Severe postpartum unipolar major depression: Choosing treatment

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INTRODUCTION

Although delivering a baby is typically a happy event, some postpartum women become depressed. Patients may manifest postpartum blues consisting of mild mood lability symptoms that are self-limited, or more severe syndromes such as unipolar major depression. Postpartum major depression is a toxic exposure for the infant that can result in short- and long-term negative consequences for the infant and family, and thus requires treatment [1-4].

This topic reviews choosing a specific treatment for severe postpartum unipolar major depression. Other topics discuss treatment of mild to moderate episodes of postpartum unipolar major depression, the clinical features and diagnosis of postpartum major depression, safety of infant exposure to psychotropic drugs through breastfeeding, the postpartum blues, and the diagnosis and treatment of antepartum unipolar major depression and postpartum bipolar mood episodes.

- (See "Mild to moderate postpartum unipolar major depression: Treatment".)
- (See "Postpartum unipolar major depression: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding".)
- (See "Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders".)

- (See "Postpartum blues".)
- (See "Unipolar major depression during pregnancy: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Mild to moderate episodes of antenatal unipolar major depression: Choosing treatment".)
- (See "Severe antenatal unipolar major depression: Choosing treatment".)
- (See "Bipolar disorder in postpartum women: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Bipolar disorder in postpartum women: Treatment".)

DEFINITIONS

Postpartum period and disorders

- **Postpartum period** – We define the postpartum period as the first 12 months after birth. Definitions of the puerperium range from the first 1 to 12 months following a live birth. (See "Postpartum unipolar major depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Definition of postpartum period'.)

- **Postpartum blues** – During the puerperium, mild, transient depressive symptoms such as dysphoria, insomnia, emotional lability, and decreased concentration occur in many women. (See "Postpartum blues".)

- **Postpartum unipolar major depression** – The diagnostic criteria for postpartum unipolar major depression are the same as those used to diagnose nonpuerperal major depression (table 1). (See "Postpartum unipolar major depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Diagnosis' and "Unipolar depression in adults: Assessment and diagnosis", section on 'Unipolar major depression'.)

Severity of illness — Factors involved in choosing a treatment for postpartum unipolar major depression include the severity of illness:

- **Mild to moderate** – Mild to moderate episodes of major depression are generally characterized by five or six depressive symptoms (table 1), as indicated by a score <20 points on the Patient Health Questionnaire – Nine Item (PHQ-9) (table 2). Alternatively, a study of patients with postpartum unipolar major depression (n >4000) empirically defined relatively mild episodes as an average score of 11 on the Edinburgh Postnatal Depression Scale (figure 1A-B), and moderate episodes as an average score of 15 [5]. The PHQ-9 and the Edinburgh Postnatal Depression Scale are discussed separately. (See "Using scales

to monitor symptoms and treat depression (measurement based care)", section on 'Patient Health Questionnaire - Nine Item' and "Postpartum unipolar major depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Screening'.)

Patients with mild to moderate illness generally do not manifest suicidal behavior or obvious impairment of functioning and are less likely to develop complications such as psychotic and catatonic features. Mild to moderate depression can typically be managed in outpatient or partial (day) hospital settings.

- **Severe** – Severe major depression is characterized by seven to nine depressive symptoms (table 1) that occur nearly every day, as indicated by a score ≥20 points on the self-report PHQ-9 (table 2). Alternatively, a study of patients with postpartum unipolar major depression (n >4000) empirically defined relatively severe episodes as an average score of 20 on the Edinburgh Postnatal Depression Scale (figure 1A-B) [5].

  Severely ill patients often report suicidal ideation and behavior, typically demonstrate obvious impairment of functioning, and often manifest poor judgement that places the patient and others (including children) at risk for imminent harm. In addition, patients are more likely to develop complications such as psychotic and catatonic features and have a history of severe or recurrent episodes. Patients with severe major depression should be referred to a psychiatrist for management and often require hospitalization [6,7]. Treating major depression with psychotic features or catatonia is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment" and "Catatonia: Treatment and prognosis".)

Difficulties may arise in determining the number of depressive symptoms present during the puerperium because changes in appetite, energy, and sleep may be due to either depression or normal postnatal-related changes. The presence of these somatic symptoms should be evaluated in the context of normal expectations for the postpartum period. As an example, postpartum patients frequently lack energy due to sleep deprivation and caring for an infant. However, lack of energy to the point that patients need to make a significant effort to initiate or maintain usual daily activities can be a mild to moderate depressive symptom, and anergia to the point that patients cannot get out of bed for hours is probably a symptom of severe depression. Persistent uncertainty as to whether an episode of major depression is mild to moderate or severe can be resolved by referral to a psychiatrist (preferably one specializing in perinatal disorders).

GENERAL PRINCIPLES

The general principles and issues that are involved in treating postpartum unipolar major depression include:

- Setting (eg, outpatient or inpatient)
- History of prior treatment
- Educating patients and families
- Adherence to treatment
- Monitoring symptoms
- Prescribing antidepressants
- Managing nonresponse
- Making referrals

These general principles are discussed in detail separately. (See "Postpartum unipolar major depression: General principles of treatment".)

CHOOSING TREATMENT FOR BREASTFEEDING PATIENTS

Overview — Many women with severe postpartum depression are likely to breastfeed their infants. One review estimated that among all women who deliver, breastfeeding is initiated by approximately 80 percent [8].

For patients with severe, postpartum unipolar major depression who are breastfeeding, acute treatment depends upon the patient's clinical history and treatment preferences, as well as the availability of specific treatments. The primary treatments include antidepressant medications such as selective serotonin reuptake inhibitors (SSRIs) and the more recently developed antidepressant brexanolone, as well as electroconvulsive therapy (ECT) [9-11]. In addition, psychotherapy is nearly always indicated as an adjuvant to pharmacotherapy, unless symptoms render the patient incapable of participating. An overview of choosing treatment is presented in the algorithm (algorithm 1).

Continuation treatment is generally indicated for patients who respond to acute treatment of unipolar major depression, and additional maintenance treatment is indicated for patients with an increased risk of recurrence. (See "Unipolar depression in adults: Continuation and maintenance treatment".)

Patients who prioritize rapid improvement — For patients with severe unipolar major depression who are breastfeeding and prioritize relatively rapid improvement over other aspects of treatment, we suggest the antidepressant brexanolone. If the drug is not available, affordable, or effective, or is declined, we suggest ECT.

- **Brexanolone** – Brexanolone, a neuroactive steroid, is a synthetic preparation of the progesterone metabolite allopregnanolone [11,12]. In 2019, intravenous brexanolone was the first antidepressant approved by the US Food and Drug Administration (FDA) specifically for treating postpartum depression [10,13,14].

  - Administration – In the United States, brexanolone is dispensed only to certified health care facilities and patients who enroll in a Risk Evaluation and Mitigation Strategy program [13-15]. The program requires on site clinicians to monitor patients for excessive sedation and sudden loss of consciousness during the intravenous infusion, and requires continuous pulse oximetry to monitor for hypoxia.

    Brexanolone is administered continuously as a single intravenous infusion for 60 hours in an inpatient facility [14]. The dosing schedule is as follows:

    - 0 to 4 hours – 30 mcg/kg/hour
    - 4 to 24 hours – 60 mcg/kg/hour
    - 24 to 52 hours – 90 mcg/kg/hour (however, 60 mcg/kg/hour is a reasonable alternative for patients who cannot tolerate the higher dose)
    - 52 to 56 hours – 60 mcg/kg/hour
    - 56 to 60 hours – 30 mcg/kg/hour

    Infusions should be immediately terminated in patients who develop excessive sedation or sudden loss of consciousness [14]. After the drug is stopped, clinicians can expect the adverse effect to remit within 15 to 60 minutes. Following resolution of the sedation/loss of consciousness, brexanolone can be resumed at the same or a lower dose.

    In addition, clinicians should immediately stop the infusion if pulse oximetry indicates that the patient is hypoxic [14]. After hypoxia resolves, the infusion should **not** be resumed.

    Additional information about administering brexanolone is available through the prescribing information approved by United States [14].

  - Efficacy – Randomized trials, in which a minority of patients received concomitant antidepressants, demonstrate that infusion of brexanolone for 60 hours can provide a rapid, beneficial response for moderate to severe postpartum unipolar major

depression. Separate pooled analyses of the same three trials compared brexanolone with placebo in a total of 209 patients [16,17]. Study drugs were administered as a single, continuous intravenous infusion in a medically monitored setting for 60 hours, during which brexanolone was titrated up to either 60 or 90 mcg/kg/hour. The primary findings included the following:

- Remission at 60 hours occurred in more women with brexanolone than placebo (50 versus 26 percent). In addition, remission 30 days after the trial remained greater with brexanolone than placebo (32 versus 16 percent).
- Response (reduction of baseline symptoms ≥50 percent) was superior with brexanolone than placebo, and the median time to onset of response was faster with active drug (24 versus 36 hours).
- Improvement of anxiety and insomnia was greater with brexanolone.

- Adverse effects – Brexanolone is usually well-tolerated. In a pooled analysis of three randomized trials that compared brexanolone with placebo (total n = 209 patients), discontinuation of treatment due to an adverse effect was similar (2 and 1 percent) [17]. In addition, results from two randomized trials (total n = 140 patients) showed that interruption of or dose reduction due to an adverse effect of brexanolone or placebo occurred in 7 and 3 percent [14].

  The incidence of the following adverse effects in patients treated with brexanolone was at least 5 percent and at least two times greater than the rate with placebo [14]:

  - Dry mouth
  - Flushing/hot flash
  - Loss of consciousness
  - Sedation/somnolence

  Sedation/somnolence may occur more frequently in patients treated with brexanolone plus antidepressants, compared with patients who receive brexanolone monotherapy [14,18]. Patients who interact with their children during the infusion with brexanolone must be accompanied, due to the risk of sedation/somnolence and loss of consciousness [14].

- Breastfeeding – For patients who are breastfeeding, we suggest that they temporarily cease nursing during treatment with brexanolone and wait until four days have elapsed before they resume breastfeeding; these were the procedures followed in the

two largest randomized trials that were conducted [19]. However, it is reasonable to continue breastfeeding during the brexanolone infusion based upon patient preferences; in this case, we suggest that a second caregiver be present.

Based upon low-quality evidence, it appears that brexanolone quickly disappears from breast milk [15]. In one small study, the drug was administered intravenously to healthy women for 60 hours according to the recommended dosing schedule, with a maximum dose of 90 mcg/kg/hour [14]. Thirty-six hours after the infusion was completed, the concentration of brexanolone in breast milk was low. In addition, the drug has low bioavailability, and it is thus expected that infant exposure would be low.

- **Electroconvulsive therapy** – ECT is particularly useful when rapidly effective treatment is imperative; specific indications include psychotic depression, plans and intent to commit suicide or infanticide, and fluid and food refusal leading to dehydration and malnutrition [20-22].

  There are few studies in breastfeeding mothers who were exposed to ECT anesthetic drugs, such as glycopyrrolate, methohexital, propofol, and succinylcholine [23]. Nevertheless, the risk of these drugs passing into breast milk appears low; after each ECT treatment, breastfeeding can be resumed when the patient recovers from anesthesia. Using ECT in patients who are breastfeeding is consistent with multiple practice guidelines, including those from the United Kingdom National Institute for Health and Care Excellence and the Canadian Network for Mood and Anxiety Treatments [23-27].

  Evidence supporting the use of ECT for severe postpartum major depression includes randomized trials that excluded lactating patients [20]. (See "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)", section on 'Acute ECT'.)

  In addition, observational studies suggest that ECT is beneficial for postpartum major depression, and is a safe option for breastfeeding mothers because there appear to be few if any adverse effects upon lactation [23,28], as well as few adverse effects for either the mother or infant [29]:

  - In one review of retrospective studies (total n = 87 postpartum patients), the authors concluded that ECT was effective and well tolerated [30].
  - A subsequent retrospective study used a national registry to identify patients with postpartum depression (n = 99) who were treated with ECT, and found that response occurred in 81 percent [31].

Further information about rapid responses with ECT in the general population of patients with unipolar major depression, including those with suicidality, is discussed separately. (See "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)".)

In addition, general information about ECT is discussed separately. (See "Overview of electroconvulsive therapy (ECT) for adults" and "Medical evaluation for electroconvulsive therapy" and "Technique for performing electroconvulsive therapy (ECT) in adults".)

Patients who respond to either brexanolone or ECT require continuation and maintenance treatment with an antidepressant. We typically use an SSRI, but it is reasonable to use other an antidepressant from a different class. (See 'Initial treatment' below.)

Detailed information about continuation and maintenance treatment for the general population of patients with unipolar depression is discussed separately. (See "Unipolar depression in adults: Continuation and maintenance treatment".)

For patients who do respond to brexanolone and ECT, we suggest an antidepressant. (See 'Initial treatment' below.)

Patients with no history of treatment for depression — Patients may present with severe, postpartum unipolar major depression and have no prior history of treatment for either perinatal (antenatal or postnatal) or nonperinatal depression. For those patients who are breastfeeding, acute treatment proceeds according to the sequence described in the subsections below. Patients receive initial treatment, and if they do not respond, progress to the next step. The primary treatments are antidepressant medications [9].

Initial treatment — For patients who present with severe, postpartum unipolar major depression and are breastfeeding, we suggest initial treatment with antidepressant medications [8,20,22]. Multiple randomized trials indicate that antidepressants are efficacious for postpartum depression [32]. In addition, the potential risks of most antidepressants to the infant are typically regarded as low, and there is a general consensus that the benefits of antidepressants outweigh the risks [9,20,33]. Antidepressants are more available than structured, evidence-based psychotherapy, and using antidepressants is consistent with multiple practice guidelines, including the United Kingdom National Institute for Health and Care Excellence and the Canadian Network for Mood and Anxiety Treatments [6,7,23-26,34,35]. The potential risks of antidepressants to breastfeeding infants are discussed separately. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding".)

For patients with severe major depression who are breastfeeding and have not been treated with antidepressants in the past, we suggest initial treatment with SSRIs because of their efficacy and tolerability for postpartum depression [8,20,22,33,36,37]. SSRIs have been used and more widely studied in breastfeeding patients than other antidepressant classes; as an example, a retrospective study of women (n = 459) who were treated for postpartum depression with antidepressants found that SSRIs were used in 90 percent [38]. Each specific SSRI can be used because the safety record for the class appears to be benign. Nevertheless, reasonable alternatives to SSRIs include serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and nortriptyline.

- **Discussing the risks** – Postpartum patients with severe major depression who are breastfeeding need to understand and weigh various risks when deciding whether to use an antidepressant [3,9,24,25,39,40]:

  - Untreated depression poses risks to the mother and infant, such as nonadherence with postnatal care, poor self-care, neglect of the infant (and other children), disrupted maternal-infant bonding, family dysfunction, child abuse, and suicidal behavior. Also, complications of depression may ensue, including psychotic features, catatonia, and comorbid substance use disorders. (See "Postpartum unipolar major depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Adverse consequences'.)

    In addition, postnatal depression is associated with:

    - Abnormal child development (see "Postpartum depression: Adverse consequences in mothers and their children", section on 'Adverse consequences for the offspring')

    - Cognitive impairment and psychopathology in the children (see "Postpartum depression: Adverse consequences in mothers and their children")

  - Maternal use of antidepressants may perhaps pose risks to breastfeeding infants. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding".)

  - Antidepressants carry the risk of maternal side effects (table 3). As an example, antidepressant-induced sedation can interfere with the mother's ability to care for her baby.

The discussion of these risks should emphasize that the benefits and harms of treatment are uncertain [24].

- **Evidence of efficacy** – Indirect evidence supporting the use of antidepressants for severe, postpartum unipolar major depression includes numerous randomized trials that demonstrated multiple antidepressants (eg, SSRIs, SNRIs, and mirtazapine) can help the general population of patients with major depression, including severe episodes. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants' and "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar major depression in adults: Choosing initial treatment", section on 'Severe major depression'.)

  Evidence supporting the efficacy of SSRIs for severe, postpartum unipolar major depression includes randomized trials [32]:

  - A meta-analysis of three trials lasting six or eight weeks compared paroxetine (10 to 40 mg/day) or sertraline (50 to 200 mg/day) with placebo in 146 patients with postpartum unipolar major depression, some of whom were breastfeeding [41,42]. Remission occurred in more patients who were treated with SSRIs than placebo (relative risk 1.8, 95% CI 1.1-3.0), and in each of the studies, the incidence of adverse effects was comparable for active drug and placebo. However, the patients generally had mild to moderate depression, sample sizes were small, and attrition was high [3].

  - A four-week trial compared antidepressants (primarily SSRIs) with usual care (nondirective counseling) in 254 patients with postpartum unipolar major depression (n = 254) [43]. More than 40 percent of the patients were breastfeeding their infants. Improvement (Edinburgh Postnatal Depression Scale (figure 1A-B) score <13) occurred in more patients who received antidepressants than usual care (45 versus 20 percent).

  Few head-to-head randomized trials have compared different antidepressants for treating postpartum depression. A 16-week trial (n = 109 patients, including 29 who breastfed) compared sertraline (50 to 200 mg/day) with nortriptyline (25 to 150 mg/day) and found that improvement was comparable [44,45].

Treatment-resistant patients — Patients with severe postpartum unipolar major depression often do not respond to initial treatment with an antidepressant [28]. As an example, a pooled analysis of three randomized trials found that among patients (n = 72) who were treated with SSRIs, response occurred in only 54 percent [41,42].

For lactating women who are resistant to initial treatment and show minimal response (eg, improvement <25 percent), we suggest switching antidepressants rather than augmentation with a second drug [20,22]. Options include switching to another SSRI, an SNRI (eg, desvenlafaxine, duloxetine, or venlafaxine), the atypical antidepressant mirtazapine, or the tricyclic nortriptyline [37]. The specific choice depends upon prior treatment history, side effects, and patient preference. Choosing next-step treatment and the process of switching antidepressants are discussed separately in the context of the general treatment of resistant depression. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Next step treatment'.)

For patients who are switching to another antidepressant, some drugs (eg, bupropion and doxepin) are typically avoided due to concerns about their safety in breastfeeding infants [20,22]. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Antidepressants'.)

For lactating women with a partial response (eg, reduction of baseline symptoms by 25 to 49 percent) to initial treatment, we add a second drug that is compatible with breastfeeding, rather than switch antidepressants [22,33]. Options for add-on pharmacotherapy include second-generation antipsychotics (eg, aripiprazole, risperidone, or olanzapine), lithium, and triiodothyronine. A small retrospective study found that among postpartum patients treated with antidepressants (n = 26), medication combinations were required for 60 percent [46]. The safety of these add-on psychotropic drugs in breastfeeding infants is discussed separately. (See "Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders".)

Severe postpartum unipolar major depression may not respond to initial and next-step treatment with antidepressants such as an SSRI, an SNRI, mirtazapine, or nortriptyline. For these patients, we suggest either brexanolone or ECT. (See 'Patients who prioritize rapid improvement' above.)

Patients treated with antidepressants during pregnancy — Antenatal unipolar major depression may remit with an antidepressant that is discontinued prior to delivery. For those patients who subsequently develop postpartum unipolar major depression and are breastfeeding, we suggest resuming the same antidepressant, even if there are better lactation safety data for other medications, because using a different antidepressant increases the number of drug exposures [3,20,22,47,48]. In addition, exposure to antidepressants that has already occurred in utero is substantially greater than exposure through breast milk. The safety of using antidepressants during breastfeeding is discussed separately. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding".)

However, patients with severe postpartum unipolar major depression may not respond to the same antidepressant that successfully treated the antenatal depressive episode. For these patients, we suggest further pharmacotherapy trials. (See 'Treatment-resistant patients' above.)

Patients treated with pharmacotherapy prior to the pregnancy — Patients who present with severe, postpartum unipolar major depression may have a history of a depressive episode that occurred prior to the pregnancy and was successfully treated with pharmacotherapy. For these patients, we suggest resuming the same regimen, provided it is compatible with breastfeeding [3,23,24,33,47]. This includes medication regimens that consisted of an antidepressant plus add-on treatment with a second-generation antipsychotic, lithium, or triiodothyronine. The safety of using psychotropic medications during breastfeeding is discussed separately. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding" and "Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders".)

Patients with severe postpartum unipolar major depression may not respond to the same pharmacotherapy regimen that successfully treated the prior depressive episode. For these patients, we suggest further pharmacotherapy trials. (See 'Treatment-resistant patients' above.)

Grossly impaired functioning — Severe, postpartum unipolar major depression may grossly impair one's functioning. Examples include patients who are bed bound, manifest poor hygiene, are not drinking and eating, and/or not interacting with the baby or other family members. For these patients, clinicians should utilize treatments that can provide relatively fast relief. (See 'Patients who prioritize rapid improvement' above.)

Psychotic depression — Treatment of unipolar psychotic major depression in breastfeeding patients is similar to treatment of nonpostpartum patients. Psychotic depression is generally treated with an antidepressant plus an antipsychotic; however, ECT is a reasonable first-line option given its relatively rapid onset of action [20,22,24,26,49]. The choice between pharmacotherapy and ECT depends upon several factors that are discussed separately, as is the administration of treatment and evidence of efficacy. (See "Unipolar major depression with psychotic features: Acute treatment", section on 'First line'.)

The safety of infant exposure to antipsychotics through breast milk is also discussed separately. (See "Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders", section on 'Antipsychotics'.)

Information about ECT for patients with postpartum unipolar major depression who are breastfeeding is discussed above. (See 'Patients who prioritize rapid improvement' above.)

Anxiety or insomnia — For breastfeeding patients with postpartum major depression that includes significant anxiety or insomnia, monotherapy with an antidepressant medication is usually preferred over the combination of an antidepressant and a benzodiazepine [24]. In particular, the antidepressant brexanolone has demonstrated efficacy for anxiety and insomnia in randomized trials that compared brexanolone with placebo [16]. (See 'Patients who prioritize rapid improvement' above.)

Nevertheless, for patients with severe anxiety or insomnia, we often prescribe an antidepressant plus a benzodiazepine at initiation of treatment [20,22]. In addition, adjunctive benzodiazepines can help with intractable anxiety or insomnia. Caution in using benzodiazepines is warranted in patients with a history of substance-related and addictive disorders [50]. In addition, benzodiazepines may result in falls and cognitive impairment.

Benzodiazepines that are added at the beginning of pharmacotherapy are prescribed at standard doses. The benzodiazepine is intended to be used for a relatively short period (eg, two weeks), and then gradually discontinued once the antidepressant begins to take effect [50,51]. However, longer use of benzodiazepines may be necessary to achieve remission of anxiety and/or insomnia. The efficacy and use of adjunctive benzodiazepines for the general treatment of anxious depression are discussed separately. (See "Unipolar depression in adults: Treatment with anxiolytics", section on 'Benzodiazepines'.)

Clonazepam and lorazepam are generally preferred for anxious depression; benzodiazepines with shorter half-lives (eg, alprazolam) can also be helpful, but long-term use (eg, four weeks) may result in maternal rebound anxiety. Lorazepam is often preferred over clonazepam because lorazepam has a shorter half-life [50].

The safety of infant exposure to benzodiazepines through breast milk is discussed separately. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Benzodiazepines'.)

Agitation — Severe unipolar major depression may include episodes of agitation, which is defined as nonproductive, excess motor activity in conjunction with inner tension [52,53]. The initial assessment of agitation in patients with a known diagnosis of unipolar major depression should focus upon determining whether the agitation is due to causes beyond depression, such as a general medical disorder, or intoxication or withdrawal from substances such as alcohol, cocaine, or methamphetamines [54]. In addition, clinicians should assess safety, including risk for suicide, and develop a treatment plan.

Hospitalized postnatal patients with severe major depression who are acutely agitated often require oral, inhaled, or intramuscular medications to manage threatening or aggressive

behavior, and may also require seclusion from other patients and physical restraints [23]. Patients placed in seclusion should be constantly observed by clinical staff. In addition, the patient should be kept hydrated and vital signs should be regularly monitored.

The goal of pharmacologic tranquilization is to rapidly eliminate the need for seclusion and restraints, and to prevent or reduce self-harm and harm to others. We suggest a second-generation antipsychotic, such as aripiprazole or olanzapine; however, first-generation antipsychotics, such as haloperidol, are reasonable alternatives. Doses are shown in a table (table 4). Another alternative for managing acute behavioral disturbances is a benzodiazepine such as lorazepam, using a dose of 0.5 to 2 mg. Intramuscular medications are typically administered in the gluteal muscle or lateral thigh. Oral rapidly dissolving formulations and short-acting intramuscular formulations generally have a calming effect within minutes.

Adjunctive psychotherapy — Patients receiving pharmacotherapy for postpartum unipolar major depression typically receive psychotherapy as an adjuvant if they are not too ill to participate in therapy. Most patients prefer combination therapy; a study of women with perinatal unipolar major depression (n = 100, including 73 postpartum patients) found that pharmacotherapy plus psychotherapy was preferred by 55 percent, whereas medication monotherapy was preferred by only 8 percent [55].

Indirect evidence supporting the use of add-on psychotherapy includes numerous, relatively large, randomized trials that excluded breastfeeding patients; these trials found that combination therapy is more efficacious than pharmacotherapy alone. Although several randomized trials in patients with postnatal depression have failed to show that combination therapy is superior to monotherapy, each study was small and underpowered, and many of the patients had mild to moderate episodes of major depression, rather than severe depression [56-59]. The efficacy of antidepressants plus psychotherapy for treating the general population of patients with severe unipolar major depression is discussed separately. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants plus psychotherapy'.)

SELECTING TREATMENT FOR PATIENTS NOT BREASTFEEDING

For patients with severe, postpartum unipolar major depression who are not breastfeeding and prioritize relatively rapid improvement over other aspects of treatment, we suggest the antidepressant brexanolone. (See 'Patients who prioritize rapid improvement' above.)

If the drug is not available, affordable, or effective, or is declined, treatment is similar to treatment in the general population of patients with severe depression. (See "Unipolar depression in adults: Choosing treatment for resistant depression" and "Unipolar major depression in adults: Choosing initial treatment", section on 'Severe major depression' and "Unipolar major depression in adults: Choosing initial treatment".)

TREATMENT THAT IS APPROVED BUT NOT YET AVAILABLE

The US Food and Drug Administration (FDA) has approved zuranolone as the first oral agent indicated for postpartum depression [60-62]. Although the drug is not yet available for clinical use, we anticipate that clinicians can begin prescribing it after the United States Drug Enforcement Administration determines its controlled substance schedule in the fourth quarter of 2023. The drug is prescribed at a dose of 50 mg/day with a fatty meal (to facilitate absorption) for 14 days, and can be used as monotherapy or in combination with other oral antidepressants [62].

Zuranolone is a neuroactive steroid that functions as a GABA-A receptor positive allosteric modulator, with a mechanism of action comparable to that of brexanolone; brexanolone is a clinically available, intravenously administered drug approved for postpartum depression [61,63]. Some patients may decide that oral administration of zuranolone represents an advantage over the 60-hour continuous infusion required for brexanolone. (See 'Patients who prioritize rapid improvement' above.)

FDA approval was granted on the basis of two randomized trials that found zuranolone was efficacious for postpartum depression [62,64]. As an example, a two-week trial compared zuranolone 30 mg/day with placebo in 150 outpatients with postpartum unipolar major depression who were not breastfeeding; concomitant antidepressants were prescribed to 19 percent [63]. Starting at day 3, remission occurred in more patients who received zuranolone than placebo (19 versus 5 percent), and remission remained greater with active medication throughout treatment and at one month after the end of treatment (53 versus 30 percent). In addition, improvement of anxiety and global maternal functioning was greater with active medication. Zuranolone was generally well tolerated, such that discontinuation of treatment due to adverse effects was similar for zuranolone and placebo (1 and 0 percent of patients).

INVESTIGATIONAL TREATMENTS

Investigational treatments for severe postpartum depression include the neuroactive steroid ganaxolone, which acts at gamma-aminobutyric acid receptors and is being tested as an oral and intravenous drug [10,18,65].

TREATMENTS WITH LITTLE OR NO EVIDENCE OF BENEFIT

The hormones progestin and estrogen are generally not used for treating postpartum depression due to the lack of supporting evidence [3,33]. A systematic review found that in one randomized trial (n = 168 patients), the benefits of progestin (single norethisterone 200 mg injection) and placebo were comparable [66]. In addition, the review identified one small, randomized trial (n = 61) that compared estrogen (transdermal 17 beta-estrogen 200 mg/day plus cyclical dydrogesterone) with placebo; improvement was greater with estrogen than placebo.

SAFETY OF INFANT EXPOSURE TO PSYCHOTROPIC DRUGS THROUGH BREASTFEEDING

The safety of infant exposure to psychotropic medications through breastfeeding is discussed separately. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding" and "Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders".)

ANTENATAL UNIPOLAR MAJOR DEPRESSION

Treatment of severe unipolar depression during pregnancy is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment".)

POSTPARTUM BIPOLAR MAJOR DEPRESSION

Treatment of postpartum patients with bipolar major depression is discussed separately. (See "Bipolar disorder in postpartum women: Treatment", section on 'Bipolar major depression'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders" and "Society guideline links: Postpartum care".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Coping with high drug prices (The Basics)" and "Patient education: Depression during and after pregnancy (The Basics)")
- Beyond the Basics topics (see "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

In addition, several lay groups offer support and education to women with postpartum mood disorders and to family members. One such group is Postpartum Support International (available at the website or call 1-805-967-7636), which holds local, state, national, and international meetings. Educational information is also available at the National Women's Health Information Center.

Furthermore, the National Maternal Mental Health Hotline provides real-time support and information; the number is 1-833-943-9746.

SUMMARY AND RECOMMENDATIONS

- **Definitions** – An episode of unipolar major depression is a period lasting at least two weeks, with five or more of the following symptoms: depressed mood, loss of interest or

pleasure in most or all activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, guilt or thoughts of worthlessness, and recurrent thoughts about death or suicide (table 1).

Severe unipolar major depression is characterized by seven to nine depressive symptoms. Severely ill patients often report suicidal ideation and behavior, typically demonstrate obvious impairment of functioning, and often manifest poor judgement that places the patient and others at risk for imminent harm. (See 'Definitions' above.)

- **General principles of treatment** – The general principles and issues involved in treating postpartum unipolar major depression include setting (eg, outpatient or inpatient), educating patients and families, adherence, monitoring symptoms, and making referrals. (See "Postpartum unipolar major depression: General principles of treatment".)

- **Overview** – An overview of choosing treatment is presented in the algorithm (algorithm 1).

- **Breastfeeding**

  - **Patients who prioritize rapid improvement** – For patients with severe unipolar major depression who are breastfeeding and want relatively rapid improvement, we suggest the antidepressant brexanolone (**Grade 2B**). If the drug is not available, affordable, or effective, or is declined, a reasonable alternative is electroconvulsive therapy. (See 'Patients who prioritize rapid improvement' above.)

  - **Patients with no history of treatment for depression** – For patients with severe, postpartum unipolar major depression, who are breastfeeding and have no prior history of treatment for depression, we suggest antidepressant medications rather than other treatments (**Grade 2B**). (See 'Initial treatment' above.)

    - For patients who have not been treated with antidepressants in the past, we suggest selective serotonin reuptake inhibitors (SSRIs) as initial treatment, rather than other antidepressants (**Grade 2B**). SSRIS have been used and more widely studied in breastfeeding patients than other antidepressant classes. Nevertheless, reasonable alternatives to SSRIs include serotonin-norepinephrine reuptake inhibitors, mirtazapine, and nortriptyline. (See 'Initial treatment' above.)

    - For patients who show a minimal response (eg, improvement <25 percent) to initial treatment with an antidepressant, we suggest switching to a different antidepressant (**Grade 2C**). For patients showing a partial response (eg, reduction

of baseline symptoms by 25 to 49 percent), we suggest augmentation with a drug that is compatible with breastfeeding, such as a second-generation antipsychotic, lithium, and triiodothyronine (**Grade 2C**). (See 'Treatment-resistant patients' above.)

- **Patients treated with antidepressants during pregnancy** – Antenatal unipolar major depression may remit with an antidepressant that is discontinued prior to delivery. For those patients who subsequently develop postpartum unipolar major depression and are breastfeeding, it is preferable to resume the same antidepressant even if there are better lactation safety data for other medications, because using a different antidepressant increases the number of medication exposures. (See 'Patients treated with antidepressants during pregnancy' above.)

- **Patients treated with antidepressants prior to the pregnancy** – Patients who present with severe, postpartum unipolar major depression and are breastfeeding may have been successfully treated with pharmacotherapy for a depressive episode that occurred prior to the pregnancy. We typically resume the same regimen for these patients, provided it is compatible with breastfeeding. (See 'Patients treated with pharmacotherapy prior to the pregnancy' above.)

- **Not breastfeeding** – For patients with severe, postpartum unipolar major depression who are not breastfeeding and prioritize relatively rapid improvement over other aspects of treatment, we suggest the antidepressant brexanolone (**Grade 2B**). (See 'Patients who prioritize rapid improvement' above.)

  If the drug is not available, affordable, or effective, or is declined, treatment is similar to that in the general population of patients with severe depression. (See "Unipolar depression in adults: Choosing treatment for resistant depression" and "Unipolar major depression in adults: Choosing initial treatment", section on 'Severe major depression' and "Unipolar major depression in adults: Choosing initial treatment".)

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