Current Psychiatry Reports (2019) 21:130
https://doi.org/10.1007/s11920-019-1111-3

REPRODUCTIVE PSYCHIATRY AND WOMEN'S HEALTH (CN EPPERSON AND L HANTSOO, SECTION EDITORS)

Bipolar Disorder in the Menopausal Transition

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Abstract

Purpose of Review We review recent data on bipolar disorder in menopausal-aged women, particularly in women undergoing the menopausal transition (MT). We discuss evidence on the severity of symptoms in bipolar women during the MT. Moreover, we address two factors in bipolar disorder and menopausal research: standardized menopausal staging and women's conceptualization of their menopausal and bipolar symptoms.

Recent Findings While there are few studies within the last 5 years on bipolar women undergoing the MT, new evidence suggest that mood symptoms in women worsen with progression through the MT. Consistent use of the standardized menopausal staging system can facilitate understanding of the timing of worsening symptoms. Moreover, whether women conceptualize their symptoms as arising from their MT or bipolar disorder can influence whether they seek hormonal therapy or psychiatric treatment, respectively.

Summary The MT is a potential time for mood instability in vulnerable women, which can manifest as first-onset development of bipolar disorder or increased symptom severity in women with pre-existing bipolar disorder. Adoption of a standardized menopausal staging may offer novel frameworks for understanding of the role of the MT in bipolar disorder.

Keywords Bipolar disorder · Mood · Perimenopause · Menopausal transition · Hormonal fluctuations · Menopausal staging

Introduction

Given that life expectancy for women worldwide has been steadily and continually increasing for the past 60 years, more women will be undergoing the menopausal transition than ever before [1]. The perimenopause, or the menopausal transition (MT), is a period leading to the cessation of menses reproductive ability. For most women the MT begins in the late 40s and lasts 4–7 years. In addition to the onset of potentially distressing physiological changes such as vasomotor, urogenital, and menstrual symptoms, the MT has been shown to be a period of increase risk of major depression and depressive symptoms [2–7]. In fact, the late perimenopause (amenorrhea 60 to 364 days) [4, 8–12] and early postmenopause (amenorrhea 1–6 years) [10, 12, 13] are well-known times of heightened risk of unipolar depression onset, recurrence, or increase in depressive symptoms.

Less is known, however, about the course of bipolar disorder through the MT. Initial work examining bipolar disorder in women of menopausal age found that women report a higher frequency of depression than during their reproductive years [14]. Moreover, menopausal-age women attend greater proportion of clinic visits in the depressed state, lower proportion in the euthymic state, and no difference in proportion of visits in the elevated/mixed state compared with similarly aged men and reproductive-age women with bipolar disorder [15]. Women transitioning from MT to postmenopause had greater depression and less euthymia and mood elevation compared with women in young-age reproductive stages [16]. Because bipolar disorder poses a significant financial and socioeconomic burden on affected individuals as well as the health care system, detecting times of risk and preventing onset is critical [17].

This article is part of the Topical Collection on *Reproductive Psychiatry and Women's Health*

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Published online: 25 November 2019

In this article, we review recent literature since 2014 on bipolar disorder in the perimenopause. We organize our review to examine new reports on the mood pattern and symptom severity of bipolar disorder and note whether the newer literature is consistent with the older findings on symptom exacerbation. In the last 5 years, studies have explored bipolar disorder mood pattern/symptom severity in early/late MT and post-menopausal years, the role of menopausal symptoms and risk factors for developing first lifetime-onset bipolar disorder, and women's understanding of the connection between bipolar disorder and menopause (see Table 1). Our review aims to provide an evaluation of the evidence regarding the development and course of bipolar disorder throughout the MT.

Symptomatic Menopausal Transition as an Indicator of Worsening Mood in Women With Bipolar Disorder

Both psychological and physiological symptoms are frequent during the MT regardless of a woman's mood history. Common symptoms include irritability, tearfulness, anxiety, depression, emotional lability, low energy and motivation, poor concentration and interrupted sleep [18], vasomotor, urogenital, and menstrual cycle disturbances [19]. While the impact of reproductive hormones on mood symptoms is still unclear, fluctuations of estradiol have been linked to psychological symptoms of irritability, anxiety, low energy, and other mood disruptions [20]. Because these psychological symptoms overlap with those of functionally impairing mood disorders, the perimenopause may place a woman at greater risk of depression (tearfulness, low energy and motivation, poor concentration, interrupted sleep) or mood elevation (irritability emotional lability, poor concentration, interrupted sleep). Additionally, recent literature has explored the overlap between psychological and physiological symptoms, leading to speculation of the role of physiological symptoms on the mood course during the MT.

Hu and colleagues [21••] have investigated the link between physiological symptoms during the MT and the incidence of bipolar disorder. The large retrospective cohort study of more than 38,000 women identified those who were diagnosed with first-onset bipolar disorders via evaluation by a clinician. Their results showed that newly diagnosed bipolar disorder following a diagnosis of a symptomatic menopausal transition (SMT) is significantly increased in women with SMT compared with those without a SMT. However, this report is notably limited by its lack of a clear definition for SMT. Hu and colleagues state that the MT is a "period late in a woman's reproductive life before the final menstrual period." They state that "symptomatic menopausal transition is a clinical diagnosis. Accordingly, laboratory testing, including determining follicle-stimulating hormone and estradiol levels, is not necessary for establishing the diagnosis, and skilled clinicians can diagnose symptomatic menopausal transition based on the characteristic symptoms such as abnormal uterine bleeding, hot flashes, and night sweats, which occur as a result of declining ovarian function." However, it is unclear if they are suggesting that the age-matched non-symptomatic menopause transition women were experiencing changes in their menstrual cycle pattern or if any change in menses frequency was considered "abnormal uterine bleeding." The author's definition is nonspecific and includes symptoms that are potentially defining of the MT, a clinical diagnosis based on menstrual cycle change, itself.

Using a similar approach, Chen and colleagues [22••] have also explored the SMT theory using the same database. They demonstrate in their cross-sectional study that the co-occurrence of major depression and SMT led to a higher incidence of conversion to bipolar disorder (at an average of 2–3 years after initial diagnosis of major depression) than with major depression alone, using the same diagnostic criteria as Hu et al. Their approach provides insight on the definition of a SMT: their non-SMT subjects were average age 47–49, which corresponds with early MT, whereas their SMT subjects were average age 50–53, which corresponds with late MT and early postmenopause. This age delineation explains why the non-SMT women may have been experiencing changes in menstrual pattern but no other menopausal symptoms, as Hu and colleagues noted in the study above. The SMT assignment may in fact be differentiating between menopausal stages, wherein non-SMT refers to late reproductive/early MT with very little/no vasomotor or urogenital symptoms and SMT to late MT/early postmenopause with a higher rate of menstrual irregularity and vasomotor symptoms. If this is the case, then the observations regarding exacerbation of mood during the SMT would be consistent with data indicating worsening of depressive symptoms in women with bipolar as they progress to later stages of the MT [23]. Not only is the risk increased during this period, it is also exacerbated through the later stages of the MT.

Influence of Hormonal Therapy on Mood During the Menopausal Transition

Older studies (greater than 5 years prior) have reported conflicting effects of hormonal therapy (HT) on mood in perimenopausal women with bipolar disorder. Several findings suggest that HT does not confer worsening or stabilizing influence on mood in perimenopausal and post-menopausal women with bipolar disorder [14, 16]. Others have indicated that HT is instead protective against worsening mood symptoms for women in the perimenopause [24]. These inconsistencies may be attributed to differences in HT formulations. However, when considering perimenopausal women with depression,

Table 1 Studies which explored bipolar disorder mood pattern/symptom severity in early/late MT and post-menopausal years, the role of menopausal symptoms and risk factors for developing first lifetime-onset bipolar disorder, and women's understanding of the connection between bipolar disorder and menopause

Study	Study design	No. of cases	Age (years)	Outcome assessment	Findings	Duration
Carranza-Lira, 2017, Mexico	Cross-sectional	202 pre-menopausal and 164 post-menopausal	45–55	Score on What's My M3? test for depression, anxiety, bipolar disorder, obsessive-compulsive disorder, and post-traumatic stress disorder	Score for bipolar disorder in the W hat's My M3 mental health assessment was significantly higher in post-menopausal women than pre-menopausal women	N/A
Perich, Sept 2017, Australia	Qualitative study of interviews	15 with bipolar disorder I or II in peri-menopause or menopause, of which 9 diagnosed with BPD during menopause, 6 diagnosed before	46–60	Interviews with questions of the following nature: Can you tell me about your experience of menopause? What features of menopause do/did you experience? Has menopause changed your bipolar disorder in any way?	Women sought mainly psychiatric or mainly somatic treatment based on whether they constructed their symptoms as due to menopause or bipolar disorder	2 months
Sramek, 2017, USA	Randomized control trial	56 lurasidone-treated and 47 placebo-treated pre-menopausal females with major depressive disorder (MDD) with mix features (defined as subthreshold hypo-manic symptoms), and 17 lurasidone-treated and 25 placebo-treated post-menopausal females (MDD) with mix features	45–51	Change in MADRS score from baseline to week 6 endpoint for two lurasidone-treated groups	Lurasidone-treated post-menopausal and pre-menopausal females responded significantly compared with placebo on the MADRS, and that post-menopausal patients had a numerically larger response (effect size = 0.96) than pre-menopausal patients (effect size = 0.64)	6 weeks
Chen, 2017, China	Cross-sectional	50,273 with major depression with ($n = 21,120$) or without ($n = 29,153$) symptomatic menopausal transition	40–60	Incidence of diagnostic conversion to bipolar disorder in women with major depression and symptomatic menopausal transition (SMT) compared to without SMT	Women with major depression and symptomatic menopausal transition had a higher incidence of the diagnostic conversion to bipolar disorder (7.3 vs. 6.6%, $p = 0.003$) than those with major depression alone	Data on women diagnosed with major depression between Jan 2002–Dec 2008, before enrollment, follow-up until Dec 2011
Hu, 2016, China	Retrospective cohort	19,718 with symptomatic menopausal transition (SMT) and 19,718 age-matched without SMT	46.4–56.9	Incidence rate and the hazard ratios of subsequent newly diagnosed psychiatric disorders	Incidence of newly diagnosed bipolar disorders, depressive disorders, anxiety disorders, and sleep disorders following a diagnosis of symptomatic menopausal transition was significantly increased	Data on women diagnosed with SMT between Jan 2000–Dec 2008
Gerber, 2015, USA	Cross-sectional	157,195 veterans, of which 16,227 used HT	> 45	Whether hormonal therapy use was associated with mental health conditions	Among women veterans of mean age 59.4 years, women with at least one diagnosis of a mental health disorder were more likely to use hormone therapy than women with no mental health diagnosis	Cross-sectional analysis of national VA administrative data for fiscal year 2009

HT has been shown to have antidepressant efficacy in several studies, regardless of differences in HT dosages between studies [25–28]. Analyzed together, this suggests that differences in formulations may not be the only reason why inconsistencies are seen in the treatment of perimenopausal women with bipolar disorder. Further exploration of the mood effects of HT, particularly in the said population, is necessary to address where these inconsistencies may be stemming from.

Using Staging of Reproductive Aging in Women as Standardized Menopausal Staging

Historically, studies reporting severe mood disturbances or worsening depression during the MT have largely relied self-reports that do not distinguish between the MT stages [24, 29]. Reporting the MT as a single period does not accurately capture the distinct, reproducible, and progressive nuances of the stages of the MT, and thus neglects the differing risks for mood symptom severity within each stage. In fact, evidence elucidate several well-reproduced phases in the MT lending it to clinical staging. The Stages of Reproductive Aging Workshop (STRAW) is the gold standard in defining reproductive, and especially, MT phases [19]. For most women, the MT lasts 4–7 years, consisting of the early stage (variable length) and the late stage (1–3 years). Postmenopause is a retrospective diagnosis given after 1 year of absence of menstruation. Delineation of the reproductive aging into a late reproductive, early MT, late MT, and early postmenopausal is clinically significant in order to clarify times of heightened mood symptom risk as women progress through the many years of the MT. Physiological symptoms, such as vasomotor symptoms, are not just high in the late MT but also in the early postmenopause making them inappropriate to use in defining a woman as in the MT. Menstrual cycle length is the most consistent criteria for defining MT staging and should be standardized across studies [23].

Even though the Stages of Reproductive Aging Workshop (STRAW) staging system is considered the gold standard and has become widespread in evaluating menopause and unipolar depression studies since its conception in 2001 [30–39], Perich et al. [40•] show, in their systemic review assessing bipolar disorder symptom severity and relapse rates in menopausal women, that only 2 out of 9 bipolar studies since 2002 in their analysis have used the STRAW staging system. Not only is this a major limitation for the comparability of bipolar studies, which is essential for facilitating clinical decisions, it hinders the advancement of other research priorities for understanding complex ovarian aging and the impact on bipolar mood course.

We used the STRAW + 10 staging system, the most updated STRAW criteria for assessing reproductive stages, in a prospective study of mood course through the MT in women with bipolar disorder. Our participants were women with known bipolar disorder, unlike Hu et al. and Chen et al., who report on bipolar onset. We did not find mood elevation symptoms (Young Mania Rating Scale or YMRS) associated with menopausal symptoms (Greene Climacteric Symptom scale) [23], and none of the women with bipolar NOS converted to full bipolar diagnosis. Rather, we report that depression (Montgomery−Åsberg Depression Rating Scale or MADRS) was significantly associated with menopausal symptoms. Both daily depression and mood elevation symptoms were significantly higher in women in the late menopausal transition/early postmenopause compared with women in the late reproductive years/early menopausal transition (hormonal replacement therapy and oral contraceptive use were exclusionary) [23]. This again demonstrates the importance of staging to support clinical decision-making.

Given these results, future research priorities include further evaluation of the MT as a risk factor for depression in particular, but also mood elevation or mixed symptoms in bipolar disorder. Also critical is the evaluation of the final menstrual period to assess the mood pattern during a transition from the late MT into early post-menopausal years, as the early postmenopause is a time of continued hormonal variability and vasomotor symptoms. However, addressing these research priorities demands continued use of the STRAW staging system.

Mood Symptom Attribution to Bipolar Disorder or to Menopause During the MT

Bipolar disorder can be challenging to diagnose and manage in general, and especially so in women who are concurrently experiencing mood symptoms during periods of hormonal fluctuations [41]. Women may delay reporting, have limited recognition, or may misattribute mood symptoms to normal physiological changes. Perich and colleagues [42••] performed a qualitative analysis of how women with bipolar disorder understand and explain their depression and mood elevation symptoms during the perimenopause. Their data indicated that while many women noted increased mood fluctuations during the MT, there was variation among how women constructed their symptoms, as resulting from their bipolar disorder, the MT, or significant life events independent from either bipolar disorder or the MT. Whether women sought mainly psychiatric or mainly somatic treatment was based on whether they constructed their symptoms as due to menopause or bipolar disorder, respectively. This is an important recent report to demonstrate that treatment approaches may vary depending on how symptoms are explained.

For example, Gerber and colleagues indicated a similar trend in a cross-sectional analysis of national VA administrative data,

which showed that among women veterans of mean age 59.4 years, women with at least one diagnosis of a mental health disorder were more likely to use hormone therapy than women with no mental health diagnosis [43]. Gerber et al. suggest that this may be due to explaining their symptoms more to MT vasomotor symptoms than to their mood disorder, which has been reported to be the case in women with similar comorbidities [44].

Conclusion

The MT is a time of normal reproductive hormone fluctuations, with symptoms such as vasomotor, urogenital, and menstrual frequency changes. The extant literature also supports the MT as a time of mood instability for vulnerable women. Increased mood symptom severity in the late MT/early postmenopause in bipolar disorder has been cited by multiple studies [22••, 21••, 23, 16]. This concurs with previous propositions that hormonal fluctuations are associated with mood exacerbation. As noted, the late MT/early postmenopause is defined by greater reproductive hormone fluctuations compared with the premenopause/early MT or reproductive years. The late MT/early postmenopause is also cited as a time of increased physiological symptoms, which further supports the notion that increased reproductive hormone fluctuations is a potential risk factor for women with bipolar disorder.

As the current evidence points strongly to increased mood disturbances in the MT for women with bipolar disorder, future research needs to focus on more specified MT staging of the bipolar mood course. However, only a small number of studies have employed the use of a menopausal staging system, in comparison with the literature on unipolar depression which has largely employed this standardization. Given that the MT can last for 4–7 years, which is a considerable duration, especially for a longitudinal study, future research studies need to appropriately stage which part of the MT they are investigating. The extant literature strongly suggested distinct presentations of mood and menopausal symptoms based on MT stage.

In addition to framing the MT through a lens of reproductive staging, future research should also consider the way women conceptualize their mood experience though the MT and consequently the treatment strategies that they seek out. Since there are many overlapping symptoms between bipolar disorder and the MT, women may find it difficult to accurately attribute the origin of their symptoms, and symptom attribution directly affects clinical decision-making for treatment approach.

Currently, little is known about whether duration of bipolar disorder since diagnosis or history of mood exacerbation during other times of hormonal variability is predictive of bipolar mood course during the MT. Studies of longer durations will also be critical for evaluating these trends, and studies of larger sample sizes will be critical for evaluating the menopausal stages as separate groups. In summary, further exploration of the specifics of bipolar mood course during the MT will require use of a standardized staging system, which may offer clarity for women's understanding of their MT experience and subsequent clinical decision-making.

Compliance with Ethical Standards

Conflict of Interest Dawn Truong and Wendy Marsh declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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