Bipolar disorder in pregnant women: Screening, diagnosis, and choosing treatment for mania and hypomania

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All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Mar 19, 2023.**

INTRODUCTION

Medications are commonly used to treat pregnant patients, including those with manic and hypomanic episodes [1]. At least one prescription drug is taken by more than 80 percent of pregnant patients across the world [2] and psychotropic drugs are taken by at least 10 percent [3].

This topic discusses pharmacotherapy for pregnant patients with mania or hypomania. Treatment of bipolar major depression during pregnancy, prenatal maintenance pharmacotherapy for bipolar disorder, the teratogenic and postnatal risks of medications used for bipolar disorder, and the general treatment of mania and hypomania are discussed separately.

- (See "Bipolar disorder in pregnant women: Treatment of major depression".)
- (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 mania and hypomania in adults: Choosing pharmacotherapy".)

DEFINITION OF BIPOLAR DISORDER

Bipolar disorder is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3) [4]. 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 of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Clinical features".)

SCREENING AND DIAGNOSIS

An overview of screening for bipolar disorder in pregnant women and making the diagnosis is presented in the algorithm (algorithm 1) [5,6]. Screening is usually performed in early pregnancy [7].

We suggest initially screening for depression using the self-report, 10-item Edinburgh Postnatal Depression Scale (figure 1 and figure 2) [8]. A reasonable alternative is the self-report, nine-item Patient Health Questionnaire (table 4) [9-13]. Screening pregnant women for depression, with services in place to ensure follow-up for diagnosis and treatment, is consistent with the practice guidelines issued by the United States Preventive Services Task Force [9,14] and the Canadian Network for Mood and Anxiety Treatments [15] and is strongly recommended by the American Psychiatric Association [16]. Patients who screen positive for depression are then screened for bipolar disorder, using the self-report, 15-item Mood Disorder Questionnaire (table 5) [17-19]. In using the Mood Disorder Questionnaire, we suggest ignoring the question about concurrent symptoms in section two and the question about psychosocial functioning in section three. A reasonable alternative to the Mood Disorder Questionnaire is the clinician administered, 12-item Composite International Diagnostic Interview (table 6) [20,21].

Evidence supporting this approach includes studies that suggest bipolar disorder is present in up to 20 percent of pregnant or postpartum women who screen positive for depression in primary care or obstetric clinics [22]. In addition, a study of women receiving prenatal care in an obstetric clinic, who were routinely administered the Edinburgh Postnatal Depression Scale and Mood Disorder Questionnaire, found that the likelihood of a positive screen for bipolar disorder was higher in women who initially screened positive for depression, than women who screened negative for depression (odds ratio 12) [23].

Although questions have been raised as to whether the Mood Disorder Questionnaire performs well enough to recommend its use [24], multiple studies in psychiatric settings have found that disregarding the question about psychosocial functioning in section three improved the instrument's psychometric properties, such that sensitivity was good to excellent and specificity was fair to excellent [17].

In addition, studies of perinatal women have also found that the Mood Disorder Questionnaire can be a useful screening tool [25]. As an example, a study enrolled pregnant (n = 95) or postpartum (n = 55) patients who were referred to a women's mental health program and administered the Mood Disorder Questionnaire and conducted diagnostic interviews [26]. After disregarding the question about concurrent symptoms in section two and the question about psychosocial functioning in section three, both the sensitivity (89 percent) and specificity (84 percent) were excellent.

Patients who screen positive for bipolar disorder require an interview to establish the diagnosis. Bipolar I disorder is diagnosed in patients with a current or past history of at least one manic episode (table 1) [27]. Bipolar II disorder is diagnosed in patients with a history of at least one episode of hypomania (table 2), at least one episode of major depression (table 3), and no history of mania. Additional information about diagnosing bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

Patients who screen positive for depression but not for bipolar disorder require an interview to establish the diagnosis of unipolar depression. Unipolar major depression (major depressive disorder) is characterized by a history of one or more major depressive episodes (table 7) and no history of mania (table 1) or hypomania (table 2) [27]. Additional information about diagnosing unipolar major depression and other unipolar depressive syndromes is discussed separately. (See "Unipolar depression in adults: Assessment and diagnosis".)

INDICATIONS FOR PHARMACOTHERAPY

Pharmacotherapy is indicated for pregnant patients with manic and hypomanic episodes that are characterized by [28]:

- 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
- Involvement in pleasurable activities that have a high potential for painful consequences (eg, unrestrained buying sprees or sexual indiscretions)

Medications may not be indicated for relatively mild episodes of hypomania. However, it is not clear which untreated hypomanic episodes will progress to mania that requires pharmacotherapy.

MANAGEMENT

General principles — Bipolar mood episodes during pregnancy are usually treated by perinatal or general psychiatrists in collaboration with obstetricians and primary care clinicians [29-33].

For manic and hypomanic pregnant patients, treatment is based upon randomized trials that excluded pregnant patients [34], as well as observational studies, birth registries, and clinical experience [35]. Preferred drugs include medications that were effective and well tolerated prior to pregnancy and have a relatively favorable reproductive safety profile [36]. For patients who are taking medications at the time of conception and are clinically stable, it is generally preferable to continue the same regimen rather than switch medications. Switching exposes the fetus to additional medications and may increase the risk of recurrent mood episodes in the mother. However, changing medications is reasonable for women who are taking valproate when they become pregnant. (See 'Drugs that are avoided' below.)

To reduce the risk of teratogenic and postnatal effects in the offspring of pregnant bipolar patients who are treated with pharmacotherapy, clinicians should attempt to use [29,36,37]:

- Drugs with fewer known teratogenic and postnatal effects
- Monotherapy
- The minimal effective dose

The risks of teratogenic and postnatal effects from medications commonly used to treat bipolar disorder are discussed separately. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy".)

Although monotherapy is desirable, medication combinations may be necessary during pregnancy and appear to be common [32,38-40]. As an example, a prospective study found that among 54 pregnant patients with bipolar disorder who were treated with psychotropic medications (eg, antipsychotics, lithium, and/or antidepressants), polypharmacy occurred in 65 percent [41].

We avoid using subtherapeutic doses because they may precipitate maternal illness and do not eliminate fetal exposure [36].

For pregnant patients with bipolar mood episodes that occur during maintenance pharmacotherapy, we favor increasing the dose within the therapeutic dose range rather than starting a second medication [29,42,43]. This includes ensuring serum concentrations are in the therapeutic range for medications such as lithium, as well as increasing the dose to achieve a higher serum level within the therapeutic range, provided that side effects do not intervene. However, as described above, many patients require medication combinations.

Setting — The setting for prenatal treatment of bipolar mood episodes depends upon the type and severity of symptoms, level of psychosocial functioning, and available support [42,44,45]:

- Inpatient hospitalization is often required for safety and stabilization of patients with severe symptoms (eg, suicidal ideation with a specific plan or intent)
- Partial hospital (day) treatment may be feasible for managing moderate symptoms (eg, suicidality that does not pose an imminent risk, such as fleeting thoughts of killing oneself with vague or nonexistent plans and no intent)
- Outpatient treatment may be suitable for patients with less acute symptoms (eg, thoughts that family members would be better off if the patient was dead, with no plan or intent to commit suicide)

Monitoring patients — The psychiatric status of pregnant bipolar patients should be regularly monitored, with particular attention to suicidal ideation and psychosis [46,47]. Patients taking medications are also assessed for therapeutic and adverse effects. In addition, serum concentrations of medications with established therapeutic levels (eg, lithium) should be checked. Monitoring pregnant patients who take lithium is discussed separately. (See "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy", section on 'Refractory patients'.)

The frequency of assessing pregnant bipolar patients generally ranges from daily to monthly, depending upon the type and severity of symptoms. Hospitalized patients are monitored daily, and patients with active suicidal ideation, a specific plan, and intent to kill themselves typically require constant observation. Outpatients who have not achieved substantial improvement in the number, intensity, and frequency of symptoms are generally seen weekly; patients who have improved substantially may be seen every two to four weeks until they remit.

Duration of an individual drug trial — We suggest treating pregnant patients with mania and hypomania for three weeks before determining whether a specific drug is beneficial, based upon the duration of most randomized trials (which excluded pregnant patients) [34]. Response is defined as stabilizing the patient's safety and substantial improvement in the number, intensity, and frequency of symptoms.

CHOOSING SPECIFIC MEDICATIONS

Despite clinical differences between mania and hypomania (eg, hypomania is less severe than mania), for the purpose of treatment these mood elevated syndromes are considered to be similar and thus treated with the same medications [42,44,45].

First-line medications — For manic and hypomanic pregnant patients, we suggest first-generation antipsychotics, which have been widely used during pregnancy [29,36,48]. Using antipsychotics as first-line treatment is consistent with practice guidelines [15,49], including the British Association for Psychopharmacology [46] and the United Kingdom National Institute for Health and Care Excellence [47].

Among antipsychotics, we prefer haloperidol, based upon its demonstrated efficacy in randomized trials (which excluded pregnant patients) [34] and other studies that suggest haloperidol is not associated with an increased risk of congenital anomalies [29,36,50]. In addition, using haloperidol is consistent with practice guidelines from the British Association for Psychopharmacology [46], and haloperidol is preferred by many experts [1,39,51]. Other first-generation antipsychotics that are reasonable alternatives to haloperidol include chlorpromazine, fluphenazine, perphenazine, thiothixene, and trifluoperazine [52]. Clinicians can expect that response to a first-generation antipsychotic will occur in approximately 50 percent of patients, based upon trials in nonpregnant patients [53].

The efficacy of haloperidol for treating mood elevated syndromes appears to be comparable to risperidone and olanzapine, and superior to quetiapine and lithium [34]. In addition, there is more experience using haloperidol during pregnancy compared with second-generation antipsychotics, and the reproductive safety profile of haloperidol is generally regarded as superior to lithium. The efficacy of haloperidol, risperidone, olanzapine, quetiapine, and lithium (in randomized trials that excluded pregnant patients) is discussed separately, as is the reproductive safety profile of these drugs, and the dose, side effect profile (table 8), and pharmacology of haloperidol. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy" and "Teratogenicity, pregnancy complications, and postnatal risks of

antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy" and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)

For pregnant bipolar patients who cannot tolerate the usual minimal therapeutic dose of haloperidol (5 to 10 mg per day) because of extrapyramidal symptoms (EPS), we suggest cautiously reducing the dose (eg, by 1 to 2 mg per day), while closely monitoring the patient for exacerbation of mood elevated symptoms. If decreasing the dose is unfeasible or inadequate, we suggest tapering and discontinuing haloperidol over one to two weeks and at the same time starting and titrating up a low-potency agent (eg, chlorpromazine). Haloperidol is tapered by the same amount for each dose decrease. As an example, haloperidol 8 mg per day is decreased by 2 mg per day every one to three days. The dose and side effects of chlorpromazine are discussed separately.

For pregnant patients receiving haloperidol who develop Parkinsonism or dystonia, a reasonable alternative to switching drugs is to add diphenhydramine. Reviews suggest that the risk of teratogenicity with antihistamines such as diphenhydramine appears to be low [54] and that fetal organ malformation appears to be less likely with diphenhydramine than amantadine, benztropine, and trihexyphenidyl [55,56]. Additional information about the treatment of EPS and the teratogenic risks of antiparkinsonian drugs is discussed separately. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Antiparkinsonian drugs used for treating extrapyramidal symptoms' and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Extrapyramidal symptoms'.)

Resistant patients — In our clinical experience, pregnant patients with manic and hypomanic episodes often do not respond to or tolerate haloperidol. (Response is defined as stabilizing the patient's safety and substantial improvement in the number, intensity, and frequency of symptoms.) For these resistant patients, we suggest in order of preference risperidone, quetiapine, or olanzapine, based upon their efficacy and side effects in randomized trials (that excluded pregnant patients) [34], as well as study findings that suggest these drugs are not associated with an increased risk of major malformations [40,57,58]. Using second-generation antipsychotics during pregnancy is consistent with the practice of many perinatal psychiatrists [39]. Up to 50 to 60 percent of patients may respond, based upon trials in nonpregnant patients [53].

The efficacy of risperidone and olanzapine appears to be superior to quetiapine and lithium; quetiapine appears to be better tolerated than olanzapine; and although the efficacy of quetiapine and lithium appear comparable, quetiapine may be better tolerated [34]. In addition, study findings suggest that second-generation antipsychotics are not associated with an

increased risk of major malformations [39,40,57,58], whereas lithium is generally regarded as teratogenic [59-61]. The preference for treating pregnant bipolar patients with risperidone, quetiapine, or olanzapine rather than lithium is consistent with practice guidelines from the United Kingdom National Institute for Health and Clinical Excellence [47].

However, second-generation antipsychotics, particularly olanzapine, may cause metabolic complications (eg, hyperglycemia and obesity) that are associated with risks to the mother and fetus [62,63]. These risks are discussed separately, as is monitoring of metabolic parameters in pregnant patients taking second-generation antipsychotics. (See "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy", section on 'Metabolic complications' and "Metabolic syndrome in patients with severe mental illness: Epidemiology, contributing factors, pathogenesis, and clinical implications" and "Modifiable risk factors for cardiovascular disease in patients with severe mental illness".)

To switch drugs, haloperidol is tapered and discontinued over one to two weeks while at the same time risperidone is started and titrated up. We generally taper haloperidol by the same amount for each dose decrease. As an example, haloperidol 8 mg per day is decreased by 2 mg per day, every one to three days. For resistant pregnant bipolar patients who do not respond to or tolerate treatment with one second-line medication, we suggest tapering and discontinuing the failed medication over one to two weeks at the same time that another second-line medication is started and titrated up. The failed medication is generally tapered by the same amount for each dose decrease. As an example, risperidone 6 mg per day is decreased by 1 to 2 mg per day, every one to three days.

The efficacy of risperidone, quetiapine, and olanzapine for treating mood elevated syndromes (in randomized trials that excluded pregnant patients) is discussed separately, as are the doses, side effects (table 8), pharmacology, and reproductive safety profiles. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy" and "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Second-generation' and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Refractory patients — Based upon clinical experience, prenatal manic and hypomanic episodes generally respond to sequential trials of haloperidol, risperidone, quetiapine, and olanzapine. (Response is defined as stabilizing the safety of the patient, as well as substantial improvement in the number, intensity, and frequency of symptoms.) However, for refractory patients who do not respond to antipsychotics, we suggest in order of preference lithium and electroconvulsive therapy (ECT) [64]. For patients unresponsive to sequential trials of lithium and ECT, other options include lithium plus an antipsychotic.

- **Lithium** – For pregnant patients with manic episodes that do not respond to multiple antipsychotics, we suggest lithium, based upon its efficacy and side effects in randomized trials (which excluded pregnant patients) [34]. Although lithium is generally regarded as teratogenic due to increased risks of cardiac defects (eg, Ebstein anomaly) [60,61,65], many experts consider the absolute risk small [1,29,38,56,65,66]. Clinicians can expect that up to approximately 50 percent of patients will respond, based upon trials in nonpregnant patients [53]. Use of lithium in pregnant patients with bipolar disorder who do not respond to antipsychotics is consistent with practice guidelines [46,67], including those from the United Kingdom National Institute for Health and Care Excellence [47].

  The dose schedule for lithium, use of serum concentrations to establish the proper dose, and lithium toxicity are discussed separately, as are using lithium during pregnancy and lithium's reproductive safety profile. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects" and "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy", section on 'Refractory patients' and "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Lithium'.)

- **Electroconvulsive therapy** – For pregnant patients with moderate to severe manic episodes that do not respond to sequential trials of antipsychotics and lithium, we suggest ECT, which is generally regarded as efficacious and safe [68,69]. The use of ECT for pregnant bipolar patients is consistent with recommendations in multiple practice guidelines [46,70,71], including those from the United Kingdom National Institute for Health and Care Excellence [47].

  ECT is typically well tolerated and there are no absolute contraindications to ECT, even among patients whose general medical status is compromised [68]. However, safety concerns regarding ECT necessitate preprocedure obstetric consultation (consistent with guideline recommendation), with emphasis upon assessing risk factors for spontaneous abortion, preterm labor, abruption, and uteroplacental insufficiency due to the association of ECT with transient increases or decreases in blood pressure and uterine contractions. The patient's general medical status is also evaluated; medical consultation prior to ECT is discussed separately, as is the use of ECT for patients with general medical conditions. (See "Medical evaluation for electroconvulsive therapy" and "Overview of electroconvulsive therapy (ECT) for adults", section on 'Patients with comorbid general medical illness'.)

  ECT is generally given three times per week on alternate days. Most patients regardless of indication remit with 6 to 12 treatments, but some patients require 20 or more. A review of

prenatal ECT found that the mean number of treatments per ECT course was 11 [69]. The number and frequency of treatments in the general use of ECT is discussed separately, as are the adjustments in ECT technique for pregnant patients. (See "Overview of electroconvulsive therapy (ECT) for adults", section on 'Treatment course' and "Technique for performing electroconvulsive therapy (ECT) in adults", section on 'Pregnancy'.)

Following a course of ECT, clinicians usually prescribe maintenance pharmacotherapy. (See "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy", section on 'Choosing a specific maintenance treatment'.)

Evidence supporting the use of ECT includes studies that found ECT is effective for mania in patients who are not pregnant. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy", section on 'Mania'.)

In addition, a review of observational studies of pregnant patients treated for mood or psychotic disorders with ECT found that among 68 cases with outcome data, at least partial remission occurred in 78 percent [69]. Among the seven patients with bipolar disorder, remission occurred in five and partial remission in one. A subsequent retrospective study of 12 pregnant bipolar patients found that remission occurred in 11 (92 percent) [72], and a case report described a pregnant patient with manic catatonia who remitted after two ECT treatments [73].

ECT during pregnancy is generally regarded as safe for the mother and fetus [68,74,75]. Many authorities think that ECT poses fewer risks than untreated bipolar mood episodes and medications that are potentially teratogenic (eg, valproate and to a lesser extent lithium) [1,68,69,76,77]. The reproductive safety profile of ECT is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment", section on 'Electroconvulsive therapy' and "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Electroconvulsive therapy'.)

The general adverse effects of ECT include cardiopulmonary events, aspiration pneumonia, fractures, dental and tongue injuries, headache, nausea, and cognitive impairment [68]. These side effects and their management are discussed separately. (See "Overview of electroconvulsive therapy (ECT) for adults", section on 'Adverse effects'.)

- **Lithium plus an antipsychotic** – For patients who do not respond to lithium monotherapy and decline or do not have access to ECT, we suggest adding either a first- or second-generation antipsychotic to lithium, based upon randomized trials that excluded pregnant patients. (Response is defined as stabilizing the safety of the patient, as well as

substantial improvement in the number, intensity, and frequency of symptoms.) For patients who do not respond to antipsychotics, lithium, and ECT, we concurrently start lithium plus an antipsychotic.

No head-to-head trials have compared medication combinations consisting of lithium plus an antipsychotic; we typically use lithium plus haloperidol, risperidone, quetiapine, or olanzapine. The choice of an antipsychotic is based upon factors including past response to medications, side effect profiles, comorbid general medical conditions, potential for drug-drug interactions, patient preference, and cost. As an example, if the patient previously showed a modest response to haloperidol and no response to risperidone, quetiapine, or olanzapine, we would choose lithium plus haloperidol.

The efficacy of lithium plus an antipsychotic in randomized trials (that excluded pregnant patients) is discussed separately, as are the doses, side effects, pharmacology, and reproductive safety profiles. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy" and "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

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

Refractory patients who do not respond to or tolerate one lithium/antipsychotic combination should be treated with a second combination. We usually taper and discontinue the failed antipsychotic at the same time that a different antipsychotic is started and titrated up. The failed antipsychotic is generally tapered over one to two weeks by the same amount for each dose decrease (eg, haloperidol 8 mg per day is decreased by 2 mg per day, every one to three days).

Severe anxiety or insomnia — For pregnant patients with mania, hypomania, or mixed episodes who also suffer severe anxiety or insomnia despite ongoing pharmacotherapy, we suggest small doses of an adjunctive benzodiazepine on an as-needed basis for as short a time as possible [1]. We prefer the high potency compounds lorazepam or clonazepam because they have shorter half-lives than diazepam and chlordiazepoxide and are thus less likely to accumulate over time and cause toxicity [1,78,79]. Alprazolam is generally discouraged because its short half-life can produce rebound anxiety. We generally use lorazepam (eg, 0.5 or 1 mg) because it has no active metabolites and may cross the placenta at a lower rate than other benzodiazepines [78]. Clonazepam (eg, 0.5 or 1 mg) is preferred for patients who require a drug with a longer half-life. The teratogenicity, pregnancy complications, and postnatal risks of

benzodiazepines are discussed separately. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Benzodiazepines'.)

Drugs that are avoided — For pregnant patients with manic episodes, we nearly always avoid valproate because of the risks of teratogenicity and adverse postnatal developmental outcomes [5,80,81]. This approach is consistent with multiple practice guidelines [46,49,67], including the American College of Obstetricians and Gynecologists [29], the Canadian Network for Mood and Anxiety Treatments [15], and the United Kingdom National Institute for Health and Care Excellence [47]. One review concluded that valproate may be more teratogenic than any other neuropsychiatric drug [82].

In addition, many regulatory agencies discourage or have banned the use of valproate in pregnant patients [80,82]:

- The European Medicines Agency in 2018 recommended that valproate be banned for bipolar disorder during pregnancy.
- The United Kingdom in 2018 banned the use of valproate in women of childbearing potential unless they enroll in a pregnancy prevention program.
- France in 2017 banned the use of valproate in women with bipolar disorder who are either pregnant or of childbearing age and not using contraception.
- The US Food and Drug Administration stated in 2016 that pregnant women with bipolar disorder should receive valproate only as a last resort.
- The New Zealand Medicines and Medical Devices Safety Authority declared in 2014 that valproate is contraindicated in pregnancy.

Evidence supporting the decision to not use valproate during pregnancy includes observational studies that were conducted largely in patients with epilepsy and yielded robust results [46,80,82]. As an example, a meta-analysis of 14 studies (n>100,000 pregnant women) found that the probability of major congenital malformations was three times greater in neonates exposed to valproate than unexposed neonates (odds ratio 3.4, 95% CI 2.5-4.5) [47]. Although these were observational studies, the results are thought to be valid because of the large magnitude of the effect as well as other factors, including the variety of adverse effects, dose-dependent relationship between exposure and risks, and consistency of results across studies [82].

Additional information about prenatal valproate and the risks of major congenital malformations and adverse neurodevelopmental outcomes is discussed in the context of treating epilepsy. (See "Risks associated with epilepsy during pregnancy and the postpartum period", section on 'Risks with specific ASMs'.)

MAINTENANCE TREATMENT

Following recovery from prenatal bipolar mood episodes with pharmacotherapy, we suggest that patients receive maintenance treatment. For patients who decline maintenance pharmacotherapy, abrupt discontinuation of medications should be avoided. Rather, clinicians should attempt to taper and discontinue drugs over the course of at least 15 days to minimize the risk of relapse, based upon observational studies [83]. Prenatal maintenance pharmacotherapy and the risk of abruptly discontinuing pharmacotherapy are discussed separately. (See "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy" and "Bipolar disorder in women: Contraception and preconception assessment and counseling", section on 'Relapse after discontinuing pharmacotherapy'.)

SUBSYNDROMAL SYMPTOMS

Pregnant patients with subthreshold symptoms of hypomania (table 2) or mania (table 1) are at risk for suffering full-blown episodes [24]. Management of subsyndromal symptoms is based primarily upon clinical experience and patient preference. One strategy is watchful waiting (eg, monitoring patients once a week) and optimizing sleep (table 9). Another strategy is prescribing a low dose of a benzodiazepine (eg, lorazepam 0.5 mg once or twice daily) or a low dose of an antipsychotic (eg, haloperidol 0.5 mg once daily or quetiapine 25 mg once or twice daily), and titrating according to efficacy and adverse effects.

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). Pregnant patients can be screened for bipolar disorder with the Edinburgh Postnatal Depression Scale (figure 1 and figure 2) and the Mood Disorder Questionnaire (table 5). An overview of screening for and diagnosing bipolar disorder in pregnant women is presented in the algorithm (algorithm 1). Patients who screen positive require a diagnostic interview to establish the diagnosis. (See 'Definition of bipolar disorder' above and 'Screening and diagnosis' above and "Bipolar disorder in adults: Clinical features" and "Bipolar disorder in adults: Assessment and diagnosis".)

- Pharmacotherapy is indicated for pregnant patients with manic or hypomanic episodes that are characterized by:

  - 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
  - Involvement in pleasurable activities that have a high potential for painful consequences (eg, unrestrained buying sprees or sexual indiscretions)

  (See 'Indications for pharmacotherapy' above.)

- Clinicians treating pregnant patients with manic or hypomanic episodes should attempt to use drugs with fewer known teratogenic and postnatal effects, monotherapy, and the minimal effective dose. An individual drug trial typically lasts three weeks before determining the medication is beneficial. (See 'General principles' above.)

- For manic and hypomanic pregnant patients, we suggest first-generation antipsychotics rather than other medications (**Grade 2C**). Haloperidol has been widely used, but

reasonable alternatives include chlorpromazine, fluphenazine, perphenazine, thiothixene, and trifluoperazine. (See 'First-line medications' above.)

- For pregnant patients with manic or hypomanic episodes who do not respond to or tolerate first-generation antipsychotics, we suggest risperidone rather than other drugs (**Grade 2C**). However, reasonable alternatives in order of preference are quetiapine and olanzapine. (See 'Resistant patients' above.)

- Pregnant patients with refractory manic or hypomanic episodes that do not respond to antipsychotics are often treated with lithium, electroconvulsive therapy, or lithium plus an antipsychotic. (See 'Refractory patients' above.)

- Small doses of an adjunctive benzodiazepine (eg, lorazepam) on an as-needed basis can be helpful for severe anxiety or insomnia. (See 'Severe anxiety or insomnia' above.)

- Subsyndromal symptoms of hypomania or mania can be managed with watchful waiting and optimizing sleep, or with a benzodiazepine or antipsychotic at a low dose. (See 'Subsyndromal symptoms' above.)

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