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REVIEW ARTICLE

Impact of menstrual cycle events on bipolar disorder course: a narrative review of current evidence

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Abstract

Several lines of research suggest that reproductive-related hormonal events may affect the course of bipolar disorder in some women. However, data on associations between bipolar disorder and menarche, menstrual cycle, and menopause are mixed. This article reviews the literature on the potential effects of menarche, menstrual cycle, and menopause on bipolar disorder. A narrative review of published articles on bipolar disorder and menstrual cycle events was conducted. The primary outcome assessed was the impact of menarche, menstrual cycle and menopause on the course of bipolar illness. Databases searched were PubMed, Ovid, Scopus, PsycINFO, Medline, and Cochrane Libraries from inception to August 2021.

Twenty-two studies were identified and included in the narrative synthesis. Research suggested that a subset of women with bipolar disorder are vulnerable to the impact of menstrual cycle events. Menarche seems to be associated with age at onset of bipolar illness especially in case of bipolar disorder type I and the specific age at menarche may predict some clinical features of the disorder. Menstrual cycle likely affects the course of bipolar disorder but the pattern of mood variability is not clear. Menopause appears to be not only a period of vulnerability to mood alteration, especially depressive episodes, and impairment of quality of life, but also a potential trigger of bipolar illness onset.

The impact of menarche, menstrual cycle, and menopause on bipolar disorder is largely understudied. Preliminary evidence suggests that a subset of women with bipolar disorder may have their mood shifts affected by menstrual cycle events, with different patterns depending on the type of bipolar disorder also. Further researches are needed to deep the impact of menarche, menstrual cycle, and menopause on bipolar illness.

Keywords Bipolar disorder · Women · Menarche · Menopause · Menstrual cycle · Hormonal mood changes

Introduction

Bipolar disorder is a lifelong episodic illness characterized by fluctuations in mood state and energy (Grande et al. 2016). The course of bipolar disorder is associated with both inter-individual variation and heterogeneity between patients and can lead to functional, occupational, and cognitive impairments (Miller and Black 2020). Thus, over a lifetime any one patient may experience many forms of the disorder including depressive and manic or hypomanic episodes, mixed emotional states, and psychosis (Vieta et al. 2011). Bipolar disorders are classified according to the longitudinal course: bipolar I disorder requires the occurrence of at least one fully syndromal lifetime manic episode, although depressive episodes are common; bipolar II disorder requires the occurrence of at least one hypomanic episode and one major depressive episode (American Psychiatric Association, 2013). The prevalence of bipolar illness is consistent across diverse cultures and ethnic groups, with an aggregate lifetime prevalence of 2.4% (Carvalho et al. 2020). Although bipolar disorder has an equal rate among men and women, some gender-related differences have been found in the clinical features of the illness(Diflorio and Jones 2010). Overall, it is reported that depressive episodes, rapid cycling, and mixed mania are more frequent in women than men

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(Altshuler et al. 2010; Marsh et al. 2012). Furthermore, there is accumulating evidence that bipolar disorder course is affected by reproductive-related hormonal events in women (Diflorio and Jones 2010). Sex differences have been hypothesized to be related to organizational and activational effects of sex hormones on the nervous system (Steiner et al. 2003). Gonadal steroids play a role in all stages of neurodevelopment, including neurogenesis, synaptogenesis, neural migration, growth, differentiation, and cell survival (Payne 2003). Furthermore, major neurotransmitter systems (i.e., serotonergic, noradrenergic, and dopaminergic systems) can be modulated by gonadal steroids and are speculated to be the link between fluctuating sex hormone levels and bipolar disorder symptoms during reproductive-related hormonal events (Frey and Dias 2014). The neuromodulatory effects of estradiol have been investigated much more extensively compared to those of other gonadal steroids. Specifically, increased estradiol levels have been shown to increase serotonergic neurotransmission, which has been associated with an improvement in mood symptoms (Freeman and Gelenberg 2005; Karpinski et al. 2017). These results are also consistent with the clinical data. Across the reproductive phase, women with bipolar disorder are at risk for mood relapses during the peripartum period and through the menstrual cycle events (i.e., menarche, menstrual cycle, and menopause) (Payne et al. 2007). All of these periods present sudden changes in estradiol parameters. Menarche and initiation of menstrual cycle are characterized by a quick maturation of hypothalamic–pituitary–adrenal (HPA) axis and consequent onset of estrogen fluctuations. During the menstrual cycle, estradiol is known to decrease around the 22nd day of a 28-day menstrual cycle; thus, an exacerbation of bipolar disorder symptoms after this time would be expected (Whybrow et al. 2003; Hardoy et al. 2006). During pregnancy, estradiol levels gradually increase over the course of the 9-month period, but labor and delivery are known to involve as much as a 1000-fold drop in estradiol levels compared to the pregnant state (Sacher et al. 2010). Therefore, some women with bipolar disorder may be more susceptible to a worsening of mood symptoms during the postpartum period (Di Florio et al., 2013). Additionally, estrogen levels become irregular and ultimately plummet during menopause and could therefore be an impetus to an increased risk of developing mood symptoms in menopausal age women (Gibbs et al. 2012). As with most other psychiatric disorders, bipolar disorder appears to have several alternative factors that contribute to the illness (McIntyre et al. 2020). While the hormonal changes during female reproductive events are a plausible mechanism for changes in bipolar disorder course, they may only serve as a precipitating factor in women already predisposed to the disorder. In fact, it is more likely that not all women with bipolar disorder have a vulnerability to hormonally triggered mood events but instead represent a subset of them (Payne 2003). While several publications have been devoted to specific issues in assessing the relationship between bipolar disorder and the peripartum period with univocal results that show an increase risk of acute mood episodes and a protective role of mood stabilizers (Maina et al. 2014; Rosso et al. 2016; Wesseloo et al. 2016), findings on bipolar disorder in relation to menarche, menstrual cycle, and menopause are scarce and conflicting. To our knowledge, there have been no systematic or narrative reviews on this topic. The pattern of mood variability related to menstrual cycle events has not been well-characterized and it is still not understood how they may affect the course of bipolar disorder. Therefore, the purpose of the present paper is to critically review the current knowledge on the impact of menarche, menstrual cycle, and menopause on the course of bipolar illness. We aim to explore the potential relationship between menstrual cycle events and bipolar disorder in clinical practice and research.

Methods

We conducted a narrative review of published articles on bipolar disorder and menstrual cycle events. Searches were made in a range of scientific databases (PubMed, Ovid, Scopus, PsycINFO, Medline, Cochrane Library) from inception to August 2021. The search terms "bipolar disorder," "BD," and "bipolar spectrum" were combined, using the boolean AND, with "reproductive cycle," "reproductive cycle events," "menarche," "age at menarche," "menstrual cycle," "menstrual cycle events," "menopause." Then, a manual search for references lists from articles selected in the previous search was done. The inclusion criteria for this narrative review were as follows: (a) participants diagnosed with bipolar disorder; (b) clinical information concerning bipolar disorder and menstrual cycle events (menarche, menstrual cycle, and/or menopause); (c) outcome clearly defined in terms of mood variability in relation to menstrual cycle events; (d) peer-reviewed English-language articles; (e) retrospective or prospective studies. The presence of comorbid medical and psychiatric disorders (either current or lifetime) did not constitute an exclusion criterion provided that bipolar disorder was the primary diagnosis. Studies were excluded if they were as follows: systematic or narrative review articles, meta-analysis articles, commentaries or editorials, case report/series. Articles were assessed for inclusion at three stages: title screening, abstract screening, and full text screening. Two reviewers (EA and GR) independently decided which articles to include according to clinical importance and eligibility criteria. In case of disagreement, the senior author (GM) was consulted to mediate consensual decision. A meta-analysis was not performed due to the small number of studies and varying outcomes reported.

Results

A flowchart of studies selected and included in the narrative review is provided in Fig. 1. From all databases combined, the initial search yielded 1229 results. After duplicates had been removed, 1197 articles remained. At title and abstract screening, 1028 articles were removed as they were not clinically relevant. A total of 169 articles were found to be suitable for inclusion in the full text screening. Full text screening of these articles eliminated 147 articles that did not meet the inclusion criteria. Twenty-two articles in total were included. Table 1, Table 2, and Table 3 list the studies that were included in the narrative synthesis.

Bipolar disorder and menarche

Menarche is shown to be a significant biological and psychosocial transition point. Several recent studies have investigated links between menarche and both clinical and subclinical psychopathology and have hypothesized a close connection between menarche and psychiatric illnesses (Graber et al. 2004; Lien et al. 2010; Joinson et al. 2011; Yazici et al. 2013; Jung et al. 2015). However, findings on putative correlation between age at menarche and bipolar disorder are particularly scarce. Tondo et al. (2017), in a study including 557 women with major depressive disorder, 301 women with bipolar disorders, and 181 women with anxiety disorders, confirmed the association between early age at menarche and earlier illness onset in women with bipolar disorder type I, in whom the peri-menarcheal onset was 2.50 times more likely than in women with major depressive disorder. Moreover, whether pubertal

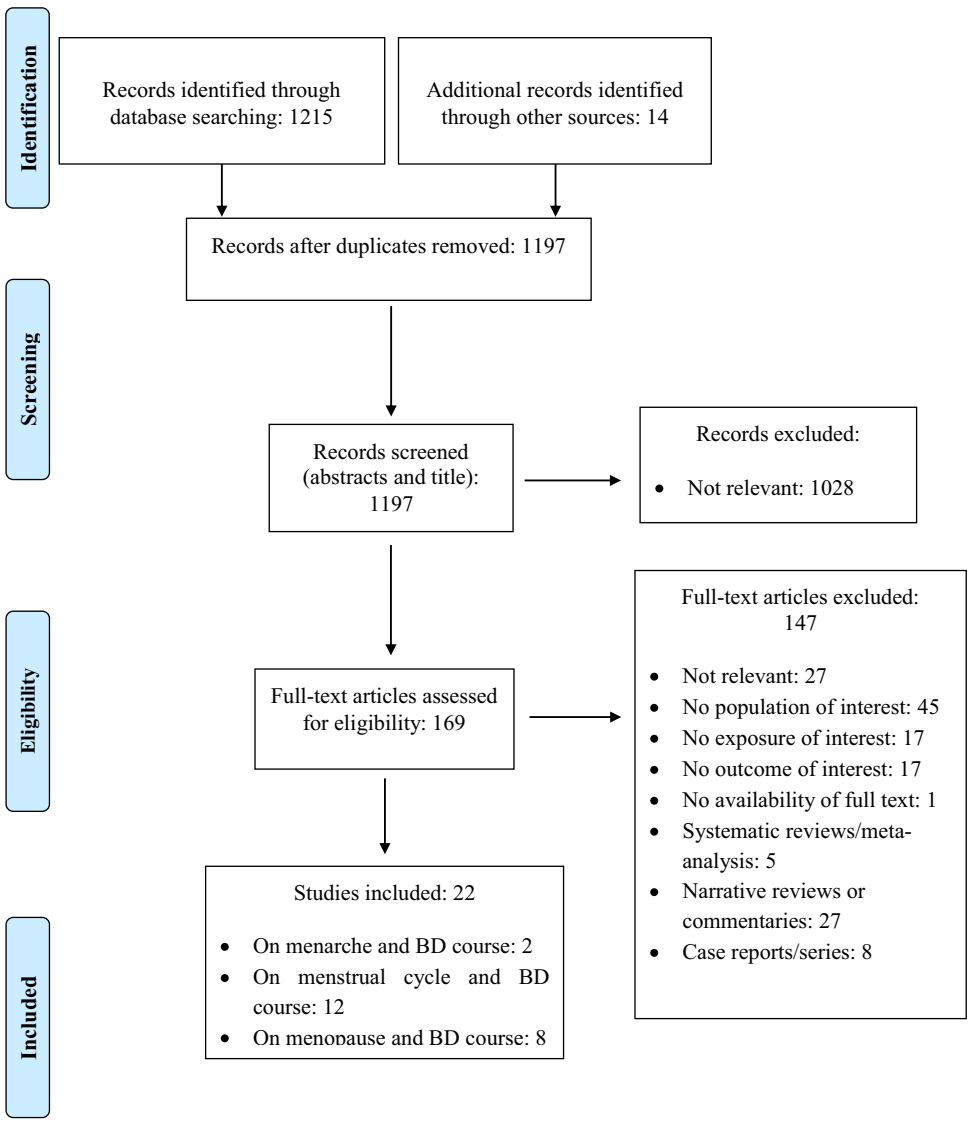

Fig. 1 Flow diagram of the narrative review. BD, bipolar disorder

Table 1 Overview of research studies on the effects of menarche on bipolar disorder

Study	Study design	Sample size	Menarche effect
Tondo et al. 2017	Retrospective cohort study	Clinical: 1139	Younger age at menarche is associated with earlier illness onset, especially among women with BD I
Rosso et al. 2020	Retrospective cohort study	Clinical: 288	Age at menarche is positively correlated to number of lifetime depressive episodes and duration of untreated illness in women with BD. Women with early menarche (≤ 11 years) have higher risk of metabolic syndrome while women with late menarche (≥ 15 years) have lower risk of peripartum mood episodes

BD, bipolar disorder; *BD I*, bipolar disorder type I

Table 2 Overview of research studies on the effects of the menstrual cycle on bipolar disorder

Study	Study design	Sample size	Menstrual cycle effect
Leibenluft et al. 1999	Prospective cohort study	Clinical: 25	No significant association between menstrual phase and mood variations in rapid cycling BD
Rasgon et al. 2003	Prospective cohort sudy	Clinical: 17	BD women report mood change across the menstrual cycle, without a consistent pattern
Wieck et al. 2003	Retrospective cohort study	Clinical: 8 Healthy controls: 9	No significant differences in premenstrual mood symptoms between patients and controls
Whybrow et al. 2003	Prospective cohort study	Clinical: 80	BD women report mood change across the menstrual cycle, without a consistent pattern
Karadag et al. 2004	Prospective cohort study	Clinical: 34 Healthy controls: 35	Premenstrual symptoms are more commonly reported by controls than by treatment-responsive BD patients
Rasgon et al. 2005	Prospective cohort study	Clinical: 45	BD women report mood change across the menstrual cycle, without a consistent pattern
Shivakumar et al. 2008	Prospective cohort study	Clinical: 41	No significant relationship between phases of the menstrual cycle and changes in depression or mania
Fornaro and Perugi 2010	Retrospective cohort study	Clinical: 92	In BD women, PMDD is a frequent co-morbid condition, in particular among patients with BD II
Choi et al. 2011	Retrospective cohort study	Clinical: 61 Healthy controls: 122	Women with BD II more than those with BD I and healthy controls reported moderate to severe PMS
Dias et al. 2011	Prospective cohort study	Clinical: 293	Women with BD and premenstrual mood exacerbation have a worse course of illness with higher risk for relapses and shorter time between affective recurrences
Sit et al. 2011	Prospective cohort study	Clinical: 11 Healthy controls: 10	No significant association between menstrual cycle and mood symptoms
Slyepchenko et al. 2017	Retrospective cohort study	Clinical: 1099	Women with BD and PMDD have earlier onset of BD, higher rates of rapid cycling, increased number of mood episodes, higher rates of other psychiatric comorbidities, closer gap between BD onset and age at menarche, and more severe symptoms during the perinatal period and while taking oral contraceptives

BD, bipolar disorder; *BD I*, bipolar disorder type I; *BD II*, bipolar disorder type II; *PMDD*, premenstrual dysphoric disorder; *PMS*, premenstrual syndrome

timing has long-term effects on bipolar disorder is not fully understood. Recently, the link between age at menarche and long-term course of bipolar illness has been explored through a retrospective study involving 288 women (Rosso et al. 2020). The research showed a positive correlation between age at menarche, number of lifetime depressive episodes, and duration of untreated illness. Furthermore, the study suggested that age at menarche may be related to clinical characteristics of bipolar disorder. Compared to women with normal menarche (12–14 years), women with late menarche (≥ 15 years) had lower probability of mood episodes with peripartum onset, while women with early menarche (≤ 11 years) showed higher risk of metabolic syndrome. Taken together, the results of the studies on this topic suggested that age at menarche may be associated with age at onset of bipolar disorder and may be related to specific clinical features of bipolar illness. Table 1 lists the

Table 3 Overview of research studies on the effects of the menopause transition period on bipolar disorder

Study	Study design	Sample size	Menopause effect
Freeman et al. 2002	Retrospective cohort study	Clinical: 50	BD women usually experience mood worsening during the menopause period
Payne et al. 2007	Retrospective cohort study	Clinical: 2524 Healthy controls: 163	Women with BD are common to experience mood symptoms during menopause
Marsh et al. 2008	Prospective cohort study	Clinical: 47	Menopausal transition age women with BD experience high frequency of affective episodes, especially depressive episodes
Marsh et al. 2015	Prospective cohort study	Clinical: 56	BD women have higher scores of depression and mania during the late menopausal phase and the early post-menopause phase compared to BD women in the early menopausal phase
Hu et al. 2016	Retrospective cohort study	Symptomatic menopausal transition: 19,028 Healthy controls: 19,028	Symptomatic menopausal transition increases risk of subsequent new onset BD
Chen et al. 2017	Prospective cohort study	Clinical: 50,273	Women with symptomatic menopause had higher risk of subsequent BD
Perich et al. 2017	Retrospective cohort study	Clinical: 158	During menopause BD women are likely to experience onset or worsening of mood symptoms. Women with early depression onset are more likely to report mood worsening during menopause
Perich et al. 2021	Retrospective cohort study	Clinical: 498	Quality of life is lower for BD women in the menopause transition period

BD, bipolar disorder

studies on bipolar disorder and menarche included in the present review and summarizes the main findings.

Bipolar disorder and menstrual cycle

Data from the investigation of menstrual cycle in women with bipolar disorder is heterogeneous. Retrospective studies indicate that 25–77% of women with bipolar disorder report premenstrual syndrome or premenstrual mood changes (Wieck et al. 2003; Karadag et al. 2004; Choi et al. 2011). Specifically, Choi et al. (2011), in a study including 61 bipolar women and 122 healthy controls, found that women with bipolar disorder type II more than those with bipolar disorder type I and age-matched controls reported moderate to severe premenstrual syndrome (52%, 23%, and 20%, respectively). Conversely, Karadag et al. (2004) found that control subjects with no history of mental disorders ($n = 35$) experienced more menstrual related mood changes compared to women with treatment-responsive bipolar disorder ($n = 34$), while Wieck et al. (2003) did not find significant differences in premenstrual mood symptoms between a sample of eight female patients with bipolar disorder and a control group of nine women. A putative association between menstrual cycle, mood variability, and rapid cycling course of bipolar disorder is up for debate (Leibenluft et al. 1999; Fornaro and Perugi 2010; Dias et al. 2011). Leibenluft et al. (1999), in a study including twenty-five women affected by rapid cycling bipolar disorder, did not find a consistent relationship between menstrual cycle phase and mood variation. Specifically, only 11 of 25 women exhibited a significant association between menstrual cycle phase and mood, without a specific pattern: 5 women reported a tendency to increased hypomania or decreased depression in the post-menstrual phase compared to the premenstrual phase; 6 women showed the opposite pattern (Leibenluft et al. 1999). These findings were confirmed by Rasgon and colleagues across three prospective studies conducted on a sample of forty-five bipolar women (Rasgon et al. 2003; Whybrow et al. 2003; Rasgon et al. 2005). The research collected daily self-reported mood ratings across 3 months using a computerized data collection software (ChronoRecord). The Chrono Record software uses a visual analogue scale between the extremes of mania and depression on which patients are told to mark their daily mood. During the study period, 55–65% of women reported significant mood alterations in at least one menstrual cycle without any defined and typical pattern of shift. More recently, two other studies examined mood ratings across the menstrual cycle. Shivakumar et al. (2008) studied depressive and manic symptoms across luteal and follicular phases of menstrual cycle. Based on a sample of 41 women with bipolar disorder, mood severity was not significantly related to the menstrual cycle: only 8 of 41women reported higher mean depression score while only 5 of 41 women showed greater mean mania score in the luteal phase compared to the follicular phase (chi-square value = 3.97, $p = 0.13$). Lastly, Sit et al. (2011) showed that symptoms of depression, mania, generalized anxiety, and suicidality, as well as psychosocial functioning and physical symptoms

did not change across the menstrual cycle in a sample of eleven bipolar women compared to a group of ten healthy controls. Concerning the relationship between menstrual cycle and long-term course of bipolar disorder, a sample of 293 female patients from the Systematic Treatment Program for Bipolar Disorder (STEP-BD) who retrospectively had exacerbation of mood symptoms during premenstrual phase were followed prospectively for 1 year (Dias et al. 2011). They showed higher risk for relapses (primarily depressive episodes) and shorter time between affective recurrences regardless of menstrual cycle phase. However, they were not more likely to have increased rates of rapid-cycling course. The association between bipolar disorder and premenstrual dysphoric disorder is also debated. Whether it has been considered among clinical markers of bipolar disorder in studies on broad bipolar spectrum (Akiskal and Pinto 1999), premenstrual dysphoric disorder is currently included in the depressive disorders section of the Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (DSM-5) (American Psychiatric Association, 2013). Fornaro and Perugi (2010), in a retrospective study run on 92 Italian patients, found that 25 women (27.2%) were affected both by bipolar disorder (especially type II) and premenstrual dysphoric disorder. By contrast, in the general population, the prevalence of premenstrual dysphoric disorder is 1.8–5.8% (American Psychiatric Association, 2013). Definitely, in a study involving 1099 female patients with bipolar disorder, women with comorbid bipolar disorder and premenstrual dysphoric disorder have been found to present a worse course of psychiatric illness with earlier onset, increased rates of rapid cycling, larger number of lifetime affective episodes (both hypomanic and depressive episodes), and more frequent comorbid psychiatric disorders (Slyepchenko et al. 2017). Furthermore, they showed a shorter gap between menarche and onset of bipolar disorder and more severe mood symptoms during the perinatal period and while taking oral contraceptives (Slyepchenko et al. 2017).

In summary, it appears that menstrual cycle may affect the course of bipolar disorder in some women, particularly those affected by bipolar disorder type II; there are no specific patterns of mood alterations according to menstrual cycle phase; menstrual-related mood symptoms and premenstrual dysphoric disorder are associated with more severe course of bipolar disorder. Table 2 details the results of the studies on bipolar disorder and menstrual cycle included in the present review.

Bipolar disorder and menopause

It is known that the menopause transition period is often marked by mood symptoms (Avis et al. 1994; Gibbs et al. 2012) with increased vulnerability to major depressive episodes and subsyndromal depressive symptoms even in women without a history of psychiatric disorders (Cohen et al. 2006; Freeman et al. 2006; Freeman et al. 2007). Although the relationship between bipolar disorder and menopause has been analyzed by few studies, there is evidence that women affected by bipolar disorder any types are at increased risk of mood changes during the menopause period (Payne et al. 2007). Specifically, in a recent study, Perich et al. (2017) found that 22 (58%) of the 38 women with bipolar disorder who have started or transitioned through menopause reported an onset or worsening of mood symptoms during this time. Furthermore, a younger age at their first lifetime depressive episode was correlated to a higher risk of mood worsening during the menopause transition period. A similar study that aimed to assess the impact of reproductive events on the course of bipolar disorder showed that among 22 bipolar patients, 12 women had increased depressive symptoms during the menopause period and many also reported an increase of irritability ($n=8$), hypomania or mania ($n=8$), and rapid cycling ($n=6$) (Freeman et al. 2002). The largest retrospective study that analyzes reproductive-related hormonal events and mood disorders included 1747 women with major depressive disorder, 665 women with bipolar disorder type I, 112 women with bipolar disorder type II, and 163 healthy controls (Payne et al. 2007). The study showed that among women with mood disorders, a larger portion of women with bipolar disorder type II reported increased mood symptoms during menopause. However, the type of symptoms was not reported. Marsh et al. (2008) analyzed data from systematic treatment enhancement program for bipolar disorder (STEP-BD) and studied the association between menopause and affective episodes that were documented during a follow-up period (12 to 24 months): 68% of women experienced major depressive episodes, 23% (hypo)mania episodes, and 13% episodes with both depressive and elevated mood. More recently, Marsh et al. (2015) conducted a prospective study that examined mood changes across menopausal transition phase over a 17-month follow-up period. Among 44 bipolar women, a larger portion of patients who were in the late menopause and early postmenopause phase had higher depression and mood elevation symptom scores compared to those who were in the early menopause stage. Only one study explored how quality of life may differs during the menopause transition period, showing that quality of life was significantly lower for bipolar women in the menopause transition group compared to women in the reproductive and postmenopause period (Perich et al. 2021).

An important but still debated topic is whether typical sex hormonal changes of menopause may be linked to development of bipolar disorder in middle-aged women. The large retrospective cohort study conducted by Hu et al. (2016) showed an association between symptomatic menopausal transition and risk of subsequent new-onset bipolar disorder.

The authors noted that women with symptomatic menopausal transition ($n = 19{,}028$), compared to those without symptomatic menopausal transition ($n = 19{,}028$), had a significantly increased risk of bipolar disorders newly diagnosis over a follow-up period of 10 years. A similar and recent study, involving 50,273 midlife women affected by major depression with ($n = 21{,}120$) or without ($n = 29{,}153$) symptomatic menopausal transition, demonstrated that women with symptomatic menopause had higher risk of subsequent bipolar disorder any types in comparison to women with major depression alone (Chen et al. 2017). In conclusion, the evidence suggests that menopausal transition may be a time of increased mood disturbances in women with bipolar disorder, particularly in case of bipolar disorder type II; furthermore, it is noteworthy that in some women menopause seems trigger the onset of bipolar disorder, although it usually starts during youth. Table 3 details the results of the studies on bipolar disorder and menopause included in the present review.

Discussion

Findings suggest that menarche, menstrual cycle, and menopause may influence the course of bipolar disorder, but results are not univocal. In line with Payne (2003), it appears that only a part of women diagnosed with bipolar disorder are vulnerable to the impact of sex hormone imbalance. This vulnerability may be genetic, a result of the organizational effects of hormones, or both (Teatero et al. 2014). Moreover, the hypersensitivity to hormonal changes may be accumulated across every menstrual cycle event (Deecher et al. 2008). Transition into puberty is associated with significant biological development and higher circulating concentrations of estrogen. A plausible relationship between these changes and onset of mood disorders is supported by findings that major cerebral neurotransmitter systems are responsive to gonadal hormones. In particular, higher changes in estrogens may modulate the neurotransmission mediated by serotonin contributing to mood alterations and bipolar disorder onset (Hall and Steiner 2013; Borrow and Cameron 2014). In addition, hormonal fluctuations that happen during menarche can exert a dysregulation of mood throughout interactions with hypothalamic–pituitary–adrenal axis, at a time of major susceptibility to external stress factors (Steiner et al. 2003). Data seem to indicate that menarche timing may influence the course characteristics of bipolar disorder: early age at menarche is shown to be associated with earlier illness onset especially in women with bipolar disorder type I (Tondo et al. 2017) and comorbid metabolic syndrome (Rosso et al. 2020). The underlying pathophysiological mechanisms involved in the association between age at menarche and metabolic syndrome remain poorly understood. However, one of the most supported explanations is that early menarche in adolescence and metabolic syndrome in adulthood are consequences of childhood obesity. On the one hand, childhood obesity may induce puberty by the production of leptin (Lim et al. 2016). Specifically, current evidence suggests that the leptin level has direct effects on gonadotropin secretion and consecutively provides initiation of puberty (Kaplowitz 2008). On the other hand, childhood obesity, if progresses to adulthood, may favor the onset of metabolic disorder. Moreover, adult obesity may impair estrogen function and influences the magnitude of hormonal fluctuations, which would lead to decreased serotonergic neurotransmission and to the worsening of mood (Baldini et al. 2021). In turn, the worsening of mood may favor unhealthy and chaotic lifestyles (increased caloric intake, cigarette smoking, alcohol abuse, and low physical activity) and increase the risk of metabolic disturbances (Kivimäki et al. 2008). Metabolic syndrome is a well-known condition in patient with bipolar disorder with prevalence rates ranging from 36 to 49% in the USA and from 18 to 26% in European countries (Murray et al. 2009). Therefore, illness-related factors, inherited biological factors (such as hypothalamic pituitary adrenal axis dysregulation, endogenous estradiol oscillations), and psychopharmacological treatments play an important role in inducing weight gain and metabolic abnormalities leading to metabolic syndrome in bipolar patients (Salvi et al. 2011; Solia et al. 2015). Given the few clinical predictors that may help to individualize the risk of metabolic disturbances in women with bipolar disorder, the association between age at menarche and metabolic disorders should be considered in clinical practice especially when choosing pharmacological treatments. Conversely, women with later age at menarche are more likely to be affected by greater number of lifetime depressive episodes, longer duration of untreated illness, and lower risk of peripartum mood episodes (Rosso et al. 2020). Taken together, these findings highlight a potential role of menarche age in predicting the course of bipolar illness from the early stages. Concerning menstrual cycle phases, they seem to trigger mood shifts in case of bipolar disorder type II especially. While the relationship between the pattern of mood alterations and menstrual cycle is not clear, a recent review speculates that hypomanic and manic episodes may be associated with follicular phase, characterized by high levels of estrogen and neuronal excitability, and, conversely, depressive episodes may be associated with luteal phase, when progesterone levels are high and cortical excitability is low (Teatero et al. 2014). Anyhow, women with mood alterations related to menstrual cycle, including premenstrual dysphoric disorder, have shown worse clinical outcomes and increased burden of bipolar illness (Slyepchenko et al. 2017). Coming to menopause, it should not be considered a period at risk for anxiety or (unipolar)

depressive disorder only. In specific cases, menopause may also lead to the onset of bipolar disorder or to the diagnostic conversion from major depression to bipolar disorder. Several possible underlying mechanisms have been hypothesized. First, it is believed that the withdrawal of estrogens may cause a change in the serotonin levels with an exacerbation of mood symptoms (i.e., more irritability), resulted to a diagnostic conversion to bipolar disorder among midlife women with major depression (Chen et al. 2017). Second, the decreased secretion of estrogens may cause a significant loss of neurotrophic and neuroprotective hormonal effects with increased levels of neuroinflammation that contributed to the pathophysiology of bipolar disorder (Yasui et al. 2007; Frey and Dias 2014). Lastly, although most evidence are in favor of a primary biological etiopathogenesis, several psychosocial stressors and sleep disturbances have also been linked to bipolar disorder onset in women during the menopause transition period (Sajatovic et al. 2006; Zambotti et al. 2015). These results are worthy of interest and should be taken into account in the choice of pharmacological treatments in menopausal age women.

The findings of the present narrative review should be evaluated considering several limitations: small number of studies on this topic with heterogeneous diagnostic criteria, assessment methods and statistical analysis; lack of large-scale longitudinal and perspective studies.

In conclusion, the relationships between bipolar disorder and hormonal changes typical of menstrual cycle events should be deepened. Far from having found specific etiopathogenic correlations, further perspective and controlled studies on larger samples, better with included hormonal assessment, are necessary to explore critical features of bipolar disorder during menstrual cycle events and expand the available data regarding the course of bipolar illnesses throughout the female lifespan. Meanwhile, in daily clinical practice, it would be helpful to analyze and monitor all reproductive-related hormonal events in view of their impact on the symptomatology and the implication on treatments in women with bipolar disorder.

Author contribution Gianluca Rosso, Giuseppe Maina, and Andrea Fagiolini designed the study. Elena Aragno and Gianluca Rosso performed the literature search and data analysis. Elena Aragno and Gianluca Rosso wrote the draft. Giuseppe Maina and Andrea Fagiolini supervised the content of the draft. All authors critically revised and approved the final version of the manuscript.

Declarations

Conflict of interest Gianluca Rosso is/has been a speaker and/or consultant from Angelini, Janssen, Lundbeck, and Otsuka. Giuseppe Maina is/has been a consultant and/or a speaker and/or has received research grants from Angelini, Boheringer Ingelheim, FB-Health, Janssen, Lundbeck, Otsuka, and Innova Pharma. Cuomo Alessandro is/has been a consultant and/or a speaker and/or has received research grants from Angelini, Lundbeck, and Otsuka. Fagiolini Andrea is/has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Apsen, Boehringer Ingelheim, Doc Generici, FB-Health, Janssen, Lundbeck, Mylan, Otsuka, Polifarma, Recordati, Sanofi Aventis, Sunovion, and Vifor. Elena Aragno and Elena Paschetta declare that they
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