CLINICAL COURSE OF BIPOLAR DISORDER DURING THE MENOPAUSAL TRANSITION: COMPARISON WITH REPRODUCTIVE AGE AND POST MENOPAUSAL WOMEN. A DISSERTATION.

A Masters Thesis Presented

By

WENDY KAY MARSH, M.D.

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Masters of Science in Clinical Investigation
Dec 31st 2010

Dedication

I dedicate this thesis

to my husband

Jude A. Kelley

who dedicated his to me once-upon-a-time

and

to our daughter

Jacqeuline Marie

who joined us during its composition.

Acknowledgments

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ABSTRACT

Introduction: The late menopausal transition is a time of increased risk of depression in the general population. Nonetheless, mood course during the late menopausal transition in women with bipolar disorder in relatively unknown.

Methods: Mood state data in 519 reproductive age women (5989 clinic visits), 116 late menopausal transition (perimenopausal) women (2046 visits), and 133 postmenopausal women (1,437 visits) with bipolar disorder who were receiving optimized naturalistic treatment in the multisite STEP-BD study over an average of 19.8±15.5 months were analyzed for proportion of clinic visits with syndromal depression, mood elevation and euthymia between the three groups. History of postpartum and perimenstrual mood exacerbation as well as hormone therapy use were evaluated as potential predictors of mood.

Results: No significant difference in the proportion of clinic visits with syndromal depression was found between reproductive age (18.1%), perimenopausal (18.1%) and postmenopausal (19.3%) women. Reproductive age women had significantly greater proportion of visits with syndromal mood elevation (5.3%) compared to perimenopausal (4.1%, Z=2.1, p<0.05) and postmenopausal (3.0%, Z=4.1, p<0.001) women. Reproductive age women also had significantly greater proportion of clinic visits in a euthymic state (29.2%) compared to postmenopausal (26.0%, Z=2.7,p<0.01) and non-signifcantly greater than perimenopausal (28.0%). Thirteen women who transitioned from perimenopause

to postmenopause during the study had significantly greater proportion of visits with syndromal depression (24.4%) χ^2 (3, N = 9960) = 19.8, p <.0002 (but not visits with mood elevation (3.2%) nor euthymia (29%)) than reproductive age women, perimenopausal women and postmenopausal women. A history of perimenstrual and or postpartum mood exacerbation did not significantly alter mood course for perimenopausal women. Hormone therapy use in perimenopausal and postmenopausal women was not associated with visits in a depressed state. Women who were excluded, most often due to lack of menstrual cycle data, had more visits depressed, compared to included subjects.

Conclusions: While proportion of clinic visits with syndromal depression did not differ among the three reproductive groups, thirteen women who had recorded transition from perimenopause to postmenopause showed significantly greater depression than reproductive age, perimenopausal or postmenopausal women. Proportion of visits with euthymia or with syndromal mood elevation decreased from reproductive age to perimenopausal to postmenopausal women. Reported history of mood exacerbation during times of hormonal fluctuation, or current use of hormone therapy, was not significantly associated with depression during the perimenopause. Limitations include women excluded due to absence of menstrual data. Future studies should include hormonal assessments.

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List of Abbreviations

ADE	Affective Disorder Evaluation
APA	American Psychiatric Association
BD	Bipolar Disorder
CES-D	Center for Epidemiologic Studies Depression Scale
CMF	Clinical Monitoring Form
DSM-IV	Diagnostic and Statistical Manual, IV edition
FMP	Final Menstrual Period
FSH	Follicular Stimulating Hormone
HT	Hormone Therapy
MADRS	Montgomery Aspberg Depression Scale
MINI	Mini International Neuropsychiatric Interview
NOS	Not Otherwise Specified
OCP	Oral Contraceptive Pill
SCID	Structured Clinical Interview for DSM IV
SD	Standard Deviation
SSRI	Selective Serotonin Reuptake Inhibitor
STEP-BD	Systematic Treatment Enhancement Protocol – Bipolar Disorder
STRAW	Stages of Reproductive Aging Workshop
SWAN	Study of Women Across the Nation
YMRS	Young Mania Rating Scale
Yr	Year

CHAPTER I

1 INTRODUCTION

1.1 Bipolar Disorder: Diagnosis, Prevalence and Dysfunction

Bipolar disorder is a common, chronic, serious psychiatric illness characterized by major depressive episodes during which an individual experiences at least two weeks of depressed mood or loss of pleasure or interest, and by mood elevation episodes (mania or hypomania) where one experiences a persistently elevated, expansive or irritable mood for at least four days. Persons with bipolar disorder can experience depression and mania simultaneously (mixed episodes) and can have psychotic symptoms (delusions, hallucinations, disorganized behavior or speech) during episodes of either polarity.

The bipolar disorders include a spectrum of diagnoses. Bipolar I may be considered the most severe, as it requires at least one mood elevation (manic or mixed) episode that is serious in the sense of entailing psychotic symptoms, hospitalization, or severe impairment of interpersonal or occupational function, commonly yielding serious adverse life events such as incarceration, bankruptcy, divorce, or employment termination. Bipolar II is characterized by hypomanias where the mood elevation is not as severe as bipolar I, but also entails depression that can be more chronic and severe than those seen in bipolar I disorder. Bipolar Disorder Not Otherwise Specified (NOS) represents a residual class of disorder that include bipolar features that do not meet criteria for bipolar I or II (APA 2000).

Bipolar disorder is a common affliction. Bipolar disorder I occurs in a proximately 1-2% of the population (Regier, Myers et al. 1984; Kessler, Berglund et al. 2005), bipolar II another 1% and bipolar NOS 2%, with a total of 3.9 to 5.5% of U.S. population affected (Angst 1998; Kessler, Berglund et al. 2005; Merikangas, Akiskal et al. 2007).

Bipolar disorder causes marked dysfunction. Bipolar disorder has been reported to have a greater prevalence of severe impairment (70%) across life domains (work, home, social) than any other psychiatric disorder as well as any chronic medical disorder (Druss, Hwang et al. 2009).

1.2 Bipolar Depression and Women

While bipolar disorder is equally diagnosed among men and women, women more frequently experience depressive episodes (Angst 1978; Altshuler, Kupka et al. 2010), rapid cycling of mood episodes (more than four mood episodes per year) (Dunner, Patrick et al. 1977; Altshuler, Kupka et al. 2010), and mixed mania which requires not only syndromal mania, but also concurrent syndromal depression (McElroy, Keck et al. 1992; Arnold, McElroy et al. 2000). Women are at particular risk of depression during times of physiological hormonal fluctuations like the postpartum (Kendell, Chalmers et al. 1987). Yet little is known about the mood episode course in bipolar disorder during the menopausal transition, another time of reproductive hormonal fluctuation.

1.3 Mood and Menopause

During the menopausal transition, the most frequent psychological symptoms for women in the general population are irritability, tearfulness, anxiety, depression, emotional lability, low energy, low motivation, poor concentration and interrupted sleep (Greene 1976; Hunter 1990; Avis, Brambilla et al. 1994). These symptoms may overlap or potentially contribute to a diagnosis of either depression or mood elevation.

1.4 Depression and Menopause

While most women do not experience a depressive episode during the perimenopausal transition, an expanding literature is replicating, both cross-sectionally and longitudinally, an increased risk of major (and minor) depression in women with a history of depression as well as those with no history of a mood disorder (Freeman, Sammel et al. 2004; Schmidt, Haq et al. 2004; Bromberger 2006; Cohen, Soares et al. 2006).

Most recently, Bromberg et al (Bromberger, Schott et al. 2010) reported from the Study of Women Across the Nation (SWAN) on a longitudinal multisite community based sample of 3302 multiethnic women 42-52 years old not using exogenous hormones. Within these women, being peri or postmenopausal compared with being premenopausal was significantly associated with increased depression with Center for Epidemiologic Studies Depression Scale (CES-D) score of 16 or higher.

Freeman et al summarized the literature noting that recent longitudinal cohort studies indicated the likelihood of depressed mood in the menopausal transition was approximately 30% to 300% greater compared with that during premenopause. Women with a history of depression were nearly five times more likely to have a diagnosis of major depression in the menopausal transition, whereas women with no history of depression were two to four times more likely to report depressed mood compared with premenopausal women. She also reviewed literature finding the early postmenopause was also associated with increased depression (Freeman 2010).

1.5 Menopausal Endocrinology and Mood

Neurobiological changes during the menopausal transition indicate the importance of evaluating the relationship between reproductive hormonal fluctuation and mood during this time period. Sex steroid receptors are found in the cognitive and mood processing regions of the brain, including the amygdala, hippocampus, cingulate cortex, locus ceruleus, midbrain raphe, and central grey matter (McEwen, Alves et al. 1997). Estradiol stimulates synaptogenesis, and leads to a significant increase in serotonin 5HT2a binding sights, increase in serotonin synthesis, decrease in monoamine oxidase concentrations, and thus in sum, to a plausible antidepressant-like effect (Kendall, Stancel et al. 1982).

Gonadal steroids such as estrogen and progesterone fluctuate greatly during the menopausal transition, especially in the early transition when menstrual

cycles start to become irregular (change by at least seven days from regular cycle frequency). It is during the late menopausal transition (greater than 60 days between menstruations) that these sex steroids have their greatest decline. After 365 days of not menstruating a woman is considered postmenopausal and estrogen and progesterone levels are low.

Higher testosterone levels may contribute to higher depressive symptoms during the menopausal transition. This association is independent of menopausal status, which remains an independent predictor of higher depressive symptoms (Bromberger, Schott et al. 2010).

1.6 Hormone Therapy and Mood

While no abnormality of ovarian hormones has been identified that distinguishes women with depression from those who remain asymptomatic during the menopausal transition, several findings suggest a role of ovarian hormones, particularly studies using hormonal therapy, in the onset of these depressions. Short term (3-6 week) double-blind, placebo-controlled trials, which used similar methodologies found that the same 17 beta estradiol preparation significantly decreased depression rating scale scores compared to placebo in perimenopausal related major depression or shortened duration until improvement of mood (Schmidt, Nieman et al. 2000; Soares, Almeida et al. 2001; Rasgon, Altshuler et al. 2002). Findings also suggest independent effects of estrogen on mood and vasomotor symptoms. Specifically, a sustained

antidepressant effect was observed after discontinuation of estradiol treatment despite recrudescence of somatic symptoms. Seven of 10 patients who remained well (MADRS<10) after estradiol discontinuation reported reemergence of moderate-to-severe hot flushes. (Schmidt, Nieman et al. 2000; Soares, Almeida et al. 2001).

In fact, when estrogen replacement treatment is combined with selective serotonin reuptake inhibitor antidepressants (SSRIs), antidepressant therapeutic effects have been found to be improved in postmenopausal women (Zanardi, Rossini et al. 2007). Estradiol depletion has also been associated with increased risk of depression (Schmidt 2005).

When considering bipolar disorder, in one report of 22 postmenopausal women with bipolar disorder, those not taking hormone replacement therapy were more likely to report worsening of mood (Freeman, Smith et al. 2002) during perimenopause. While depression may be influenced by estrogen, no studies were found regarding the effect estrogen or other reproductive hormones during the menopausal transition on mania.

1.7 Bipolar Disorder and Menopause

To date, prior studies of women with bipolar disorder in the menopausal transition have been small (Kukopulos, Reginaldi et al. 1980; Marsh, Templeton et al. 2005; Marsh, Ketter et al. 2009) or retrospective, that is, dependent on subject recall (Blehar, DePaulo et al. 1998; Freeman, Sammel et al. 2004). Most

involved cross-sectional or retrospective assessment of mood (Kukopulos, Reginaldi et al. 1980; Blehar, DePaulo et al. 1998; Freeman, Smith et al. 2002). None compared mood episodes in menopausal transition women with those in women of reproductive age and postmenopausal women with bipolar disorder.

Nonetheless, the literature in bipolar disorder suggests an increase in mood instability during the menopausal transition (Kukopulos, Reginaldi et al. 1980; Blehar, DePaulo et al. 1998; Freeman, Smith et al. 2002; Marsh, Templeton et al. 2005), particularly an increase in depression (Freeman, Smith et al. 2002; Marsh, Templeton et al. 2005) or high rate of depression (Marsh, Ketter et al. 2009).

One retrospective report (Blehar, DePaulo et al. 1998) found that approximately 20% (11/ 56) of postmenopausal women with bipolar I reported severe emotional disturbances during the menopausal transition, wth the majority of those having depression (13%), and the others experiencing mania (4%), and anxiety/agitation (4%). In another study, 55% (12/22) of postmenopausal women with bipolar disorder had perimenopausal worsening of mood episodes, and all 55% with such worsening experienced increased depressive symptoms while over a third (36%, 8/22) also experienced worsening of mood elevations (Freeman, Smith et al. 2002).   Kukopulos et al (1980) found 32% of 77 women with 'continuous cycling' and 25% of 60 women who developed rapid cycling bipolar disorder did so during the menopausal transition (20).

1.8 Perimenstrual Mood Symptoms and Postpartum Mood Episodes

Perimenstrual symptoms and postpartum mood episodes have unclear relationships with mood during the perimenopause. For example, perimenopausal women who were depressed reported more premenstrual symptoms over the course of one menstrual cycle than perimenopausal women who were not depressed (Richards, Rubinow et al. 2006). In a population-based cohort, reporting symptoms of premenstrual syndrome predicted an increased risk of depression during perimenopause (Freeman, Sammel et al. 2004).

Among women with bipolar disorder, the evidence is mixed as to whether a postpartum episode indicates greater risk of a mood episode during natural menopause (Payne, Roy et al. 2007; Marsh, Templeton et al. 2008; Robertson Blackmore, Craddock et al. 2008). For example, when looking at women with bipolar disorder, a reported history of mood disturbance postpartum or across the menstrual cycle did not convey an increased risk of mood dysregulation during perimenopause (Marsh, Templeton et al. 2005; Payne, Roy et al. 2007).

On the other hand, among women with unipolar major depressive disorder, a postpartum depression may likely confer a greater risk of depression during the natural menopause (Payne, Roy et al. 2007).

1.9 Objectives (Overview)

- We used prospectively collected systematic clinical data to test the primary hypothesis that among women with bipolar disorder, those in

the late menopausal transition (perimenopause) experience a greater proportion of clinic visits with a major depressive episode than reproductive premenopausal women and postmenopausal women.

- To place the depression results in the larger context of mood course in bipolar disorder across reproductive phases, we examined the proportion of visits in an elevated mood between the three cohorts, without expectation of a significant difference between them.

- Likewise, we compared the proportion of visits in a euthymic state between the three reproductive groups with the hypothesis that the perimenopausal group would have fewer visits in euthymia than the pre and postmenopausal women.

- In examining the reproductive continuum, we assessed whether reporting a prior experience of mood exacerbation related to reproductive events (postpartum, perimenstrual or both) was associated with an increased proportion of clinic visits with syndromal depressive or mood elevation episodes during the menopausal transition.

- To look for an association of hormone therapy and mood in women with bipolar disorder, we compared the proportion of visits with syndromal depressive or mood elevation episodes between menopausal transition and postmenopausal women taking hormone therapy (HT) to those who were not taking HT.

- Women transitioning from late perimenopause to postmenopause had their mood course compared to that of the reproductive age, non-transitioning perimenopasual and postmenopausal women.

CHAPTER II

2 RELATED WORK

2.1 Bipolar Disorder

Dr. Marsh has focused her research on bipolar disorder and women. With respect to bipolar disorder, she has published not only regarding effective medication treatment of mania (Ketter, Wang et al. 2005), but also, more relevant to this thesis on women, regarding the clinical effectiveness of medications for bipolar depression: lamotrigine (Ketter, Brooks et al. 2008), quetiapine (Ketter, Brooks et al. 2010) and antidepressants (Bauer, Rasgon et al. 2006). She has also reported on phenomena such as 'brief' mood episodes (those with subthreshold duration) (Bauer, Grof et al. 2006; Bauer, Glenn et al. 2007; Bauer, Glenn et al. 2009); and symptoms such as sleep (Bauer, Glenn et al. 2008; Bauer, Glenn et al. 2009) related to the potential overlap of mood disorders and menopausal symptoms.

2.2 Reproductive Events

In her work focusing on women with mood disorders she has first-authored a review paper on bipolar disorder in women discussing the impact of each reproductive phase on mood (Marsh and Vemuri 2006) and presented a case study characterized by menstrually entrained mood symptoms in rapid cycling bipolar disorder (Becker, Rasgon et al. 2004). In the context of her thesis, she has published articles based on data acquired during the Systematic Treatment

Enhancement Program for Bipolar Disorder (STEP-BD) (Ketter, Brooks et al. 2008; Marsh, Templeton et al. 2008; Marsh, Ketter et al. 2009; Ketter, Brooks et al. 2010) and her first authored works are detailed below.

2.3 Bipolar Disorder and Perimenopause

In related work, Dr. Marsh found a significant increase in the frequency of syndromal depressive episodes in the perimenopause compared to the reproductive years in women receiving treatment for bipolar disorder. Specifically 68% of the 47 perimenopausal age women with bipolar disorder (I,II, or NOS) met criteria for experiencing at least one major depressive episode over an average of 17 months of prospective monitoring. Depression (but not mood elevation) episode frequency significantly increased during the menopausal transition compared to reported frequency during patients' reproductive years. However, a history of premenstrual and or postpartum mood exacerbations did not predict perimenopausal mood episodes. (Marsh, Templeton et al. 2008).

She found with longitudinal assessment (mean 21 ±18 months) that 78% of women age 45- 55 experienced a major depressive episode and that this was significantly increased compared to self-report of prior depressive episode frequency. However the mood elevation episode frequency at 32% did not significantly increase from subject's report of prior years (Marsh, Templeton et al. 2008).

CHAPTER III

3   DETAILS OF RESEARCH

3.1 Subjects

3.1.1   Subject Selection and Mood Evaluation

Prospectively collected systematic clinical data were analyzed for 268

women with a DSM IV diagnosis of bipolar disorder type I, II, or NOS or

schizoaffective disorder, bipolar type, who were ages 28 to 38, 42 to 60, and over

60 at enrollment in STEP-BD (Sachs, Thase et al. 2003). STEP-BD included

4108 female and male participants enrolled between September 1998 and

September 2005 and treated guided by model practice procedures, which

included published pharmacotherapy guidelines (Sachs, Thase et al. 2003) at

twelve academic U.S. sites (Baylor College of Medicine, Case Western Reserve

University, Massachusetts General Hospital, Portland Veteran's Administration

Medical Center, Stanford University, University of Colorado, University of

Massachusetts, University of Oklahoma Health Sciences Center, University of

Pennsylvania Medical Center, University of Pittsburg, University of Texas Health

Science Center at San Antonio, and seven community partners). The STEP-BD

ClinicalTrials.gov identifier is NCT00012558 .

DSM IV diagnoses were based on assessments using the STEP-BD

Affective Disorders Evaluation (ADE) (Sachs, Thase et al. 2003), which includes

the mood disorders module of the Structured Clinical Interview for DSM-IV

(SCID) (First, Spitzer et al. 1996) and independently confirmed using the Mini International Neuropsychiatric Interview (MINI) (Sheehan, Lecrubier et al. 1998). Longitudinal observation of mood episodes was performed with the STEP-BD Clinical Monitoring Form (CMF) (Sachs, Guille et al. 2002) based on DSM IV mood episode criteria. All assessors were psychiatrists trained to use standardized criteria for mood and symptom ratings. Mood at each visit was categorized as recovering/recovered (i.e. euthymic), roughening/continued symptomatic (i.e. subsyndromal depressive or mood elevation symptoms), syndromal depression, or syndromal mood elevation (i.e. syndromal manic, hypomanic, or mixed episode)

3.1.2 Subject Cohort Classification

Reproductive age, premenopausal, women were defined as being 28-38 years old and having menstruation recorded every 60days or fewer. Self-report of regular menstruation was considered evidence of non-pregnancy and intact uterus (no hysterectomy). All women meeting the 60days or less menstrual cycle frequency criteria were included.

Menopausal transition, or perimenopausal women, were defined as women 42 to 60 years old who had 60 to 365 days between the first days of consecutive reported menstruations according to STRAW criteria for the late menopausal transition (Soules, Sherman et al. 2001). Using a 60 day compared to a 90 day lower limit between menses is more inclusive, and has been found to be as accurate in predicting final menstrual period (Harlow, Cain et al. 2006).

Any woman between the ages of 42 and 60 who at one point during her participation in STEP-BD menstruated between 60 and 365days apart was considered perimenopausal (even if future cycles were recorded at greater than 365 days apart). All of her visits were then included in the perimenopausal analysis, based on the assumption that a) there continues to be significant hormonal withdrawal within the first months of postmenopause and b) given the high degree of missing menstrual cycle data there is a likelihood menstrual cycles may have occurred but not have been reported.

Postmenopausal women were defined as over 42years old and having a reported menstrual cycle after which 365 days passed without further menstruation (i.e. if at any time she had two menstrual cycles less than 365 days apart, she was considered perimenopausal). If over 60 years old she was considered postmenopausal even if no menstrual cycle data was recorded.

Transitioning Perimenopausal to postmenopausal women were defined as a subgroup of perimenopausal women whose menstrual cycle frequency changed from 60 to 365 days to greater than 365 days without menstruation during her participation in STEP-BD. This group was used for a separate analysis.

3.2 Procedure

The STEP-BD protocol was approved by the human subjects review panel of each site, and subjects provided verbal and written informed consent prior to participation. Baseline demographic, diagnostic, illness history, psychiatric

comorbidity and reproductive data were obtained from the baseline STEP-BD ADE assessments. Longitudinal data regarding mood status as defined by DSM IV, treatment received, and menstrual status at each visit were obtained from the STEP-BD CMF assessments performed at each clinical visit.

Specific baseline variables used from the ADE included age, sex, bipolar diagnosis, current comorbid psychiatric diagnoses including substance use and anxiety disorders, medication at intake (specifically, hormone therapy), age of first syndromal mood episode (mood elevation or depression), rapid cycling status, history or perimenstrual mood exacerbation, history of postpartum mood exacerbation, menstrual and reproductive history including regularity, and parity. Variables used from the CMF assessments included current clinical mood status (syndromal depression, syndromal mood elevation, or neither syndromal depression nor syndromal mood elevation), medications taken (specifically, hormone therapy), and self-reported date of first day of most recent menses.

3.3 Statistical Analysis

Initial analysis by clinic visit for an <u>overall difference</u> in proportion of clinic visits with differing mood states between reproductive age, perimenopausal and postmenopausal was performed by Chi square test. The overall analysis was also performed by averaging within woman clinic visits by mood state and compared across reproductive groups using a generalized linear model.

3.3.1 Bipolar Depression

The primary hypothesis that women with bipolar disorder in the late menopausal transition would have a greater proportion of clinic visits in syndromal depression than concurrent reproductive age women and postmenopausal women was tested by Chi square analyses. Pair-wise comparison between any of the two reproductive groups for difference in proportion of clinic visits with syndromal depression was performed using a Z test of proportions.

3.3.2 Mood Elevation and Euthymia

The secondary hypotheses examining the proportion of visits in a) syndromal mood elevation and b) euthymic state between the reproductive age, perimenopausal and postmenopausal groups, were examined using an analogous analysis to that described above for syndromal depression.

3.3.3 Perimenstrual and Postpartum Mood Exacerbation

To examine whether the presence compared to the absence of a reported history of postpartum and/or perimenstrual mood exacerbation was associated with an increased proportion of clinic visits with syndromal depression or syndromal mood elevation in the menopausal transition women a within-woman analysis using a Z test of proportions, or Z score was used.

3.3.4 Hormone Therapy

The proportions of clinic visits with syndromal depression in women with bipolar disorder taking and not taking hormonal therapy (HT) in both the perimenopausal and postmenopausal women were compared using a within-woman Z test of proportions.

3.3.5 Transitioning Peri to Postmenopause

Proportion of clinic visits in syndromal depression, elevation and euthymia for women transition from late perimenopause to postmenopause was compared that of reproductive age, non-transitioning perimenopausal and postmenopausal women was compared using a Chi square analysis similar to that described in bipolar depression. A within-woman comparison of mood states in the perimenopause compared to postmenopause was performed by t-test.

3.3.6 Covariates, Age and Missing Data

Differences between reproductive, menopausal transition and postmenopausal women in known covariates of mood severity were examined. Possible predictors of recurrence in bipolar disorder were assessed for presence of significant differences between reproductive age, perimenopausal and postmenopausal women including bipolar diagnostic subtype, rapid cycling status, age at onset (Schurhoff, Bellivier et al. 2000), and current comorbid anxiety (Simon, Otto et al. 2004) and substance use (Goldstein, Velyvis et al. 2006) disorders.

A statistical description of mood course by 5 year <u>age</u> groupings was also performed to screen for an age effect.

An ordinal logistic regression model was used to look at whether reproductive stage predicted pervasiveness of mood states. Euthymia was set as the base reference.

Due to high rate of <u>missing data</u>, a comparison of proportion of visits in each mood state (depressed, elevated and euthymic) of included versus excluded women was performed by chi square analysis.

CHAPTER IV

4   RESULTS

4.1 Study Sample

Of 4,108 participants who enrolled in STEP-BD and had an initial diagnostic

assessment with the ADE, in the final deliverable 1,740 had complete baseline

data. Of the original 4,108 enrolled subjects 2,196 were women, 1,548 of whom

had a recorded age (though not necessarily complete base line data), 488

women were under the age of 28 and were not included in this analysis.   768

women met inclusion criteria for one of the three reproductive groups below.

Total visit count for the three groups was 9960.

The mean ± SD duration of longitudinal monitoring was 19.8 ± 15.5 months

overall, with an average of 0.8 ± 0.6 visits a month for the three reproductive

groups.

4.1.1   Reproductive Age Women

There were 640 women (8943 visits) age 28-38 years of whom 533 (6279 visits)

had information on menses. 107 women (2664 visits) had no information on

menses. Of the 533 women with menses information, 519 women (5989 visits)

met the inclusion criteria of menses within sixty days from consent. 29.7% of

clinic visits in this age group were missing menstrual cycle data.

4.1.2 Menopausal Transition Women

There were 810 women (with 11803 visits) between 42 and 60 years old. Of these women, 369 had information on menses. From the women with information on menses, 116 women (2046 visits) met the criteria to be included in the analysis (a record of menses within 60-365days). 43 (488 visits) of the 369 women with information on menses had a record of menses greater than 365 days from consent and are considered part of the postmenopausal analysis 68.8% of clinic visits of women between 42 and 60 years old were missing menstrual cycle data. The final perimenopausal women data included 2046 clinic visits in 116 women.

4.1.3 Postmenopausal Women

Postmenopausal women were between 42 and 83 years old on study entry.   43 (488 visits) women were under 60 years old and had a record of menses greater than 365 days from. 98 women (with 1437 visits) were over the age of 60 and of these women 133 women and 1924 visits for the postmenopausal analysis. 99.5% of women over 60 years old were missing menstrual data, presumably because the clinician assumed they were past the final menstrual period.

4.1.4 Transitioning Peri to Postmenopausal Women

Within the perimenopausal women, thirteen met criteria to have transitioned from perimenopause into postmenopause by progressing to greater than 365 days since final menstrual period.

4.2 Sample Characteristics

The majority (almost 90%) of the subjects were Caucasian and there was no significant difference between the three reproductive groups in bipolar subtype (I, II, or NOS) or rapid cycling status. Table 1.

Age of first syndromal mood episode (for both mania and depression) was significantly different between the three reproductive groups with postmenopausal women having the oldest age of onset and reproductive age women the youngest.   Also, rates of comorbid anxiety disorders were significantly differed across reproductive groups (p=0.002) with the highest rates in reproductive age women (39%), the lowest in postmenopausal women (24%) and perimenopausal women (36%) in between. There were no significant differences across the three groups with respect to comorbid alcohol or substance use disorders. Table 1.

Reproductive characteristics varied across the three reproductive cohorts (Table 2). All three groups reported similar age of menarche and number of miscarriages, however postmenopausal women had more births and fewer abortions than the younger two groups. While there was no significant difference between the three groups in the percentage of women who reported postpartum mood exacerbation, significantly fewer postmenopausal women compared to the younger cohorts reported a history of perimenstrual mood exacerbation.

4.3 Overall Mood State Description by Reproductive Group

There was a significant overall difference in number of visits in different mood states (recovered, symptomatic, depressed or elevated) at clinic visits between the reproductive age, perimenopausal and postmenopausal women with bipolar disorder, c^2 (6, N = 9959) = 31.6, p <0.0001.

An ordinal logistic regression model revealed a gradient of worsening mood state from reproductive age to perimenopausal (OR=1.08, 95% CI 0.906 – 1.289, p=0.4) and perimenopausal to postmenopausal women (OR=-0.07, 95% CI -0.32 – 0.18, p=0.6). While there was no significant difference between the proportion of visits in a depressed, elevated or euthymic state between the three reproductive groups χ^2 (2, N = 768) = 2.3, p=0.3 by generalized estimating equations, there was a significant increase in the proportion of visits in a symptomatic state from reproductive age (48±32%) to perimenopausal (51±28%) to postmenopausal (55±32%) women F(2, N=768) 3.0, p=0.05.Figure 2.

4.4 Primary Hypothesis: Proportion of Visits with Syndromal Depression Across Reproductive Stages

There was no significant difference in the proportion of visits with syndromal depression among reproductive age, perimenopausal and postmenopausal women when analyzed by clinic visit, χ^2 (2, N = 9960) = 1.6, p=0.4. Nor were any of the reproductive group pair-wise comparisons significantly different in the proportion of clinic visits depressed. Table 3.

Similarly, when using a within woman analysis, there was no significant difference in the proportion of visits in a depressed state across reproductive age (17.8±2.5%) perimenopausal (18.2±2.3%) and postmenopausal (14.5±2.1%) women F(2, N=768) 1.09, p=0.3. Figure 2.

4.5 Secondary Hypotheses

4.5.1 Proportion of Visits with Syndromal Mood Elevation across Reproductive Stages

There was a significant overall difference in the proportion of visits with syndromal mood elevation (manic, hypomanic or mixed episodes) among reproductive age (5.3%), perimenopausal (4.1%) and postmenopausal (3.0%) women with bipolar disorder when analyzed by visit χ^2 (2, N = 9960) = 19.5, p <0.0001. Figure 1.

In a pair-wise comparison, reproductive age women had a significantly greater proportion of clinic visits in mood elevation than either postmenopausal (Z-test=4.1, p<0.0001) or perimenopausal women (Z-test=2.1, p=0.03); while postmenopausal compared to perimenopausal women did not significantly differ in proportion of visits with syndromal mood elevation. Table 3.

However, when analyzed by woman, there was no significant difference in the proportion of visits in a syndromal mood elevation between reproductive age (5.3±13%) perimenopausal (3.4±6%) and postmenopausal (3.2±8%) women F(2, N=765) 2.3 p=0.1. Figure 2.

4.5.2 Proportion of Visits in a Euthymic Mood across Reproductive Stages

There was a significant overall difference in the proportion of visits in a euthymic healthy mood among the reproductive age (29.2%), perimenopausal (28.0%) and postmenopausal (26.0%) women with bipolar disorder when analyzed by visit χ^2(2, N=9960)=7.7,p=0.02. Figure 1.

In a pair-wise comparison, postmenopausal women had a significantly smaller proportion of clinic visits in euthymic mood than reproductive age (Z-test=7.5, p<0.006) while there was no significant difference in the proportion of visits in a euthymic mood between reproductive age women and perimenopausal women (Z-test=1.2,p=0.3) or peri and postmenopausal women (Z-test=1.9,p=0.2). Table 3.

When analyzed by woman, there was no significant difference in the proportion of visits in a euthymic state between reproductive age (29±26%) perimenopausal (28±21%) and postmenopausal (27±23%) women F(2, N=768) 0.8,p=0.5. Figure 2.

4.5.3 History of Perimenstrual and or Postpartum Mood Exacerbation

Of perimenopausal women with bipolar disorder, 46% gave a history of perimenstrual mood exacerbation, 42% gave a history of no perimenstrual mood exacerbation and 12% had missing data. Women with versus without a history of perimenstrual mood exacerbation did not significantly differ in proportion of visits

with syndromal depression (18% vs 19%) or with syndromal mood elevation (4% vs 4%) during the perimenopause.

Of perimenopausal women with bipolar disorder, 30% gave a history of postpartum mood exacerbation, 40% gave a history of no postpartum mood exacerbation and 30% had missing postpartum mood data. Women with versus without a history of postpartum mood exacerbation did not significantly differ in proportion of visits with syndromal depression (18% vs 14%) or with syndromal mood elevation (3% vs 4%) during the perimenopause.

Likewise, perimenopausal women with bipolar disorder who reported both perimenstrual and postpartum mood exacerbations (29%) did not significantly differ from those who reported no mood exacerbation at either time (24%) in the proportion of visits in a depression (18% vs 14%) or mood elevation (3% vs 3%) during the perimenopause. Table 4.

4.5.4 Hormone Therapy Use

In the 28% of perimenopausal and postmenopausal women with bipolar disorder who used HT, 16% of their clinic visits were with syndromal depression and 2% were with syndromal mood elevation. These ratios did not significantly differ from those of the 72% of women not using HT, in whom 16% of visits were with syndromal depression and 4% were with syndromal mood elevation. Similarly, use of oral contraceptive pill by reproductive age women was not associated with a difference in proportion of visits elevated or depressed. Table 5.

Hormone Therapy use did not predict a greater proportion of visits in a depressed state by logistic regression χ^2(2, N=768)=1.9,p=0.38.

4.5.5 Women Transitioning from Perimenopause to Postmenopause

Thirteen women had a recorded menstrual cycle transition from late menopausal transition to postmenopause. These women experienced a significantly greater proportion of clinic visits in a syndromal depression women (24.4±18%) compared to reproductive age, non-transitioning perimenopausal or postmenopausal women χ^2 (3, N = 9960) = 19.8, p <0.0002. However, while a significant difference in proportion of visits in euthymia (29±14%) on comparison of the four reproductive groups was found χ^2 (3, N = 9960) = 9, p =0.046, there was no notable difference of transition peri to postmenopausal women on a pairwise comparisons with reproductive age, non-transitioning perimenopausal and postmenopausal women. Likewise, no significant difference in proportion of visits in a mood elevation (3.2±0.5%) was found in a pairwise comparison of the transitioning peri to post group compared to reproductive age, non-transitioning perimenopausal and postmenopausal women.

These thirteen women did not have a significant within woman change in the proportion of clinic visits in a syndromal depression t (24)=0.8,p=0.4, syndromal elevation t (24)=-0.34,p=0.7 or euthymia t (24)=-0.7,p=0.5, from late transition to early postmenopause.

4.5.6 Mood state of included compared to excluded subjects

There was an overall significant difference between included reproductive age, perimenopausal and postmenopausal women compared to excluded women of the corresponding age group in the proportion of clinic visits in euthymic, syndromal elevation, syndromal depression and symptomatic states χ^2 (15, N = 21989) = 138, p <0.0001.

There was a significantly greater proportion of visits in a syndromal depression in excluded versus included premenopausal , χ^2 (1, N = 8922) = 24, p <.0001, perimenopausal χ^2 (1, N = 10990) = 12, p <.0005 and postmenopausal women χ^2 (1, N = 2174) = 8.9 p <.003. However, there was no significant difference in the proportion of visits in a euthymic mood or syndromal elevation in included versus excluded women within the reproductive age, perimenopausal or postmenopausal age groups, χ^2 (5, N = 22086) = 7.1, p=0.2). Table 6.

4.5.7 Mood State by Age

For a visual comparison, the proportion of visits in the four mood states across five year age cohorts in women with bipolar disorder is presented in Figure 3. The proportion of visits in a syndromal mood elevation declines as age advances. However, it is difficult to comment proportion of visits by age cohort in the other three mood groups as the sample size decreases significantly in the seventy years old and older groupings.

CHAPTER V

5   CONCLUSIONS

5.1 Summary of Findings

5.1.1   Syndromal Bipolar Depression

In contrast to our hypothesis, our findings did not show a significant difference in the proportion of clinic visits in a depressed state between reproductive age women, late transition perimenopausal women and postmenopausal women in either by visit or by woman analysis.

5.1.2   Syndromal Mood Elevation

The pervasiveness of syndromal mood elevations significantly decreased from reproductive age to perimenopausal to postmenopausal women with both perimenopausal and postmenopausal women experiencing significantly lower proportion of clinic visits in a mood elevated state than reproductive age women when analyzed by visit. While postmenopausal women had the numerically lowest proportion of visits in a syndromal mood elevation, the proportion did not differ significantly from perimenopausal women. No significant difference in proportion of mood elevation visits by reproductive group was seen in a within woman analysis. In examining mood elevation by increasing five year age groups, a reduction of the proportion of visits in an elevated state by age was visually apparent.

5.1.3 Euthymic Mood

The proportion of visits in a healthy euthymic mood significantly decline from reproductive age to perimenopausal to postmenopausal women giving a statistically lower proportion of euthymic clinic visits in postmenopausal compared to reproductive age women in the by visit analysis. When analyzing within woman, no significant difference in visits in euthymic mood emerged.

5.1.4 History of Mood Disruption Associated with Reproductive Events

A reported history of mood exacerbation associated with the menstrual cycle and or postpartum was not associated with altered pervasiveness of syndromal depression or syndromal mood elevation during the perimenopause.

5.1.5 Hormone Therapy

Perimenopausal and postmenopausal women with bipolar disorder who used of hormone therapy compared to those who did not use HT, did not have a significantly different proportion of clinic visits with syndromal depression or mood elevation.

5.1.6 Women Transitioning from Peri to Post Menopause

The thirteen women who transitioned from perimenopause to postmenopause during study participation had a significantly greater proportion of clinic visits in a syndromal depression than the reproductive age, non-transitioning perimenopausal and postmenopausal women. Within these thirteen

transitioning women, the proportion of visits in a depressed state did not significantly differ during their perimenopausal time to their postmenopausal time.

5.1.7 Mood State in Included compared to Excluded Women

Excluded (primarily due to missing menstrual cycle data) reproductive age, perimenopausal age and postmenopausal age women had a significantly greater proportion of clinic visits in a syndromal depression than included like aged women; excluded women had no significant difference in the proportion of euthymic or syndromal elevation visits than included women.

5.2 Discussion and Comparison to Published Data

5.2.1 Bipolar Depression in Menopausal Transition

This study found no significant difference in the proportion of clinic visits in a syndromal depression experienced by reproductive age, late perimenopausal transition or postmenopausal women. This is in contrast to the few small studies in women with bipolar disorder that report significant or notable worsening of depression during the perimenopause compared to younger reproductive years either within woman by retrospective report (Freeman, Smith et al. 2002) or in contrast to a longitudinal report in concurrent cohort (Marsh, Templeton et al. 2008; Marsh, Ketter et al. 2009). This study's results are in accordance with a 16 year prospective study on clinical course of 95 patients with bipolar disorder finding 'individual patients do not tend to go into depression with increasing age' (Angst 1978).

However, the thirteen women who transitioned from late perimenopause into postmenopause during study participation had a significantly greater proportion of visits in a syndromal depression than any of the original three reproductive groups. Within the thirteen women who transitioned from late perimenopause to postmenopause there was no significant difference in rates of depression from the former to latter reproductive phase. In the unipolar depression literature, both the menopausal transition and early postmenopause have been found to have an increased rate of depression (Bromberger, Schott et al. 2010; Freeman 2010).

5.2.2 Mood Elevation in Menopausal Transition

Our findings of a decrease in syndromal mood elevations by aging reproductive group are consistent with a previous report of no increased risk of syndromal mood elevation during the perimenopause compared to the reproductive years (Marsh, Ketter et al. 2009). Another study reported the perimenopause as a time of increased mood cycling in bipolar disorder (Kukopulos, Reginaldi et al. 1980). Our study may be the first to report a <u>decreased</u> rate of syndromal mood elevation in the perimenopause and postmenopause compared to reproductive years.

5.2.3 Euthymia and Menopausal Transition

This study reports decreasing proportion of visits in a healthy euthymic state from the youngest reproductive age group to the oldest postmenopausal group; a result in accordance with the assertion that the natural course in bipolar disorder

is a worsening of symptoms over time, in this case apparent despite treatment. While a different design, in a recent 7yr prospective naturalistic follow up study individuals were found over time to have an increase in the number of euthymic visits (Altshuler, Kupka et al. 2010).

5.2.4 Potential Confounders

Previous studies found substance use associated with worse mood course in bipolar disorder. In our subjects, substance use between the three reproductive groups did not differ significantly, thus was unlikely to be a factor in mood episode differences.

However, age of first mood episode (mania or depression) was significantly different between the three reproductive groups with onset being earliest in reproductive age group, intermediate in perimenopausal group, and latest in postmenopausal women. This difference may be explained by a) earlier recognition of bipolar currently than in the past, b) postmenopausal women having a higher threshold until the disorder hit awareness, or c) a survivor effect in the women with later onset having less severe mood course and thus more often reaching the older postmenopausal age. Nevertheless, studies of pooled (male and female) adults with bipolar disorder have reported later onset in older than in younger subjects (Depp and Jeste 2004). Earlier age of onset has been associated with worse mood course in STEP-BD (Perlis, Miyahara et al. 2004).

Comorbid anxiety disorders have been associated with a worse mood course in bipolar disorder (Simon, Otto et al. 2004; Gaudiano and Miller 2005; Keller 2006;

Perlis, Ostacher et al. 2006; Altshuler, Kupka et al. 2010), and in the current study, were more prevalent in the reproductive age group, followed by the perimenopausal group, followed in turn by the postmenopausal group, a finding that has not been found previously reported. In a prior analysis of STEP-BD anxiety was associated with decreased time recovered (Simon, Otto et al. 2004) and yet in this study the reproductive age group had the greatest proportion of visits in a euthymic (recovering + recovered) state of the three groups. Comorbid anxiety disorders have also been associated with increased rates of depression in bipolar disorder (Gaudiano and Miller 2005; Altshuler, Kupka et al. 2010) and yet the reproductive group did not experience a greater rate of depression. Rather the reproductive age group experienced the greatest proportion of mood elevations which has not been reported associated with anxiety.

5.2.5 History of Mood Exacerbation with Reproductive Events

Reporting a history of mood exacerbation in association with the postpartum period or menstrual cycle or both did not predict syndromal depression or syndromal mood elevation in the perimenopause in women with treated bipolar disorder. Thus, women with bipolar disorder in this study did not carry a lifelong vulnerability to mood episodes associated with reproductive events. This is in agreement with other retrospective studies (Payne, Roy et al. 2007; Marsh, Templeton et al. 2008). However, our finding is in contrast to a case series of five women reporting increased risk of mood recurrence in the perimenopause in

women with a history of postpartum psychosis (Robertson Blackmore, Craddock et al. 2008).

5.2.6 Bipolar Mood Episodes and Hormone Therapy

Use of hormone therapy in perimenopausal and postmenopausal women with treated bipolar was not associated with lower proportion of visits with syndromal depression in this analysis. While from this study it would appear that in women treated for bipolar disorder, HT did not confer antidepressant-like effects, HT may improve mood of users to that of non users. In a retrospective report of women with bipolar disorder, women who were not using hormone therapy were significantly more likely than those who were using HT to report worsening of symptoms during perimenopause (Freeman, Smith et al. 2002). However, as previously reported by this author in a smaller study, women age 45-55 years who did and did not take HT had statistically similar proportions of clinic visits with syndromal depression (Marsh, Templeton et al. 2008).

5.3 Strengths and Limitations

5.3.1 Strengths

Strengths of this study include its large sample size compared to previous studies in the field. Longitudinal assessment averaged approximately a year and a half per patient. The non-randomized, open, naturalistic treatment subjects received generally reflects that seen in optimized evidence-based clinical practice. It is the first study to assess menstrual status in conjunction with mood

course in bipolar disorder. This study took a continuum approach to female reproductive life – from the reproductive years to perimenopause to postmenopause. Mood at each clinic visit was classified by rigorous DSM-IV criteria, (although a less sensitive measure than other mood rating instruments). Analysis of mood state was performed both by clinic visit and by within woman comparison. Characteristics that may influence mood course for the worse in bipolar disorder were assessed. Similarly a visual representation of the potential confounder of age compared to mood was included. For thirteen women we were able to perform a within-individual comparison of mood state from perimenopause to postmenopause.

5.3.2 Limitations

Limitations include a significant amount of missing data from the database, particularly menstrual cycle reporting. Thus, perimenopausal women may have been mistakenly classified as postmenopausal if a menstrual cycle occurred but was not reported. Proportion of clinic visits in a mood state does not necessarily translate into duration of a mood episode, as patients likely attend doctor visits more often during syndromal mood episode than when euthymic. Thus, while presence of mood episode was defined, the duration and severity of mood episodes were not accounted for in the analysis of the impact of reproductive phase upon mood.

The absence of baseline and longitudinal endocrinological assessment, as well as systematic assessments of medical and psychosocial stressors represent additional limitations.

The relatively brief duration of the current study did not permit more than thirteen transitioning perimenopausal to postmenopause within-individual comparisons of mood across reproductive phases.

It could be that smaller sample size and hence more limited statistical power could have attenuated ability to demonstrate differences between the reproductive groups.

Limitations: Included vs Excluded Women

Exclusion of women in the correct reproductive group age ranges was primarily due to missing menstrual cycle data. While these excluded women did not differ from included women in proportion of visits in a syndromal mood elevation or euthymic state, they were significantly more likely to be in a syndromal depressed than included women in all three reproductive age groups. This brings to question whether there may have been a nonrandom reason for the missing data. For example, in excluded women clinic time was prioritized for discussing options for difficult to treat bipolar depression and not on obtaining menstrual cycle data. This missing data might have modified findings of this study.

5.4 Future Work

Future studies are warranted, including research prospectively tracking menstrual cycle and mood course in women with bipolar disorder through the early and late perimenopause and early postmenopause. In such research, at entry women ought to undergo a diagnostic interview based on DSM-IV diagnostic criteria and provide detailed histories of menstrual status. Via a staged study design, women in each reproductive category need to be followed for several (at least four) months with daily mood, medication, life events, and menstrual cycle assessments using mood tracking software (such as ChronoRecord) and monthly with standardized mood ratings and reproductive endocrinological assessment of estradiol and follicle stimulating hormone (FSH). Clinical Global Impression scale should also be performed monthly as a sensitive measure to change in mood severity. Such a design would address several important limitations (missing menstrual cycle reporting, unclear duration and severity of mood episodes, lack of endocrinological assessments, lack of structured assessments of social stressors) of the current study.

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TABLES and FIGURES

Table 1. Subject Characteristics

	Premenopausal[1] (n=519)	Perimenopausal[2] (n=116)	Postmenopausal[3] (n=133)	Premenopausal, Perimenopausal, and Postmenopausal Groups Combined (n=768)	P-value
	N (%)	N (%)	N (%)	N (%)	
Number of clinical observations	5989	2046	1925	9960	XXXXX
Race					
White or Caucasian	460 (89)	102 (88)	119 (89)	681 (89)	0.0464
Black or African American	30 (6)	13 (11)	10 (8)	53 (7)	
Other	29 (5)	1 (1)	4 (3)	34 (4)	
Bipolar Diagnosis					
Bipolar I	317 (61)	67 (58)	87 (65)	471 (61)	0.7943
Bipolar II	166 (32)	42 (36)	37 (28)	245 (32)	
Bipolar NOS	31 (6)	5 (4)	8 (6)	44 (6)	
Schizoaffective Disorder	5 (1)	2 (2)	1 (1)	8 (1)	
Rapid cycling					
Yes	160 (31)	39 (34)	35 (26)	234 (30)	0.0596
No	152 (29)	34 (29)	57 (43)	243 (32)	
Current Substance Abuse or Dependency					0.3219*
Yes	14 (3)	3 (3)	1 (1)	18 (2)	
No	505 (97)	112 (97)	131 (99)	748 (98)	
Current Alcohol Abuse or Dependency					
Yes	31 (6)	7 (6)	5 (4)	43 (6)	0.6051
No	486 (94)	106 (91)	126 (95)	718 (93)	
Number of Previous Episodes					
0	3 (0.6)	2 (2)	5 (4)	10 (1)	0.0002*
1-2	20 (4)	0 (0)	5 (4)	25 (3)	
3-4	34 (7)	5 (4)	2 (2)	41 (5)	
5-6	160 (31)	46 (39)	61 (46)	267 (35)	
7	109 (21)	21 (18)	17 (13)	147 (19)	
Anxiety Diagnosis					
Yes	201 (39)	44 (38)	30 (23)	275 (36)	0.0021
No	318 (61)	72 (62)	103 (77)	493 (64)	
HRT Use					
Yes	65 (13)	20 (17)	49 (37)	134 (17)	<.0001
No	454 (87)	96 (83)	84 (63)	634 (83)	
	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	P-value (ANOVA)
Age at entry	33.09 (3.21) 28-38	47.96 (3.80) 42-59	60.95 (8.68) 42-83	XXXXX	<.0001
Height (inches)	65.05 (3.05) 53-74	64.68 (2.97) 59-77.50	64.69 (3.27) 56.50-78	64.93 (3.08) 53-78	0.4021
Weight (pounds)	164.71 (44.69) 95-379	179.36 (42.15) 105-288	173.55 (42.68) 102-376	168.21 (44.29) 95-379	0 0076
Total Bipolar Index	72.13 (16.07) 25-100	71.51 (14.79) 30-100	72.37 (15.79) 25-100	72.08 (15.82) 25-100	0 9075
Age at Onset of Depression	16.40 (6.59) 3-37	19.32 (9.94) 5-46	25.88 (13.41) 4-61	18.45 (9.32) 3-61	<.0001
Age at Onset of Mania	20.32 (6.90) 2-36	24.98 (10.76) 5-45	30.08 (13.58) 6-67	22.72 (9.76) 2-67	<.0001
Months in Clinic	17.29 (14.23) 0-57.50	28.65 (17.02) 0-60.88	22.15 (15.73) 0-59.30	19.84 (15.49) 0-60.88	<.0001
Average Number of Visits	11.54 (11.78) 1-86	17.64 (13.39) 1-72	14.47 (12.74) 1-63	12.97 (12.39) 1-86	<.0001
Average Number of Visits a Month	0.86 (0.67) 0.04-4.35	0.72 (0.44) 0.11-2.61	0.78 (0.55) 0.12-4.68	0.82 (0.62) 0.04-4.68	0 0562

*P-values for categorical variables from chi-square test unless asterisk is present. Asterisk designates p-value from likelihood ratio chi-square.
[1] Premenopausal: 28-38 years old, 0-60 days since last menstrual cycle
[2] Perimenopausal: 42-60 years old with history of a menstrual cycle in last 2-12 months
[3] Postmenopausal: over 42 years old with no menstruation for at least 12 months

Table 2. Reproductive History of Subjects

	Premenopausal[1] (n=519)	Perimenopausal[2] (n=116)	Postmenopausal[3] (n=133)	Premenopausal, Perimenopausal, and Postmenopausal Groups Combined (n=768)	P-value
	N (%)	N (%)	N (%)	N (%)	
History of Postpartum Exacerbation of Depression					
Yes	116 (22)	35 (30)	42 (32)	193 (25)	0.5963
No	151 (29)	47 (41)	69 (52)	267 (35)	
History of Perimenstrual Exacerbation of Depression					
Yes	258 (50)	53 (46)	33 (25)	344 (45)	<.0001
No	214 (41)	49 (42)	87 (65)	350 (46)	
Number of Miscarriages					
0	172 (33)	45 (39)	68 (51)	285 (37)	0.8754*
1	42 (8)	15 (13)	12 (9)	69 (9)	
2	14 (3)	5 (4)	5 (4)	24 (3)	
3+	10 (2)	3 (3)	4 (3)	17 (2)	
Number of Abortions					
0	141 (27)	41 (35)	77 (58)	259 (34)	0.0001
1	62 (12)	16 (14)	8 (6)	86 (11)	
2	28 (5)	5 (4)	1 (0.8)	34 (4)	
3+	10 (2)	5 (4)	2 (2)	17 (2)	
Number of Live Births					
0	63 (12)	12 (10)	5 (4)	80 (10)	<.0001
1	76 (15)	17 (15)	12 (9)	105 (14)	
2	72 (14)	24 (21)	40 (30)	136 (18)	
3+	38 (7)	19 (16)	37 (28)	94 (12)	
Current Contraceptive Method					
None	158 (30)	53 (46)	74 (56)	285 (37)	<.0001
Oral birth control	80 (15)	5 (4)	4 (3)	89 (12)	
Barrier	92 (18)	6 (5)	2 (2)	100 (13)	
Abstinence	54 (10)	8 (7)	5 (4)	67 (9)	
Other	83 (16)	30 (26)	29 (22)	142 (18)	
	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	P-value (ANOVA)
Age at First Menarche	12.61 (1.68) 8-18	12.57 (1.71) 9-18	12.69 (1.75) 8-19	12.62 (1.70) 8-19	0.8771
Number of Live Births	1.42 (1.20) 0-7	1.83 (1.29) 0-6	2.41 (1.26) 0-6	1.72 (1.29) 0-7	<.0001

*P-values for categorical variables from chi-square test unless asterisk is present. Asterisk designates p-value from likelihood ratio chi-square.
[1] Premenopausal: 28-38 years old, 0-60 days since last menstrual cycle
[2] Perimenopausal: 42-60 years old with history of a menstrual cycle in last 2-12 months
[3] Postmenopausal: over 42 years old with no menstruation for at least 12 months

Table 3. Pair-wise Comparisons of Proportion of Clinic Visits in Depression, Mood Elevation or Euthymia by Reproductive Cohort

Pair-wise Comparison	Mood State	Proportion of Visits in Mood State (%)	Z-test for Proportion Value; P value
	Syndromal **Depression**		
Reproductive age vs Perimenopause		18.1 vs 18.1	Z=-0.01. p=0.9
Reproductive age vs Postmenopause		18.1 vs 19.3	Z=1.1; p=0.2
Peri- vs Post-Menopause		18.1 vs 19.3	Z=0.9; p=0.3
	Syndromal **Elevation**		
Reproductive age vs Perimenopause		5.3 vs 4.1	Z=2.1; p=0.03*
Reproductive age vs Postmenopause		5.3 vs 3.0	Z=4.1, p<0.001*
Peri- vs Post-Menopause		4.1 vs 3.0	Z=1.8. p=0.06
	Euthymia		
Reproductive age vs Perimenopause		29.2 vs 28.0	Z=1.0, p=0.3
Reproductive age vs Postmenopause		29.2 vs 26.0	Z=2.7, p=0.007*
Peri- vs Post-Menopause		28.0 vs 26.0	Z=1.4;p=0.2

P-values are from a z-test of two proportions (a test used to compare the proportions from two independent groups to determine if they are significantly different from one another)
*P-values significant at 0 05 level.

Table 4. Proportion of Visits in a Depression or Mood Elevation by Reproductive Group Reporting a Positive or Negative History of Perimenstrual and or Postpartum Mood Exacerbation.

Reproductive Group	Perimenstrual Exacerbation (by woman) N (%)	Average Proportion (%) of visits in a Syndromal **Depression**	P-Value*	Average Proportion (%) of visits in Syndromal **Mood Elevation**	P-Value*
Premenopausal (N_women=519)			Z=-0.12 P=0.90		Z=-0.21 P=0.83
PM +	258 (50)	18		5	
PM -	214 (41)	18		5	
Perimenopausal (N_women=116)			Z=-0.13 P=0.90		Z=-0.51 P=0.61
PM +	53 (46)	18		4	
PM -	49 (42)	19		4	
Postmenopausal (N_women=133)			Z=0.87 P=0.38		Z=-0.024 P=0. 98
PM +	33 (25)	18		2	
PM -	87 (65)	10		4	
Reproductive Group	**Postpartum** Mood Exacerbation (by woman) N (%)				
Premenopausal (N_women=519)			Z=0.67 P=0.50		Z=0.46 P=0.64
PP +	116 (22)	21		6	
PP -	151 (29)	17		4	
Perimenopausal (N_women=116)			Z=0.19 P=0.85		Z=-0.35 P=0.72
PP +	35 (30)	18		3	
PP -	47 (40)	14		4	
Postmenopausal (N_women=133)			Z=-0.013 P=.089		Z=-0.29 P=0.77
PP +	42 (32)	14		2	
PP -	69 (52)	15		3	
Reproductive Group	**Perimenstrual and Postpartum** (by woman) N (%)				
Premenopausal (N_women=519)			Z=0.81 P=0.41		Z=0.22 P=0.82
Both	74 (14)	20		6	
Neither	89 (17)	14		4	
Perimenopausal (N_women=116)			Z=0.004 P=0.99		Z=-0.72 P=0.46
Both	23 (29)	18		3	
Neither	28 (24)	14		3	
Postmenopausal (N_women=133)			Z=0.-029 P=0.97		Z=0.053 P=0.95
Both	15 (11)	14		0.4	
Neither	54 (41)	10		4	

PM = history of perimenstrual exacerbation (+ = yes; - = no)
PP = history of poatpartum exacerbation (+ = yes; - = no)
Both = history of PM and PP
Neither = No history of PM nor PP
*P-values are from a z-test of two proportions (a test used to compare the proportions from two independent groups to determine if they are significantly different from one another)

Table 5. Proportion of Visits in a Depression or Mood Elevation by Exogenous Hormone Use

Reproductive Group	Exogenous Hormone Use (by woman) N (%)	Average Proportion (%) of visits in a Syndromal **Depression**	P-Value*	Average Proportion (%) of visits in Syndromal **Mood Elevation**	P-Value*
Premenopausal (N_women=519)			Z=0.62 P=0.54		Z=0.041 P=0.97
OCP +	65 (13)	14		6	
OCP -	454 (87)	18		5	
Peri & Postmenopausal (N_women=249)			Z=-0.19 P=0.85		Z=-0.40 P=0.69
HT +	69 (28)	16		2	
HT -	180 (72)	16		4	

HT = Hormone Therapy
OCP = Oral Contraceptive Pill
*P-values are from a z-test of two proportions (a test used to compare the proportions from two independent groups to determine if they are significantly different from one another)

Table 6. Proportion of Visits in Mood State by Reproductive Age Group: Included vs Excluded Women

Mood State	Reproductive Age Group						
	Pre Included n=519	Pre Excluded n=118	Peri Included n=116	Peri Excluded n=654	Post Included N=133	Post Excluded n=5	Total visits
Syndromal Depression	18.66%	29.10% *	18.61%	21.96% *	19.73%	32.00% *	4475
Syndromal Mood Elevation	5.71%	6.35%	4.18%	4.12%	2.99%	2.00%	1027
Euthymic	28.30%	30.16%	27.30%	27.14%	26.00%	32.00%	6067
Symptomatic	47.33%	34.39%	49.90%	46.77%	51.28%	34.00%	10420
Total Number of Visits	8303	567	2509	8437	2073	100	21989

*p<0.05

Figure 1. Proportion of Clinic Visits in Mood State by Reproductive Cohort of Women with Bipolar Disorder, by Visit
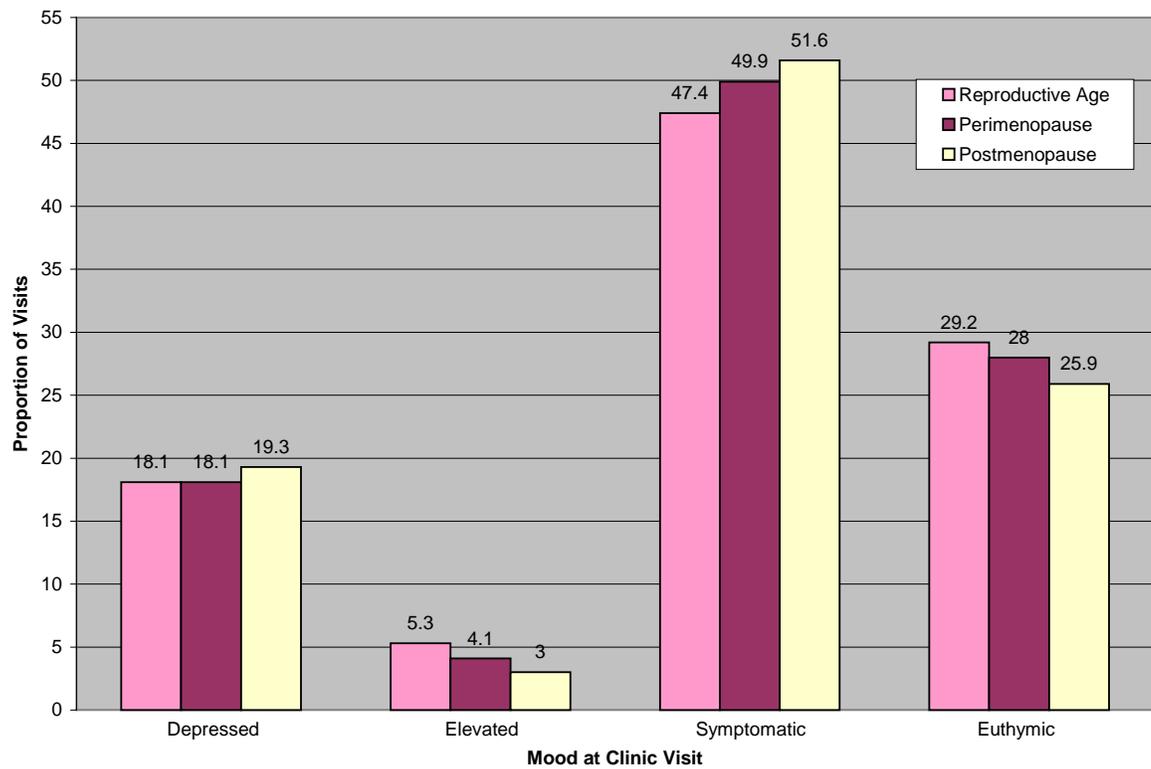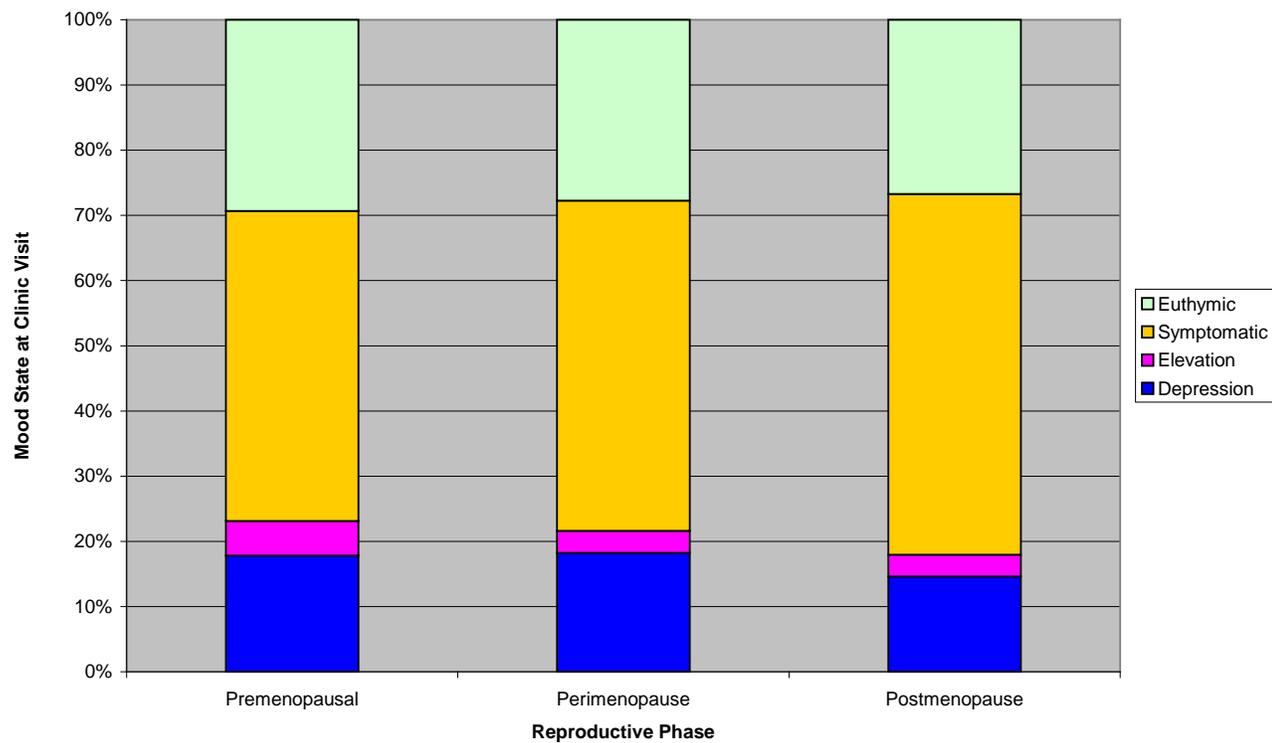
Figure 2. Proportion of Clinic Visits in Mood State by Reproductive Phase in Women with Bipolar Disorder, by Woman

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