is not suicidal or psychotic but feels that she cannot cope. What would you advise?**

## THE CLINICAL PROBLEM

POSTPARTUM DEPRESSION IS A DISABLING BUT TREATABLE MENTAL DISORDER that represents one of the most common complications of childbearing.<sup>1</sup> Postpartum depression is included in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), as a major depressive episode "with peripartum onset if onset of mood symptoms occurs during pregnancy or within 4 weeks following delivery"<sup>2</sup> (Table 1). However, depression that begins later than 4 weeks after delivery or does not meet the full criteria for a major depressive episode may still cause harm and require treatment.<sup>3</sup> In clinical practice and in clinical research, postpartum depression (i.e., nonpsychotic puerperal depression) is variably defined as depression that occurs within 4 weeks after childbirth, or 3 months, 6 months, or up to 12 months<sup>2-4</sup> after childbirth.

The estimated prevalence of postpartum depression ranges from 6.5 to 12.9% or even higher in lower-income and middle-income countries.<sup>1,4,5</sup> Some studies have shown increased rates of depression among new fathers,<sup>6</sup> whereas others have not.<sup>5</sup> Symptoms of postpartum depression often include sleep disturbance (beyond that associated with the care of the baby), anxiety, irritability, and a feeling of being overwhelmed, as well as an obsessional preoccupation with the baby's health and feeding. Suicidal ideation and worries about causing harm to the baby have also been reported.<sup>7</sup> The strongest risk factor for postpartum depression is a history of mood and anxiety problems and, in particular, untreated depression and anxiety during pregnancy.<sup>7</sup> The rapid decline in the level of reproductive hormones after childbirth probably contributes to the development of depression in susceptible women,<sup>8</sup> although the specific pathogenesis of postpartum depression is unknown; in addition to hormonal changes,<sup>8,9</sup> proposed contributors include genetic factors<sup>10,11</sup> and social factors including low social support, marital difficulties, violence involving the intimate partner, previous abuse, and negative life events.<sup>1,12</sup> The natural course of postpartum depression is variable. Although it may resolve spontaneously within weeks after its onset, approximately 20% of women with postpartum depression still have depression beyond the first year after delivery, and 13% after 2

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## KEY CLINICAL POINTS

## POSTPARTUM DEPRESSION

- Postpartum depression is a common, disabling, and treatable problem that affects the woman, infant, and family.
- Sensitive inquiry about mental health symptoms should occur at all postpartum consultations, and comprehensive evaluation should be sought when core symptoms of depression, such as low mood or loss of interest, are present.
- Clinicians should be alert to symptoms that suggest bipolar disorder or postpartum psychosis because these require a management strategy that is different from that for postpartum depression.
- Treatment for postpartum depression depends on the severity of symptoms and the level of functional impairment. Mild depression may be addressed with psychosocial strategies, including peer support and nondirective counseling, and psychological therapy is recommended for moderate depression; pharmacotherapy (generally a selective serotonin reuptake inhibitor [SSRI] as first-line treatment) is recommended for severe depression, for lack of response to nondrug therapy, or in accordance with patient preference.
- Most SSRIs pass into breast milk at a dose that is less than 10% of the maternal level and are generally considered to be compatible with breast-feeding of healthy, full-term infants.

years; approximately 40% of women will have a relapse either during subsequent pregnancies or on other occasions unrelated to pregnancy.<sup>13</sup> Postpartum depression results in maternal suffering and diminished functioning and is associated with increased risks of marital conflict and impaired infant–caregiver attachment, as well as increased risks of impaired emotional, social, and cognitive development in the child,<sup>14</sup> and in rare cases, suicide or infanticide.<sup>15,16</sup>

## STRATEGIES AND EVIDENCE

## SCREENING AND DIAGNOSIS

The best method for detecting postpartum depression remains controversial. Sensitive clinical inquiry about mood during postpartum visits facilitates case finding. Administration of the 10-item Edinburgh Postnatal Depression Scale (EPDS)<sup>17</sup> is recommended by both the American College of Obstetricians and Gynecologists<sup>18</sup> and the American Academy of Pediatrics<sup>19</sup> as a method of identifying possible postpartum depression. The U.S. Agency for Healthcare Research and Quality suggests that serial testing, beginning with the use of a sensitive, two-question screening tool relating to feelings of depression or hopelessness and of a lack of interest or pleasure in activities, followed by the use of a second, more specific instrument for women who give a positive answer to either screening question, may be a reasonable strategy to reduce both false positive and false negative results.<sup>20</sup> The United

Kingdom’s National Institute for Health and Care Excellence<sup>21</sup> recommends asking all women in the postpartum period these same two questions (Fig. 1), which show consistently high pooled sensitivity (0.95; 95% confidence interval [CI], 0.88 to 0.99) and modest pooled specificity (0.65; 95% CI, 0.56 to 0.74) across a range of scenarios; few women who answer “no” to both questions are depressed.<sup>23</sup> A positive response to either question can be followed by the use of either the EPDS<sup>17</sup> or the Patient Health Questionnaire 9 (PHQ-9)<sup>22</sup> (Fig. 1). Positive findings from screening questionnaires should lead to a comprehensive clinical interview to ascertain a diagnosis.<sup>21</sup>

The evaluation of women with possible postpartum depression requires careful history taking to ascertain the diagnosis, identify coexisting psychiatric disorders, and manage contributing medical and psychosocial issues. Approximately 70% of new mothers have mild depressive symptoms called “baby blues,” which peak between 2 and 5 days after delivery and typically include weepiness, sadness, mood lability, irritability, and anxiety. “Blues” do not seriously impair functioning or include psychotic symptoms; typically, these symptoms begin to abate spontaneously within 2 weeks, although some cases will progress to postpartum depression.<sup>24</sup> Distinguishing between postpartum blues and postpartum depression can be difficult, but assessment of mood and of severity of symptoms at multiple time points may facilitate making this distinction.

During the process of history taking, special attention should be given to a personal or family history of depression, postpartum psychosis, or bipolar disorder, especially if depression or bipolar disorder had been associated with pregnancy. Because depression may be a presenting feature of bipolar disorder, all women who are depressed should be asked whether they have ever had 4 or more continuous days during which they had abnormally high, expansive, or irritable mood and increased activity or had a level of energy that was a change from their usual level, that other persons thought was not characteristic of their normal self, or that got them into troublesome situations.<sup>24</sup> Positive responses require further evaluation because treatment with antidepressants alone may worsen bipolar disorder. Coexisting anxiety and obsessive–compulsive symptoms are common among women with postpartum depression and should be investigated further by involved clinicians.

Women should be asked about social support as well as substance abuse and violence involving an intimate partner. An examination to assess mental status should be conducted, as well as a physical examination if symptoms suggest a medical cause. Laboratory investigations should be performed as indicated; measurement of hemoglobin and thyroid-stimulating hormone levels are generally recommended. Women should be asked directly whether they have had any thoughts of harming themselves, their infants, or anyone else. A positive response should prompt emergency referral for psychiatric assessment and care to promote safety.<sup>21</sup> Women who are unable to care adequately for themselves or their infant should also be referred urgently.<sup>1,21</sup>

Postpartum psychosis, which can be related diagnostically to primary psychoses, manic episodes, or depressive episodes with psychotic features, typically begins within the first days or weeks after delivery and manifests as delusions, hallucinations, bizarre behavior, confusion, or disorganized thoughts, accompanied by depressed or elevated mood.<sup>24</sup> Postpartum psychosis has an estimated prevalence of 1 to 2 cases per 1,000 births and is often a manifestation of bipolar disorder. Postpartum psychosis represents a psychiatric emergency that usually requires hospitalization owing to its rapidly changing course and the danger of suicide or harm to the infant.<sup>1</sup>

**Table 1. Diagnostic Criteria for Major Depressive Episode.\***

**At least five symptoms present for at least 2 weeks, for most of nearly every day**

One symptom must include

Depressed mood

Markedly diminished interest or pleasure in all or most activities

Other symptoms

Clinically significant weight loss when not dieting or clinically significant weight gain, or increase or decrease in appetite

Insomnia or hypersomnia

Psychomotor agitation or retardation

Fatigue or loss of energy

Feelings of worthlessness or excessive or inappropriate guilt

Diminished ability to think or concentrate or indecisiveness

Recurrent thoughts of death or suicidal ideation (with or without a specific plan)

**Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of function**

**Symptoms not due to direct physiological effects of a substance or another medical condition, not better explained by schizoaffective disorder or other psychotic disorders, and there has never been a manic or hypomanic episode**

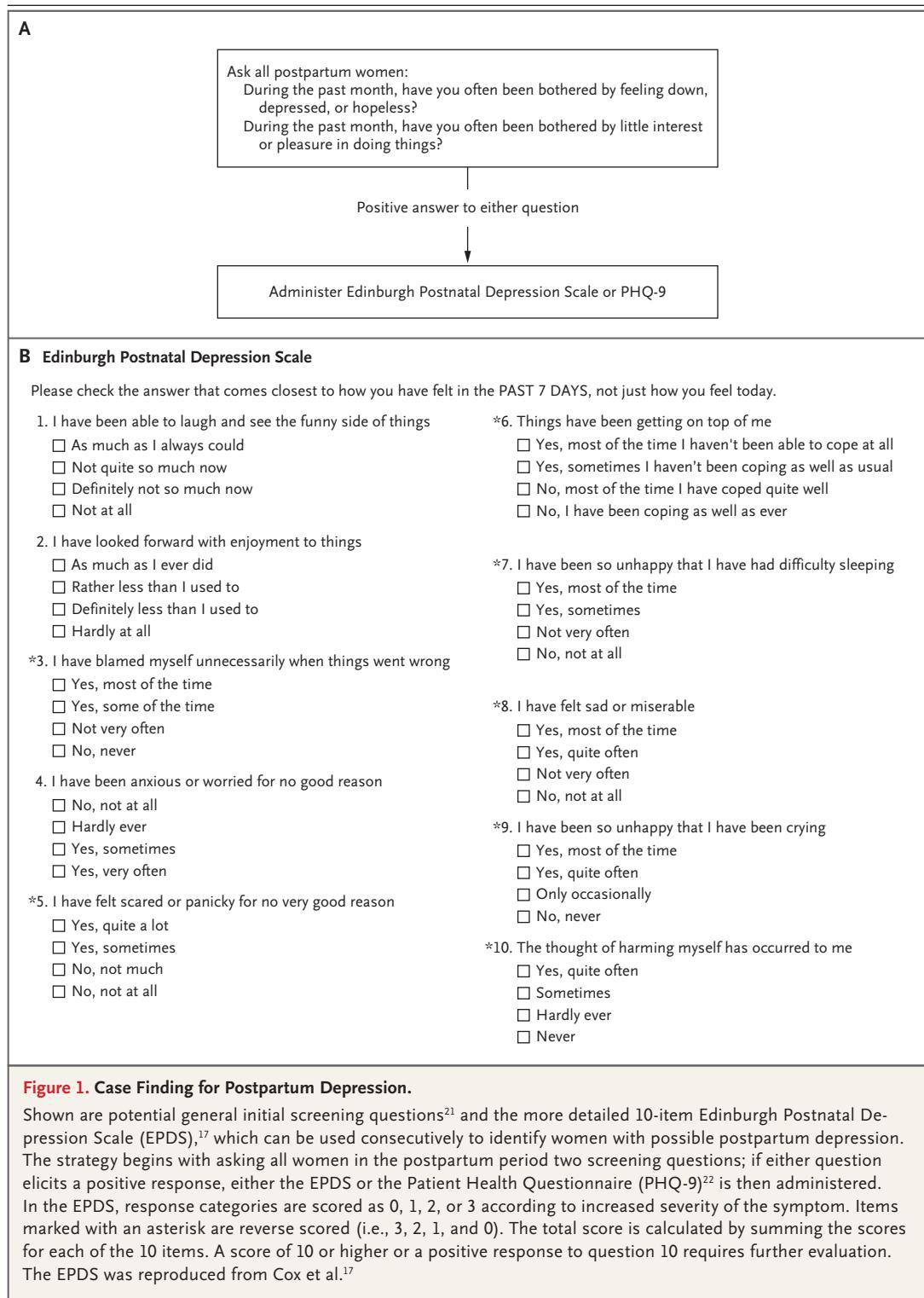
Specifier: With peripartum onset

This specifier can be applied to the current or, if full criteria are not currently met for a major depressive episode, the most recent episode of major depression if onset of mood symptoms occurs during pregnancy or in the 4 weeks following delivery.

\* This list of criteria is adapted from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition.<sup>2</sup>

#### PREVENTION

Women who have untreated depression during pregnancy have a risk of postpartum depression that is more than seven times that of women who have no antenatal symptoms of depression; therefore, treatment of antenatal depression is important for the prevention of postpartum depression.<sup>25</sup> In one small observational study involving 78 women who received a diagnosis of depression in the first trimester of pregnancy, postpartum depression developed in none of the women whose depression was treated with either psychotherapy or pharmacotherapy, as compared with 92% of the women with untreated depression.<sup>26</sup> Among women who had either symptoms of depression that fell below the threshold for the definition of postpartum depression or who had clinically significant risk factors for postpartum depression, a pooled analysis of 20 randomized trials showed that the use of supportive



and psychological care (e.g., home visits, telephone-based peer support, or interpersonal therapy) was associated with a lower risk of postpartum depression than that associated with standard care (e.g., information booklets, routine antenatal classes, and routine antenatal and post-

partum care by a primary care provider) (pooled rates of postpartum depression, 13.8% vs. 16.6%; pooled risk ratio, 0.78; 95% CI, 0.66 to 0.93).<sup>27</sup> These supportive and psychological interventions are more effective when delivered postnatally (pooled risk ratio from 12 trials, 0.73; 95% CI, 0.59 to 0.90) than when they are initiated during pregnancy (pooled risk ratio from 10 trials, 0.96; 95% CI, 0.75 to 1.22). Healthful nutrition, regular exercise, and adequate sleep are also recommended, although evidence for reducing the risk of postpartum depression on the basis of these factors is limited.

#### PSYCHOLOGICAL TREATMENT

Appropriate options for the treatment of postpartum depression vary according to the severity of the woman's symptoms and her functional status, including her ability to care for, and relate to, the newborn. Mild or moderate symptoms may be managed within the primary care setting, but psychiatric referral is warranted when symptoms do not respond to initial treatment and is indicated urgently in cases of severe illness, especially when thoughts of harm to self or others, mania, or psychosis are present.<sup>21</sup> Barriers to care for postpartum depression include shame, stigma, and practical problems such as finances, transportation, and child care, as well as limited specialty care.<sup>28</sup> Strategies that have been proposed to improve uptake of care include collocation of mental health services in primary care or obstetrical services, provider training, and collaborative care programs.<sup>29</sup>

For women with mild symptoms, psychosocial interventions that enhance support, such as peer support and nondirective counseling by trained health professionals (e.g., in support groups or by nurses in home visits), are considered to be first-line interventions.<sup>21</sup> A meta-analysis of five trials showed that women who were treated with psychosocial interventions were less likely to remain depressed at 1 year post partum than women who received standard postpartum primary care by a health visitor, public health nurse, or primary care practitioner (pooled rates of persistent depression, 32% vs. 46%; pooled risk ratio, 0.61; 95% CI, 0.39 to 0.94).<sup>30</sup>

For women with moderate illness, and for those with mild illness that does not respond to psychosocial interventions alone, formal psychotherapy that addresses the challenges of the

transition to parenthood is recommended. Most research focuses on time-limited, structured psychotherapies (i.e., cognitive behavioral therapy and interpersonal therapy) that can be delivered in either group or individual format over a period of 12 to 16 weeks. Cognitive behavioral therapy focuses on changing maladaptive thought patterns, behaviors, or both, to effect positive change in emotional state. Interpersonal therapy links mood to interpersonal relationships and life events and therefore focuses on improving interpersonal relationships to assist with the transition to parenthood. A systematic review of 5 trials that compared cognitive behavioral therapy with usual care and 1 trial that compared interpersonal therapy with usual care showed pooled remission rates of 60.3% for cognitive behavioral therapy or interpersonal therapy versus 48.1% for usual care (pooled risk ratio for persistent depression, 0.75; 95% CI, 0.63 to 0.88; effect sizes were similar for interpersonal therapy and cognitive behavioral therapy).<sup>30</sup> A systematic review of 11 trials that evaluated online psychosocial interventions included 7 small randomized trials that showed benefits for the treatment of postpartum depression that were similar to those of in-person care.<sup>31</sup>

#### DRUG THERAPIES

Antidepressant medication is recommended when symptoms of postpartum depression do not resolve with psychological treatment alone, when symptoms are severe and require rapid treatment, or when antidepressant medication is preferred by the patient.<sup>21</sup> A Cochrane systematic review of six trials that evaluated antidepressant use for postpartum depression included three randomized trials that compared depression response and remission rates among women assigned to receive selective serotonin reuptake inhibitors (SSRIs) with those among women assigned to a placebo group. Response rates (52.2% vs. 36.5%; pooled risk ratio, 1.43; 95% CI, 1.03 to 2.03) and remission rates (46.0% vs. 25.7%; pooled risk ratio, 1.79; 95% CI, 1.08 to 2.98) were higher in the SSRI group.<sup>32</sup> Trials of postpartum depression that compare the effect of a combination of drug therapy and psychotherapy with that of drug treatment alone are lacking. In non-postpartum populations, there is evidence of some benefit of combined therapy for functional outcomes.<sup>33</sup>

Most SSRIs pass into breast milk at a dose that is less than 10% of the maternal dose, and drugs in this class are generally considered to be compatible with breast-feeding of healthy, full-term infants (Table 2).<sup>34</sup> Although data on long-term child development are limited, in most cases breast-feeding need not be discouraged among women who are taking an antidepressant medication. However, clinicians should support women in the choice not to breast-feed when difficulties in the breast-feeding process or lack of sleep are perpetuating depressive symptoms. Despite some variability among SSRIs in terms of their passage into breast milk, switching the antidepressant medication because of lactation is not usually recommended for women who had previously been receiving effective treatment with a given agent, owing to the risk of a relapse of depression. In new-onset postpartum depression, sertraline is often recommended as first-line therapy because it passes minimally through breast milk.<sup>34</sup> Since more than 50 cases have been reported in which women who were breast-feeding were taking fluoxetine or citalopram with minimal evident adverse effects for the neonate, these medications would also be considered first-line choices. Serotonin norepinephrine reuptake inhibitors (SNRIs) or mirtazapine are commonly used either when SSRIs are ineffective or when a woman has previously had a positive response to these agents since available data also suggest minimal passage into breast milk. Data on safety for these agents remain limited,<sup>34,40</sup> however, since fewer than 50 cases have been reported in which women who were breast-feeding were taking either SNRIs or mirtazapine (Table 2).<sup>35</sup> Because of case reports of infant seizure with bupropion, other antidepressant medications (such as those referenced above) are preferred when possible.<sup>42</sup> Newer antidepressants for which safety data during lactation are not available should be used only when other medications are either unavailable or ineffective. Monoamine oxidase inhibitors are rarely used given their potential adverse effects; their safety with respect to breast-feeding is also unknown.<sup>42</sup> Tricyclic agents are generally avoided during lactation given their potential passage into breast milk (unlike the preferred agents noted above), as well as other concerns (e.g., cardiac risk); in addition, case reports of infant respiratory depression, poor sucking, hypotonia, and vomiting have been reported

with doxepin.<sup>43</sup> Although data to guide the duration of treatment for postpartum depression are lacking, it is generally recommended that to reduce the risk of relapse, antidepressant medications be continued for 6 months to 1 year, then reduced gradually and discontinued after symptoms have abated during a first episode of depression.<sup>44</sup> For women who have recurrent episodes of depression, a longer duration of treatment is probably required.<sup>44</sup>

In cases of severe depression, additional drug therapy may be indicated. Benzodiazepine agents may be used temporarily for severe anxiety, insomnia, or both until the antidepressant medication takes effect. Adjunctive antipsychotic agents may be required for women who have depression with psychotic features. Hospitalization, a somatic intervention such as electroconvulsive therapy, or both may be required for severe cases that are unresponsive to drug therapy or when active suicidal intent or psychosis is present.<sup>1,21</sup>

#### OTHER POSSIBLE TREATMENTS

Because fluctuation in hormone levels is thought to trigger postpartum depression in some women, hormonal interventions have been studied in prevention and treatment. The results of one small trial suggested that transdermal estrogen therapy may reduce symptoms of postpartum depression,<sup>45</sup> but further study is needed. In another trial, a synthetic progestin increased the risk of postpartum depression.<sup>45</sup> A small randomized trial involving 14 patients with postpartum depression who underwent repetitive transcranial magnetic stimulation, a focal brain-stimulation treatment, showed greater reductions in depressive symptoms with transcranial magnetic stimulation than with a sham procedure,<sup>46</sup> but this finding requires confirmation from other trials. Complementary and alternative-medicine treatment options, such as omega-3 fatty acids, folate, S-adenosylmethionine, St. John's wort, bright-light therapy, exercise, massage, and acupuncture, have been used, but little rigorous evidence exists regarding their efficacy.<sup>47</sup>

#### AREAS OF UNCERTAINTY

More data are needed with regard to genetic factors in postpartum depression, and an international genetics consortium on postpartum depression is collecting such data.<sup>48</sup> Uncertainty

**Table 2. Available Data for Antidepressant Drug Safety in Lactation.\***

Drug	No. of Trials/ Total No. of Patients	Infant Age Range	Dose Range	Range of Relative Infant Dose	Range of Milk-to- Plasma Ratio	Range of Plasma Level of Drug in Infants	Range of Steady- State Plasma Level in Adults <sup>36</sup>	Adverse Events <sup>†</sup>
		wk	mg	%		ng/ml	mg/ml	
Selective serotonin reuptake inhibitor (SSRI)								
Sertraline	16/269	0–141	25–200	0.5–3.0	0.42–4.8	ND–87	20–200	None reported
Citalopram	7/98	0–42	10–60	0.2–5.2	0.9–4.3	ND–2.1	40–300	Colic and decreased feeding (2 patients); irritability, restlessness, or both (1 patient); “transient neurodevelopmental delay” (resolved) (1 patient)
Escitalopram	3/31	3–32	10–20	4.5–5.3	1.6–2.7	ND	3.75–75 <sup>37</sup>	None reported
Fluoxetine	13/228	0–52	10–60	0.54–6.5	0.01–3.9	ND–84	90–300	Decreased postnatal growth (5 patients); colic (2 patients)
Fluoxamine	4/9	0–94	25–300	0.2‡	1.0–1.2	ND	20–500	None reported
Paroxetine	11/186	0–156	5–50	0.7–2.9	0.06–1.3	ND–188	10–600	Hypotonia, lethargy, and poor weight gain (1 patient); irritability (1 patient)
Serotonin norepinephrine reuptake inhibitor (SNRI)								
Venlafaxine	2/23	8–41	75–300	3.2–5.2	2.4–2.5	ND–49	1–145 <sup>38</sup>	None reported
Duloxetine§	1/6	0–12	40	0.14	0.25	NA	30–182 <sup>39</sup>	None reported
Other antidepressants								
Mirtazapine	2/9	6–56	22.5–120	1.5–4.4	1.1¶	ND–1.9 <sup>40</sup>	5–100 <sup>41</sup>	None reported

\* Data are from Orsolini and Bellantuono.<sup>34</sup> Data from case reports and trials that were confounded by patient exposure to other psychotropic drugs were excluded from this summary because of the potential for bias. In instances where fewer than 50 cases have been reported in the literature, the recommendation according to the Breastfed Infant Antidepressant Safety Index is that safety should continue to be considered unknown.<sup>35</sup> NA denotes not available, and ND nondetectable.

† None of these trials included comparison groups; therefore, it is unclear whether reported events were caused by exposure to study medication.

‡ Relative infant dose was measured in only one of the four prospective cohort trials included in this analysis, so only one point estimate is given (no range).

§ Because only one dose level was evaluated in this trial, only one value is included for all ranges except for that of the plasma level at steady state in adults.

¶ Because case reports were not included, data from only one trial were available, and only the mean relative infant dose was reported in that trial.

|| This value is expressed in micrograms per milliliter rather than nanograms per milliliter.

remains about the benefits and harms of universal screening for postpartum depression as compared with a targeted case-finding approach.<sup>20</sup> More data are needed regarding the passage of various antidepressants into breast milk including any potential adverse effects, although information that is currently available with respect to commonly used agents is reassuring.<sup>34</sup> The long-term outcomes for children and families with various treatment strategies for postpartum depression require further study.<sup>14</sup> Treatment of the mother's depression alone may not be sufficient to improve the mother–infant relationship; further study is needed to determine whether mother–infant dyadic, couple, and family therapies are more effective.

#### GUIDELINES

Recommendations in this article are generally consistent with those of existing guidelines, including those from the National Institute for Health and Care Excellence in the United Kingdom (2014),<sup>21</sup> the Guidelines Expert Advisory Committee of the National Health and Medical Research Council in Australia (2011),<sup>49</sup> the Scottish Intercollegiate Guidelines Network in Scotland (2012),<sup>50</sup> the Canadian Network for Mood and Anxiety Treatments (2016),<sup>44</sup> and the American Psychiatric Association (in the section addressing perinatal depression) (2010).<sup>51</sup>

#### CONCLUSIONS AND RECOMMENDATIONS

Untreated postpartum depression affects the health of the woman, infant, and family. Pregnant women should receive information about the signs and symptoms of postpartum depression and its effects. Perinatal care providers should inquire about mood and anxiety during all visits and can use the brief screening tools

described in Figure 1. If postpartum depression is diagnosed, patients should be informed about all treatment options. Management depends on the patient's medical history, the severity of the symptoms, the effects on functioning, the woman's preferences, available expertise, and resources.

The woman described in the vignette has a history of untreated depression and meets the DSM-5 diagnostic criteria for major depression with peripartum onset. She is not suicidal or psychotic and has symptoms of moderate severity. We would take a careful history to assess past psychiatric symptoms, social support, her relationship with any intimate partner, and other life stressors, and we would check her hemoglobin level and thyroid function. She should be offered peer support but also formal psychotherapy (interpersonal therapy or cognitive behavioral therapy) individually, in a group format, or online, since these are effective treatments for moderately severe depression. If this approach is unsuccessful or if she prefers pharmacotherapy, an antidepressant that is considered to be compatible with breast-feeding should be prescribed. We would generally favor sertraline, especially given the availability of reassuring data regarding its safety during lactation; we would typically initiate treatment at a dose of 50 mg daily, reassess at 1 week for side effects and suicidality, and then increase the dose as needed (e.g., by 50 mg every 2 weeks; maximum daily dose, 200 mg) until complete remission is achieved. Pharmacotherapy is generally continued for at least 6 to 12 months after complete remission to reduce the risk of relapse. The patient should be advised to seek care if symptoms of depression recur.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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