Mild to moderate episodes of antenatal unipolar major depression: Choosing treatment

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INTRODUCTION

Unipolar major depression is common in pregnant women and is often not treated [1]. In a nationally representative survey in the United States that identified pregnant and nonpregnant women with major depression, pregnant women were less likely to receive mental health treatment than nonpregnant women (49 versus 57 percent) [2]. Untreated disease causes maternal suffering and is associated with poor nutrition, comorbid substance use disorders, poor adherence with antenatal care, postpartum depression, impaired relationships between the mother and her infant and other family members, and an increased risk of suicide [3,4].

Barriers to treatment of antenatal depression include cost, reluctance to engage in treatment (eg, fear of exposing the fetus to antidepressant medication or lack of interest in psychotherapy), unavailability of clinicians, and stigma [3,4]. In addition, many clinicians are uncomfortable prescribing medications because they lack sufficient experience and expertise [5], and the literature describing pharmacotherapy for antenatal depression is often inconsistent [6].

This topic reviews choosing a specific treatment for mild to moderate episodes of antenatal unipolar major depression. Other topics discuss the treatment of severe episodes of antenatal unipolar major depression; general principles of treatment; risks of antidepressants during pregnancy; and the epidemiology, clinical features, assessment, and diagnosis of antenatal depression.

- (See "Severe antenatal unipolar major depression: Choosing treatment".)
- (See "Unipolar major depression in pregnant women: General principles of treatment".)
- (See "Antenatal use of antidepressants and the potential risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors".)
- (See "Antenatal use of antidepressants and risks of teratogenicity and adverse pregnancy outcomes: Drugs other than selective serotonin reuptake inhibitors".)
- (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes".)
- (See "Unipolar major depression during pregnancy: Epidemiology, clinical features, assessment, and diagnosis".)

DEFINITIONS

Unipolar major depression — Unipolar major depression (major depressive disorder) is diagnosed in patients who have suffered at least one major depressive episode and have no history of mania or hypomania [7]. An episode of unipolar major depression is a period lasting at least two weeks, with five or more of the following nine 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). Additional information about the clinical presentation and diagnosis of unipolar major depression is discussed separately. (See "Unipolar depression in adults: Clinical features" and "Unipolar depression in adults: Assessment and diagnosis".)

Severity of illness — When selecting a treatment for antenatal major depression, clinicians should determine the severity of illness:

- **Mild to moderate** – Mild to moderate episodes of unipolar major depression are generally characterized by five or six depressive symptoms (table 1), as indicated by a score <20 points on the self-report Patient Health Questionnaire – Nine Item (PHQ-9) (table 2). However, the instrument includes items about changes in appetite, energy, and sleep, which may reflect the physical effects of pregnancy rather than depression. Additional information about the PHQ-9 is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

  Patients with mild to moderate illness do not manifest suicidal behavior or obvious impairment of functioning and are less likely to develop complications such as psychotic

features and catatonia, compared with patients who are severely ill. Mild to moderate depression can typically be managed in outpatient or partial hospital settings.

- **Severe** – Severe unipolar major depression is characterized by seven to nine depressive symptoms (table 1), as indicated by a score ≥20 points on the PHQ-9 (table 2). Severely ill patients often report suicidal ideation and behavior, typically demonstrate obvious impairment of functioning, and frequently manifest poor judgment that places the patient and others (including children) at risk for imminent harm [8]. In addition, patients with severe depression can develop complications such as psychotic features and catatonic features, and often have a history of severe or recurrent depressive episodes [7]. Patients with severe major depression should be referred to a psychiatrist for management and may require inpatient hospitalization [9,10].

Difficulties may arise in determining the number of depressive symptoms that are present during pregnancy because changes in appetite, energy, and sleep may be due to depression, or may represent normal pregnancy-related changes. The presence of these somatic symptoms should be evaluated in the context of normal expectations for pregnancy. As an example, although food aversions can occur during pregnancy, patients with anorexia who fail to gain weight may have mild to moderate depression, and pregnant patients with anorexia who lose weight may have severe depression. In the same vein, pregnancy can cause fatigue. 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 during the day 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).

This topic discusses choosing a specific treatment for mild to moderate episodes of antenatal major depression. Treating severe episodes is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment".)

GENERAL PRINCIPLES

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

- Setting
- History of prior treatment

- Educating patients and families
- Adherence
- Monitoring symptoms
- Prescribing antidepressants
- Managing nonresponse
- Making referrals

These general principles are discussed in detail separately. (See "Unipolar major depression in pregnant women: General principles of treatment".)

CHOOSING TREATMENT

Overview — We suggest that acute treatment of pregnant patients with mild to moderate episodes of unipolar major depression proceed according to the sequence described in the subsections below. Patients generally start with initial therapy and progress through each step until they respond. The best evidence supports using a structured psychotherapy such as cognitive-behavioral therapy (CBT) or interpersonal psychotherapy (IPT) as the primary treatment. However, many patients receive antidepressant medications, and some patients receive psychotherapy plus an antidepressant. As part of treatment, all patients should receive psychoeducation about depression, with emphasis upon self-care including rest, time for self, adequate sleep, keeping a consistent schedule, minimizing stressors, and asking for and accepting support. (See "Unipolar major depression in pregnant women: General principles of treatment", section on 'Educating patients and families'.)

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".)

Initial treatment — Initial treatment of mild to moderate episodes of antenatal unipolar major depression consists of pharmacotherapy (antidepressants) or psychotherapy. The choice depends upon multiple factors, including the patient's history, preferences, and availability of treatment [1,4,8,11-17]:

- For patients with a prior history of unipolar major depression, we frequently use an antidepressant as initial treatment of antenatal major depression [18]. Antidepressants are also indicated if psychotherapy is not available, and for patients who prefer pharmacotherapy (eg, they previously responded well to antidepressants, they perceive

psychotherapy as too time consuming, or they previously did not respond to psychotherapy).

- For patients who present with mild to moderate antenatal unipolar major depression, and have no prior history of major depression, we recommend a structured psychotherapy as first-line treatment. We typically choose either CBT or IPT, which are likely to be most effective in patients who are psychologically minded. Ideally, the psychotherapy is modified for use in pregnant patients.

  Psychotherapy is also a reasonable alternative to pharmacotherapy for patients who prefer it, including patients who were successfully treated in the past for major depression with antidepressants but have never received psychotherapy. Some pregnant patients prefer psychotherapy over pharmacotherapy.

  Initial treatment of mild to moderate antenatal major depression with antidepressants is consistent with practice guidelines from the Canadian Network for Mood and Anxiety Treatments [19], and administering structured psychotherapy as initial treatment is consistent with multiple treatment guidelines, including those from the American Psychiatric Association, American College of Obstetricians and Gynecologists, and the United Kingdom National Institute for Health and Care Excellence [17,19-22].

It is important to assess the benefit of previous treatment to guide selection of a specific antidepressant or psychotherapy for antenatal major depression [18]. If pharmacotherapy is indicated and the patient was successfully treated with a particular antidepressant prior to pregnancy, the same drug is typically used during pregnancy. Additional information about choosing an antidepressant for antenatal depression is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment", section on 'Initial treatment'.)

Similarly, if structured psychotherapy is indicated and the patient was successfully treated with a particular psychotherapy prior to pregnancy, the same therapy generally is used during pregnancy. For patients who were not previously treated successfully with a structured psychotherapy, we typically choose either CBT or IPT. These two therapies have been more widely studied in perinatal populations than other psychotherapies, and are also the most widely studied in the general population of patients with depression. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Selecting a specific psychotherapy'.)

The specific choice between CBT and IPT is guided by availability and patient preference, as well as specific depressive symptoms:

- In patients with prominent dysfunctional thoughts, beliefs, and attitudes (eg, “I’m going to be a terrible mother”), or marked symptoms of anxiety, we use CBT. For depression that includes marked inactivity, we use CBT that emphasizes behavioral activation.

  CBT for major depression combines cognitive therapy and behavioral therapy. Cognitive therapy attempts to modify dysfunctional thoughts and illness beliefs; one technique is cognitive restructuring, which involves reframing distorted thoughts (eg, “I’m no good”) by empirically testing them and considering more benign explanations. Behavioral therapy aims to change problematic behaviors that occur in response to dysfunctional thoughts, depressive symptoms, and environmental stimuli; specific techniques include behavioral activation (counteracting inertia and avoidance by assigning rewarding activities for patients to complete between treatment sessions), problem solving (identifying the problem, generating multiple solutions, considering the consequences of each solution, choosing one solution, and acting upon it), progressive muscle relaxation, abdominal breathing exercises, and physical exercise.

- If the depressive syndrome occurs in the context of role disputes (conflicts with others over different expectations about the relationship, such as conflicts with one’s partner), role transitions (major changes in life roles or circumstances such as difficulty in adjusting to pregnancy), or grief, we suggest IPT. The therapy focuses upon improving problematic interpersonal relationships or circumstances that are directly related to the current depressive episode.

  Additional information about IPT for unipolar depression in the general population is discussed separately. (See "Interpersonal Psychotherapy (IPT) for depressed adults: Indications, theoretical foundation, general concepts, and efficacy" and "Interpersonal Psychotherapy (IPT) for depressed adults: Specific interventions and techniques".)

Structured psychotherapy for unipolar major depression is usually time-limited (eg, 6 to 10 sessions); thus, patients treated with CBT or IPT generally receive a full course of therapy, regardless if nonresponse persists through the middle phases of treatment.

If psychotherapy is indicated for mild to moderate episodes of antenatal unipolar major depression, and CBT and IPT are not available, a reasonable alternative is a different psychotherapy. (See 'Treatment-refractory patients' below.)

For mild to moderate episodes of antenatal major depression that are initially treated with pharmacotherapy or psychotherapy, we suggest also prescribing adjunctive treatments, depending upon patient preferences and availability. (See 'Adjunctive treatments' below.)

Relationship conflict — For pregnant patients with mild to moderate depressive disorders that stem from poor family functioning and relationship problems, family/couples therapy may be used as a primary or adjunctive treatment, based upon randomized trials in patients who usually were not pregnant. Using couples therapy for mild to moderate antenatal major depression is consistent with practice guidelines from the Canadian Network for Mood and Anxiety Treatments [19].

During evaluations for family therapy, women should be assessed individually to assure privacy, particularly when screening for intimate partner violence, and again with her partner to assess any relationship discord. The assessment of families and efficacy and administration of family therapy are discussed separately. (See "Unipolar depression in adults: Family and couples therapy".)

Evidence of efficacy

- **Antidepressants** – Although no randomized trials have evaluated the efficacy or safety of antidepressants during pregnancy, numerous trials that excluded pregnant patients have demonstrated that antidepressants are efficacious for treating the general population of patients with major depression [20]. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants'.)

- **Psychotherapy** – Evidence supporting the use of psychotherapy for antenatal depression includes numerous randomized trials that found psychotherapy was efficacious in the general population of adults with depression. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of psychotherapy'.)

  In particular, many randomized trials in the general population of patients with depression have found that CBT is efficacious [23-26]. As an example, a meta-analysis of 115 trials (number of patients not reported) compared CBT with a control condition (waiting list, usual care, or pill placebo) and found a significant, clinically moderate to large effect favoring CBT [27].

  Likewise, evidence for the efficacy of IPT includes numerous randomized trials in the general population of patients with unipolar major depression [28,29]. (See "Interpersonal Psychotherapy (IPT) for depressed adults: Indications, theoretical foundation, general concepts, and efficacy", section on 'Evidence of efficacy'.)

  In addition, randomized trials have demonstrated that CBT and IPT are each efficacious in patients with antenatal depression [1,12,17,30,31]. As an example:

- A meta-analysis of seven trials (n = 1300) compared CBT with control conditions (eg, usual care, psychoeducation, or supportive counseling) and found a significant, clinically moderate to large effect favoring CBT [32]. In addition, the benefit of CBT was consistent across studies.

- A meta-analysis of four randomized trials compared IPT with a control condition (usual care, peer support group, or parenting education) in patients with antenatal depression (n = 277) [32]. Outcomes were superior with IPT and the clinical benefit was moderate to large. However, heterogeneity across studies was large.

  Subsequently, a randomized trial compared IPT with usual care in 234 patients with depression, as determined by a score on the Edinburgh Postnatal Depression Scale (figure 1 and figure 2) ≥10 [33]. Active treatment was administered by a team that included IPT therapists who administered eight 50-minute individual, weekly sessions that were tailored for pregnant patients and culturally relevant. IPT focused upon skills to reduce conflict and increase interpersonal support. Usual care included maternity support services, as well as psychotherapy (not IPT or CBT) as indicated. Pharmacotherapy was permitted for both groups. Improvement of depression was greater with IPT than usual care, and the clinical effect was moderate.

Treatment-resistant patients — Patients with mild to moderate episodes of antenatal major depression who receive initial treatment with an antidepressant may not respond; response is typically defined as reduction of baseline symptoms ≥50 percent. These patients typically receive next step pharmacotherapy; however, adding on or switching to structured psychotherapy is a reasonable alternative. Next step pharmacotherapy is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment", section on 'Treatment-resistant patients'.)

For patients with antenatal major depression of mild to moderate severity who do not respond to initial treatment with a structured psychotherapy (eg, CBT or IPT), next step treatment depends upon the degree to which the initial treatment is beneficial:

- For patients who achieve a partial response (eg, reduction of baseline symptoms of 25 to 49 percent), we suggest increasing the total number of sessions (eg, providing 12 to 16 sessions rather than 8), based upon our clinical experience. In addition, some clinicians increase the frequency of treatment (eg, administering two sessions/week rather than one/week).

- For patients who are treated with either CBT or IPT and achieve only a minimal response (eg, improvement <25 percent), we suggest switching to the other psychotherapy, based

upon our clinical experience. If switching is not feasible due to lack of availability, a reasonable alternative is switching to a psychotherapy other than CBT or IPT. (See 'Treatment-refractory patients' below.)

However, whether patients respond partially or minimally to initial treatment with psychotherapy, it is reasonable to switch from psychotherapy to pharmacotherapy. Antidepressants are standard treatment for severe antenatal depression, and choosing and prescribing an antidepressant for mild to moderate antenatal depression is the same as it is for severe antenatal depression. The drug is titrated in the same manner and clinicians should treat to remission. (See "Severe antenatal unipolar major depression: Choosing treatment", section on 'Initial treatment'.)

In addition to the primary next step treatment that is prescribed for treatment-resistant antenatal depression, we suggest that clinicians also use adjunctive treatments, depending upon patient preference and availability. If one adjunctive treatment has previously not been helpful, we suggest switching to a different one. (See 'Adjunctive treatments' below.)

Treatment-refractory patients — Patients with mild to moderate episodes of antenatal major depression who receive initial and second-line treatment with an antidepressant may not respond. These patients typically receive next step pharmacotherapy; however, adding on or switching to structured psychotherapy is a reasonable alternative. Next step pharmacotherapy is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment", section on 'Treatment-resistant patients'.)

In addition, patients with mild to moderate antenatal depression may not respond to sequential courses of CBT and IPT or may decline these therapies, or CBT and IPT may not be available. For these patients, we suggest antidepressants or using a psychotherapy other than CBT or IPT, such as:

- Behavioral activation – Behavioral activation is a type of behavioral therapy and is a primary element of CBT. Behavioral activation consists of clinical strategies that include self-monitoring, structuring and scheduling rewarding activities, reducing avoidance behavior, and improving problem solving skills. Using behavioral activation is consistent with practice guidelines for treating the general population of patients with major depression [34].

  Evidence supporting behavioral activation for antenatal depression includes multiple randomized trials in the general population of patients with major depression [34]. In addition, one randomized trial compared usual care plus behavioral activation (10 sessions) with usual care alone in pregnant patients with depressive symptoms (n = 163)

[35]. Behavioral activation was tailored for antenatal depression, and usual care included other psychotherapies and pharmacotherapy. The rate of remission three months postpartum was greater in patients who received adjunctive behavioral activation than usual care alone (56 versus 30 percent). In addition, improvement of anxiety and perceived stress was superior with behavioral activation.

Additional information about the administration and efficacy of behavioral activation in the general population of patients with major depression is discussed separately. (See "Behavioral activation therapy for treating unipolar major depression".)

- Mindfulness-based cognitive therapy – Although there is no evidence from high-quality studies that mindfulness-based treatments are beneficial in pregnant women [36], multiple studies in the general population of patients with unipolar major depression indicate that mindfulness-based cognitive therapy is efficacious [34]. Mindfulness-based cognitive therapy is a skills-training group program that combines the clinical application of mindfulness meditation with elements of CBT. Using mindfulness-based cognitive therapy for antenatal depression is consistent with practice guidelines from the Canadian Network for Mood and Anxiety Treatments [19]. Additional information about the administration and efficacy of mindfulness-based cognitive therapy is discussed separately. (See "Unipolar major depression: Treatment with mindfulness-based cognitive therapy".)

- Psychodynamic psychotherapy (short-term) – Short-term psychodynamic psychotherapy is based upon the idea that childhood experiences, past unresolved conflicts, and previous relationships significantly influence an individual's current situation in life. Adult relationships are understood to be a byproduct of unconscious patterns that begin in childhood, and psychodynamic psychotherapy uncovers the unconscious patterns of interpersonal relationships, conflicts, and desires that cause depression. Using short-term psychodynamic psychotherapy for mild to moderate antenatal major depression is consistent with practice guidelines from the Canadian Network for Mood and Anxiety Treatments [19]. Additional information about the administration and efficacy of psychodynamic psychotherapy in the general population of patients with major depression is discussed separately. (See "Unipolar depression in adults: Psychodynamic psychotherapy".)

- Supportive psychotherapy – Supportive psychotherapy treats depression by improving self-esteem, psychological functioning, and adaptive skills; the therapy focuses upon current, problematic relationships and maladaptive patterns of behavior and emotional responses. Using supportive psychotherapy for mild to moderate antenatal major

depression is consistent with practice guidelines from the Canadian Network for Mood and Anxiety Treatments [19]. Additional information about the administration and efficacy of supportive psychotherapy in the general population of patients with major depression is discussed separately. (See "Unipolar depression in adults: Supportive psychotherapy", section on 'Evidence of efficacy'.)

For pregnant patients with mild to moderate major depression who do not respond to initial and next step treatments, another option is repetitive transcranial magnetic stimulation (TMS). Prescribing TMS for mild to moderate antenatal major depression is consistent with practice guidelines, including those from the Canadian Network for Mood and Anxiety Treatments [19,22]. Information about using TMS for antenatal depression, and the administration, efficacy, and safety of TMS in the general population of patients with major depression, is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment", section on 'Other options' and "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)" and "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)".)

In addition to the primary next step treatment that is prescribed for refractory antenatal depression, we suggest that clinicians also use adjunctive treatments, depending upon patient preference and availability. If one adjunctive treatment has previously not been helpful, we suggest switching to a different one. (See 'Adjunctive treatments' below.)

Adjunctive treatments — For patients with mild to moderate antenatal depression who do not respond to initial and subsequent therapies, we suggest the following options as adjunctive interventions [37]. Multiple adjunctive treatments can be used concurrently. The specific choice depends upon patient preferences and availability.

- Acupuncture
- Bibliotherapy
- Bright light therapy
- Exercise/yoga
- Folic acid
- Massage therapy
- Omega-3 fatty acids
- Peer support/support groups
- Psychoeducation
- S-adenosyl methionine

Additional information about these treatments, including evidence of efficacy, is as follows:

- Acupuncture – Although the evidence is insufficient to recommend the use of acupuncture for the general population of patients with depression [38], randomized trials have reported that acupuncture may be efficacious for antenatal depression:

  - An eight-week trial compared acupuncture specific for depression (12 sessions) with acupuncture not specific for depression in pregnant women with unipolar major depression (n = 101) [39]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received active treatment than controls (63 versus 38 percent). The rate of adverse events (eg, feeling tired after treatment) for the two groups was comparable.

  - Another trial from the same research group compared acupuncture specific for depression (12 sessions over eight weeks) with acupuncture not specific for depression in pregnant women with unipolar major depression (n = 35) [40]. Response occurred in more patients who received active treatment than controls (11/16 versus 9/19 [69 versus 47 percent]); although this difference was not statistically significant, a difference of this magnitude, if real, would be clinically meaningful.

  Using acupuncture for mild to moderate antenatal major depression is consistent with practice guidelines, including those from the Canadian Network for Mood and Anxiety Treatments [19,22].

  General information about acupuncture is discussed separately. (See "Overview of the clinical uses of acupuncture".)

- Bibliotherapy – Bibliotherapy involves reading hard copy or online material about the clinical features and treatment of major depression. Using bibliotherapy is consistent with practice guidelines for treating the general population of patients with major depression [34].

- Bright light therapy – Bright light therapy can be beneficial for seasonal affective disorder as a stand-alone treatment, and can also help patients with nonseasonal depressive syndromes [41-45]. As an example, randomized trials indicate that in the general population of patients with nonseasonal, unipolar major depression, bright light therapy can be efficacious as augmentation. (See "Unipolar depression in adults: Investigational and nonstandard treatment", section on 'Bright light therapy'.)

  In addition, bright light therapy may perhaps be useful for antenatal depression. A small, five-week randomized trial compared bright light therapy (7000 lux bright white light) with placebo (70 lux dim red light) in pregnant patients with nonseasonal major depression (n =

27) [46]. Each study treatment was administered for one hour/day. Most patients received no other treatment, but four patients had initiated a selective serotonin reuptake inhibitor prior to the study and continued the drug during the study. Remission occurred in more patients who received bright light therapy than placebo (11/16 versus 4/11 [69 versus 36 percent]). No clinically meaningful side effects were observed and all pregnancy deliveries occurred without complication. However, an even smaller randomized trial in 10 pregnant patients found that bright light therapy and placebo were comparable [47].

Using bright light therapy for mild to moderate antenatal major depression is consistent with practice guidelines, including those from the Canadian Network for Mood and Anxiety Treatments [19,22]. Information about the administration, safety, and side effects of bright light therapy is discussed separately. (See "Seasonal affective disorder: Treatment", section on 'Bright light therapy'.)

- Exercise/yoga – For mild to moderate antenatal major depression, we suggest exercise or yoga. The use of exercise/yoga is consistent with practice guidelines from the Canadian Network for Mood and Anxiety Treatments [19]. In addition, the general population of pregnant women who do not have medical or obstetric complications are typically encouraged to exercise. (See "Exercise during pregnancy and the postpartum period".)

  Evidence supporting the use of exercise (eg, yoga) for antenatal depression includes randomized trials [48-50]. For example:

  - A meta-analysis of six randomized trials compared exercise with a control condition in patients with antenatal depressive symptoms (n = 348) [48]. Five of the trials utilized yoga as the exercise intervention; one trial used aerobic exercise. The control conditions included usual care, waiting list, social support group, or parenting education. The analysis found a significant effect favoring exercise over the comparators, and the clinical benefit was moderately large. However, the quality of the trials was low to moderate, heterogeneity across studies was moderate to large, and the safety and incidence of adverse events was not discussed in any of the trials.

  - A meta-analysis of four randomized trials lasting 12 weeks compared yoga with control conditions (eg, usual care, social support group, or parenting education) in pregnant women with depressive symptoms (n = 234) [49]. The yoga interventions were administered once or twice per week, with each session lasting 20 minutes. Improvement of depression was greater with yoga and the clinical benefit was moderate. However, heterogeneity across studies was moderate to large.

The efficacy and use of exercise in the general population of patients with depression is discussed separately. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Exercise'.)

- Folic acid – Folic acid is recommended for all pregnant women to prevent neural tube defects. (See "Nutrition in pregnancy: Dietary requirements and supplements", section on 'Folate/folic acid' and "Preconception and prenatal folic acid supplementation".)

  In addition, indirect evidence suggests that adjunctive folic acid may perhaps be beneficial for antenatal depression:

  - A randomized trial compared folic acid (500 micrograms/day) plus fluoxetine (20 mg/day) with placebo plus fluoxetine as initial treatment in patients with unipolar major depression (n = 127; females who were pregnant were excluded) [51]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received adjunctive folic acid than placebo (82 versus 62 percent). The benefit appeared to be greater for women than men.

  - An observational study of pregnant women (n = 709) included women with clinically significant depressive symptoms (n = 51, 7 percent) [52]. Serum folate concentrations were lower in the pregnant women with depressive symptoms than the pregnant women without depressive symptoms.

  However, randomized trials studying the use of folate in the general population of patients with treatment-resistant patients have found that the benefit is modest at best. (See "Unipolar depression in adults: Investigational and nonstandard treatment", section on 'Complementary and alternative treatments'.)

- Massage therapy – Multiple randomized trials by the same group of investigators indicate that maternal massage can be helpful for antenatal depression [53,54]:

  - A six-week trial compared massage therapy plus group IPT with group IPT alone in patients with antenatal depression (n = 112); each treatment was administered once per week [55]. Improvement of depression was greater in the group that received adjunctive massage therapy; anxiety also improved more with massage therapy.

  - A 16-week trial (n = 56 patients with depressive symptoms) compared massage therapy with progressive muscle relaxation; each treatment was administered twice per week [56]. Improvement of depression was greater with massage therapy than muscle relaxation. In addition, anxiety and leg and back pain improved more with massage

therapy. The incidence of prematurity and low birthweight were each less with massage therapy, and neonatal functioning was better in babies of mothers treated with massage therapy.

- A 12-week trial compared massage therapy (two sessions per week) with usual care in pregnant patients with major depression (n = 149) [57]. Improvement of depressive symptoms was greater with massage therapy than usual care. In addition, prematurity and low birth weight occurred in fewer babies of mothers treated with massage therapy and neonatal functioning was better in babies of mothers treated with massage therapy.

- Omega-3 fatty acids – We suggest that patients with antenatal depression consume foods with omega-3 (n-3) polyunsaturated fatty acids (eg, seafood), consistent with the recommendation that the general population of pregnant women consume these foods. (See "Fish consumption and marine omega-3 fatty acid supplementation in pregnancy".)

  For patients with mild to moderate antenatal unipolar depression, we use supplements with omega-3 fatty acids to augment standard treatment with antidepressants or psychotherapy. One rationale for administering supplemental omega-3 fatty acids to pregnant women with depression is that antenatal depression appears to be associated with low serum levels of these essential fatty acids [58]. A meta-analysis of six observational studies in women with antenatal depression and healthy controls (total n >2600) found that serum levels of omega-3 fatty acids were lower in depressed women than controls [59].

  However, we do not prescribe omega-3 fatty acids as primary treatment because the evidence supporting their use is limited. Meta-analyses of randomized trials that compared omega-3 fatty acids with placebo in the general population of patients with unipolar major depression have yielded conflicting results. (See "Unipolar depression in adults: Investigational and nonstandard treatment", section on 'Omega-3 fatty acids'.)

  In addition, it is not clear that omega-3 fatty acids are useful for treating depression specifically in pregnant women [60-62]. The relatively few randomized trials that have been conducted used different types of omega-3 fatty acids with different doses in small samples [60]. Also, some trials enrolled patients with perinatal depression (either antenatal or postnatal depression), rather than focusing solely on antenatal depression, or they enrolled euthymic patients who were not depressed [63]. The evidence regarding omega-3 fatty acids for treating depression in pregnant women includes the following:

- A meta-analysis of three randomized trials compared omega-3 fatty acids with placebo in patients with perinatal depression (n = 110), and found that improvement was comparable for the two groups [64]. However, two of the trials included patients with postpartum depression [65,66]. A subsequent meta-analysis of the same three trials also found no advantage for omega-3 fatty acids over placebo [32].

- A meta-analysis identified a different, overlapping set of three randomized trials that compared omega-3 fatty acids with placebo in 172 patients, and found that the benefit was comparable for the two groups [67]. However, one of the trials included patients with postpartum depression [65] and one of the trials evaluated omega-3 fatty acids for preventing depression in women at increased risk for depressive symptoms [68].

- Each meta-analysis included an eight-week trial that compared omega-3 fatty acids (eicosapentaenoic acid 2.2 grams/day and docosahexaenoic acid 1.2 grams/day) with placebo (olive oil) solely in pregnant women with unipolar major depression (n= 33) [69]. Improvement was greater with omega-3 fatty acids than placebo, no obstetric complications occurred in any of the study patients, and all of the newborns were healthy.

Multiple practice guidelines that address antenatal depression concur that the data regarding omega-3 fatty acids are weak or inconsistent [17,62], and other guidelines do not mention omega-3 fatty acids [18,19,70].

- Peer support/support groups – Peer support includes self-help groups and services provided by trained peers. We suggest peer support as adjunctive treatment for patients with mild to moderate antenatal unipolar depression who are receiving standard treatment with antidepressants or psychotherapy. This approach is consistent with practice guidelines from the Canadian Network for Mood and Anxiety Treatments [34].

  Evidence supporting the effectiveness of peer support includes randomized trials in pregnant women:

  - A 12-week randomized trial compared peer support (weekly group sessions, each lasting 20 minutes) with IPT (weekly group sessions, each lasting 60 minutes) in pregnant patients with a depressive syndrome [71]. Compared with patients treated with IPT, patients assigned to peer support had a lower socioeconomic status and a higher level of baseline depression as assessed with a rating scale. Despite the differences in the intensity of treatment and baseline treatment group differences, improvement of depression, as well as anxiety symptoms, was comparable for the two treatments.

- A randomized trial compared peer support plus usual care with usual care alone in pregnant women (n = 236) with at least moderate depressive symptoms [72]. Laywomen in the community were trained to deliver peer support consisting primarily of behavioral activation; the intervention was administered over 6 to 14 individual sessions (each lasting 30 to 45 minutes), over 7 to 12 months. Usual care included information about treatment guidelines and referring patients for treatment. At six months postpartum, recovery occurred in more patients who received peer support plus usual care than usual care alone (53 versus 41 percent).

  A second randomized trial by the same investigators compared peer support plus usual care with usual care alone in pregnant women (n = 406) with at least moderate depressive symptoms [73]. Peer support and usual care were comparable to the interventions in the first trial. At six months postpartum, recovery occurred in more patients who received peer support plus usual care than usual care alone (35 versus 26 percent).

- Psychoeducation – All pregnant patients with unipolar major depression should receive psychoeducation about the illness as part of treatment. Psychoeducation includes explaining the clinical features of major depression and treatment options [74]. The material that is presented should be tailored for antenatal depression. As an example, clinicians can clarify that somatic symptoms of major depression, such as changes in sleep, energy level, and appetite, overlap with changes observed in pregnant women who are not depressed. Educating patients about antenatal major depression can help them accept their illness, and improve adherence to treatment and treatment outcomes. (See "Unipolar major depression in pregnant women: General principles of treatment", section on 'Educating patients and families'.)

- S-adenosyl methionine – S-adenosyl methionine may be useful for patients with antenatal depression, based upon studies in the general population of patients with treatment-resistant depression. (See "Unipolar depression in adults: Investigational and nonstandard treatment", section on 'S-adenosyl methionine'.)

In addition, five randomized trials that evaluated S-adenosyl methionine for cholestasis during pregnancy found no adverse effects in mothers or their infants [37,75].

SEVERE ANTENATAL UNIPOLAR MAJOR DEPRESSION

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

UNPLANNED PREGNANCIES AND DISCONTINUING ANTIDEPRESSANTS DURING PREGNANCY

Unplanned pregnancies and discontinuing antidepressants during pregnancy are discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment", section on 'Unplanned pregnancies and discontinuing antidepressants during pregnancy'.)

MINOR DEPRESSION

Unipolar minor depression is diagnosed in patients with two to four depressive symptoms lasting for a period of at least two weeks, and no history of mania or hypomania (table 3). (See "Unipolar minor depression in adults: Epidemiology, clinical presentation, and diagnosis", section on 'Diagnosis'.)

Management of minor depression is discussed separately. (See "Unipolar minor depression in adults: Management".)

BIPOLAR DEPRESSION

Depression can occur in the context of bipolar disorder, which is marked by episodes of hypomania (table 4) or mania (table 5). Distinguishing bipolar depression from unipolar depression is discussed separately, as is treatment of bipolar major depression during pregnancy. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Unipolar major depression' and "Bipolar disorder in pregnant women: Treatment of major depression".)

ANTIDEPRESSANTS AND BREASTFEEDING

The safety of antidepressants in lactating women is discussed separately. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Antidepressants'.)

POSTPARTUM DEPRESSION

Treatment of postpartum unipolar depression and postpartum bipolar depression are discussed separately. (See "Severe postpartum unipolar major depression: Choosing treatment" and "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".)

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

SUMMARY AND RECOMMENDATIONS

- 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). (See 'Unipolar major depression' above.)

- Mild to moderate episodes of unipolar major depression are generally characterized by five or six depressive symptoms. Patients with mild to moderate illness do not manifest suicidal behavior or obvious impairment of functioning, are less likely to develop complications such as psychotic features, and can typically be managed in outpatient or partial hospital settings.

  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 judgment that places the patient and others at risk for imminent harm. In addition, patients with severe depression can develop complications such as psychotic features, and often have a history of severe or recurrent depressive episodes. Patients with severe major depression should be referred to a psychiatrist for management and often require inpatient hospitalization. (See 'Severity of illness' above.)

- The general principles and issues involved in treating unipolar major depression during pregnancy include setting, history of prior treatment, educating patients and families, adherence, monitoring symptoms, prescribing antidepressants, managing nonresponse, and making referrals. (See "Unipolar major depression in pregnant women: General principles of treatment".)

- Initial treatment of mild to moderate episodes of antenatal unipolar major depression consists of antidepressants or psychotherapy:

  - For patients with antenatal major depression and a prior history of major depression, we suggest antidepressants as initial treatment rather than watchful waiting (**Grade 2C**). However, psychotherapy is a reasonable alternative if patients have previously responded to it or if pharmacotherapy is declined.

  - For patients who have no prior history of major depression, we suggest structured psychotherapy as initial treatment rather than antidepressants (**Grade 2C**). We typically choose either cognitive-behavioral therapy (CBT) or interpersonal psychotherapy (IPT), which are likely to be most effective in patients who are psychologically minded. However, if psychotherapy is not available or acceptable, antidepressants are a reasonable alternative.

  (See 'Initial treatment' above.)

- Patients with mild to moderate episodes of antenatal major depression, who receive initial treatment with an antidepressant and do not respond, are typically treated with next step pharmacotherapy. However, a reasonable alternative is to add or switch to structured psychotherapy.

  In addition, patients with mild to moderate antenatal depression may not respond to initial treatment with either CBT or IPT. Next step treatment depends upon the degree to which the initial treatment is beneficial:

  - Patients who achieve a partial response typically receive more sessions of the same psychotherapy (eg, 12 to 16 sessions rather than 8), and may be seen more frequently (eg, two sessions/week rather than one/week).

  - Patients who achieve only a minimal response are typically switched to another psychotherapy (eg, from CBT to IPT).

  However, whether patients respond partially or minimally to initial treatment with psychotherapy, it is reasonable to switch from psychotherapy to pharmacotherapy. (See 'Treatment-resistant patients' above.)

- Patients with mild to moderate episodes of antenatal major depression, who receive initial and second-line treatment with an antidepressant and do not respond, are typically treated with next step pharmacotherapy. However, switching to structured psychotherapy is a reasonable alternative.

  In addition, patients with mild to moderate antenatal depression may not respond to sequential courses of CBT and IPT or may decline these therapies, or CBT and IPT may not be available. These patients are generally treated with either antidepressants or a psychotherapy other than CBT or IPT, such as behavioral activation, mindfulness-based cognitive therapy, psychodynamic psychotherapy, or supportive psychotherapy. Another option is repetitive transcranial magnetic stimulation. (See 'Treatment-refractory patients' above.)

- Patients with mild to moderate episodes of antenatal major depression typically receive one or more adjunctive therapies in addition to the primary treatment that is prescribed. Adjunctive therapies include acupuncture, bibliotherapy, bright light therapy, exercise/yoga, folic acid, massage therapy, omega-3 fatty acids, peer support/support groups, psychoeducation, and S-adenosyl methionine. (See 'Adjunctive treatments' above.)

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