Bipolar disorder in pregnant women: Treatment of major depression

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INTRODUCTION

Medications are commonly used to treat pregnant patients, including those with bipolar major depression [1]. At least one prescription drug is taken by more than 60 percent of pregnant patients [2], and psychotropic drugs are taken by 21 to 33 percent [3,4].

This topic discusses treatment of pregnant patients with bipolar major depression. Treatment of manic and hypomanic episodes during pregnancy, prenatal maintenance pharmacotherapy for bipolar disorder, the teratogenic and postnatal risks of pharmacotherapy for bipolar disorder, and the general treatment of bipolar major depression are discussed separately.

- (See "Bipolar disorder in pregnant women: Screening, diagnosis, and choosing treatment for mania and hypomania".)
- (See "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy".)
- (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy".)
- (See "Bipolar major depression in adults: Choosing treatment".)

DEFINITION OF BIPOLAR DISORDER

Bipolar disorder is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3) [5]. The subtypes of bipolar disorder include bipolar I and bipolar II. Patients with bipolar I disorder experience manic episodes, and nearly always experience major depressive and hypomanic episodes. Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes. Additional information about the clinical features and diagnosis of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Clinical features" and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

INDICATIONS

Pharmacotherapy is indicated for pregnant patients with bipolar major depression that is characterized by [6]:

- Suicidal or homicidal ideation or behavior
- Aggressive behavior
- Psychotic features (delusions or hallucinations)
- Poor judgement that places the patient or others at imminent risk of being harmed
- Moderate to severe impairment of social or occupational functioning

GENERAL PRINCIPLES AND MANAGEMENT

Bipolar mood episodes during pregnancy are usually treated by perinatal or general psychiatrists in collaboration with obstetricians and primary care clinicians [4,7-10].

For pregnant patients with bipolar major depression, treatment is based upon randomized trials that excluded pregnant patients [11-14], as well as observational studies, birth registries, and clinical experience [15].

Additional information about the general principles and management of treating bipolar mood episodes during pregnancy are discussed separately, as is the general treatment of bipolar major depression. (See "Bipolar disorder in pregnant women: Screening, diagnosis, and choosing treatment for mania and hypomania", section on 'Management' and "Bipolar major depression in adults: Choosing treatment".)

Duration of individual drug trial — We suggest treating pregnant patients with bipolar major depression for six to eight weeks before determining whether a specific drug is beneficial, based upon the duration of most randomized trials (which excluded pregnant patients) [11-

13,16]. Response is defined as stabilizing the patient's safety and substantial improvement in the number, intensity, and frequency of symptoms.

SELECTING TREATMENT

Bipolar major depression during pregnancy is typically treated with pharmacotherapy because it is easier to administer, more widely available, and more acceptable to patients than electroconvulsive therapy (ECT). However, refractory patients may benefit from ECT.

First line treatment — For pregnant patients with bipolar major depression, we suggest lamotrigine as first line treatment, based upon efficacy in a meta-analysis of randomized trials that excluded pregnant patients [14]. Up to 40 to 50 percent of patients may respond (defined as stabilizing the patient's safety and substantial improvement in the number, intensity, and frequency of symptoms). In addition, the reproductive safety profile of lamotrigine is generally regarded as favorable [4,17,18]. The efficacy of lamotrigine and quetiapine appear to be comparable, but there is more experience using lamotrigine during pregnancy than quetiapine. In addition, there is more evidence supporting the efficacy of lamotrigine compared with fluoxetine plus olanzapine or lamotrigine plus lithium, and prenatal treatment with monotherapy is preferable to treatment with drug combinations due to concerns about teratogenic effects.

The efficacy of lamotrigine, quetiapine, fluoxetine plus olanzapine, and lamotrigine plus lithium; reproductive safety profile of these drugs; and the dose schedule, side effects (table 4 and table 5) (including life-threatening skin rash), and pharmacology of lamotrigine are discussed separately.

- (See "Bipolar major depression in adults: Choosing treatment".)
- (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy".)
- (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Lamotrigine'.)
- (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Lamotrigine'.)

Treatment resistance — For pregnant patients with bipolar major depression who do not respond to lamotrigine or cannot tolerate it, we suggest quetiapine [19], based upon randomized trials that excluded pregnant patients [20-23]. Up to 50 to 60 percent of patients may respond (defined as stabilizing the patient's safety and substantial improvement in the

number, intensity, and frequency of symptoms). In addition, other studies suggest that quetiapine is not associated with teratogenic effects [24], and use of quetiapine for bipolar major depression during pregnancy is consistent with practice guidelines from the United Kingdom National Institute for Health and Clinical Excellence [25,26]. There is more evidence supporting the efficacy of lamotrigine compared with fluoxetine plus olanzapine or lamotrigine plus lithium, and prenatal treatment with monotherapy is preferable to treatment with drug combinations due to concerns about teratogenic effects.

We generally taper and discontinue lamotrigine at the same time that quetiapine is started and titrated up. Lamotrigine is usually tapered by the same amount for each dose decrease over a one to two week period. As an example, lamotrigine 200 mg per day is decreased by 50 mg per day every three to four days.

Second-generation antipsychotics may cause metabolic complications (eg, hyperglycemia and obesity) that are associated with risks to the mother and fetus [27,28]. These risks are discussed separately, as are monitoring of metabolic parameters in pregnant patients taking second-generation antipsychotics and the efficacy, dose, reproductive safety, pharmacology, and side effects of quetiapine.

- (See "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy", section on 'Metabolic complications'.)
- (See "Bipolar major depression in adults: Choosing treatment".)
- (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Second-generation'.)
- (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Refractory patients — Pregnant patients with bipolar major depression often do not respond to sequential trials of lamotrigine and quetiapine. For these refractory patients, we suggest tapering and discontinuing quetiapine over one to two weeks at the same time that another medication regimen is started and titrated up. (Response is defined as stabilizing the safety of the patient and others, as well as substantial improvement in the number, intensity, and frequency of symptoms.) Quetiapine is generally tapered by the same amount for each dose decrease. As an example, quetiapine 600 mg per day is decreased by 50 to 100 mg per day, every one to two days.

We suggest using the following treatments in sequence for pregnant patients with refractory bipolar major depression, based upon their efficacy in randomized trials (which excluded pregnant patients), reproductive safety profiles, and adverse effects. Although the benefit of

fluoxetine plus olanzapine and the combination of lamotrigine and lithium appear to be comparable, neither fluoxetine nor olanzapine appear to be associated with teratogenic effects. By contrast, lithium is generally regarded as teratogenic [29-31]. The proportion of patients who respond to any of the following treatment regimens may be as high as approximately 50 percent, based upon trials in nonpregnant patients [11,12].

- **Fluoxetine plus olanzapine** – Fluoxetine plus olanzapine is efficacious for bipolar major depression in nonpregnant patients [12,32]. However, second-generation antipsychotics, especially olanzapine, may cause metabolic complications (eg, hyperglycemia and obesity) that are associated with risks to the mother and fetus [27,28]. These risks are discussed separately, as are monitoring of metabolic parameters in pregnant patients taking second-generation antipsychotics and the efficacy, dose, reproductive safety, pharmacology, and side effects of fluoxetine and olanzapine.

  - (See "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy", section on 'Metabolic complications'.)
  - (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy".)
  - (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)
  - (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)
  - (See "Bipolar major depression in adults: Choosing treatment".)

  The dose of fluoxetine may need to be increased during pregnancy, especially after 20 weeks gestation, because the volume of distribution (eg, plasma volume) increases during pregnancy, and the activity of hepatic enzymes that metabolize the drug may also increase during pregnancy [33]. However, pharmacokinetic changes during pregnancy vary widely among patients.

  The fluoxetine dose that is prescribed during the third trimester is typically maintained at the end of pregnancy and immediately following delivery [33]. There are no data that support tapering and discontinuing fluoxetine during the third trimester in an effort to avoid neonatal symptoms. However, following delivery, if adverse effects occur in the mother, the dose should be decreased.

- **Lamotrigine plus lithium** – For pregnant patients with bipolar major depression who do not respond to or tolerate fluoxetine plus olanzapine, we suggest lamotrigine plus lithium [11]. Fluoxetine plus olanzapine are usually tapered and discontinued concurrently over a

period of one week, and subsequently lamotrigine and lithium are started and titrated up. Fluoxetine is generally tapered by the same amount for each dose decrease, as is olanzapine. As an example, fluoxetine 40 mg per day is decreased by 10 mg per day every two days, and olanzapine 15 mg per day is decreased by 5 mg per day every three days. Use of lithium in pregnant patients with bipolar disorder who do not respond to antipsychotics is consistent with practice guidelines from the United Kingdom National Institute for Health and Care Excellence [34].

Although lithium is generally regarded as teratogenic due to increased risks of cardiac defects (eg, Ebstein anomaly) [29-31], many authorities consider the absolute risk small [1,4,18,35,36]. The reproductive safety profile of lamotrigine is generally regarded as favorable [4,17,18], based primarily upon studies of patients with epilepsy. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Lithium' and "Risks associated with epilepsy during pregnancy and the postpartum period".)

The dose schedule, side effects (table 4 and table 5) (including life-threatening skin rash), and pharmacology of lamotrigine are discussed separately; as are the use of lithium during pregnancy, dose, use of serum concentrations to establish the proper dose, side effects, and pharmacology of lithium.

- (See "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy", section on 'Refractory patients'.)
- (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects".)
- (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Lamotrigine'.)
- (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Lamotrigine'.)

Specific medication interactions that can occur may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

- **Electroconvulsive therapy (ECT)** – For refractory pregnant patients with bipolar major depression that does not respond to sequential trials of lamotrigine, quetiapine, fluoxetine plus olanzapine, and lamotrigine plus lithium, we suggest electroconvulsive therapy (ECT). Lamotrigine and lithium are tapered and discontinued over a period of one to two weeks prior to starting ECT. Lamotrigine is generally tapered by the same amount for each dose decrease, as is lithium. As an example, lamotrigine 200 mg per day is decreased by 50 mg

per day every three to four days, and lithium 1200 mg per day is tapered by 300 mg per day every three to four days.

Reviews have found that ECT is efficacious and safe for patients with bipolar major depression who are not pregnant, as well as patients who are pregnant [37,38]; ECT is thus recommended by several practice guidelines [7,34,39,40]. The efficacy, adverse maternal and fetal effects, and reproductive safety of ECT are discussed separately, as is the technique for performing ECT during pregnancy.

- (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy", section on 'Bipolar major depression'.)
- (See "Bipolar disorder in pregnant women: Screening, diagnosis, and choosing treatment for mania and hypomania", section on 'Refractory patients'.)
- (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Electroconvulsive therapy'.)
- (See "Technique for performing electroconvulsive therapy (ECT) in adults", section on 'Pregnancy'.)

ADJUNCTIVE TREATMENT

Psychotherapy — For pregnant patients with bipolar major depression who are treated with pharmacotherapy, we suggest adjunctive psychotherapy based upon randomized trials in nonpregnant patients [2,6,41]. As an example, a one-year randomized trial compared intensive psychotherapy plus pharmacotherapy with brief psychoeducation plus pharmacotherapy in 293 nonpregnant patients with bipolar major depression [42]. Intensive psychotherapy consisted of family therapy, cognitive-behavioral therapy, or interpersonal and social rhythm therapy, with up to 30 sessions (50 minutes each) administered over nine months; brief psychoeducation included three 50-minute sessions instructing patients about the clinical features and treatment of bipolar disorder. Recovery occurred in more patients who received adjunctive intensive psychotherapy compared with brief psychoeducation (64 versus 52 percent), and outcome did not differ significantly among the three intensive therapies. Using psychotherapy is also supported by randomized trials in pregnant patients with unipolar major depression [43], and is consistent with treatment guidelines [26].

Omega-3 fatty acids — For pregnant patients with bipolar major depression, dietary supplementation with omega-3 fatty acids (eg, eicosapentaenoic acid 1 to 2 grams per day) as adjunctive treatment is reasonable, based upon limited evidence in meta-analyses of

randomized trials (which excluded pregnant patients) and the apparent lack of serious side effects. In addition, prenatal intake of omega-3 fatty acid supplements may have modest beneficial effects on fetal neurodevelopment, and do not have known harmful effects. The efficacy of omega-3 fatty acids for bipolar depression and the risks and benefits during pregnancy are discussed separately. (See "Bipolar major depression in adults: Investigational and nonstandard approaches to treatment", section on 'Omega-3 fatty acids' and "Fish consumption and marine omega-3 fatty acid supplementation in pregnancy".)

RESIDUAL INSOMNIA

Bipolar major depression in pregnant patients often includes insomnia, which may persist despite resolution of the depressive syndrome. For patients with residual insomnia, we suggest behavioral therapy, including education about sleep hygiene (table 6) and stimulus control (table 7). Patients unresponsive to behavior therapy typically receive additional treatment with low dose doxepin. Treatment of insomnia is discussed separately. (See "Overview of the treatment of insomnia in adults".)

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: Bipolar disorder".)

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: Bipolar disorder (The Basics)" and "Patient education: Coping with high drug prices (The Basics)".)

- Beyond the Basics topics (See "Patient education: Bipolar disorder (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)".)

These educational materials can be used as part of psychoeducational psychotherapy. (See "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies", section on 'Group psychoeducation'.)

The National Institute of Mental Health also has educational material explaining the symptoms, course of illness, and treatment of bipolar disorder in a booklet entitled "Bipolar Disorder," which is available online at the website or through a toll-free number, 866-615-6464. The web site also provides references, summaries of study results in language intended for the lay public, and information about clinical trials currently recruiting patients.

More comprehensive information is provided in many books written for patients and family members, including The Bipolar Disorder Survival Guide: What You and Your Family Need to Know, written by David J. Miklowitz, PhD (published by The Guilford Press, 2002); An Unquiet Mind: A Memoir of Moods and Madness, written by Kay Jamison, PhD (published by Random House, 1995); and Treatment of Bipolar Illness: A Casebook for Clinicians and Patients, by RM Post, MD, and GS Leverich, LCSW (published by Norton Press, 2008).

The Depression and Bipolar Support Alliance (available at the website or 800-826-3632) is a national organization that educates members about bipolar disorder and how to cope with it. Other functions include increasing public awareness of the illness and advocating for more research and services. The organization is administered and maintained by patients and family members, and has local chapters.

The National Alliance on Mental Illness (available at the website or 800-950-6264) is a similarly structured organization devoted to education, support, and advocacy for patients with any mental illness. Bipolar disorder is one of their priorities.

SUMMARY AND RECOMMENDATIONS

- Bipolar disorder is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3). (See 'Definition of bipolar disorder' above and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

- Pharmacotherapy is indicated for pregnant patients with bipolar major depression that is characterized by (see 'Indications' above):
  - Suicidal or homicidal ideation or behavior
  - Aggressive behavior
  - Psychotic features (delusions or hallucinations)
  - Poor judgement that places the patient or others at imminent risk of being harmed
  - Moderate to severe impairment of social or occupational functioning
- An individual drug trial for pregnant patients with bipolar major depression typically lasts six to eight weeks before determining whether treatment is beneficial. (See 'General principles and management' above.)
- For pregnant patients with bipolar major depression, we suggest lamotrigine as first line treatment rather than other medications (**Grade 2C**). (See 'First line treatment' above.)
- For pregnant patients with bipolar major depression who do not respond to lamotrigine or cannot tolerate it, we suggest quetiapine rather than other medications (**Grade 2C**). (See 'Treatment resistance' above.)
- Pregnant patients with refractory bipolar major depression that does not respond to lamotrigine or quetiapine are often treated with fluoxetine plus olanzapine, lamotrigine plus lithium, or electroconvulsive therapy. (See 'Refractory patients' above.)
- For pregnant patients with bipolar major depression who are treated with pharmacotherapy, we suggest adjunctive psychotherapy (**Grade 2B**). (See 'Psychotherapy' above.)

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