Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy

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INTRODUCTION

Euthymic bipolar patients often receive maintenance pharmacotherapy prior to conception and during pregnancy [1,2]. Onset of bipolar disorder in women typically occurs during childbearing years [3], and most patients are at risk for recurrent mood episodes [2].

This topic reviews preconception and prenatal maintenance pharmacotherapy for bipolar patients. Indications for maintenance pharmacotherapy during pregnancy, the teratogenic risks of medications used for bipolar disorder, preconception counseling and care for bipolar disorder, and the general maintenance treatment of bipolar disorder are discussed separately.

- (See "Bipolar disorder in women: Indications for preconception and prenatal maintenance pharmacotherapy".)
- (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy".)
- (See "Bipolar disorder in women: Contraception and preconception assessment and counseling".)
- (See "Bipolar disorder in adults: Choosing maintenance treatment".)

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 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'.)

MANAGEMENT

General principles — Preconception and prenatal maintenance treatment for bipolar patients is usually provided by perinatal or general psychiatrists in collaboration with obstetricians and primary care clinicians [5-8].

After considering medical advice about the risks of fetal exposure to medications and the risks of avoiding preconception and prenatal maintenance pharmacotherapy, bipolar patients can choose to [9]:

- Maintain existing pharmacotherapy throughout conception, the pregnancy, and birth.
- Switch medications before they try to conceive to avoid drugs with a greater risk of teratogenicity.
- Discontinue pharmacotherapy prior to conception and restart medications during the second or third trimester (when organogenesis is completed).
- Discontinue pharmacotherapy prior to conception and remain medication-free throughout conception, the pregnancy, and delivery.

For bipolar patients who plan to or do become pregnant, we suggest maintenance pharmacotherapy to prevent mood episodes, based upon prospective observational studies that found untreated pregnant patients were at increased risk of recurrent mood episodes [1,10], as well as our clinical experience and that of several authorities [2,11-14]. However, for patients with a mild lifetime course of illness, it is reasonable to try to avoid pharmacotherapy during pregnancy. Indications for preconception and prenatal maintenance pharmacotherapy, risks of avoiding maintenance pharmacotherapy, and specific drugs suggested as preconception and prenatal maintenance treatment are discussed separately. (See "Bipolar disorder in women: Indications for preconception and prenatal maintenance pharmacotherapy"

and 'Risks of avoiding pharmacotherapy' below and 'Choosing a specific maintenance treatment' below.)

In prescribing preconception and prenatal maintenance pharmacotherapy, clinicians should attempt to use [2,5,15]:

- Drugs with fewer known teratogenic effects
- Monotherapy
- Doses at the low end of the therapeutic range

For euthymic bipolar patients who are receiving preconception or prenatal maintenance treatment with lamotrigine, a second-generation antipsychotic, or lithium, we suggest continuing the same drug [15,16]. For patients who are currently treated with valproate or carbamazepine, we suggest switching treatment to avoid the teratogenic effects of these two antiepileptics [11,17]. (See 'Switching from valproate or carbamazepine to less teratogenic drugs' below and "Risks associated with epilepsy during pregnancy and the postpartum period", section on 'Effects of ASMs on the fetus and child'.)

Female bipolar patients who want to conceive and continue maintenance treatment with valproate or carbamazepine can consider in vitro fertilization and use of a gestational carrier [8]. (See "Gestational carrier pregnancy".)

Medication doses generally need to be increased over the course of pregnancy, especially in the second and third trimesters, to prevent decreases in serum concentrations [18-21]. This is because pregnancy causes physiologic changes that alter pharmacokinetics (eg, increased extracellular fluid volume and body fat increase the volume of distribution, increased activity of hepatic enzymes increases metabolism, and increased renal blood flow and glomerular filtration rate increase renal elimination).

Recurrent bipolar mood episodes may occur despite preconception or prenatal maintenance pharmacotherapy because of problems with adherence [9]. Suggestions for improving adherence are discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Second-line'.)

Risk of adverse pregnancy and birth outcomes — The risk of adverse pregnancy and birth outcomes in women with bipolar disorder who receive pharmacotherapy and women with bipolar disorder who are not treated with pharmacotherapy is discussed separately. (See "Bipolar disorder in women: Contraception and preconception assessment and counseling", section on 'Risk of pregnancy complications'.)

Teratogenic and postnatal risks of pharmacotherapy — Following the first trimester, the risk of teratogenesis decreases and it is safer to prescribe drug combinations and higher doses. The teratogenic and postnatal risks of medications commonly used to treat bipolar disorder are discussed separately. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy".)

Risks of avoiding pharmacotherapy — For bipolar patients who are receiving preconception or prenatal maintenance pharmacotherapy, discontinuing treatment includes the following risks [1,10,12,17,22]:

- It is not known if maintenance drugs that are discontinued provide the same level of prophylactic efficacy after they are restarted.
- Stopping treatment may increase the risk of recurrent mood episodes, particularly if medications are discontinued abruptly (eg, in less than two weeks). (See "Bipolar disorder in women: Contraception and preconception assessment and counseling", section on 'Relapse after discontinuing pharmacotherapy'.)
- Treating recurrent episodes during pregnancy may be difficult and expose the fetus to more medications at higher doses compared with pharmacologic maintenance of euthymia.
- Postpartum mood episodes may occur more frequently in patients who are not treated with maintenance pharmacotherapy during pregnancy. A meta-analysis of eight prospective and retrospective observational studies found that postpartum mood episodes occurred in more patients who were medication free during pregnancy (n = 385), compared with patients who used prophylactic pharmacotherapy during pregnancy (n = 60; 66 versus 23 percent) [23].

Switching from valproate or carbamazepine to less teratogenic drugs — For bipolar patients who plan to become pregnant, are treated with valproate or carbamazepine, and are clinically stable (eg, euthymic for at least six months), we suggest that clinicians attempt to switch maintenance treatment to other drugs [11,24]. Valproate and carbamazepine are generally regarded as teratogens, primarily based upon observational studies of epilepsy patients [2,5,25,26]. In addition, prenatal exposure to these medications, particularly valproate, is associated with developmental delay and lower intelligence quotient scores [27,28]. Specific drugs suggested as preconception and prenatal maintenance treatment and the teratogenic effects of valproate and carbamazepine are discussed separately. (See 'Choosing a specific maintenance treatment' below and "Risks associated with epilepsy during pregnancy and the postpartum period", section on 'Effects of ASMs on the fetus and child'.)

For bipolar patients who plan to become pregnant and decide to switch from maintenance treatment with valproate or carbamazepine to a less teratogenic drug, we suggest changing pharmacotherapy at least three to six months before patients try to conceive, to assess the effectiveness of the new medication. Valproate or carbamazepine are tapered and discontinued over 15 to 30 days; this approach appears to be associated with a lower risk of recurrence than a faster taper [1]. The medication is tapered by the same amount for each dose decrease. As an example, valproate 2000 mg per day is decreased by 250 to 500 mg per day, every three to seven days. At the same time, the new medication is started and titrated up.

However, alternative medications may not work as well as valproate or carbamazepine, and switching medications can precipitate a recurrence of bipolar mood symptoms [29]. Thus, for patients with a history of poor outcomes using other medications, such as lamotrigine, quetiapine, risperidone, and lithium, it is reasonable to maintain valproate or carbamazepine, rather than switching to another medication. Patients treated with valproate or carbamazepine during pregnancy should also receive high doses of folic acid (eg, 4 to 5 mg per day), although the efficacy of folate supplementation in reducing the risk of neural tube defects is not clear [30]. Managing pregnant patients who receive valproate or carbamazepine is discussed separately in the context of epilepsy, including the use of folic acid. (See "Management of epilepsy during preconception, pregnancy, and the postpartum period", section on 'Management during pregnancy' and "Preconception and prenatal folic acid supplementation", section on 'Maternal use of antiseizure medications'.)

For bipolar patients who are maintained on valproate or carbamazepine and unexpectedly become pregnant, we suggest switching medications. (See 'Unplanned pregnancies' below.)

Monitoring patients — Bipolar patients receiving preconception or prenatal maintenance pharmacotherapy should be regularly monitored for recurrence of manic and depressive symptoms as well as medication side effects. Particular attention is given to suicidal ideation and to psychotic symptoms. Stable patients can be seen every one to two months. For patients who remit from an acute mood episode and remain stable, monitoring can be tapered, with progressively longer intervals between assessments. As an example, a patient who is seen every two weeks at the time of remission can be seen every two weeks for one to three more visits, then every one to two months until parturition. More frequent visits should be scheduled for patients who develop symptoms or side effects; monitoring acutely ill patients is discussed separately. (See "Bipolar disorder in pregnant women: Screening, diagnosis, and choosing treatment for mania and hypomania", section on 'Monitoring patients'.)

Adjunctive psychotherapy — For bipolar patients who receive preconception or prenatal maintenance pharmacotherapy, we suggest adjunctive psychoeducation or cognitive-behavioral

therapy (CBT), based upon randomized trials that excluded pregnant patients. Although no head-to-head trials have compared these psychotherapies, we generally choose psychoeducation because there are more data supporting its use, it is easier to administer than CBT and thus usually more available, and psychoeducation is generally an element of CBT. The evidence of efficacy for reducing recurrent mood episodes with other psychotherapies, such as family therapy and interpersonal and social rhythm therapy, is not as strong. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Choosing adjunctive psychotherapy'.)

CHOOSING A SPECIFIC MAINTENANCE TREATMENT

There are no randomized trials in bipolar patients who plan to or do become pregnant to guide preconception and prenatal maintenance pharmacotherapy; the benefits and risks of treatment are thus based upon randomized trials that excluded pregnant patients [31-33], as well as observational studies, birth registries, and clinical experience [18].

For euthymic bipolar patients who are receiving preconception or prenatal maintenance treatment with lamotrigine, a second-generation antipsychotic, or lithium, we suggest continuing the same drug (see 'General principles' above). For euthymic bipolar patients who plan to or do become pregnant and are not receiving preconception or prenatal maintenance treatment, we suggest maintenance treatment according to the sequence described in the subsections below. Patients initially receive first line therapy and progress through each step until they respond.

First line — For euthymic bipolar patients who plan to or do become pregnant, we suggest lamotrigine as first line maintenance treatment [5], based upon randomized trials that excluded pregnant patients. There are more data supporting the efficacy of lamotrigine for the general maintenance treatment of bipolar disorder compared with quetiapine and risperidone. In addition, a prospective observational study of euthymic, pregnant bipolar patients found that relapse occurred in significantly fewer patients who continued lamotrigine (n = 10) than patients who stopped pharmacotherapy (n = 16; 30 versus 100 percent) [10]. A second study of eight pregnant bipolar patients who received maintenance treatment with lamotrigine found that at delivery, the infants were full term, healthy, and without congenital malformations; in addition, none of the infants developed a rash [34]. The reproductive safety profile of lamotrigine is generally regarded as favorable [5,25,35], and there is more experience using lamotrigine during pregnancy compared with quetiapine and risperidone. Although there are more data supporting the efficacy of lithium than lamotrigine for the general maintenance treatment of

bipolar disorder, the reproductive safety of lamotrigine is generally regarded as comparable or superior to lithium.

Serum concentrations of lamotrigine should be measured prior to conception or as soon as possible in patients who present during pregnancy [34]. Concentrations are regularly monitored (eg, every four weeks) during pregnancy and the dose adjusted accordingly. Serum-level-to-dose ratios generally decrease during the first trimester due to increased drug clearance, and reach their lowest level during the third trimester. A dose increase of 20 to 25 percent from preconception baseline is often required to maintain baseline serum concentrations and euthymia.

After delivery, clearance of lamotrigine decreases and thus decreased doses are frequently necessary to maintain baseline serum concentrations and avoid toxicity. (See "Bipolar disorder in postpartum women: Treatment", section on 'Patients not breastfeeding'.)

Evidence for the efficacy of lamotrigine, quetiapine, risperidone, and lithium for delaying or preventing bipolar mood episodes is discussed separately, as are the reproductive safety profile of these drugs, and the dose schedule, side effect profile, and pharmacology of lamotrigine. (See "Bipolar disorder in adults: Choosing maintenance treatment" and "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy" and "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Lamotrigine'.)

Resistant patients — Maintenance treatment for bipolar disorder with lamotrigine is often not efficacious, based upon randomized trials (which excluded pregnant patients) [31]. For resistant bipolar patients who do not respond to or tolerate preconception or prenatal maintenance lamotrigine, we suggest quetiapine or risperidone, based upon their efficacy and adverse effects in randomized trials that excluded pregnant patients [32,36]. (Response is defined as psychopathology that is considerably less than full criteria for a mood episode, eg, no more than two moderately or three mildly intense symptoms.) No head-to-head trials have compared quetiapine and risperidone. The specific choice is thus based upon other factors, including past response to medications, side effect profiles, comorbid general medical conditions, patient preference, and cost.

Although there are more data supporting the maintenance efficacy of lithium than quetiapine or risperidone, study findings suggest that quetiapine and risperidone are not associated with an increased risk of major malformations [37-40], whereas lithium is generally regarded as teratogenic [24,41,42]. In addition, the preference for treating pregnant bipolar patients with quetiapine or risperidone rather than lithium is consistent with practice guidelines from the

United Kingdom National Institute for Health and Clinical Excellence [9,43]. However, second generation antipsychotics may cause metabolic complications. (See 'Metabolic complications' below.)

To switch drugs, lamotrigine is tapered and discontinued over one to two weeks while at the same time quetiapine or risperidone is started and titrated up. We generally taper lamotrigine by the same amount for each dose decrease. As an example, lamotrigine 200 mg per day is decreased by 50 mg per day, every two to three days.

For resistant bipolar patients who do not respond to preconception or prenatal maintenance treatment with either quetiapine or risperidone, we suggest tapering and discontinuing the failed medication over one to two weeks while at the same time the other drug is started and titrated up. The failed medication is generally tapered by the same amount for each dose decrease.

The efficacy of quetiapine and risperidone for the general maintenance treatment of bipolar disorder is discussed separately, as is the dose, side effect profile (table 4), pharmacology, and reproductive safety profile. (See "Bipolar disorder in adults: Choosing maintenance treatment" and "Bipolar mania and hypomania in adults: Choosing pharmacotherapy" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Second-generation'.)

Metabolic complications — Second-generation antipsychotics may cause hyperglycemia [44]. In pregnant women with diabetes, hyperglycemia is associated with increased risks of spontaneous abortion, congenital malformations, and macrosomia. (See "Pregestational (preexisting) diabetes: Preconception counseling, evaluation, and management".)

In addition, second-generation antipsychotics may cause obesity [44,45]. Obesity during pregnancy is associated with an increased risk of multiple obstetric complications, including gestational diabetes mellitus and pre-eclampsia. (See "Obesity in pregnancy: Complications and maternal management".) Although many clinicians use second-generation antipsychotics during pregnancy [46], some authorities generally avoid them due to concerns about excessive weight gain and gestational diabetes [25,26,47]. A review of observational studies (primarily case reports) found that gestational diabetes mellitus has been observed in patients who have taken clozapine, olanzapine, quetiapine, or risperidone [48].

Clinicians using second-generation antipsychotics in pregnant patients should manage potential metabolic complications by monitoring [9,24,43]:

- Weight gain.
- Blood pressure.
- Fasting serum glucose, cholesterol, and triglyceride concentrations. The normal reference range for cholesterol and triglycerides is generally higher in pregnant women compared with nonpregnant individuals (table 5). (See "Normal reference ranges for laboratory values in pregnancy".)

Patients are assessed at baseline and every one to three months during pregnancy [17,24]. In addition, a glucose tolerance test is performed every four months. (See "Gestational diabetes mellitus: Screening, diagnosis, and prevention".)

Refractory patients — Based upon clinical experience, many bipolar patients do not respond to or tolerate sequential trials of preconception or prenatal maintenance lamotrigine, quetiapine, and risperidone. (Response is defined as psychopathology that is considerably less than full criteria for a mood episode, eg, no more than two moderately or three mildly intense symptoms.) For these refractory patients, we suggest lithium [11,17]. Evidence for the efficacy of lithium includes the following:

- Randomized trials (that excluded pregnant patients) have demonstrated the benefit of maintenance treatment with lithium in bipolar disorder; these trials are discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Lithium'.)
- A prospective observational study found that relapse occurred in fewer pregnant bipolar patients who continued pharmacotherapy (n = 27, 85 percent received lithium) than patients who stopped pharmacotherapy (n = 62; 37 versus 86 percent) [1].
- A prospective observational study found that relapse occurred half as often in pregnant bipolar patients who received maintenance pharmacotherapy (n = 31, 97 percent received lithium) than patients who did not (n = 10; 19 versus 40 percent) [15].

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 [49].

Although lithium is generally regarded as teratogenic due to increased risks of cardiac defects (eg, Ebstein anomaly) [24,41,42], many authorities consider the absolute risk small [5,25,26,50]. For pregnant patients using lithium, we suggest prenatal screening for anomalies with high-resolution ultrasonography at 16 to 18 weeks gestation, and depending upon the results, fetal

echocardiography, which can aid decisions about pregnancy termination, referral for delivery at a hospital with the appropriate level of neonatal care, and postnatal interventions for congenital malformations [8,26,51]. The teratogenic effects of lithium are discussed separately. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Lithium'.)

For pregnant patients treated with lithium, we suggest using the lowest amount necessary to achieve a therapeutic serum concentration [41,52]. The total daily dose is often given in two to three divided doses (rather than a single daily dose) using controlled release preparations, to avoid high peak serum levels [15,53,54]; however, it is not known whether this reduces the risk of teratogenic effects [53]. Serum lithium concentrations are checked every two to four weeks during pregnancy, until 36 weeks gestation, at which point levels should be checked weekly [7,24,55]. The dose schedule for lithium, use of serum concentrations to establish the proper dose, and lithium toxicity are discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects".)

Additional laboratory monitoring of lithium includes thyroid and renal function tests that are checked at baseline and repeated every three months [24]. Normal reference ranges for laboratory tests often differ for gravid and nongravid patients (table 5). (See "Normal reference ranges for laboratory values in pregnancy".)

Serum lithium concentrations generally decrease during pregnancy and the doses required to effectively prevent bipolar mood episodes thus increase [2,19]. These changes are a consequence of increases in maternal glomerular filtration rate and extracellular fluid volume and their impact upon pharmacokinetics. As an example, renal excretion of lithium may increase 30 to 100 percent [41,54,55]. During the second and third trimesters, twice the prepregnancy dose of lithium may be required to achieve therapeutic serum concentrations [53]. In addition, serum lithium concentrations can be altered by concomitant medications and other clinical factors (eg, diarrhea). (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Prescribing lithium'.)

Frequent urination, thirst, weight gain, and nausea are common during pregnancy and can be exacerbated by lithium. Side effects of lithium are discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Managing lithium adverse effects'.)

For pregnant patients treated with lithium, delivery should occur in facilities with the ability to resuscitate neonates, given the risks of postnatal complications [24]. Postnatal toxicity and withdrawal secondary to lithium are discussed separately. (See "Teratogenicity, pregnancy

complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Lithium'.)

To avoid lithium toxicity, we suggest withholding lithium for one to two days before a scheduled delivery or at the onset of labor, consistent with the practice of many perinatal psychiatrists [7,20,56]. Although a brief reduction in serum lithium concentrations may possibly precipitate a postpartum relapse, the risk seems small. In a prospective observational study of nine pregnant bipolar patients treated with lithium in the third trimester, lithium was withheld for one to two days before a scheduled delivery or at the onset of labor; maternal serum concentrations decreased from a mean of 0.8 mEq/L (0.8 mmol/L) to 0.5 mEq/L (0.5 mmol/L), and none of the patients became symptomatic [56]. However, rather than withholding lithium as a means of avoiding lithium toxicity, it is reasonable to increase hydration close to the time of delivery [20].

For pregnant patients treated with lithium, adequate hydration must be maintained throughout labor, especially if the serum level drawn at the time of delivery is high. During labor and delivery, vascular volume can decrease through loss of blood as well as diaphoresis [19]. If oral intake is insufficient to maintain adequate hydration, adjunctive intravenous fluids are used to prevent dehydration and lithium toxicity [7,17].

After delivery, lithium is resumed when patients are medically stable (provided breastfeeding is not planned) at doses lower than those used during the third trimester, because maternal glomerular filtration rates rapidly decrease to pregravid levels [56,57]. Patients treated with lithium prior to conception are restarted on the prepregnancy dose. Patients not treated with lithium prior to conception are usually started at a dose of 600 to 900 mg per day, which is then increased by 300 to 600 mg every one to five days based upon response, tolerability, and body mass index. Serum concentrations are measured 24 hours after delivery and every three to five days until they stabilize at a therapeutic level. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Lithium dose and serum concentrations'.)

The newborn should be monitored for symptoms of lithium toxicity for up to 10 days after delivery [41,57], even if the maternal serum lithium concentration at delivery is within normal limits. Signs of neonatal toxicity at the time of delivery should prompt a cord serum level [24] and a neonatal electrocardiogram [41,57]. Neonatal lithium toxicity and withdrawal are discussed separately. (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Lithium'.)

For pregnant bipolar patients who do not respond to prenatal maintenance pharmacotherapy, become acutely ill, and respond to an acute course of electroconvulsive therapy (ECT), we

suggest maintenance ECT. Support for this approach comes from small observational studies that suggest ECT may be efficacious for pregnant bipolar patients and appears to be safe for perinatal patients. [58]. The efficacy and safety of using ECT in bipolar patients who are pregnant, as well as the technique, are discussed separately. (See "Bipolar disorder in pregnant women: Screening, diagnosis, and choosing treatment for mania and hypomania", section on 'Refractory patients' and "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Electroconvulsive therapy' and "Technique for performing electroconvulsive therapy (ECT) in adults", section on 'Pregnancy'.)

UNPLANNED PREGNANCIES

Unintended pregnancies in bipolar patients are common and may precipitate mood episodes. Two prospective observational studies of pregnant bipolar patients (n = 89 and 26) found that the pregnancy was not planned in 34 and 58 percent, and that unplanned pregnancy was associated with recurrent prenatal mood episodes [1,10].

For euthymic bipolar patients who unintentionally become pregnant during maintenance treatment with lamotrigine, a second-generation antipsychotic, or lithium, we suggest continuing the same drug [15,16].

For bipolar patients who are maintained on valproate or carbamazepine and unexpectedly become pregnant, we suggest switching medications. We typically titrate up the new drug as rapidly as tolerated, and then taper and discontinue the antiepileptic over the course of a few days. The antiepileptic is decreased the same amount for each dose reduction. As an example, valproate 1500 mg per day is decreased by 500 mg every one to two days. The choice of a new drug is discussed elsewhere in this topic, as is management of patients who decline switching medications. (See 'Choosing a specific maintenance treatment' above and 'Switching from valproate or carbamazepine to less teratogenic drugs' above.)

Bipolar patients who unexpectedly become pregnant may decide to discontinue maintenance pharmacotherapy. However, stopping medications (particularly over a period of less than two weeks) may increase the risk of recurrent mood episodes. (See "Bipolar disorder in women: Contraception and preconception assessment and counseling", section on 'Relapse after discontinuing pharmacotherapy'.)

Determining the gestational age will inform the decision to use maintenance pharmacotherapy in bipolar patients with unplanned pregnancies. The period of greatest risk for the teratogenic

effects of medications is between the third and eighth week of gestation (weeks of gestation are counted from the first day of the last menstrual period) (figure 1 and figure 2). Many unplanned pregnancies are discovered after this period of greatest risk has passed [59]; thus, discontinuing or switching treatment at this point often puts the mother at risk for relapse of a mood episode and provides minimal benefit to the fetus [46].

FOLIC ACID SUPPLEMENTATION

Folic acid is recommended for every woman planning to conceive a child and is discussed separately. (See "Preconception and prenatal folic acid supplementation" and "Nutrition in pregnancy: Dietary requirements and supplements", section on 'Folate/folic acid' and "Management of epilepsy during preconception, pregnancy, and the postpartum period", section on 'Folic acid supplementation'.)

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 their 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 their 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 their 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

- **Definition of bipolar disorder** – 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'.)

- **Prescribing maintenance pharmacotherapy** – Bipolar disorder is a highly recurrent illness. For bipolar patients who plan to or do become pregnant, we suggest maintenance pharmacotherapy rather than no treatment (**Grade 2C**). However, for patients with a mild lifetime course of illness, it is reasonable to try to avoid pharmacotherapy during pregnancy. (See 'General principles' above and "Bipolar disorder in women: Indications for preconception and prenatal maintenance pharmacotherapy" and 'Risks of avoiding pharmacotherapy' above.)

- **Avoiding teratogens**

  - In prescribing preconception or prenatal maintenance pharmacotherapy for bipolar patients, clinicians should attempt to use drugs with fewer known teratogenic effects, monotherapy, and doses at the low end of the therapeutic range. Following the first trimester, the risk of teratogenesis decreases and it is safer to prescribe drug combinations and higher doses. (See 'General principles' above.)

  - Valproate and carbamazepine are generally regarded as teratogens. For stable bipolar patients who plan to or do become pregnant and are currently treated with valproate and carbamazepine, we suggest switching treatment to a less teratogenic drug rather than maintaining valproate or carbamazepine (**Grade 2C**). However, it is reasonable to maintain valproate or carbamazepine for patients with a history of poor outcomes using other medications. (See 'Switching from valproate or carbamazepine to less teratogenic drugs' above.)

- **Choosing a specific maintenance treatment**

  - First line – For bipolar patients who plan to or do become pregnant, we suggest lamotrigine as first line maintenance treatment rather than other medications (**Grade 2C**). (See 'First line' above.)

  - Resistant patients – For patients who are unresponsive to or intolerant of lamotrigine, we suggest quetiapine or risperidone rather than other medications (**Grade 2C**). (See 'Resistant patients' above.)

  - Refractory patients – For refractory patients who do not respond to sequential maintenance treatment trials with lamotrigine, quetiapine, and risperidone, lithium is a reasonable option. Although lithium is generally regarded as teratogenic due to increased risks of cardiac defects, the absolute risk is considered low. Maintenance ECT may help patients unresponsive to maintenance pharmacotherapy. (See 'Refractory patients' above.)

- **Unplanned pregnancies** – For bipolar patients with unplanned pregnancies, determining the gestational age will inform the decision to use maintenance pharmacotherapy. The period of greatest risk for the teratogenic effects of medications is between the third and eighth week of gestation (figure 1 and figure 2). (See 'Unplanned pregnancies' above.)

- Folic acid **supplements** – Every woman planning to conceive a child should receive folic acid. (See "Preconception and prenatal folic acid supplementation" and "Nutrition in pregnancy: Dietary requirements and supplements", section on 'Folate/folic acid' and "Management of epilepsy during preconception, pregnancy, and the postpartum period", section on 'Folic acid supplementation'.)

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