Issues in the Treatment of Women With Bipolar Illness

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Gender differences in bipolar illness have been relatively neglected, but the course of the illness does appear to differ between men and women. Compared with bipolar men, bipolar women are clearly more likely to develop the rapid cycling form of the illness and may also suffer from more episodes of depression. Therefore, the literature concerning the treatment of rapid cycling bipolar disorder and of bipolar depression is reviewed. In addition, effects of bipolar illness on the female reproductive cycle are discussed. Since bipolar women are at high risk to develop postpartum episodes, the use of mood stabilizers in pregnancy is discussed. *(J Clin Psychiatry 1997;58[suppl 15]:5–11)*

At first glance, gender may not appear to be an important variable to consider when discussing the treatment of patients with bipolar illness. Unlike unipolar illness, which is two to three times more common in women than men, bipolar illness is equally prevalent in both sexes.[1,2] However, as will be discussed, the conclusion that gender is irrelevant in discussions of bipolar illness is untenable for two reasons. First, while the illness itself is equally common in women and men, its course appears to differ between the sexes. Second, female reproductive events not only affect the course of bipolar illness, but also influence the treatment decisions that are made at various points in a woman's life.

The most clearly documented gender difference in the course of bipolar illness is the observation that rapid cycling is approximately three times more common in women than men. Rapid cycling bipolar disorder, as first defined by Dunner and Fieve,[3] occurs when a bipolar patient experiences four or more affective episodes in a year (an affective episode being one of mania, hypomania, or depression). Ten studies have reported samples of rapid cycling patients that include at least 20 patients.[4–13] In these studies, the percentage of women in the samples ranges from 58% to 92%, and the weighted mean percentage of female patients is 71%. The reasons for this gender imbalance are unclear, although gender differences in the hypothalamic-pituitary-thyroid (HPT) axis,[14] the hypothalamic-pituitary-gonadal (HPG) axis, the prescription of antidepressant medication,[15] or some combination have all been suggested as possible causes. Whatever its cause(s), the observation that rapid cycling bipolar disorder is more common in women than in men has important treatment implications, since patients with rapid cycling comprise a particularly challenging clinical population.

Other possible gender differences in the course of bipolar illness have received more limited research attention, and the data concerning them are more equivocal. However, some data support the conclusion that bipolar women, like women in general, are at higher risk than bipolar men to develop depressive syndromes. Specifically, three studies[16–18] indicate that bipolar women have more frequent depressive episodes (and less frequent manic episodes) than bipolar men, although there are also two negative studies[10,19] on this point. Second, of the eight studies that report the gender composition of samples including patients with mixed (dysphoric) and pure mania, five[20,21] indicate that bipolar women are more likely than bipolar men to develop the mixed syndrome. Again, these observations have important clinical consequences, since both bipolar depression and mixed affective states are often difficult to treat.

BIPOLAR ILLNESS AND THE FEMALE REPRODUCTIVE CYCLE

With regard to the effects of female reproductive events on the course of bipolar illness, only the postpartum period has received much systematic study (Table 1). A number of studies[22–25] have shown that bipolar women are at high risk to have an affective episode in the postpartum period. For example, Kendell et al.[24] found that 21.4% of women with the ICD-9 diagnosis of manic-depressive illness, manic or

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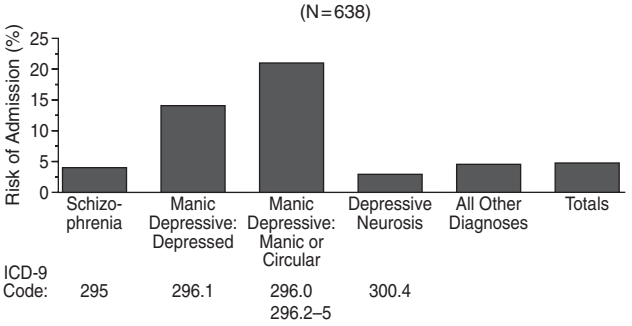
Table 1. Effects of the Female Reproductive Cycle on the Course of Bipolar Illness*

Reproductive Event	Summary of Literature
Puberty/menarche	None available
Menstrual cycle	Increased hospitalizations in luteal phase among women in lithium clinic[44] High rate of severe premenstrual syndrome in women with RCBD,[45] or no effect in women with RCBD[13] Cases of systematic relationship between menstrual cycle and mood cycle, some treated with oral contraceptives or clomiphene citrate[87,88]
Pregnancy	Hospitalization rates unaffected[43]
Postpartum	Many studies demonstrate high risk of episode[22–25,89]
Lactation	None available
Menopause	1/3 of women converting to "continuous circular course" did so at this time, or no effect[13]

*Abbreviation: RCBD = rapid cycling bipolar disorder.

Figure 1. Risk of Psychiatric Admission Within 90 Days of Childbirth by Prior Psychiatric Diagnosis*



*Data from Kendell et al.[24]

circular, and 13.3% of the women diagnosed with manic-depressive illness, depressed, were admitted to a psychiatric hospital within 30 days of giving birth, compared with 3.4% of the women with a diagnosis of schizophrenia (Figure 1). Dean et al.[23] highlighted the recurrent nature of bipolar postpartum relapse when they found that 50% of women with a history of both a puerperal and a nonpuerperal affective episode (most of whom were bipolar) once again relapsed after a subsequent pregnancy and delivery.

While the phenomenon of postpartum recurrence in bipolar women has been well documented, its etiology has received little research attention. It is interesting to note that both the HPT axis and the circadian system, which may be involved in the pathophysiology of bipolar mood cycling,[14,26] undergo significant stress in the postpartum period.[27] Studies suggest that a precipitous fall in estrogen levels[28] or dysfunction in the hypothalamic-pituitary-adrenal (HPA)[29,30] or HPT axes[31,32] may contribute to postpartum mood dysregulation, but these hypotheses have not been tested in bipolar women.

The high prevalence of postpartum episodes in bipolar women, coupled with the fact that many women continue to have affective episodes throughout pregnancy, makes the possible teratogenicity of mood stabilizers a clinically relevant issue. While the risk of Ebstein's anomaly in fetuses exposed to lithium in the first trimester was originally thought to be 400 times greater than that of controls, two more recent studies put the risk ratio for cardiac malformations at 1.2 or 7.7.[33] Thus, while lithium does appear to increase the risk of such malformations, the level of risk is not as great as had initially been suggested. In women whose bipolar illness is so severe that lithium maintenance is necessary throughout all or part of the first trimester, Cohen et al.[33] suggest fetal echocardiography and high-resolution ultrasound examination at 16 to 18 weeks of gestation.

In addition to its first-trimester teratogenic risk, lithium in late pregnancy has also been associated with other adverse consequences, including polyhydramnios[34,35] and "floppy baby syndrome."[36] In addition, one study showed an association between maternal lithium exposure and premature delivery. Specifically, 32% of 58 bipolar women treated with lithium delivered babies at 37 weeks or earlier, compared with 14% of 292 bipolar women who had not received lithium and 11% of 350 unaffected women.[37]

Unfortunately, the anticonvulsant mood stabilizers are also associated with teratogenic risk. While teratogenicity in bipolar women treated with valproate or carbamazepine has not been well studied, an extensive literature examines such risk in the offspring of epileptic women. This literature appears to indicate an increased risk of spina bifida in the offspring of women treated with anticonvulsants during pregnancy, with the risk being approximately 0.5% to 1% for carbamazepine, 1% to 5% for valproate, and 0.06% for controls.[38] The administration of folate may have some protective effect in unmedicated women, although its efficacy in women on anticonvulsant therapy has not been documented. Serum α-fetoprotein levels and ultrasound may help to detect such anomalies in utero.[39] In addition, anticonvulsants have been reported to lower vitamin K–dependent coagulation factors, making the administration of vitamin K to both mother and child advisable.[40]

Outside of the postpartum period, there are few systematic studies concerning the effects of reproductive events on the course of bipolar illness. While clinical lore generally holds that pregnancy has a protective effect against mood disorders, several studies of unipolar depressives refute that assumption.[41,42] In bipolar illness, the one existing study of pregnancy examined only hospitalization rates, which were unaffected.[43] Concerning menopause, one study[10] found that one third of the women who converted to a "continuous circular" course (i.e., one in which manic and depressive episodes alter-

nate, with no intervening euthymia) did so in the perimenopausal period, while another[13] found that menopause had no effect on the course of rapid cycling bipolar disorder.

Finally, with respect to the menstrual cycle, there have been a number of case reports of bipolar women whose menstrual and mood cycles appeared to vary in concert. However, outside of these individual cases, there are only three systematic studies of possible effects of the menstrual cycle on the course of bipolar illness. One of these showed an increase in hospitalization rates during the luteal phase,[44] the second showed a high rate of retrospectively reported premenstrual syndrome among women with rapid cycling bipolar disorder,[45] but the third showed no systematic relationship between menstrual cycle and mood in a sample of patients with rapid cycling bipolar disorder.[13]

In sum, bipolar women are more likely than bipolar men to develop a rapid cycling course, and they may be more likely to develop both depressive episodes and episodes of mixed (as opposed to pure) mania. They clearly are at high risk to relapse during the postpartum period, but the effects of other reproductive events on the course of bipolar illness are unclear. Since both rapid cycling and bipolar depression are common in women but difficult to treat, the remainder of this paper will review the literature concerning their pharmacologic management.

TREATMENT OF RAPID CYCLING BIPOLAR DISORDER

Approximately 20% of bipolar patients presenting to research studies are rapid cycling.[4,9,10] Patients with rapid cycling bipolar disorder can be among the most challenging in a psychiatrist's practice. Management of their depressive episodes is often particularly difficult, since aggressive treatment with antidepressant medication may not only precipitate a switch into mania (a risk described below), but may also increase cycle frequency.[13,46,47] Clinician and patient may then be left to choose between faster cycles (if an antidepressant is begun or its dose increased) and severe, incapacitating depressive episodes (if the antidepressant is withheld). In this clinical setting, the utility of maximizing mood-stabilizing medications becomes apparent. In addition, it is crucial that the patient record daily mood ratings, since antidepressant-induced cycle acceleration can be subtle and difficult to detect retrospectively.[48]

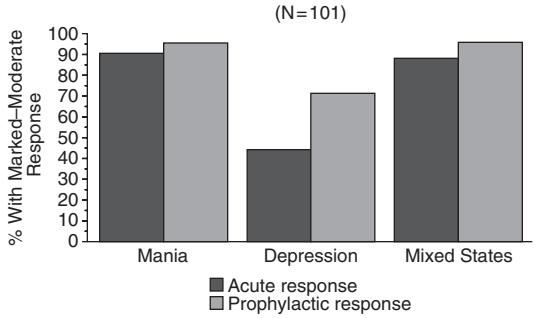
Which mood-stabilizing medication is most effective in the treatment of rapid cycling? Our ability to answer this question is limited by the fact that double-blind, random-assignment clinical trials in patients with rapid cycling bipolar disorder are virtually nonexistent. Some investigators conducting controlled trials with bipolar patients have performed post hoc analyses that compare the response of the rapid cycling patients in the sample with that of the non–rapid cycling patients.[3,10] Given the treatment-resistant nature of this population, however, the majority of studies have been uncontrolled and open.

The original description of rapid cycling was based on a sample of lithium nonresponders in a controlled trial of lithium versus placebo.[3] In this study, Dunner and Fieve became the first not only to define rapid cycling, but also to present data indicating that rapid cycling patients were less likely than non–rapid cycling bipolar patients to respond to lithium. Specifically, 82% of the rapid cyclers in their sample failed to respond to lithium, compared with 41% of the non–rapid cycling bipolar patients. However, both of these investigators[4] and others[49] later suggested that, while lithium may fail to decrease episode frequency in rapid cycling patients, it can frequently decrease episode severity and duration.

The data concerning the efficacy of carbamazepine as a treatment for rapid cycling bipolar disorder are limited and mixed. In a recent review, Calabrese and Woyshville[50] note 20 open and three "controlled or quasi-controlled" studies, with the latter category including only 10 patients. Calabrese and Woyshville note an overall response rate for carbamazepine in rapid cycling patients of 32% for acute depression, 52% for acute mania, 57% for the prevention of depression, and 59% for the prevention of mania.[50] However, they note that the majority of patients in these studies required adjunctive treatments, including antidepressants and often lithium. In addition, Okuma[51] reported an open study in which 53% of rapid cycling patients had a marked or moderate response to 2 years or more of carbamazepine treatment, compared with 30% of rapid cycling patients who responded to similarly lengthy trials of lithium. However, the report does not state whether the patients were receiving other medications or which ones if they were. Therefore, at this point, it appears that carbamazepine may have a role in the treatment of rapid cycling bipolar disorder, but its efficacy as either a sole or an adjunctive agent remains to be clearly defined.

Six open trials have examined the efficacy of valproate in the treatment of rapid cycling bipolar disorder. In the largest of these, Calabrese et al.[52] followed 43 rapid cycling patients on valproate therapy alone and 58 rapid cycling patients on combination therapy of valproate and other mood stabilizers. Fifty-nine percent of these patients had failed lithium treatment, 24% had failed carbamazepine treatment, and 25% had failed the combination of lithium and carbamazepine. Response to the acute treatment was measured after 6 weeks, while prophylactic effects were assessed after an average of 17.2 months of treatment. These investigators found that valproate was remarkably effective in the prevention and treatment of both mania and mixed states, with response rates approximating 90% (Figure 2). In the case of depression, the response rates were lower, particularly with regard to acute depres-

Figure 2. Efficacy of Valproate in Rapid Cycling Bipolar Disorder*



*Data from Calabrese et al.[52]

sion. Only 42% of acutely depressed patients responded to valproate, but 72% of patients did experience a prophylactic effect against future depressive episodes.

An emerging body of literature indicates that clozapine may be useful in the treatment of patients with refractory bipolar illness, including those with rapid cycling.[50,53–56] One of these studies[54] appears to indicate that clozapine alone is effective, without the concomitant use of other mood-stabilizing agents. High-dose thyroid supplementation and calcium channel blockers have also received some study as possible treatments for rapid cycling bipolar disorder. For example, Bauer and Whybrow found increased mood stabilization when they added levothyroxine (titrated to increase free T_4 levels to 150% of baseline) to stable medication regimens in a sample of 10 patients with rapid cycling bipolar disorder.[6] Nimodipine was reported to have some mood-stabilizing effect in eight patients with ultra-rapid cycling; it is unclear whether this possible effect also extends to other, less expensive calcium channel blockers.[57] It is interesting to note that both clozapine and levothyroxine, like the other mood stabilizers discussed above, appear to be more effective in the prevention and treatment of mania than in the prevention and treatment of depression.[6,56]

In sum, the treatment of patients with rapid cycling bipolar disorder is likely to remain a clinical challenge for some time to come. The hallmark of good treatment is systematic medication trials, with daily documentation of mood so that both short- and long-term treatment effects can be detected. Given the possibility that antidepressants may either precipitate mania or decrease cycle length, it is advisable to maximize the use of mood-stabilizing agents and minimize the use of antidepressants in patients with rapid cycling bipolar disorder. In some patients, combinations of mood-stabilizing medications appear to be useful. However, as noted above, mood-stabilizing agents are generally more effective at preventing and treating mania than at preventing and treating depression. Therefore, it is not uncommon for patients with rapid cycling bipolar disorder to suffer from severe depressive episodes. When a rapid cycling patient (or other bipolar patient) becomes acutely depressed, how effective are the mood-stabilizing agents in treating that depression? What are the risks and benefits of adding an antidepressant medication to the treatment regimen of a depressed, bipolar patient? These questions will now be addressed.

TREATMENT OF BIPOLAR DEPRESSION

Almost all bipolar patients experience depressive episodes, episodes that are frequently disabling and may involve significant suicidal ideation. Despite this fact, there are remarkably few clinical studies on the treatment of bipolar depression. This dearth of data may result from the fact that bipolar patients are often excluded from antidepressant trials because of concern that the medication will precipitate a manic episode. The rate at which this adverse effect occurs (and, indeed, the very question of whether it occurs) has been debated in the literature. In a review, Wehr and Goodwin[58] note that between 44% and 100% of bipolar patients in long-term antidepressant trials experienced a switch into hypomania or mania. Interestingly, there is evidence that women may be at higher risk than men to develop antidepressant-induced hypomania or mania.[13,47,59,60]

Data indicate that serotonin reuptake inhibitors (SRIs), monoamine oxidase inhibitors (MAOIs), and bupropion may be less likely to induce mania than tricyclic antidepressants (TCAs).[61–65] For example, in a review of published, controlled studies of bipolar depression, Zornberg and Pope[66] reported no cases of treatment-emergent mania in the 34 patients treated with SRIs, compared with an 11% switch rate among the 107 patients treated with TCAs. However, case reports of possible drug-induced switching exist even for the newer agents.[67–71] One study indicates that manic episodes induced by antidepressants are milder and more short-lived than manic episodes that arise spontaneously.[72] This same study also suggested that manic episodes induced by MAOIs or bupropion may be milder than those associated with TCAs or fluoxetine.[72]

Since antidepressants may cause bipolar patients to switch into hypomania or mania, and since most bipolar patients are maintained on one or more mood-stabilizing medications, the antidepressant effects of the mood stabilizers are of great clinical importance. How effective are each of the mood-stabilizing agents in treating acute depression in bipolar patients? Of all the available mood stabilizers, lithium has been best studied in this regard. Goodwin and Jamison[73] reviewed the seven studies comparing lithium with placebo in the treatment of acute depression and found that 79% of bipolar depressed patients, compared with 36% of unipolar depressed patients, had a complete or partial response to lithium.

Zornberg and Pope[66] used a stricter criterion to evaluate the same studies, calling patients "unequivocal" responders if they relapsed after the lithium was withdrawn. Using this criterion, they found a 36% unequivocal response rate in the bipolar depressed patients. In two other studies comparing lithium with imipramine in the treatment of bipolar depressed patients, one small study found lithium to be as effective as imipramine,[74] while a second, larger one found a superior response rate for imipramine.[75] These studies have generally maintained patients at serum lithium levels between 0.7 and 1.5 mEq/L,[73] but the issue of optimal lithium levels in the treatment of bipolar depression has not received systematic study.

The literature on the efficacy of carbamazepine and valproate in the treatment of acute bipolar depression is more limited than that concerning lithium. Two studies found that carbamazepine was superior to placebo in the treatment of bipolar depression.[76,77] Seven of the 16 patients in these studies had a good response to carbamazepine, while 2 had a partial response, for an overall response rate of 56%. A third study added lithium to the treatment of depressed bipolar patients who had not responded to carbamazepine alone, and found that 6 of 13 responded to the combination.[78]

With respect to valproate, there have been no controlled trials of the efficacy of valproate in the treatment of bipolar (or unipolar) depression. Summarizing the four uncontrolled studies in the literature, McElroy et al.[79] concluded that 30% of 195 depressed bipolar patients had experienced an antidepressant response to valproate. It is interesting to note that one of these studies[80] found that men were more responsive than women to the prophylactic antidepressant effects of valproate.

In sum, then, the literature indicates that the proportion of depressed bipolar patients responding to the antidepressant effects of mood-stabilizing agents may vary from a high of nearly 80% for lithium to a low of 30% for valproate (with carbamazepine in the middle at 56%). However, the literature concerning carbamazepine and valproate is so limited that these numbers could well change if larger studies were conducted. In addition, the one study that tested the antidepressant efficacy of carbamazepine and lithium combined,[78] as well as clinical experience, suggests that bipolar patients taking one mood stabilizer who become depressed may respond to the addition of a second mood-stabilizing medication.

Nonetheless, there are many bipolar patients whose depressive episodes do not respond to mood-stabilizing agents alone. For these patients, which antidepressants are likely to be most effective? Again, the available literature is surprisingly scant. Two studies on the same patient sample indicate that the MAOI tranylcypromine is more effective than imipramine in the treatment of atypical (i.e., anergic) bipolar depression. In the first of these studies, 81% of the patients who received tranylcypromine responded, compared with 48% of the patients who received imipramine.[62] In the second study, the patients who did not respond to the first treatment were then treated with the second.[81] Here, 75% of the patients who did not respond to imipramine responded to tranylcypromine, whereas only 25% of the patients who did not respond to tranylcypromine responded to imipramine. Given this favorable result with an MAOI, it is interesting to note the results of Ketter et al.,[82] who added phenelzine or tranylcypromine to the treatment regimen of 10 patients taking carbamazepine (with or without lithium). The combination was well tolerated by all 10 patients and effective in four.

Unfortunately, only one study has tested the efficacy of SRIs in the treatment of bipolar depression.[83] In this study, fluoxetine was more effective than imipramine, which in turn was more effective than placebo, in the treatment of bipolar depression. Although this study had a large sample size (N = 89), the dropout rate was high. Furthermore, the interpretation of the results is complicated by the fact that a relatively high percentage of the patients in the fluoxetine group received lithium in addition to the experimental treatment.[73,83] Obviously, more information is needed about the efficacy of fluoxetine, paroxetine, sertraline, and venlafaxine in the treatment of bipolar depression. In addition, a head-to-head comparison of an SRI with an MAOI in the treatment of bipolar depression would be a particularly informative study.

Of the newer antidepressants, bupropion has received the most attention in the treatment of bipolar depression. This interest was sparked by early reports of high response rates coupled with a low risk for mania or rapid cycling.[61,65] However, the two most recent studies have had more mixed results. Thus, Sachs et al. found that only 1 of 11 bipolar patients treated with bupropion switched into hypomania,[84] while Fogelson et al.[68] reported that 6 of 11 bipolar patients required discontinuation of the medication because of such switches.

Finally, it is important to note that electroconvulsive treatment (ECT) appears to be quite effective in the treatment of bipolar depression. As reviewed by Zornberg and Pope, five of the seven studies comparing ECT with antidepressants (TCAs and, in some instances, MAOIs) found ECT to be more effective than medication.[73] For example, in one of the larger studies, 61% of patients treated with ECT, compared with 25% of patients treated with TCAs or MAOIs, responded.[85] Of the nonresponders to medication who were then treated with ECT, 56% responded. However, ECT, like antidepressant medication, can cause switches into mania or hypomania.[86]

In sum, there are many gaps in our knowledge concerning the treatment of bipolar depression. While the available mood-stabilizing medications are better antimanic than antidepressant agents, these medications do nonetheless have significant antidepressant efficacy. Such efficacy has been most clearly demonstrated for lithium, but prob-

ably also exists in the case of valproate and carbamazepine. When a depressed, bipolar patient is treated with antidepressant medication, it is important that he or she document his or her mood on a daily basis so that the clinician can detect the onset of drug-induced cycling. Although the MAOIs, SRIs, and bupropion are less likely than the TCAs to induce hypomania or mania, all of the available antidepressants appear to be capable of causing such an adverse side effect. In addition, MAOIs appear to be more effective than TCAs in the treatment of bipolar anergic depression, and one study (albeit with some methodological difficulties) did show fluoxetine to be superior to imipramine. ECT should also be considered when other treatments are ineffective or cannot be tolerated.

CONCLUSION

While bipolar illness affects roughly equal numbers of women and men, its manifestations differ by gender. Bipolar women are three times more likely than bipolar men to develop rapid cycling. Bipolar women may also be more likely than bipolar men to develop depressive episodes and to experience dysphoric (rather than mixed) mania. Indeed, it is conceivable that bipolar women develop rapid cycling more frequently than do bipolar men because they are treated more frequently and/or more aggressively with antidepressants.[15]

These observations highlight the primary importance of mood stabilizers in the treatment of bipolar women, as well as the need for new antidepressant treatments that do not induce mania or rapid cycling. Relative to the TCAs, the SRIs and bupropion probably represent an advance in that regard. However, even the newer antidepressants appear to be capable of inducing mania (albeit at a lower rate than the TCAs) and therefore probably also cause rapid cycling. Continued research is warranted to develop antidepressant treatments that do not cause this adverse effect. In addition, given the limited literature on the treatment of bipolar depression and rapid cycling bipolar disorder, more clinical trials are needed to guide clinicians in the treatment of these frequently severe, and sometimes deadly, syndromes.

Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol and others), clomiphene citrate (Clomid and others), clozapine (Clozaril), fluoxetine (Prozac), imipramine (Tofranil and others), levothyroxine (Synthroid and others), nimodipine (Nimotop), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor).

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