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Mood symptoms in pregnant and postpartum women with bipolar disorder: a naturalistic study

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Abstract

Objective: We conducted a prospective naturalistic study of pregnant women with bipolar disorder (BD) to evaluate symptoms of BD across childbearing and assess whether pharmacotherapy reduced their severity.

Methods: Assessments were scheduled at 20, 30, and 36 weeks' gestation and 2, 12, 26, and 52 weeks postpartum. Symptoms were assessed using the Structured Interview Guide for the Hamilton Depression Rating Scale–Atypical Depression Supplement (SIGH-ADS) and Mania Rating Scale (MRS).

Results: Pregnant women (N=152) with BD were evaluated; 88 women (58%) were treated and 64 untreated (42%) with psychotropic drugs during pregnancy. Among the 88 women treated, 23 (26%) discontinued their medication in the first trimester and the remaining 65 (74%) were exposed throughout pregnancy or in the second and third trimesters. More than two-thirds (73%) of the women who remained in the study took psychotropic agents postpartum. The mean scores on the SIGH-ADS were in the mild range of depressive symptoms in both the psychotropic-treated and untreated groups in both pregnancy and postpartum. The majority of women had no or few symptoms of mania. Of the pregnant women treated with psychotropic agents, 66% received a guideline-concordant drug, and 34% received either antidepressant mono-therapy (for BD I) or mono-or polypharmacy with a variety of other agents.

Conclusions: This sample of perinatal women with BD was characterized by mild residual symptoms of depression independent of pharmacotherapy, which poses a risk for recurrence and impaired parenting. The treatment of childbearing women with BD deserves urgent clinical and research attention to improve psychiatric outcomes.

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Keywords

Psychotropic agents; bipolar disorder; pregnancy; pharmacokinetics; perinatal; mental health

1 | INTRODUCTION

Childbearing is a major life event with a profound impact on mental health,¹ particularly for women with bipolar Disorder (BD). Mothers with BD are highly vulnerable to postpartum affective episodes, which are often depressive or mixed,^{2–5} and postpartum psychosis is a manifestation of BD.⁶ Contributors to this postbirth vulnerability are the rapid gonadal steroid withdrawal that occurs at delivery,⁷ sleep deprivation from labor and infant care with disrupted circadian rhythms,⁸ and postbirth activation of the immune system.⁹ The first month after birth is an especially high-risk time for mood destabilization and carries a relative risk of 23 for psychiatric admission for women with BD compared to nonpostpartum women with BD.¹⁰

Few studies have examined the course of BD through pregnancy and after birth. Viguera et al.¹¹ conducted a prospective observational cohort study to determine the magnitude of risk and time to recurrence for a new episode in 89 women with BD. The overall risk for recurrence in pregnancy was a striking 71%. For women who discontinued vs continued pharmacotherapy, the recurrence risk was twice as high, the median time to recurrence was four times shorter, and the proportion of weeks ill during pregnancy was five times greater. The median recurrence latency was 11 times shorter after abrupt or rapid vs gradual discontinuation of pharmacotherapy. Most recurrences (47%) occurred during the first trimester and the majority were depressive or mixed (74%).

Freeman et al. studied the influence of reproductive events on the course of BD in 50 women.⁵ Two-thirds of the women with children had a postpartum mood episode after their first birth, and all of these women had recurrences after subsequent pregnancies. Postpartum episodes were almost exclusively depressive, and increased depressive symptoms in pregnancy were significantly associated with postpartum mood episodes. Wesseloo et al.¹² reported that postpartum relapse rates were significantly higher among those who were medication free during pregnancy (66%) compared to women who used prophylactic medication (23%). Patients with chronic BD were significantly less likely to experience severe episodes postpartum (17%) compared to women with a history of only postpartum psychosis (29%), who have a specific vulnerability to postbirth relapse. In a prospective observational study of pharmacotherapy in 37 women with BD II across child-bearing, Sharma et al.¹³ reported that the majority of women (54%) did not take psychotropic medication, approximately one-third received monotherapy, and the remainder were treated with combination therapy. During the postpartum period, the majority (86%) of women were treated with psychotropic medication; about one-third received monotherapy, and over half were treated with combination therapy. While 14% of participants were taking three or more psychotropic drugs during pregnancy, 22% required three or more psychotropic drugs after childbirth in order to manage their symptoms.

The impact of pregnancy on the course of BD across childbearing is an important area of clinical investigation. As the mainstay of treatment is pharmacotherapy, the benefits to the woman and family of BD treatment must be weighed against the risks of drug treatment across childbearing. This decision-making process is a challenging task. Both groups of pregnant women with BD (treated and untreated with pharmacotherapy) have a greater risk for multiple adverse reproductive events (cesarean delivery, preterm birth, and infants with microcephaly, small for gestational age, and with neonatal hypoglycemia) compared to women without BD.^{14,15} Evolving research on the association between adversity during pregnancy (fetal programming) and lifelong health has highlighted the risks of uncontrolled disease.^{16,17} To contribute information on the course of BD and the impact of pharmacotherapy on symptom expression across childbearing, we conducted a prospective study of a community cohort of pregnant women with BD. We characterized symptoms of depression and mania throughout pregnancy and the first year after birth and compared symptom levels of psychotropic-treated women to those of nonpsychotropic-treated women. Our hypothesis was that psychotropic-treated women would have less symptom burden and functional impairment across childbearing compared to women who were not receiving pharmacotherapy.

2 | METHODS

2.1 | Subjects

Women between 18 and 44 years of age from Pittsburgh, PA, were enrolled between July 2006 and March 2011, into the Antimanic Use during Pregnancy (AMUP, R01 MH 075921; K. Wisner, PI) study at or prior to 20 weeks' gestation. The investigation was approved by the University of Pittsburgh Institutional Review Board. Subjects were referred by physicians, community health practitioners, rural regional medical centers, and by advertising. Eligible women were English-speaking and had a DSM-IV diagnosis of BD I, II, or not otherwise specified (NOS), according to the Structured Clinical Interview for DSM-IV (SCID) by Master's-level clinicians with extensive experience in assessing mood disorders. All women provided written informed consent.

Pregnant women were excluded if they did not have obstetrical care or were taking medications in the Food and Drug Administration (FDA)-assigned D or X categories other than the psychotropic drugs of interest. Although these FDA categories have been eliminated,¹⁸ they were in effect during the time of the study. Smoking, alcohol, and illicit substance use information history was obtained. Women who tested positive by urine screen for a nonprescription, illicit drug at intake were not eligible for the study; however, we enrolled women who tested positive for cannabis because its use was so frequent that excluding them would have limited both the sample accrual and generalizability.

All subjects received consultation regarding the management of BD, and a summary of the recommendations was sent to participants and community prescribers. Decisions about treatment were made by participants and community healthcare professionals. The choice to accept or decline treatment or to implement investigators' clinical recommendations did not dictate study inclusion or retention.

2.2 | Assessments

Maternal assessments were scheduled at 20, 30, and 36 weeks' gestation and 2, 12, 26, and 52 weeks postpartum. Evaluations were held in our specialized women's mental health center, conducted at the participants' homes or by telephone to minimize barriers in collecting data. In addition to establishing the diagnosis of BD, the SCID was administered to determine comorbid and lifetime diagnoses. At all study visits, subjects were interviewed about tobacco, illicit substance, and alcohol use. Symptom severity was assessed using the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS), which contains the familiar 17-item Hamilton Rating Scale for Depression (HAM-D-17).¹⁹

The SIGH-ADS also captures eight atypical symptoms of depression, which are more common in women²⁰ and individuals with BD.²¹ A score of 8 indicates remission, 9–17 indicates mild depression, and 18 indicates moderate to severe depression.

The Mania Rating Scale (MRS), derived from the Schedule for Affective Disorders and Schizophrenia Research Diagnostic Interview, was used to evaluate hypomanic/manic symptoms.²² Notably, five of 11 items on the scale require at least “1 other manic-like symptom” in order to score any points; therefore, the MRS is a discontinuous measure with a score distribution heavily weighted toward zero. Given the skewness of MRS scores, we used the dichotomized MRS (zero vs nonzero) in all analyses. Secondary functional measures included the Global Assessment Scale (GAS) and the 12-item Short-Form (SF-12) health survey, which yields summary scores for the physical (PS) and mental (MS) subscales.

2.3 | Statistical methods/data analysis

The primary outcome measure was the SIGH-ADS score. Demographic and clinical measures obtained at study enrollment were compared among women who took psychotropic agents only during the first trimester of pregnancy (Stop T1), or during the second and/or third trimester (OnT2/T3), and nonpsychotropic-treated women (No Psych Med) at any point during pregnancy. Women in the Stop T1 group stopped medication upon discovering they were pregnant. Women in the OnT2/T3 group continued medication throughout pregnancy or had exposure only during Trimester 2 and 3. The SIGH-ADS scores of women receiving psychotropic medication at any point postpartum were compared to women who did not receive them. A wide variety of psychotropic drug classes were prescribed; therefore, we characterized exposure broadly as psychotropic drug vs no psychotropic drug. Medications prescribed for nonpsychiatric disorders (such as antihypertensive drugs, antibiotics) were not included in either group.

For continuous demographic and clinical measures, the group comparisons employed *t* tests or analysis of variance (ANOVA) when empirical distributions appeared normal, and Mann-Whitney U or Kruskal-Wallis tests otherwise. For categorical measures, the groups were compared using chi-squared tests and Fisher's exact tests when expected cell sizes were small (less than five). In the event of significant findings at the 5% level across three groups

for any comparison, further post hoc pairwise comparisons were evaluated using Bonferroni correction for multiple comparisons.

Because the clinical and functional measures were assessed at each study visit, additional analyses employed repeated-measures mixed models, assuming an unstructured covariance matrix random subject effect and fixed effects (psychotropic use during pregnancy or postpartum, time, and their interaction). All analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, Version 3.2.0). All statistical tests were two-sided, with a significance level of 0.05, except in cases utilizing Bonferroni correction.

3 | RESULTS

A total of 159 pregnant women with BD were enrolled (Figure 1). Seven participants were lost to follow-up during pregnancy (N=152) and an additional 45 were lost to follow-up during the postpartum period (N=107). A total of 88 women (58% of women with BD) were exposed to medication during pregnancy; however, about a quarter of these women discontinued their treatment in the first trimester (Stop T1) and the remainder continued pharmacotherapy into the second and third trimesters (OnT2/T3). There were 64 women (42%) who were not exposed to psychotropic medication (No Psych Med) during pregnancy. About three-quarters (n=78, 73%) of the women were treated with psychotropic agents (Psych Med) after birth.

The demographics of the subjects, for the overall diverse sample and divided by exposure group in pregnancy and postpartum, are displayed in Table 1. The sample was 26.3 ± 6.2 years of age, about one-third (33%) from minority groups, with the majority having high school and/or some college education (85%), being unemployed (68%), and being single (60%). Nearly 60% of the participants had the BD I subtype. Self-reported substance use across pregnancy was common: 40% of the women smoked cigarettes, 19% drank alcohol, and 27% used illicit drugs (primarily cannabis) after study enrollment. The most common lifetime comorbidities in these women with BD included anxiety disorders (51%), alcohol abuse (11%), and cannabis use disorders (10%).

Compared to women in the No Psych Med group, those who continued pharmacotherapy during pregnancy (OnT2/T3) were significantly older, more likely to be educated, less likely to be single or widowed, more likely to have BD I and a history of psychiatric hospitalization, and more likely to have a lifetime comorbid alcohol use disorder (Table 1). Of the variables examined, the only significant difference between women in the Stop T1 group and those in the OnT2/T3 group was that the former were more likely to be single. No significant demographic differences were observed between the women in the No Psych Med group vs those in the Stop T1 group. In the group of women who provided postpartum data, those in the No Psych Med group were significantly younger than those who were treated with psychotropic agents.

A total of 88 (58%) pregnant women were treated with psychotropic agents; however, substantial changes in both the class of drug prescribed and the individuals treated were observed across pregnancy (Table 2). At any point in pregnancy, 66% of women received a guideline-concordant drug²³ for BD, defined as lithium alone/combination (n=9; 8%), anticonvulsant alone/combination (n=22; 19%), antipsychotic agent alone/combination (n=34; 30%), or, for BD II or BD NOS, antidepressant monotherapy or combined with another psychotropic (n=10; 9%). The remaining subjects received nonguideline-concordant treatment: antidepressant monotherapy for BD I (n=10; 9%) or mono- or polypharmacy with a variety of agents, including gabapentin, hydroxyzine, zolpidem, amphetamines, methylphenidate, atomoxetine, diphenhydramine, benzodiazepines, and buspirone (n=28; 25%). After recognition of pregnancy in the first trimester, discontinuation of and switches in medication were common. In the second and third trimesters, the number of women treated with antipsychotic monotherapy doubled, while the number treated with anticonvulsants declined. Following birth, the proportion of women treated with guideline concordant drugs was similar (60%) to proportion of guideline concordant drug treatment across pregnancy (66%).

At all three assessment points in pregnancy, mean SIGH-ADS scores were of mild to moderate severity. The mean scores were similar for SIGH-ADS (16.5–19.6; the primary outcome measure) and HAM-D-17 (10.4–12.8) in all three groups of women with BD (Table 3). No statistically significant differences in the mixed-effect models were observed for comparison of depression symptom levels among the three groups. During the postpartum period (Table 4), the ranges of the mean SIGH-ADS (12.6–17.4) and HAM-D (7.8–11.3) scores across the four assessments tended to be lower than those observed during pregnancy for both the psychotropic-treated and untreated groups. Similar to pregnancy, no significant differences in the mixed models were observed in psychotropic treated vs untreated women.

On the MRS, the majority of pregnant women scored a zero, and the proportion of women who had a nonzero score did not differ significantly among the three groups. After birth, the proportion of women endorsing any symptoms on the MRS did not differ significantly between psychotropictreated and untreated subjects. Surprisingly, no substantial elevation in manic or depression symptom scores was observed in the immediate postbirth period at week 2.

Among the functional measures for pregnant women, the only significant difference was for the SF-12-MS scores; however, the group difference was no longer significant when we adjusted for multiple comparisons ($p=.24$ and $p=.10$ for the No Psych Med vs Stop T1 and OnT2/T3 groups comparisons, respectively). Mean scores at the assessments ranged from 33.4 to 43.3 in the Stop T1 and OnT2/T3 groups, and 39.3 to 45.3 in the No Psych Med group. As expected, these mental subscale scores in childbearing women with BD were lower than the average SF-12 MS score for a general population of American women of 50.8.²⁴ The SF-12 PS mean score ranges over-lapped for the three groups: 40.2–43.9 for No Psych Med, 33.6–48.8 for Stop T1, and 41.5–45.5 for OnT2/T3. These scores were similar to the mean SF-12 PS score for American women of 46.1.²⁴ After birth, the SF-12 MS mean scores were higher in both the psychotropic-treated and untreated groups (range 37.3–45.1)

compared to pregnancy. The SF-12 PS mean scores also improved (range 44.5–51.1) in the postpartum period compared to during pregnancy.

During pregnancy, the mean GAS scores (59.9–65.8) were generally in the 61st to 70th decile both for treated and untreated women. This decile is described as “some mild symptoms or some difficulty in social, occupational, or school functioning, but generally functioning pretty well, and has some meaningful interpersonal relationships”.²⁵ After birth, for both psychotropic-treated and untreated women, the mean GAS scores (62.4–74.1) improved overall, which is consistent with the increase observed for the SF-12 MS and PS scores. At 12 and 26 weeks postpartum, the mean scores were in the 71st to 80th decile for the No Psych Med group (“if symptoms are present, they are transient and expectable reactions to psychological stressors; no more than slight impairment in social, occupational, or school function”).²⁶ Although not statistically significant, the psychotropic treated women had worse symptom scores, on average, compared to the No Psych Med group ($p=.055$).

4 | DISCUSSION

In the present observational study of a community sample of women with BD, slightly more than half received psychotropic drugs during pregnancy and more than a quarter of the women stopped their medication in the first trimester. After birth, about two-thirds of the women were treated with psychotropic drugs. Compared to nonpsychotropic-treated women with BD, those who continued psychotropic pharmacotherapy through pregnancy were older, more educated, and more likely to be married, have BD I, and have a history of both hospitalization and comorbid alcohol use disorder. These characteristics suggest that women who continued pharmacotherapy beyond the first trimester of pregnancy had more severe psychiatric illness but more resources and access to psychiatric treatment. Some subjects reported abruptly stopping psychotropic medication in the first trimester without physician consultation or having difficulty in locating a practitioner who would prescribe psychotropic agents during pregnancy.

About two-thirds of the women received guideline-concordant drug therapy, with antipsychotic agents as the most commonly pre-scribed agents. These results are similar to those of Huang et al.²⁶ for nonpregnant patients with BD. In that investigation and ours, more than half received guideline-concordant therapy, and antipsychotic agents represented the modal monotherapy choice. In our study, a third of the treated women received either antidepressant monotherapy (for BD I) or polypharmacy with a variety of other agents. Other non-drug treatments, such as psychotherapy and nutritional supplements, were used instead of or in addition to mood stabilizers for some study participants. Several explanations for the lack of, or nonguideline-concordant, drug treatment are likely. Patient factors include a preference for nonprescription drug treatments and concern about the adverse effects of antimanic agents for the fetus.¹⁴ Prescriber-level factors include minimal training in the pharmacological treatment of perinatal women with BD²⁷ and reticence to prescribe antimanic drugs during pregnancy due to liability concerns.¹⁴ Variability among clinical practice guidelines for the general population of BD patients leads to uncertainty about pharmacotherapy on the part of healthcare providers, policy makers, and patients.²⁸

The application of guidelines for BD to pregnant and breastfeeding women presents additional challenges, and reviews are available.^{14,29}

Our data are consistent with previous studies of perinatal women, in that depression was the predominant manifestation of BD both during pregnancy and after birth.^{10,11,30} Depression is strongly associated with perceived poor quality of life,³¹ and our subjects consistently reported problems with functioning. Comorbid psychiatric disorders are also associated with lower scores on functional measures in patients with BD.³² Consistent with epidemiological and clinical studies of BD, our sample also had a high rate of lifetime comorbid anxiety disorders (about 50%).^{33–35} For these patients, the course of BD is likely to be more severe, with shorter periods in euthymia, more rapid time to relapse, slower time to remission, and poorer functioning and quality of life.^{34,36} This comorbidity and the resulting effects on illness course contribute to chronic symptoms and the negative impact on parenting.¹⁴

The rates of self-reported smoking, alcohol, and illicit drug use during pregnancy in our subjects are similar to those in a study demonstrating that perinatal women with BD have more substance use compared to perinatal women with psychiatric diagnoses other than BD.³⁷ Even with the exclusion of alcohol- and substance-dependent women at intake by urine drug screen and focused interview, the women with BD who were enrolled in the study smoked (40%), drank alcohol (19%), and used illicit drugs, particularly cannabis (27%), at some point during pregnancy. Substance use comorbidity contributes to poor response to treatment. Providing targeted substance use education and intervention is an opportunity to improve pregnancy outcomes in women with BD,³⁸ and collaborative care treatment models that integrate mental health and pregnancy care also enhance outcomes.³⁹

We did not confirm our hypothesis that women who received psychotropic medication would have less symptom burden and functional impairment compared to women in the No Psych Med group. Depression and mania scores were relatively constant across pregnancy and the postpartum period in all groups. We propose several explanations for these results. About a third of women were treated with medications without established efficacy for BD. Additionally, maintaining therapeutic doses of psychotropic drugs is challenging due to the changing physiological milieu of pregnancy and the induction of cytochrome P 450 enzymes, which reduce plasma drug concentrations.^{40,41}

We did not observe a substantial increase in either depressive or manic symptoms in the postpartum period, which contrasts with our expectations based upon epidemiological studies. Our subjects experienced lower levels of depressive and manic symptoms after birth than during pregnancy, in contrast to studies which suggest that pregnancy is a low-risk period for recurrence of BD.^{3,42,43} However, our data corroborate the findings of investigators who report that women with chronic BD are at risk for a worsening of mood symptoms during pregnancy.^{5,11} Consistent with our results, Bergink et al.⁴⁴ reported that women with chronic BD (as in our sample), compared to women with a history of acute postpartum episodes only, had a similar rate of relapse during pregnancy (24%) as postpartum (22%), regardless of lithium treatment. The symptom course of our subjects improved on all measures after birth, and the majority resumed psychotropic medication in the postpartum period. Another explanation is that about two-thirds of the treated women

were taking an antimanic agent, most often antipsychotic drugs, in the third trimester, which may have reduced the risk of postbirth mania.

The strengths of the present investigation include multiple observations of a difficult-to-study population—women with chronic BD who are coping with pregnancy and childbirth. The diversity in this community sample of women being treated and/or monitored for BD enhances the generalizability of results; however, the subjects were able to provide informed consent, meet eligibility criteria, and participate in follow-up assessments, which suggests that women who did not participate may have had more severe disorders. Despite intense effort by the study team, another limitation was that the follow-up rate postdelivery was only 70%; therefore, it is possible that worsening of illness and inability to be reached for follow-up accounted for postpartum attrition.

The treatment of pregnant and postpartum women with BD is a clinical challenge, as elegantly described by Burt et al.⁴⁵ The mental health of the mother is a priority in optimizing pregnancy outcomes, and the risks of poorly controlled disease must be balanced against those of drug treatment for the mother and fetus. This clinical conundrum has received policy attention from the Center for Disease Control and Prevention's Treating for Two, which aims to improve the health of women and infants by identifying the safest treatment options for the management of common disorders during pregnancy (www.cdc.gov/pregnancy/meds/treatingfortwo/). Pregnancy is a clinical context that compels the use of psychotropic agents, with demonstrated efficacy as a reduction in disease burden is the justification for exposure of the maternal-fetal pair. In a summary of management strategies for BD in pregnancy, Yonkers et al.¹⁴ emphasized the need for professional education to improve the treatment of women with BD. More recently, Osborne et al.²⁷ provided evidence of the gap between clinical need and education in reproductive psychiatry and argued that all psychiatrists should receive training in managing pregnant women to ensure the competent care of this vulnerable group. Improving psychiatric care for childbearing women with BD deserves further urgent clinical and research attention, to improve psychiatric treatment delivery and to optimize perinatal mental health⁴⁶.

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FIGURE 1.

Study flow chart. AMUP, Antimanic Use in Pregnancy; MDD, major depressive disorder; No Psych Med, nonpsychotropic-treated women; Stop T1, women who took psychotropic agents only during the first trimester of pregnancy; OnT2/T3, women who continued medication throughout pregnancy or had exposure only during Trimester 2 and 3 [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1
Demographic and clinical measures by use of psychotropic agents in pregnant and postpartum women

Characteristic	Overall		During pregnancy N=152		Post hoc pairwise comparison		Postpartum N =107		P-value
	N=152	No Psych Med (N=64)	StopTI (N=23)	OnT2/T3 (N=65)	No Psych Med vs StopTI	StopTI vs OnT2/T3	No Psych Med (N=29)	Medicated (N=78)	
Age (years)	26.3±6.2	23.9±5.2	26.9±5.0	28.5±6.7	<.001	0.800	24.2±5.3	27.4±6.2	.014
Race					.113				.170
White	102 (67.1)	37 (57.8)	17 (73.9)	48 (73.8)			12 (41.4)	55 (70.5)	
Black	42 (27.6)	24 (37.5)	6 (26.1)	12 (18.5)			23 (29.9)	18 (23.1)	
Other	8 (5.3)	3 (4.7)	0	5 (7.7)			1 (3.4)	5 (6.4)	
Hispanic	3 (2.0)	0	0	3 (5.8)	.348		0	3 (4.7)	.571
Education level					.002	0.999			.399
<High school	22 (14.7)	17 (26.6)	1 (4.5)	4 (6.2)			5 (17.2)	8 (10.3)	
High school	42 (28.0)	21 (32.8)	8 (36.4)	13 (20.3)			10 (34.5)	19 (24.4)	
Some college	60 (40.0)	20 (31.3)	9 (40.9)	31 (48.4)			10 (34.5)	35 (44.9)	
College	18 (12.0)	5 (7.8)	2 (9.1)	11 (17.2)			4 (13.8)	11 (14.1)	
Graduate school	8 (5.3)	1 (1.6)	2 (9.1)	5 (7.8)			0 (0.0)	5 (6.4)	
Employed	47 (32.0)	14 (22.6)	10 (45.5)	23 (36.5)	.084		6 (21.4)	24 (31.2)	.464
Marital status					<.001	0.008			.560
Single	91 (59.9)	45 (70.3)	18 (78.3)	28 (43.1)			19 (65.5)	42 (53.8)	
Married/cohabitating	53 (34.9)	19 (29.7)	3 (13.0)	31 (47.7)			10 (34.5)	30 (38.5)	
Divorced/separated	7 (4.6)	0	1 (4.3)	6 (9.2)			0 (0.0)	5 (6.4)	
Widowed	1 (0.7)	0	1 (4.3)	0			0	1 (1.3)	
Use during study period ^a									
Smoked tobacco	60 (40.0)	28 (43.8)	8 (36.4)	24 (37.5)	.718		9 (32.1)	30 (40.0)	.615
Drank alcohol	29 (19.3)	15 (23.4)	2 (9.1)	12 (18.8)	.335		7 (25.0)	13 (17.3)	.552
Used illicit drugs	41 (27.3)	22 (34.4)	5 (22.7)	14 (21.9)	.267		11 (40.7)	16 (21.1)	.073
Bipolar subtype					.050	0.350			.496
I	89 (58.6)	32 (50.0)	11 (47.8)	46 (70.8)			15 (51.7)	49 (62.8)	
II	42 (27.6)	24 (37.5)	7 (30.4)	11 (16.9)			10 (34.5)	19 (24.4)	

Characteristic	Overall		During pregnancy N=152		Post hoc pairwise comparison		Postpartum N =107		P-value
	N=152	No Psych Med (N=64)	Stop T1 (N=23)	OnT2/T3 (N=65)	P-value	No Psych Med vs Stop T1	No Psych Med vs OnT2/T3	No Psych Med (N=29)	Medicated (N=78)
NOS	21 (13.8)	8 (12.5)	5 (21.7)	8 (12.3)				4 (13.8)	10 (12.8)
Lifetime comorbidities									
Anxiety	77 (50.7)	31 (48.4)	12 (52.2)	34 (52.3)	.897			13 (44.8)	42 (53.8)
Alcohol abuse	17 (11.2)	1 (1.6)	3 (13.0)	13 (20.0)	.001	0.165	0.999	2 (6.9)	13 (16.7)
Cannabinoid	15 (9.9)	6 (9.4)	1 (4.3)	8 (12.3)	.577			3 (10.3)	7 (9.0)
Psychiatric hospitalization	13 (8.6)	2 (3.1)	1 (4.3)	10 (15.4)	.037	0.999	0.826	1 (3.4)	12 (15.4)
Parity					.078				
1	41 (32.5)	15 (30.0)	2 (11.1)	24 (41.4)				11 (37.9)	29 (38.7)
2	43 (34.1)	21 (42.0)	7 (38.9)	15 (25.9)				11 (37.9)	20 (26.7)
3+	42 (33.3)	14 (28.0)	9 (50.0)	19 (32.8)				7 (24.1)	26 (34.7)

Data presented as mean ± standard deviation SD and n (%).

NOS, not otherwise specified; No Psych Med, nonpsychotropic-treated women; Stop T1, women who took psychotropic agents only during the first trimester of pregnancy; OnT2/T3, women who continued medication throughout pregnancy or had exposure only during Trimester 2 and 3.

^aPresented as use at any point in pregnancy (or postpartum) by an individual woman.

TABLE 2

Medication use by women by trimester of pregnancy and postpartum

Psychotropic (psych) agent(s)	First trimester	Second trimester	Third trimester	Any time point during pregnancy	0–2 weeks PP	2 weeks to 3 months PP	3 months to 6.5 months PP	6.5 months to 12 months PP	Any time point during PP
N ^a	74	59	59	88	60	66	62	43	77
Lithium only	2 (2.7%)	3 (5.1%)	4 (6.8%)	5 (4.4%)	4 (6.8%)	2 (3.4%)	2 (3.2%)	0(0%)	5 (4.8%)
Lithium + antipsychotic	1 (1.4%)	0(0%)	0(0%)	1 (0.9%)	0(0%)	2 (3.4%)	0(0%)	1 (2.3%)	3 (2.9%)
Lithium + antidepressant	2 (2.7%)	3 (5.1%)	2 (3.4%)	3 (2.7%)	2 (3.4%)	2 (3.4%)	2 (3.2%)	2 (4.7%)	2 (1.9%)
Lithium + anticonvulsant	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1 (2.3%)	1 (1.0%)
Anticonvulsant only	4 (5.4%)	3 (5.1%)	3 (5.1%)	10 (8.8%)	5 (8.5%)	3 (5.1%)	1 (1.6%)	2 (4.7%)	5 (4.8%)
Anticonvulsant + antipsychotic	3 (4.1%)	2 (3.4%)	2 (3.4%)	5 (4.4%)	2 (3.4%)	2 (3.4%)	1 (1.6%)	2 (4.7%)	4 (3.8%)
Anticonvulsant + antidepressant	6(8.1%)	1 (1.7%)	2 (3.4%)	7 (6.2%)	1 (1.7%)	3 (5.1%)	3 (4.8%)	2 (4.7%)	4 (3.8%)
Antipsychotic only	7(9.5%)	16(27.1%)	14 (23.7%)	19 (16.8%)	13 (22%)	16(27.1%)	16(25.8%)	6 (14.0%)	20(19.2%)
Antipsychotic + antidepressant	12 (16.2%)	9 (15.3%)	12 (20.3%)	14 (12.4%)	8 (13.6%)	9 (15.3%)	5 (8.1%)	0(0%)	10 (9.6%)
Antipsychotic + other psych med	0(0%)	1 (1.7%)	0(0%)	1 (0.8%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Antidepressant only (BD I only)	4 (5.4%)	7(11.9%)	4 (6.8%)	8 (7.1%)	5 (8.3%)	4(6.1%)	4 (6.5%)	3 (7.0%)	6 (5.8%)
Antidepressant only (BD II and NOS)	8 (10.8%)	5 (8.5%)	7(11.9%)	9 (8.0%)	6 (10%)	6(9.1%)	6 (9.7%)	5 (11.6%)	8 (7.7%)
Antidepressant + other psych med (BD I only)	2 (2.7%)	0(0%)	0(0%)	2 (1.8%)	1 (1.7%)	1 (1.7%)	0(0%)	0(0%)	1 (1.0%)
Antidepressant + other psych med (BD II and NOS)	1 (1.4%)	0(0%)	0(0%)	1 (0.8%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Benzodiazepine only	0(0%)	0(0%)	1 (1.7%)	1 (0.8%)	1 (1.7%)	2 (3.4%)	0(0%)	0(0%)	2 (1.9%)
Other psych med only	2 (2.7%)	2 (3.4%)	1 (1.7%)	4 (435%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Other combinations of 2 meds	6(8.1%)	2 (3.4%)	1 (1.7%)	7 (6.2%)	1 (1.7%)	0(0%)	2 (3.2%)	1 (2.3%)	4 (3.8%)
Combinations of 3 or more psych meds	14 (18.9%)	5 (8.5%)	6 (10.2%)	16 (14.2%)	11 (18.6%)	14 (23.7%)	20 (32.3%)	18 (41.9%)	29 (27.9%)

Guideline-concordant pharmacotherapy is highlighted in green. Med, medication; PP, postpartum

^aN is the number of women providing data at the assessment point. Note that the N for “at any time” during pregnancy or postpartum refers to individual subjects, but the denominator for calculated percentages is higher due to changes in medications prescribed in the same patient at varying points in pregnancy or postpartum (denominator = 113 in pregnancy and 104 postpartum).

[Colour table can be viewed at wileyonlinelibrary.com]

TABLE 3

Symptom measures for women by psychotropic drug use during pregnancy

Measure	No Psych Medication				Stop T1		OnT2/T3			
	Week 20 N ^b =54	Week 30 N=38	Week 36 N=33	Week 20 N=18	Week 30 N=11	Week 36 N=11	Week 20 N=57	Week 30 N=45	Week 36 N=47	
SIGH-ADS	18.6±7.4	17.5±7.5	16.5±7.3	19.6±8.7	17.5±8.0	18.7±6.3	19.3±9.6	17.2±9.2	16.6±8.5	
HAM-D	11.7±5.2	11.2±5.8	10.4±5.9	12.8±7.3	11.2±5.1	11.7±4.3	12.8±6.9	10.7±5.9	10.5±6.0	
GAS	64.4±11.2	65.8±13.1	64.5±14.4	62.4±10.9	63.1±12.1	59.9±8.4	63.0±11.5	63.1±10.6	63.8±10.5	
SF12 mental scale ^a	39.3±11.6	41.5±12.1	45.3±14.6	33.4±10.0	35.0±9.4	42.2±13.2	33.8±14.4	38.8±14.2	43.3±12.3	
SF12 physical scale	43.2±8.8	43.9±8.7	40.2±8.7	48.8±9.1	44.6±11.5	33.6±10.2	45.5±10.6	43.9±9.3	41.5±10	
MRS>0	21 (38.9)	10 (26.3)	11 (33.3)	2 (11.1)	2 (18.2)	3 (27.3)	21 (36.8)	12 (26.7)	8 (17.0)	

Data presented as mean ± standard deviation and n (%).

GAS, Global Assessment Scale; HAM-D, 17-item Hamilton Rating Scale for Depression; MRS, Mania Rating Scale; Psych, psychotropic; SF-12, 12-item Short-Form health survey; No Med, No Medications in Pregnancy; SIGH-ADS, Structured Interview Guide for the Hamilton Depression Rating Scale– Atypical Depression Supplement; Stop T1, stopped medication upon discovering they were pregnant; OnT2/T3, continued medication throughout pregnancy or had exposure only during Trimester 2 and 3..

^aSignificant group effect ($P<.05$) was found. No Med vs Stop T1: $P=.08$; Stop T1 vs OnT2/T3: $P=.79$; and No Psych Med vs OnT2/T3: $P=.034$.

^bN is the number of women providing data at the assessment point.

TABLE 4

Symptom measures for women by use of psychotropic agents postpartum

Measure	No Psych Medication			Medicated		
	Week 2 N ^a =21	Week 12 N=14	Week 26 N=14	Week 52 N=14	Week 2 N=67	Week 12 N=53
SIGH-ADS	15.3±8.3	12.6±8.1	14.3±7.4	15.2±8.0	16.6±9.0	14.8±8.5
HAM-D	10.1±6.2	8.1±6.1	7.8±5.0	9.1±5.4	11.3±6.6	9.6±5.9
GAS	69.0±11.9	74.1±12.3	70.8±10.2	62.4±12.1	63.9±10.6	64.7±9.3
SF12 Mental scale	42.4±11.2	45.1±9.7	43.4±11.5	39.7±11.6	40.7±12.9	37.3±11.8
SF12 Physical scale	45.2±9.7	51.1±6.4	50.3±7.2	45.2±15.8	46.8±10.0	48.7±11.1
MRS>0	7 (33.3)	3 (21.4)	2 (14.3)	4 (28.6)	21 (31.3)	17 (32.1)
						11 (27.5)
						9 (22.5)

GAS, Global Assessment Scale; HAM-D, 17-item Hamilton Rating Scale for Depression; MRS, Mania Rating Scale; SF-12, 12-item Short-Form health survey; SIGH-ADS, Structured Interview Guide for the Hamilton Depression Rating Scale–Atypical Depression Supplement.

^aN is the number of women providing data at the assessment point.