# The Relationship Between Postpartum Psychosis and Bipolar Disorder: A Review

Linda H. Chaudron, M.D., M.S., and Ronald W. Pies, M.D.

***Background:*** The evidence for a spectrum of bipolar disorders is mounting. Of particular interest and importance is the evolution and recurrence of bipolar disorder in the postpartum period and its relationship to postpartum psychosis. Understanding whether such a phenomenological link exists has diagnostic, prognostic, and treatment implications.

***Objectives:*** A comprehensive review of (1) the literature regarding the relationships between postpartum psychosis and bipolar affective disorder, (2) the data regarding prophylactic treatment and acute management of postpartum psychosis and bipolar disorder in the puerperium, and (3) critical areas for future research.

***Study Design:*** MEDLINE and PubMed (1966–2002) databases were searched for English-language articles using the keywords *postpartum/puerperal depression*, *puerperal/postpartum psychosis*, *bipolar disorder*, *lithium*, *anticonvulsants*, *antipsychotics*, and *breastfeeding*.

***Results:*** Evidence from studies of women with a history of bipolar disorder, longitudinal studies of women with puerperal episodes of psychosis, and family studies support a link between postpartum psychosis and bipolar disorder.

***Conclusions:*** Understanding the relationship between postpartum psychosis and bipolar disorder has implications for perinatal and long-term treatment. Prophylactic treatment of women with bipolar disorder and/or a history of postpartum psychosis may be indicated. Epidemiological, genetic, and pharmacologic research must be completed to understand, prevent, and adequately treat postpartum psychosis.

*(J Clin Psychiatry 2003;64:1284–1292)*

*Received Jan. 2, 2003; accepted July 21, 2003.* *From the University of Rochester School of Medicine and Dentistry, Rochester, N.Y. (Dr. Chaudron); Tufts University School of Medicine, Boston, Mass. (Dr. Pies); and Harvard Medical School, Cambridge, Mass. (Dr. Pies).*

*Supported by an unrestricted grant from GlaxoSmithKline.*

*Dr. Chaudron has received honoraria from and has served on the speakers/advisory boards for Forest, GlaxoSmithKline, Pfizer, and Eli Lilly. Dr. Pies has received research funding from various pharmaceutical and related corporate entities; has received ad hoc stipends from Abbott, Janssen, GlaxoSmithKline, and other pharmaceutical or related corporate entities; and is a consultant for Apothecom Associates.*

*The authors acknowledge the editorial assistance and content contributions of Jacqueline Brooks, M.B.B.Ch., M.R.C.Psych.*

*Corresponding author and reprints: Linda H. Chaudron, M.D., M.S., Department of Psychiatry, University of Rochester School of Medicine and Dentistry, 300 Crittenden Boulevard, Box PSYCH, Rochester, NY 14642 (e-mail: linda_chaudron@urmc.rochester.edu).*

The mental health of women in the weeks and months following childbirth is of critical importance to the well-being of the mothers, their children, and their families. For more than 2 decades, researchers have tried to elucidate the prevalence, presentation, and treatment of postpartum mental disorders. Postpartum "blues" may affect more than half of women who give birth,[1–4] and nonpsychotic major depressive disorder occurs in 10% to 20% of women within 6 months of delivery.[5–9] In contrast, postpartum psychosis affects only 0.1% to 0.2% of women.[10] Understandably, most studies and scientific reviews have focused on postpartum blues and depression.[11–13] Changes in the definition of postpartum psychosis, confusion over its classification, and disagreements over its clinical presentation have all contributed to the paucity of research on this serious disorder. This is unfortunate, since postpartum psychosis often has severe consequences for both mothers and their children.

In addition, researchers have long suspected, but have not confirmed, a link between postpartum psychosis and bipolar disorder. Given the high prevalence, morbidity, and mortality of bipolar disorder, and the implications for prevention and treatment, it is essential that this possible link be explored.

Thus, the goals of this literature review are (1) to review the current body of knowledge regarding the established and hypothesized relationships between bipolar disorder and postpartum psychosis, (2) to review the current recommendations for prophylaxis and management of postpartum psychosis, and (3) to identify critical areas for future research.

MEDLINE and PubMed (1966–2002) databases were searched for English-language articles using the keywords *postpartum/puerperal depression*, *puerperal/postpartum psychosis*, *bipolar disorder*, *lithium*, *anticonvulsants*, *antipsychotics*, and *breastfeeding*.

## DEFINITIONS AND CLASSIFICATIONS

Two primary areas of confusion in the nosology of all postpartum psychiatric disorders are (1) whether these are discrete diagnostic entities, and (2) what time frame should govern the use of the term *postpartum.*

Opinion regarding postpartum psychosis falls into 3 main "camps"[14]: those who regard it as a unique diagnos-

Table 1. Postpartum Syndromes

| Syndrome | Onset/Course | Features | Management |
|---|---|---|---|
| Postpartum blues | Peaks 3–5 days after delivery and lasts from several days up to 2 weeks | Crying, emotional lability, irritability; psychotic features not present | Usually self-limited; reassurance, education, emotional support; counseling may be useful |
| Postpartum depression | Within 6 months of delivery; usually 2–4 weeks postpartum | Nonpsychotic major depressive disorder with low mood, anxiety, altered sleep (initial insomnia), appetite disturbance, fatigue, poor concentration, feelings of maternal inadequacy; thoughts of harming infant, if present, usually not acted upon | Individual and group psychotherapy; reduction of psychosocial stressors; antidepressant medication often useful; consider hospitalization in severe cases |
| Postpartum psychosis | Usually within 3 weeks of childbirth | Delusions, confusion, hallucinations, thought process disorder, agitation, insomnia | Hospitalization; medical workup to rule out organic factors; mood stabilizers; antipsychotics; electroconvulsive therapy; caution regarding use of antidepressants |

Data from Burt and Hendrick.[21]

tic entity,[15] those who see it as a variant of bipolar disorder,[16] and those who regard childbirth as a nonspecific stressor that can trigger a wide variety of psychotic illnesses.[17] We will review pertinent studies that support and refute each of these opinions.

In contrast to much of the European literature, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision (DSM-IV-TR) does not recognize "postpartum" or "puerperal" psychiatric disorders as discrete diagnoses; rather, it permits the term *postpartum onset* to be used only as a specifier. Thus, postpartum onset may be applied to a major depressive episode, a manic or mixed episode in bipolar I or bipolar II disorder, and a brief psychotic disorder.[18]

The second major area of nosological debate concerns the time frame for the designation *postpartum*. The most restrictive definition is that of the DSM-IV-TR, which requires the onset of illness to occur within 4 weeks of childbirth. Researchers often use a less restrictive boundary of 3 months, because the peak prevalence of psychiatric illness and hospitalization occurs within 3 months of childbirth.[10] Many clinicians and some researchers use a very liberal boundary of 1 year,[19,20] contributing to the lack of consensus.

Given the confusion in these 2 areas—discreteness of diagnosis and expansiveness of time frame—it is often difficult to interpret and compare studies of postpartum psychiatric illnesses. Another confound is the widespread use of ill-defined terms, such as *puerperal psychosis*, *psychotic states*, *affective episodes*, *affective states*, *depressive states*, *postpartum depression*, *postpartum psychiatric illness*, and *postpartum mood symptom.*

## VARYING CLINICAL SYNDROMES

Despite the "official" designations in the DSM-IV-TR, clinicians often use the term *postpartum depression* or *postpartum psychosis* to describe a variety of psychiatric disorders occurring after labor and delivery. In fact, postpartum mood states form at least 3 distinct clinical entities (postpartum blues, postpartum depression, postpartum psychosis), though symptoms of each may overlap and be mistaken for one another. The clinical features of postpartum blues and postpartum depression have been reviewed elsewhere[11,12,21] and are summarized in Table 1.

Postpartum psychosis most often has an abrupt onset. Studies consistently find that more than two thirds of women who develop postpartum psychosis do so within the first 2 weeks following childbirth.[22–24] Women may present in any mood state, including depressed, manic, or mixed states. Many authors have noted a "delirious" or "perplexed" presentation with a waxing and waning confusional state that some propose may be unique to postpartum psychosis.[22,25,26] No typical presentation has been determined. However, women often present with delusions, disorganized behavior, and/or hallucinations. Delusions often revolve around the infant or children and must be carefully assessed, since women with postpartum psychosis commonly have thoughts of harming their infants[25,26] and sometimes act on these thoughts.[25–27] Whereas suicide is rare in the postpartum period,[28] women with severe postpartum episodes requiring hospitalization have very high rates of suicide.[19] Among postpartum women who commit infanticide, filicide, or suicide, the predominant affective symptom is depression rather than mania.[27]

## POSTPARTUM PSYCHOSIS AND BIPOLARITY: EXPLORING THE LINK

Evidence of a link between bipolar disorder and postpartum psychosis exists in 4 areas: symptom presentation, diagnostic and longitudinal outcomes, family history, and recurrences in women with bipolar disorder.

### Symptomatology

Few studies have systematically described the puerperal psychosis symptom presentation. One of the most detailed studies compared 58 women with puerperal psychosis to 52 women with nonpuerperal psychosis.[16]

  

Manic symptoms, defined as elation, mood lability, rambling speech, distractibility, observed euphoria, and increased activity, were significantly more common and more severe in the puerperal group. The authors also found greater severity of confusion and "incompetence" among this group. Pressured speech, decreased need for sleep, and grandiosity were not significantly more common in the puerperal group, but a trend in this direction was found. Systematic delusions, persecutory ideas, auditory hallucinations, odd affect, and social withdrawal were less common among women with puerperal psychosis.

Another detailed study compared women with childbearing-related (N = 21) and nonchildbearing-related (N = 96) psychotic episodes.[26] The authors found that cognitive disorganization, bizarre behavior, and homicidal ideation were more prominent among women with a childbearing-related episode of psychosis. They did not find manic symptoms, defined as elated mood, pressured speech, flight of ideas, or lability of mood, to be more common.

A smaller study compared 20 hospitalized women diagnosed with puerperal psychosis with 20 age-matched hospitalized women diagnosed with mania.[29] More delusions of control, auditory hallucinations, blunted affect, and emotional turmoil were found among the puerperal psychosis group. There were no differences regarding clouding of consciousness, disorientation, or poor concentration, but there were more reports of "perplexity" among the women with puerperal psychosis (although not of statistical significance). Symptoms commonly associated with mania, such as grandiosity and decreased need for sleep, were more commonly found in the bipolar group. Because of these differences, the authors rejected the hypothesis that puerperal psychosis is the "same as bipolar disorder."[29]

Finally, another small study comparing postpartum onset versus nonpostpartum onset in women with bipolar disorder found symptoms such as thought broadcasting, thought control, "experiences of influence," auditory hallucinations, and primary delusions to be more prominent in the postpartum group (62% vs. 28%, $p < .005$).[30] These differences in psychotic presentation led the authors to conclude that postpartum psychosis supports "heterogeneity within the bipolar syndrome."[30]

In summary, while some studies do suggest a preponderance of manic symptoms in postpartum psychosis, inconsistent classification of manic symptoms across studies complicates interpretation.

### Diagnosis and Longitudinal Outcome

Several longitudinal diagnostic studies suggest that initial diagnosis of postpartum psychosis is often associated with long-term diagnosis of a specific Axis I mood or psychotic disorder; for example, women with an index episode of postpartum psychosis risk developing further affective episodes, both puerperal and nonpuerperal.[25,31–33]

A review of 16 studies found that between 18% and 37% of women with puerperal psychosis had a subsequent puerperal episode, while 39% to 81% had a subsequent nonpuerperal episode (E. K. Robertson, Ph.D., written communication, Oct. 2002).[22,24,25,31–43] Two studies have determined that the index diagnosis, made during the puerperal episode, remained stable over time, even if subsequent episodes were nonpuerperal.[24,33]

A third study compared women with childbearing-related onset of psychiatric illness to women with nonchildbearing-related onset of illness.[44] The initial diagnoses between the groups did not differ, but upon reclassification by Research Diagnostic Criteria (RDC) 5 years later, 95% of women with childbearing-related onset, compared with 75% of women with nonchildbearing-related onset, had an affective disorder. Furthermore, "all women with DSM-III–defined nonaffective psychoses were reassigned by RDC to affective disorder diagnoses for the initial episode."[44] All of these women received a diagnosis of schizoaffective disorder, manic disorder, or bipolar disorder.

Some recent data support these findings. Thus, at the 2002 Marcé Society International Biennial Scientific Meeting, Robertson and colleagues[45] presented results from a recent longitudinal follow-up study, reporting that "86% of 110 women who experienced a puerperal psychotic episode subsequently met the criteria for bipolar I disorder" (E. K. Robertson, Ph.D., oral communication, Sept. 2002).

Another more limited study compared 20 women with postpartum psychosis with 20 women with bipolar disorder.[29] This study found a greater proportion of women with a history of treatment for schizophrenia among the women with postpartum psychosis, and only 35% of the women with postpartum psychosis met DSM-III-R criteria for bipolar disorder. This study had 2 important limitations: its cross-sectional design did not permit follow-up, and its use of a 90-day postpartum period makes it hard to compare with studies using shorter (e.g., 2 week) postpartum periods. Therefore, its findings must be interpreted cautiously.

In summary, most longitudinal studies suggest that postpartum psychosis is not a discrete nosologic entity, but a postpartum presentation of an underlying mood disorder. In many, if not most, cases, this underlying disorder appears to be within the bipolar spectrum.

### Family History

Family studies have consistently found the risk for psychiatric illness among first-degree relatives of women with puerperal psychosis to be between 10% and 50%, which is substantially higher than comparative rates in the general population.[32,35,36,46] However, these studies have provided contradictory data regarding the relationship between bipolar disorder and postpartum psychosis. Studies

that support the link find that the risk of having an affective episode among first-degree relatives of women with puerperal psychosis is similar to the risk among first-degree relatives of patients with bipolar disorder.[24,36,46] Other studies have produced conflicting findings; that is, they found either a lower risk[30,32] or an even greater risk for affective illness and other psychiatric disorders among family members of women with puerperal psychosis than that among nonpuerperal bipolar controls.[35]

Due to methodological differences, it is difficult to compare the studies' outcomes. For example, most studies questioned subjects about family history, whereas Dean et al.[35] used a family study method including direct interviews of first-degree relatives. Furthermore, comparison groups differed between studies.

Despite these uncertainties, further family research has shown that women with bipolar disorder who have a family history of puerperal psychosis have twice the rate of puerperal episodes than do women with bipolar disorder whose families do not have such a history.[47]

### Women With Bipolar Disorder

Substantial evidence for a postpartum psychosis–bipolar link derives from studies of women with bipolar disorder. Thus, Leibenluft points out that a female patient with bipolar disorder has the highest episode risk during the postpartum period.[48] A recent study found 260 episodes of psychosis per 1000 deliveries among women with bipolar disorder, in comparison with the rate of 1 to 2 episodes per 1000 deliveries estimated in the general population.[47] These rates are consistent with previous studies showing that women with bipolar disorder have a 100-fold higher risk of developing postpartum psychosis than do women without a history of bipolar disorder.[49]

In addition, several studies have found the rate of postpartum relapse in women with bipolar disorder to be approximately 30% to 50%.[10,34,35,50–52] In the largest study to date, Kendell and colleagues[10] found that the risk of psychiatric admission in the first 30 days after childbirth was 21.4% for women with a history of bipolar disorder, manic or circular type, and 13.3% for women with a history of bipolar disorder, depressed type. In comparison, women with a history of schizophrenia and depressive neurosis had rates of 3.4% and 1.9%, respectively.[10] Yet, despite the evident impact of the postpartum period on recurrence of bipolar disorder, the reasons for this association remain unclear.[53]

In summary, the majority of these studies do suggest that many, but not all, episodes of puerperal psychosis may be variants or atypical forms of bipolar disorder. Therefore, psychiatrists should suspect bipolar disorder in any patient presenting with postpartum depression or mania, particularly when psychotic features are present. Indicators of a possible bipolar diagnosis include a previous history of "missed" or misdiagnosed mood episodes, any evidence of previous mania or hypomania, and a strong family history of bipolar disorder or puerperal psychosis.[54]

## MANAGEMENT OF POSTPARTUM PSYCHOSIS

To our knowledge, there are no established treatment guidelines for postpartum psychosis. Because women with postpartum psychosis are usually severely ill, psychiatric hospitalization is almost always indicated.[21,55] A thorough medical evaluation to rule out underlying organic etiologies, such as postpartum thyroiditis, vitamin $B_{12}$ deficiency, seizures, or tumors, is recommended. Treatment regimens are based on clinical assessment of the prominent psychotic and/or affective symptoms. Randomized, controlled studies of psychotropic medication for postpartum psychosis are virtually nonexistent.

### Antipsychotics

Postpartum psychosis has historically been treated with neuroleptic medications.[14] The only treatment study using antipsychotic medication was an investigation of 10 women, 5 of whom received chlorpromazine and 5 of whom received propranolol.[56] Propranolol appeared to have an advantage, but the small sample size, as well as other methodological details, limits the interpretation of the results. To our knowledge, no further investigations of typical or newer atypical antipsychotic medications have been conducted, although interest exists in the treatment possibilities associated with the atypical antipsychotics.[57]

### Mood Stabilizers and Antidepressants

Because growing evidence supports a link between bipolar disorder and postpartum psychosis, experts currently advise initiation of mood stabilizers and antipsychotic medication for acute psychosis, mania, and agitation in the postpartum period.[21,55] Whereas antidepressants may be indicated for postpartum psychosis with prominent depressive features, caution is advised because antidepressants may precipitate rapid cycling in this population. This concern arises from evidence suggesting that antidepressants may worsen the long-term prognosis of bipolar disorder by promoting rapid cycling and treatment resistance.[58–60] Although not all studies support this conclusion,[61] we believe that if an antidepressant is used at all in postpartum psychosis, a mood stabilizer should also be prescribed. This rationale, though not yet confirmed in controlled studies of postpartum psychosis, derives from current treatment guidelines of bipolar disorder.[62–64] There is, as yet, no consensus regarding which mood stabilizer (lithium, divalproex, or others) or antipsychotic is the drug of choice in the acute management of postpartum psychosis.

### Alternative Therapeutics

There are no rigorously controlled studies of the use of electroconvulsive therapy in the treatment of postpartum

  

**Table 2. Postpartum Prophylaxis for Puerperal Episodes**

| Study and Population | N | Design | Method | Results: Recurrent Cases | Results: Timing of Recurrence | Results: Symptoms or Diagnosis at Recurrence |
|---|---|---|---|---|---|---|
| Cohen et al[67] DSM-III-R bipolar disorder | 14 | Treatment group (lithium, carbamazepine, or combination) | Within 48 hours postpartum (N = 3); during pregnancy (N = 11) | 1 | "in the first 3 months postpartum" | "Affective instability" |
| | 13 | Nontreatment group | N/A | 8 (p = .004) | "in the first 3 months postpartum" | Manic or depressive |
| Austin[68] RDC bipolar disorder, puerperal affective psychosis | 9 | Lithium treatment group | Within 48 hours postpartum (N = 2); during pregnancy (N = 7) | 2 | Day 10 | Mania |
| | 8 | Nontreatment group | N/A | 6 (p < .05) | 1 week to 12 weeks (4/6 within 3 weeks) | Mania (psychotic) |
| Stewart et al[69] RDC bipolar I disorder, major depressive disorder, schizoaffective disorder, unspecified functional psychosis | 21 | Lithium treatment group | Within 24 hours postpartum (N = 16); during pregnancy (N = 5) | 2 | Day 6 (N = 1)<br>Day 8 (N = 1) | Major depressive disorder without psychotic features<br>Not described, puerperal psychosis |
| Stewart[70] Postpartum psychosis | 4 | Lithium treatment group | Within 24 hours | 0 | Day 9 | Mild confusion, insomnia |

Abbreviations: N/A = not applicable; RDC = Research Diagnostic Criteria.

psychosis. However, many experts have reported it to be an effective treatment,[65] and therefore it is often recommended as an alternative, especially in refractory or rapidly progressing cases.[11,14]

Finally, a recent small, open-label pilot study using sublingual 17β-estradiol to treat postpartum psychosis had promising results.[66] It found a dramatic decrease in psychotic symptoms as measured by the Brief Psychiatric Rating Scale within 2 weeks of treatment. Further research is required to confirm the effectiveness of these treatments.

## PROPHYLACTIC MANAGEMENT

Because the risk of a psychotic episode or the recurrence of a depressive or manic episode in the postpartum period is undisputedly high for women with bipolar disorder, prophylaxis with mood stabilizers must be considered. The few studies to date that have assessed efficacy of prophylaxis (primarily with lithium) during late pregnancy or in the postpartum period show promising results (Table 2).[67–70] A recent open-label, flexible-dosing study of transdermal 17β-estradiol did not show evidence of preventing postpartum "affective psychosis."[52] In the sample of 29 high-risk women, 12 experienced a recurrence. Because of the high risk of recurrence, despite the limited data, prophylactic treatment with a mood stabilizer is recommended during the postpartum period for women with bipolar disorder or a history of postpartum psychosis.

No consensus exists regarding the most suitable time to reintroduce prophylaxis.[71] While some authors suggest reinstituting mood stabilizers in the second or third trimester of pregnancy[72] when the teratogenesis risk is lower, many patients may prefer to defer prophylaxis until immediately after delivery. Some particularly vulnerable women may require medication throughout pregnancy.

## SPECIAL CONSIDERATIONS

Women who experience a postpartum psychotic episode will fall into one of 2 categories. The first is women who have no history of a psychiatric disorder and for whom the postpartum psychosis is an initial onset of illness. For this group, acute treatment, rather than prevention, is the focus. The second category is women who have a known psychiatric disorder, such as bipolar disorder. For this group, prevention of a recurrent episode during pregnancy or postpartum is the focus.

A risk-benefit discussion of the use of medications during each trimester and during breastfeeding is required. Prophylactic use of medication as well as treatment of current symptoms must be taken into consideration. Comprehensive reviews[73–83] of the risk-benefit analysis for antidepressant,[73,74] mood stabilizer,[75–83] and antipsychotic[75] use in pregnancy and lactation are available to assist the clinician in this discussion. In addition, an American Psychiatric Association consensus work group has produced guidelines for the management of bipolar disorder in pregnancy and postpartum, which are currently under

review (K. Yonkers, M.D., written communication, May 2003). When available, these may be helpful in guiding the clinician and patient through difficult decisions. Therefore, we present only a brief overview of the major risks of mood stabilizer prophylaxis and treatment during pregnancy and breastfeeding.

### Risks During Pregnancy

The teratogenic effects of existing bipolar treatments are major concerns. Maternal exposure to carbamazepine or valproate in the first trimester is associated with a markedly increased risk of neural tube defects (1%[84] and 3%–8%,[85,86] respectively). Historically, lithium was considered unsafe to use during pregnancy because of the increased risk of cardiac anomalies,[87] but the risk is substantially less than originally believed.[88] Indeed, while cardiac abnormalities such as Ebstein's anomaly are associated with first-trimester lithium use, the risk is only about 0.05%, with a relative risk of between 1.2 and 7.7 times that of the general population.[88] Therefore, experts regard lithium as the safest mood stabilizer to use during pregnancy in comparison with valproate or carbamazepine.[89] While these risks are important, the patient's clinical history, including medication response and risk for decompensation, must be taken into account in choosing a mood stabilizer during pregnancy.

Another consideration is medication discontinuation. While discontinuing existing mood-stabilizer therapy promotes a high relapse risk,[90–92] abrupt discontinuation (e.g., immediately upon learning of a pregnancy) is associated with an even higher relapse risk.[90–94] Viguera et al.[95] reported that among 33 subjects who discontinued their mood stabilizer during pregnancy, 26 relapsed (78.8%). Those who gradually discontinued maintenance mood stabilizer were at lower risk for relapse (N = 21; [62%]) than were those who abruptly (1 day to < 2 weeks) discontinued their mood stabilizer (N = 10; [100%]).[95] Therefore, if discontinuation of medication is indicated during the first trimester, avoiding a rapid taper is recommended.

### Postpartum and Lactation

All psychotropic medications are excreted through breast milk to varying degrees. The amount of medication in breast milk and the infant's absorption, metabolism, and excretion of the drug, as well as the drug's half-life and active metabolites, may all affect the infant's drug exposure. Because of the limited information about most drugs during lactation, a "safe" value has been described as 10% or less of the "therapeutic dose for infants (or the adult dose standardized by weight)."[96] Both valproate and carbamazepine are currently classified by the American Academy of Pediatrics (AAP) as "usually compatible" with breastfeeding because they meet this criterion.[97] However, these drugs should still be used with caution as each has been associated with at least 1 case report of hepatic dysfunction.[98–100] The AAP has changed lithium's categorization from contraindicated to "should be given to nursing mothers with caution."[97] Reports of lithium concentrations in breast milk range from 24% to 72% of maternal serum concentrations.[83, 101–106] Two cases of lithium toxicity related to breast milk exposure have also been reported.[101,102] While breast milk levels are an important indicator of infant exposure, infant serum levels are the most reliable source to determine exposure. As with the risk-benefit analysis done during pregnancy, consideration of medication use while breastfeeding must take into account the mother's history of medication response, side effects, and infant-related factors.[73]

### Investigational Treatments

Clinicians managing bipolar spectrum disorders are no longer confined to the traditional options of lithium, valproate, and carbamazepine. Olanzapine is the only atypical antipsychotic that is U.S. Food and Drug Administration (FDA)-approved for the treatment of acute mania.[107,108] While not FDA-approved for treatment of bipolar disorder, studies of atypical antipsychotics (ziprasidone[109] and risperidone[110,111]) and new anticonvulsants (oxcarbazepine[112]) hold promise as treatment options for mania. Lamotrigine, a new anticonvulsant that is also not FDA-approved for treatment of bipolar disorder, does appear especially useful for bipolar depression.[113] Atypical antipsychotics and newer anticonvulsants have not been systematically studied in pregnant women with bipolar disorder, in women during the postpartum period, or in those with postpartum psychosis. Nevertheless, these agents may be appropriate for selected patients. As with other medications used in these populations, data regarding their use and safety during pregnancy or breastfeeding are limited and confined to individual case reports.[114–125]

Given the complexities of managing these patients, including the difficult risk-benefit issues that must be weighed, psychiatrists should work closely with the patient's treating team (e.g., obstetrician, primary care or family physician, pediatrician, and nurses), regardless of whether the patient is taking maintenance medications.

## CONCLUSION

Despite the finding that not all cases of puerperal psychosis fall into the bipolar spectrum, there is substantial evidence for a fundamental link between bipolar disorder and postpartum psychosis. Therefore, clinicians should always consider bipolar disorder in the differential diagnosis of any woman who presents with a new onset affective disorder in the puerperium, especially if psychotic symptoms are present. Psychiatrists must carefully consider the use of antidepressants in women with puerperal psychosis, given the observed risks of antidepressants in bipolar patients. We recommend a treatment approach consistent

  

with that of bipolar disorder, unless a psychiatric history of a supervening Axis I disorder (e.g., schizophrenia) exists. Women with bipolar disorder are known to be at high risk in the postpartum period. Therefore, a comprehensive risk-benefit analysis and treatment plan during pregnancy and postpartum are essential in coordination with the patient's obstetrician and pediatrician.

Future research should include epidemiologic and genetic studies of postpartum psychosis in order to clarify its symptomatic presentation and nosologic status. Such studies are needed to help identify those factors, beyond an established bipolar disorder diagnosis, that put women at risk for this severe illness. Such data will help guide treatment and prevention strategies. Randomized, controlled, prospective studies are also needed to determine the best treatment and prevention strategies for postpartum psychosis. Such studies should include both newer and established agents used in managing bipolar disorder.

*Drug names:* carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), divalproex (Depakote), lamotrigine (Lamictal), olanzapine (Zyprexa), oxcarbazepine (Trileptal), propranolol (Inderal and others), risperidone (Risperdal), ziprasidone (Geodon).

## REFERENCES


1. Gotlib I, Whiffen V, Mount J, et al. Prevalence rates and demographic characteristics in pregnancy and the postpartum. J Consult Clin Psychol 1989;57:269–274
2. Miller L, Rukstlis M. Beyond the blues: hypotheses about postpartum reactivity. In: Miller L, ed. Postpartum Mood Disorders. Washington, DC: American Psychiatric Press, Inc; 1999:3–19
3. Stein G, Marsh A, Morton J. Mental symptoms, weight changes, and electrolyte excretion in the first postpartum week. J Psychosom Res 1981;25:395–408
4. Stowe Z, Nemeroff C. Women at risk for postpartum-onset major depression. Am J Obstet Gynecol 1995;173:639–645
5. Pop V, Essed G, Geus C, et al. Prevalence of postpartum depression—or is it post-puerperium depression? Acta Obstet Gynecol Scand 1993;72:354–358
6. Hearn G, Iliff A, Jones I, et al. Postnatal depression in the community. Br J Gen Pract 1998;48:1064–1066
7. Georgiopoulos A, Bryan T, Yawn B, et al. Population-based screening for postpartum depression. Obstet Gynecol 1999;93:653–657
8. Josefsson A, Berg G, Nordin C, et al. Prevalence of depressive symptoms in late pregnancy and postpartum. Acta Obstet Gynecol Scand 2001;80:251–255
9. O'Hara M, Neunaber D, Zekoski E. Prospective study of postpartum depression: prevalence, course and predictive factors. J Abnorm Psychol 1984;93:158–171
10. Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses. Br J Psychiatry 1987;150:662–673
11. Miller LJ. Postpartum depression. JAMA 2002;287:762–765
12. Wisner KL, Parry BL, Piontek CM. Postpartum depression. N Engl J Med 2002;347:194–199
13. Harris B. Postpartum depression. Psychiatr Ann 2002;32:405–415
14. Brockington I. Puerperal psychosis. In: Motherhood and Mental Health. New York, NY: Oxford University Press; 1999:200–284
15. Hamilton JA. Postpartum psychiatric syndromes. Psychiatr Clin North Am 1989;12:89–103
16. Brockington IF, Cernik KF, Schofield EM, et al. Puerperal psychosis: phenomena and diagnosis. Arch Gen Psychiatry 1981;38:829–833
17. Foundeur M, Fixser C, Triebel WA, et al. Postpartum mental illness: a controlled study. Arch Neurol Psychiatry 1957;77:508–512
18. American Psychiatric Association. Postpartum onset specifier. In: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Publishing, Inc; 2000:422–423
19. Appleby L, Mortensen PB, Faragher EB. Suicide and other causes of mortality after post-partum psychiatric admission. Br J Psychiatry 1998;173:209–211
20. Beeghly M, Weinberg MK, Olson KL, et al. Stability and change in level of maternal depressive symptomatology during the first postpartum year. J Affect Disord 2002;71:169–180
21. Burt VK, Hendrick VC. Postpartum psychiatric disorders. In: Concise Guide to Women's Mental Health. Washington, DC: American Psychiatric Press, Inc; 1997:63–77
22. Rohde A, Marneros A. Postpartum psychoses: onset and long-term course. Psychopathology 1993;26:203–209
23. Klompenhouwer JL, van Hulst AM. Classification of postpartum psychosis: a study of 250 mother and baby admissions in The Netherlands. Acta Psychiatr Scand 1991;84:255–261
24. Protheroe C. Puerperal psychoses: a long term study, 1927–1961. Br J Psychiatry 1969;115:9–30
25. Videbech P, Gouliaev G. First admission with puerperal psychosis: 7–14 years of follow-up. Acta Psychiatr Scand 1995;91:167–173
26. Wisner KL, Peindl K, Hanusa BH. Symptomatology of affective and psychotic illnesses related to childbearing. J Affect Disord 1994;30: 77–87
27. Brockington I. Infanticide. In: Motherhood and Mental Health. New York, NY: Oxford University Press; 1999:430–468
28. Appleby L, Turnbull G. Parasuicide in the first postnatal year. Psychol Med 1995;25:1087–1090
29. Oosthuizen P, Russouw H, Roberts M. Is puerperal psychosis bipolar mood disorder? a phenomenological comparison. Compr Psychiatry 1995;36:77–81
30. Kadrmas A, Winokur G, Crowe R. Postpartum mania. Br J Psychiatry 1979;135:551–554
31. Davidson J, Robertson E. A follow-up study of post partum illness, 1946–1978. Acta Psychiatr Scand 1985;71:451–457
32. Schopf J, Rust B. Follow-up and family study of postpartum psychoses, pt 1: overview. Eur Arch Psychiatry Clin Neurosci 1994;244:101–111
33. Robling SA, Paykel ES, Dunn VJ, et al. Long-term outcome of severe puerperal psychiatric illness: a 23 year follow-up study. Psychol Med 2000;30:1263–1271
34. Reich T, Winokur G. Postpartum psychoses in patients with manic depressive disease. J Nerv Ment Dis 1970;151:60–68
35. Dean C, Williams RJ, Brockington IF. Is puerperal psychosis the same as bipolar manic-depressive disorder? a family study. Psychol Med 1989; 19:637–647
36. Platz C, Kendell RE. A matched-control follow-up and family study of "puerperal psychoses." Br J Psychiatry 1988;153:90–94
37. Arentsen K. Postpartum psychoses with particular reference to the prognosis. Dan Med Bull 1968;15:97–100
38. Bratfos O, Haug JO. Puerperal mental disorders in manic-depressive females. Acta Psychiatr Scand 1966;42:285–294
39. Kirpinar I, Coskun I, Caykoylu A, et al. First-case postpartum psychoses in eastern Turkey: a clinical case and follow-up study. Acta Psychiatr Scand 1999;100:199–204
40. McNeil TF. A prospective study of postpartum psychoses in a high-risk group: relationship to life situation and experience of pregnancy. Acta Psychiatr Scand 1988;77:645–653
41. Muller C. On the nosology of post-partum psychoses. Psychopathology 1985;18:181–184
42. Schopf J, Bryois C, Jonquiere M, et al. On the nosology of severe psychiatric post-partum disorders: results of a catamnestic investigation. Eur Arch Psychiatry Neurol Sci 1984;234:54–63
43. Terp IM, Engholm G, Moller H, et al. A follow-up study of postpartum psychoses: prognosis and risk factors for readmission. Acta Psychiatr Scand 1999;100:40–46
44. Wisner KL, Peindl KS, Hanusa BH. Psychiatric episodes in women with young children. J Affect Disord 1995;34:1–11
45. Robertson E, Jones I, Craddock N. Predicting non-puerperal episodes of illness in women with bipolar affective puerperal psychosis [abstract]. Presented at the Marcé Society international biennial scientific meeting; Sept 25–27, 2002; Sydney, Australia
46. Whalley LJ, Roberts DF, Wentzel J, et al. Genetic factors in puerperal affective psychoses. Acta Psychiatr Scand 1982;65:180–193

47. Jones I, Craddock N. Familiality of the puerperal trigger in bipolar disorder: results of a family study. Am J Psychiatry 2001;158:913–917
48. Leibenluft E. Women with bipolar illness: clinical and research issues. Am J Psychiatry 1996;153:163–173
49. Pariser SF. Women and mood disorders: menarche to menopause. Ann Clin Psychiatry 1993;5:249–254
50. Jefferson JW, Greist JH, Ackerman DL, et al. Pregnancy. In: Lithium Encyclopedia for Clinical Practice. 2nd ed. Washington, DC: American Psychiatric Press; 1987:504–511
51. Marks MN, Wieck A, Checkley SA, et al. Contribution of psychological and social factors to psychotic and non-psychotic relapse after childbirth in women with previous histories of affective disorder. J Affect Disord 1992;24:253–263
52. Kumar C, McIvor RJ, Davies T, et al. Estrogen administration does not reduce the rate of recurrence of affective psychosis after childbirth. J Clin Psychiatry 2003;64:112–118
53. Leibenluft E. Women and bipolar disorder: an update. Bull Menninger Clin 2000;64:5–17
54. Attia E, Downey J, Oberman M. Postpartum psychoses. In: Miller LJ, ed. Postpartum Mood Disorders. Washington, DC: American Psychiatric Press, Inc; 1999:3–20
55. Sichel DA. Postpartum psychiatric disorders. In: Steiner M, Yonkers K, Eriksson E, eds. Mood Disorders in Women. London: Martin Dunitz Ltd; 2000; 313–328
56. Steiner M, Latz A, Blum, I, et al. Propranolol versus chlorpromazine in the treatment of psychoses associated with childbearing. Psychiatr Neurol Neurochir 1973;76:421–426
57. Kornhuber J, Weller M. Postpartum psychosis and mastitis: a new indication for clozapine? Am J Psychiatry 1991;148:1751–1752
58. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995;152:1130–1138
59. Sachs GS. Bipolar mood disorder: practical strategies for acute and maintenance phase treatment. J Clin Psychopharmacol 1996;16(suppl 2): 32S–47S
60. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. J Clin Psychiatry 2000;61:804–808
61. MacQueen GM, Trevor YL, Marriott M, et al. Previous mood state predicts response and switch rates in patients with bipolar depression. Acta Psychiatr Scand 2002;105:414–418
62. Goodwin FK, Jamison KR. Manic-depressive illness. New York, NY: Oxford University Press; 1990
63. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Bipolar Disorder [Revision]. Am J Psychiatry 2002;159(suppl 4):1–50
64. Sachs GS, Printz DJ, Kahn DA, et al. The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. Postgrad Med 2000;Spec No:1–104
65. Reed P, Sermin N, Appleby L, et al. A comparison of clinical response to electroconvulsive therapy in puerperal and non-puerperal psychoses. J Affect Disord 1999;54:255–260
66. Ahokas A, Aito M, Rimon R. Positive treatment effect of estradiol in postpartum psychosis: a pilot study. J Clin Psychiatry 2000;61:166–169
67. Cohen LS, Sichel DA, Robertson LM, et al. Postpartum prophylaxis for women with bipolar disorder. Am J Psychiatry 1995;152:1641–1645
68. Austin MP. Puerperal affective psychosis: is there a case for lithium prophylaxis? Br J Psychiatry 1992;161:692–694
69. Stewart DE, Klompenhouwer JL, Kendell RE, et al. Prophylactic lithium in puerperal psychosis: the experience of three centres. Br J Psychiatry 1991;158:393–397
70. Stewart DE. Prophylactic lithium in postpartum affective psychosis. J Nerv Ment Dis 1988;176:485–489
71. Viguera AC, Cohen LS. The course and management of bipolar disorder during pregnancy. Psychopharmacol Bull 1998;34:339–346
72. Grof P, Robbins W, Alda M, et al. Protective effect of pregnancy in women with lithium-responsive bipolar disorder. J Affect Disord 2000;61:31–39
73. Burt VK, Suri R, Altshuler L, et al. The use of psychotropic medications during breast-feeding. Am J Psychiatry 2001;158:1001–1009
74. Wisner KL, Zarin DA, Holmboe ES, et al. Risk-benefit decision making for treatment of depression during pregnancy. Am J Psychiatry 2000;157:1933–1940
75. Ernst CL, Goldberg JF. The reproductive safety profile of mood stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. J Clin Psychiatry 2002;63(suppl 4):42–55
76. Spigset O, Hagg S. Excretion of psychotropic drugs into breast milk: pharmacokinetic overview and therapeutic implications. CNS Drugs 1998;9:111–134
77. Baugh CL, Stowe ZN. Treatment issues during pregnancy and lactation. CNS Spectr 1999;4:34–39
78. Altshuler LL, Cohen L, Szuba MP, et al. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996;153:592–606
79. Stowe ZN, Calhoun K, Ramsey C, et al. Mood disorders during pregnancy and lactation: defining issues of exposure and treatment. CNS Spectr 2001;6:150–166
80. Miller LJ. Pharmacotherapy during the perinatal period. Essent Psychopharmacol 1998;2:263–286
81. Cohen LS, Rosenbaum JF. Psychotropic drug use during pregnancy: weighing the risks. J Clin Psychiatry 1998;59(suppl 2):18–28
82. Llewellyn A, Stowe ZN, Strader JR. The use of lithium and management of women with bipolar disorder during pregnancy and lactation. J Clin Psychiatry 1998;59(suppl 6):57–64
83. Chaudron LH, Jefferson JW. Mood stabilizers during breastfeeding: a review. J Clin Psychiatry 2000;61:79–90
84. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. N Engl J Med 1991;324:674–677
85. Omtzigt JGC, Los FJ, Grobbee DE, et al. The risk of spina bifida aperta after first-trimester exposure to valproate in prenatal cohort. Neurology 1992;42 (suppl 5):119–125
86. Holmes LB, Wyszynski D, Mittendorf R. Evidence for an increased risk of birth defects in the offspring of women exposed to valproate during pregnancy: findings from the AED Pregnancy Registry [poster]. Presented at the 23rd annual meeting of the Society for Maternal-Fetal Medicine; Feb 3–8, 2003; San Francisco, Calif
87. Nora JJ, Nora AH, Toews WH. Lithium: Ebstein's anomaly and other congenital heart defects. Lancet 1974;2:594–595
88. Cohen LS, Friedman JM, Jefferson JW, et al. A reevaluation of risk of in utero exposure to lithium. JAMA 1994;271:146–150
89. Cohen L. Bipolar disorder in pregnancy. Clin Psychiatry News 2002;30:20
90. Suppes T, Baldessarini RJ, Faedda GL, et al. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry 1991;48:1082–1088
91. Baldessarini RJ, Tondo L, Faedda GL, et al. Effects of the rate of discontinuing lithium maintenance treatment in bipolar disorders. J Clin Psychiatry 1996;57:441–448
92. Baldessarini RJ, Tondo L, Floris G, et al. Reduced morbidity after gradual discontinuation of lithium treatment for bipolar I and II disorders: a replication study. Am J Psychiatry 1997;154:551–553
93. Faedda GL, Tondo L, Baldessarini RJ, et al. Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. Arch Gen Psychiatry 1993;50:448–455
94. Viguera AC, Nonacs R, Cohen LS, et al. Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. Am J Psychiatry 2000;157:179–184
95. Viguera AC, Cohen LS, Reminick A, et al. Risk of recurrence among pregnant women with bipolar disorder. In: Abstracts on Disk of the 155th Annual Meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa. Abstract NR284
96. Ito S. Drug therapy for breast-feeding women. N Engl J Med 2000; 343:118–126
97. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics 2001;108: 776–789
98. Stahl MM, Neiderud J, Vinge E. Thrombocytopenic purpura and anemia in a breast-fed infant whose mother was treated with valproic acid. J Pediatr 1997;130:1001–1003
99. Frey B, Schubiger G, Musy JP. Transient cholestatic hepatitis in a neonate associated with carbamazepine exposure during pregnancy and breast-feeding. Eur J Pediatr 1990;150:136–138
100. Merlob P, Mor N, Litwin A. Transient hepatic dysfunction in an infant of an epileptic mother treated with carbamazepine during pregnancy and breastfeeding. Ann Pharmacother 1992;26:1563–1565
101. Tunnessen WW Jr, Hertz CG. Toxic effects of lithium in newborn


  

infants: a commentary. J Pediatr 1972;81:804–807
102. Skausig OB, Schou M. Breast feeding during lithium therapy. Ugeskr Laeger 1977;139:400–401
103. Weinstein MR, Goldfield M. Lithium carbonate treatment during pregnancy. Dis Nerv Syst 1969;30:828–832
104. Fries H. Lithium in pregnancy. Lancet 1970;1:1233
105. Sykes PA, Quarrie J, Alexander FW. Lithium carbonate and breast-feeding. Br Med J 1973;2:138
106. Skausig OB, Schou M. Breast-feeding during lithium treatment. Ugeskr Laeger 1977;139:400–401
107. Tohen M, Sanger TM, McElroy SL, et al, and the Olanzapine HGEH Study Group. Olanzapine versus placebo in the treatment of acute mania. Am J Psychiatry 1999;156:702–709
108. Tohen M, Jacobs TG, Grundy SL, et al, for the Olanzapine HGGW Study Group. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. Arch Gen Psychiatry 2000;57:841–849
109. Keck PE Jr, Ice K. A three-week, double-blind, randomized trial of ziprasidone in the acute treatment of mania [abstract]. Presented at the 153rd annual meeting of the American Psychiatric Association; May 13–18, 2000; Chicago, Ill
110. Vieta E, Herraiz M, Parramon G, et al. Risperidone in the treatment of mania: efficacy and safety results from a large, multicentre, open study in Spain. J Affect Disord 2002;72:15–19
111. Sachs GS, Grossman F, Ghaemi SN, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry 2002;159:1146–1154
112. Emrich HM. Studies with oxcarbazepine (Trileptal) in acute mania. In: Emrich HM, Schiwy W, Silverstone T, eds. Carbamazepine and Oxcarbazepine in Psychiatry. London: Clinical Neuroscience Publishers; 1990:83–88
113. Calabrese JR, Bowden CL, Sachs GS, et al, for the Lamictal 602 Study Group. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J Clin Psychiatry 1999;60:79–88
114. Tomson T, Ohman I, Vitols S. Lamotrigine in pregnancy and lactation: a case report. Epilepsia 1997;38:1039–1041
115. Morrell MJ. The new antiepileptic drugs and women: efficacy, reproductive health, pregnancy, and fetal outcome. Epilepsia 1996;37(suppl 6):S34–S44
116. Goldstein DJ, Corbin LA, Fung MC. Olanzapine-exposed pregnancies and lactation: early experience. J Clin Psychopharmacol 2000;20: 399–403
117. Rambeck B, Kurlemann G, Stodieck SR, et al. Concentrations of lamotrigine in a mother on lamotrigine treatment and her newborn child. Eur J Clin Pharmacol 1997;51:481–484
118. Kirchheiner J, Berghofer A, Bolk-Weischedel D. Healthy outcome under olanzapine treatment in a pregnant woman. Pharmacopsychiatry 2000;33:78–80
119. Dickson RA, Dawson DT. Olanzapine and pregnancy [letter]. Can J Psychiatry 1998;43:196–197
120. Hill RC, McIvor RJ, Wojnar-Horton RE, et al. Risperidone distribution and excretion into human milk: case report and estimated infant exposure during breast-feeding. J Clin Psychopharmacol 2000;20:285–286
121. Goldstein DJ, Corbin LA, Fung MC. Olanzapine-exposed pregnancies and lactation: early experience. J Clin Psychopharmacol 2000;20: 399–403
122. Goldstein DJ, Corbin LA, Wohlreich MM. Olanzapine use during breast-feeding [abstract]. Schizophr Res 2002;53:185
123. Littrell KH, Johnson CG, Peabody CD, et al. Antipsychotics during pregnancy [letter]. Am J Psychiatry 2000;157:1342
124. Mendhekar DN, War L, Sharma JB, et al. Olanzapine and pregnancy. Pharmacopsychiatry 2002;35:122–123
125. Croke SJ, Buist AE, Norman TR, et al. Presence of olanzapine in breast milk [abstract]. Aust N Z J Psychiatry 2000;34(suppl):A16