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Catamenial fluctuations in Lithium and Valproate serum levels: a systematic review.

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Corresponding Author:	Claudia Del Grande, M.D. Universita degli Studi di Pisa Pisa, ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Universita degli Studi di Pisa
Corresponding Author's Secondary Institution:	
First Author:	Claudia Carmassi, M.D. PhD
First Author Secondary Information:	
Order of Authors:	Claudia Carmassi, M.D. PhD
	Claudia Del Grande, M.D.
	Isabella Masci, MD
	Danila Caruso, M.D.
	Laura Musetti, M.D.
	Andrea Fagiolini, Full Professor
	Liliana Dell'Osso, Full Professor
Order of Authors Secondary Information:	
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Abstract:	Several women affected by mood disorders experience higher affective instability during the premenstrual phase. On the assumption that fluctuations in drug levels might contribute to the worsening of mood symptoms, we provided a systematic review of available studies that had investigated changes in Lithium and Valproate concentrations in relation to menstrual phases. We selected five studies, 4 of which assessing catamenial fluctuations of Lithium levels and 1 those of Valproate. Study samples included women affected by bipolar disorder, healthy and epileptic women of fertile age. Preliminary results proved a close relationship between cyclic premenstrual exacerbation in affective symptoms and a significant decrease of Lithium levels during the luteal phase, despite a constant oral dose, in bipolar women. Lithium concentration instead was influenced neither by menstrual cycle phases or oral contraceptives use in healthy women. Valproate concentrations in epileptic women showed just a little, not significant decline of Valproate level during the mid-luteal phase. Pharmacokinetic gender differences in adsorption, volume distribution, hepatic metabolism and renal excretion of mood stabilizers have been supposed to partly explain such catamenial fluctuations. A better understanding in this field could help to counteract the distress related to premenstrual phase improving the therapeutic management of mood disorders.

UNIVERSITÀ DI PISA
Dipartimento di Medicina Clinica e Sperimentale

To:
Stuart A. Montgomery, Professor
Editor-in-Chief
Emeritus Professor Imperial College, London, UK

October 30th 2018

Dear Editor,

We should greatly appreciate your kind consideration of the enclosed manuscript entitled **"Catamenial fluctuations in Lithium and Valproate serum levels: a systematic review."**, Authors: Claudia Carmassi, Claudia Del Grande, Isabella Masci, Danila Caruso, Laura Musetti, Andrea Fagiolini, Liliana Dell'Osso, for its publication as a Review in the journal *International Clinical Psychopharmacology*. The paper aims to provide a systematic review of available studies that have investigated changes in the serum concentrations of Lithium and Valproate in relation to the menstrual phases, that are supposed to partly account for the exacerbation of mood symptoms experienced by several women with bipolar and related disorders during the premenstrual phase. We particularly focused on the gender pharmacokinetic differences potentially implicated in catamenial fluctuations of these mood stabilizers concentration.

The submitting authors warrant that the article is original, does not infringe upon any copyright or other proprietary right of any third party, and is not under consideration by another journal.

All submitting authors have contributed to the work, seen and approved the submitted version.

Yours faithfully,

Claudia Del Grande, M. D.
on behalf of the submitting authors

Department of Clinical and Experimental Medicine, Section of Psychiatry, University of Pisa
Via Roma 67, 56126 Pisa, Italy

Tel +39 050 2219760; fax: +39 050 2219787
e-mail: claudiadelgrande83@gmail.com

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Running head: Mood stabilizers and menstrual cycle

Carmassi Claudia[1], Del Grande Claudia[1*], Masci Isabella[1], Caruso Danila[1], Musetti Laura[1], Fagiolini Andrea[2], Dell'Osso Liliana[1]

[1] University of Pisa, Department of Clinical and Experimental Medicine, Psychiatric Clinic

[2] University of Siena, Department of Molecular and Developmental Medicine, Psychiatric Clinic

***Corresponding Author:**

Claudia Del Grande, M.D.

Department of Clinical and Experimental Medicine, Section of Psychiatry, University of Pisa

Via Roma 67, 56126 Pisa, Italy

Tel +39 050 2219760; fax: +39 050 2219787

e-mail: claudiadelgrande83@gmail.com

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Abstract

Several women affected by mood disorders experience higher affective instability during the premenstrual phase. On the assumption that fluctuations in drug levels might contribute to the worsening of mood symptoms, we provided a systematic review of available studies that had investigated changes in Lithium and Valproate concentrations in relation to menstrual phases. We selected five studies, 4 of which assessing catamenial fluctuations of Lithium levels and 1 those of Valproate. Study samples included women affected by bipolar disorder, healthy and epileptic women of fertile age. Preliminary results proved a close relationship between cyclic premenstrual exacerbation in affective symptoms and a significant decrease of Lithium levels during the luteal phase, despite a constant oral dose, in bipolar women. Lithium concentration instead was influenced neither by menstrual cycle phases or oral contraceptives use in healthy women. Valproate concentrations in epileptic women showed just a little, not significant decline of Valproate level during the mid-luteal phase. Pharmacokinetic gender differences in adsorption, volume distribution, hepatic metabolism and renal excretion of mood stabilizers have been supposed to partly explain such catamenial fluctuations. A better understanding in this field could help to counteract the distress related to premenstrual phase improving the therapeutic management of mood disorders.

Keywords: lithium; valproate; mood stabilizers; serum level; menstrual cycle; mood disorders

Introduction

A growing body of research has investigated possible gender differences in clinical manifestations, illness course, response to medications and neurobiological background of many mental disorders, in particular mood disorders (Baldassano et al., 2005, Barnes and Mitchell, 2005, Benedetti et al., 2007, Carmassi et al., 2018, Freeman et al., 2002, Kawa et al., 2005, Suominen et al., 2009). Women with Bipolar Disorder (BD) have been reported to be often misdiagnosed with unipolar depression for 1.9 years longer than men and to receive therefore inadequate treatment, that has been estimated on average for 5.5 years longer than men (Viguera et al., 2000). Bipolar women usually experience more episodes of depression ("depressive diathesis") over the course of their illness than men, who conversely report predominant manic episodes (Dell'Osso et al., 1991, Leibenluft, 1996, Robb et al., 1998). Depressive episodes in women are described to last longer, more refractory to treatment, more frequently occurring in autumn and winter (Baldassano et al., 2005) and more likely to precede a hypomanic/manic episode (Zornberg and Pope, 1993) than depressive episodes in males. Mixed episodes, characterized by the contemporary presence of manic and depressive symptoms are more common in females than in males(Akiskal et al., 1998, Benazzi and Akiskal, 2003, Braunig et al., 2009, Kessing, 2004, McElroy et al., 1992, Miller and Ghadiali, 2015), and are known to be associated with a worse clinical course, high rates of comorbidity with anxiety and alcohol or substance abuse disorders, head trauma or other neurological problems, greater prevalence of mood incongruent psychotic features, poor treatment outcome and higher suicide risk (Balazs et al., 2006, Dell'Osso et al., 1991, Fagiolini et al., 2015, Goldberg et al., 1998, Kruger et al., 2005, Perugi et al., 2014, Swann et al., 2013, Vieta, 2005). Compared to men, women more frequently report changes in weight and appetite, hypersomnia and difficulty on maintaining sleep at night during bipolar depression (Benazzi and Akiskal, 2003, Kawa et al., 2005). In contrast, fewer women than men report problematic behaviors, grandiosity, hyperactivity or increased sexual interest during manic episodes (Barnes and Mitchell, 2005). For that concern the course of the disease, women are more likely than men to experience a rapid cycle pattern, that is defined by at least four mood episodes within a 12 months'

time frame (Kessing, 2004). The hypotheses that have been formulated to explain this greater probability of having rapid cycling in females include gonadal steroid effects, hypothyroidism and greater use of antidepressant drugs in women (Leibenluft, 1996, Leibenluft, 2000).

It is of note that mood disorders and affective instability frequently occur or are exacerbated in the framework of life experiences related to hormonal changes: menarche, menstrual cycle, pregnancy, postpartum and perimenopausal periods (Steiner et al., 2003). These evidences lead to suppose that, in a subgroup of women, physiological hormonal changes may underlie the mood changes associated with reproductive events in both unipolar and bipolar disorders. Similarly, a relationship between the stages of the menstrual cycle and a greater vulnerability to the development of a new episode or exacerbation of mood symptoms has been suggested for a subgroup of women (Soares and Zitek, 2008). Premenstrual Dysphoric Disorder (PMDD), as defined by American Psychiatric Association (APA) and assumed by The American College of Obstetricians and Gynecologists (ACOG), is recognized as a severe and pervasive mood disorder that affects a small, although significant, percentage of women, and is characterized by physical, cognitive, affective and behavioral symptoms. The distress related to the premenstrual symptoms, occurring in the luteal phase of the menstrual cycle and resolving rapidly in the follicular phase, is relevant and causes a severe social and working impairment (Freeman et al., 2002). Moreover, as highlighted in a recent review (Teatero et al., 2014), the effects of the menstrual cycle are more common in women with BD-II compared to BD-I. Among all types of mood disorders, rapid cycling BD has been hypothesized to have the strongest relationship with the menstrual cycle (Teatero et al., 2014). In addition, the development of rapid cycling appears to be associated with antidepressant use prior the onset of manic episodes in women but not in men (Freeman and Gelenberg, 2005). The symptomatic exacerbations that occur in some phases of the menstrual cycle may be due to the fluctuations of estrogen and progesterone levels; in fact, gonadal steroids can modulate the central activity of serotonin, noradrenaline and γ-aminobutyric acid (GABA) (Barnes and Mitchell, 2005). Higher rates of hospitalization, mainly due to severe depressive episodes, have been described during the premenstrual period, as well as increased suicide attempts

or completed suicides (Endicott, 1993). Overall, reproductive cycle appears to add complexity to the management of bipolar women and should be taken into account in the evaluation of treatment.

Lithium (Li^{++}) is still the first-line prophylactic treatment for BD, as also recommended by international guidelines (Goodwin et al., 2016, Grunze et al., 2018). Its efficacy for the long-term management of bipolar patients has been continuously supported by several observational and randomized clinical trials (Hayes et al., 2016, Kessing et al., 2018, Kessing et al., 2011, Muzina and Calabrese, 2005, Nolen, 2015), and increasing evidences also highlight the potential benefits of Li^{++} salts on neuroprotection and neuroregeneration (Dell'Osso et al., 2016). Among anticonvulsants approved for BD prophylaxis, Valproate (VPA) is the most commonly used and is prescribed mainly to patients with negative predictors of response to Li^{++}, such as mixed states, psychotic features, and comorbidity with anxiety and substances or alcohol abuse (Fountoulakis et al., 2017, Goodwin et al., 2016, Malhi et al., 2015, Verdolini et al., 2018).

It is known that the attainment of a steady state plasma level in a certain range is necessary to obtain an optimal therapeutic effect, although studies showing the possible influence of menstrual cycle on the mood stabilizers serum concentrations as cause of symptomatic exacerbation are lacking. Moreover, no studies have been conducted on female population in childbearing, according to the guidelines, as this condition represents exclusion criteria from clinical studies for the possible side and teratogenic effects of Li^{++} and VPA.

The purpose of this systematic review was to investigate changes in Li^{++} and VPA serum concentrations in relation to the menstrual cycle phases and to discuss the potential research implication of our findings.

Methods

Search strategy and selection of studies

We performed a systematic review, based on PRISMA guidelines, of articles published up till May 2018, and indexed in the following databases: MEDLINE, PubMed and Cochrane Library. The search

strategies used MeSH headings and keywords for *"lithium" OR lithium serum level" OR "valproate" OR "valproate serum level" AND "menstrual cycle".* The searches were limited to the English Language, studies conducted on adult human populations, adult participants over 18 years old, longitudinal, cross-sectional, or case-control studies, case reports, systematic reviews or meta-analyses, analyzing the relationship between Li^{++} and VPA serum levels and menstrual cycle.

Initial literature search returned 191 records, 120 after exclusion of duplicates. Following preliminary screening of the titles, 73 of the retrieved articles were excluded; then 42 records were excluded after reading of abstracts and full-texts (Figure 1).

Results

Five independent studies were retained and included in the qualitative analysis (Table 1). These investigations were classified according to the studied parameters: 4 out of the 5 studies explored Li^{++} serum levels variations during the menstrual cycle, while only 1 study explored those of VPA.

The first preliminary report (Libusova et al., 1975) included 35 women affected by mood disorder with psychotic features on prophylactic treatment with Li^{++} for at least two years (600-1500 mg/day; serum lithium level maintained between 0.5 to 1.0 mEq/l). The close monitoring of Li^{++} levels in blood and urine in different phases of menstrual cycle showed that in 19 patients of fertile age serum Li^{++} levels highly decreased 24-48 hours before menstruation ($p=0.01$). Moreover, the women who became pregnant under prophylactic Li^{++} treatment showed between the 42^{nd} to 70^{th} day of pregnancy a fall in the serum Li^{++} levels by one half of the mean values prior to pregnancy, despite a more than double increase of Li^{++} doses. In this preliminary report, authors proved that blood Li^{++} concentration was dependent on hormonal fluctuations related to menstrual phases in childbearing women and in the first three months of pregnancy.

Ten years later, some Authors (Conrad and Hamilton, 1986, Kukopoulos et al., 1985) described the cases of two women with marked fluctuations in serum Li^{++} concentrations in relation to menstrual cycle, with a significant/considerable decline in Li^{++} concentrations detected during the premenstrual

phase resulting in cyclic premenstrual mood changes or exacerbation of symptoms. Koukopoulos et al. (1985) analyzed a 28-year-old woman, for a period of 84 days, treated with Li^{++} monotherapy at the constant dosage of 16.2 mmol/day, and found a clear and typical relationship between psychopathological switches and menstrual cycle. This patient experimented, every month, a premenstrual manic-depressive cycle beginning with a hypomanic episode approximately two weeks before menstruation followed by severe depressive symptoms during the 2 days prior to onset of menses, which improved with menstruation. During the observation period, fluctuations in Li^{++} serum levels were measured through serial assays of Li^{++} concentrations on blood, red blood cells (RBC), and urinary samples. Levels of sexual hormones, estradiol and progesterone, in plasma and urine were also performed. Authors observed that Li^{++} serum levels oscillated in a regular and inverse relationship to the mood changes, although the patient received the same dosage of drug: the highest value of Li^{++} was recorded at the same time of the greatest severity of depressive symptoms (1.10 mmol/l), while its lowest value during the hypomanic period, corresponding to the luteal phase (0.30 mmol/l). Conversely, only small oscillations in serum Li^{++} levels, around 0.5 mmol/l, were showed when the patient was in a euthymic state. The Li^{++} concentration in RBC followed the same pattern of serum levels, ruling out a potential role of the RBC transport mechanisms in the variations of Li^{++} concentrations.

Conrad and Hamilton (1986) reported the case of a 16-year-old female adolescent who met DSM-III criteria for BD, mixed episode with psychotic features, and repeatedly exhibited a premenstrual exacerbation in symptoms (5-10 days preceding onset of menses). Authors observed that this exacerbation in her manic and psychotic symptoms coincided with a progressive decline in Li^{++} serum concentration (from mid-cycle to onset of menses) from the 1.0-1.2 mEq/l maintenance range to 0.6-0.8 mEq/l, despite a constant 1500 mg oral dose, and symptoms spontaneously remitted within the first two days of menstruation. They evaluated the prophylactic use of higher oral dose (2100-2700 mg) of Li^{++} during the patient's luteal phase (1 week prior to expected onset of menses) to compensate the premenstrual decline in serum concentrations. The higher doses typically produced serum Li^{++}

concentrations between 1.0 and 1.3 mEq/L and it was able to prevent the symptomatology exacerbation without toxic effects.

Chamberlain et al. (Chamberlain et al., 1990) analyzed serum Li^{++} concentrations in 13 healthy women not suffering from premenstrual syndrome or other mood disorders (6 women with regular and natural menstrual cycle and 7 women taking oral contraceptives (OC)) during the mid-follicular, mid-luteal, and premenstrual phases after they had received 300 mg of Li^{++} carbonate orally. After the loading dose, serum concentrations fluctuated from the lower limit of detection to a maximum of 0.4 mmol/l 2-3 hours after ingestion, with a return to baseline between 12 and 24 hours afterward. For both groups of women, the representative curves of Li^{++} serum concentration over time were overlapping independently of the phase of menstrual cycle and the OC interference. So, the Authors concluded that were no significant differences between groups or between cycle phases.

To the best of our knowledge, to date only one study analyzed whether the natural variation in reproductive steroid levels during different phases of the menstrual cycle or the use of Combined OC (COC) may affect VPA serum levels, as well as Lamotrigine (LTG) (Herzog et al., 2009). This investigation included 48 epileptic women (13-45 years), 12 of which were on VPA, 12 on VPA plus COC, 12 on LTG and 12 on LTG plus COC. VPA and LTG serum levels were measured at two-time points during a single menstrual cycle, the mid-luteal phase (between days 20-24) and the early mid-follicular phase (between days 3-7), in the groups of women not on COC. In women on COC, VPA and LTG levels were detected during the third week of active pill use and at the end of the week of the inactive pill use. In the COC groups, both VPA and LTG serum levels were significantly lower when measured during the week of active COC use than the week of inactive pill. The non-COC VPA group, instead, showed the least change of any group between the two measured time points, with a decline of 8.3% in VPA serum levels during the mid-luteal phase.

Discussion

The aim of this systematic review was to describe available evidences in literature regarding possible influences of menstrual cycle phases on the variation of Li^{++} and VPA serum concentrations. The underlying hypothesis is that these fluctuations in serum concentrations might be a factor contributing to the affective symptoms exacerbation experienced during premenstrual phase by a subset of bipolar women, and that these women might by more susceptible to physiological hormonal changes.

Despite substantial researches focusing on the impact of mood stabilizers on menstrual cycle have mainly assessed side effects and hormonal fluctuations, clinical studies regarding how menstrual cycle phases may affect blood levels variations of Li^{++} and VPA are scant and have gained limited interest of research until now.

We selected and included in our review only 5 old studies that have evaluated the relationship between catamenial fluctuations and mood stabilizers (Li^{++} and VPA) serum levels; 4 out of these studies explored Li^{++} serum levels variations according to menstrual cycle phases (Chamberlain et al., 1990, Conrad and Hamilton, 1986, Kukopoulos et al., 1985, Libusova et al., 1975) while only 1 study explored those of VPA (Herzog et al., 2009). Two of the 5 studies also evaluated the effect of OC use on Li^{++} and VPA serum levels (Chamberlain et al., 1990, Herzog et al., 2009). Clinical studies on catamenial fluctuations of VPA levels are lacking because most of studies focused on VPA-induced side effects on menstrual cycle regularity, or VPA teratogenic effects, or concerned the association between VPA and PCOS and have been conducted especially in epileptic women (Akdeniz et al., 2003, Kenna et al., 2009, McIntyre et al., 2003). Since 1990 for Li^{++}, and since 2009 for VPA, no research has been conducted on that topic.

Firstly, a close monitoring of Li^{++} levels in blood and urine in different phases of menstrual cycle in 35 women of fertile age affected by mood disorder with psychotic features showed a significant decrease of serum Li^{++} levels 24-48 hours before menstruation ($p=0.01$), as well as a fall in the serum Li^{++} levels in the first three months of gravidity in women who became pregnant under prophylactic Li^{++} treatment (Libusova et al., 1975). These preliminary findings proved the close relationship

between the phase of the hormonal cycle and Li^{++} concentration. Subsequently, two case reports of women affected by BD on prophylactic treatment with Li^{++} who exhibited a cyclic premenstrual exacerbation in symptoms showed similar results (Conrad and Hamilton, 1986, Kukopoulos et al., 1985). Koukopoulos et al. (1985), in a longitudinal single-case study performing serial assays of Li^{++} concentration on blood, RBC and urinary sample, observed that Li^{++} serum levels cyclically oscillated in a regular and inverse relationship to the mood changes, although the patient received the same oral dosage of Li^{++}, with the lowest concentration (0.30 mmol/l) during the luteal phase correlated to a typical hypomanic switch, and the highest (1.10 mmol/L) at the time of the greatest severity of depression during the 2 days prior to onset of menses. Similarly, Conrad and Hamilton (1986) reported the case of an adolescent BD patients in which Li^{++} serum levels cyclically decreased from the 1.0-1.2 mEq/l maintenance range to 0.6-0.8 mEq/l, despite a constant 1500 mg oral dose, 5-10 days before menstruation concomitantly with exacerbation in her affective psychosis. Therefore, they effectively evaluated the administration of higher Li^{++} oral dose, up to 2700 mg per day, during the patient's luteal phase (1 week prior to expected onset of menses) to prevent relapses.

Finally, Chamberlain et al. (1990), did not report significant catamenial changes in Li^{++} concentration in a sample of 13 healthy women not affected by premenstrual syndrome or other mood disorders, with both natural and artificial cycle induced by OC steroids. In this study, Li^{++} serial assays were performed before administration of drug and then after ingestion of a single dose of Li^{++} (300 mg). Representative curves of Li^{++} serum concentration over time were overlapping independently of the menstrual cycle phase and the OC interference. Since then, no other study using similar approach has been conducted in women with bipolar or unipolar illness.

To date, only one observational study (Herzog et al., 2009) investigated the catamenial changes in VPA concentration. The sample analyzed was not composed by bipolar women but by epileptic women, half of them using COC. Women with regular menstrual cycle and without COC showed a decline (8.3%) of VPA level during the mid-luteal phase, but there were no statistically significant differences compared to the early-mid follicular phase.

Although these findings overall pointed out a significant reduction of Li^{++} serum concentrations during the premenstrual phase and, at a lesser extent, of VPA concentration, related to a concomitant exacerbation of depressive and dysphoric symptoms, the underlying mechanism is not clear (Endicott, 1993). One of the possible explanation is based on pharmacokinetic gender differences. Some studies have underlined the importance of these differences on the management of psychopharmacological treatments (Giudicelli and Tillement, 1977, Leibenluft, 1996). As women have a reduced gastric secretion and a slower gastric emptying than men, they consequently have low absorption rates that could influence the serum concentrations of drugs. It seems due to progesterone hormone level in the luteal phase that causes a reduction of gastric acid secretion and slowing gastric emptying (Yonkers et al., 1992). Lean and fat mass of the adipose tissue could also influence the distribution of drugs. Females generally have a lower ratio between lean mass and adipose tissue (Seeman, 2004), so lipophilic drugs should have a greater volume of distribution in females especially during chronic and multiple drugs administration. Thus, the half-life may be prolonged and serum levels may be higher in patients with less lean mass.

Menstrual phases changes could modify trans capillary fluid dynamics, with consequent fluid displacements between intravascular and extravascular spaces (Oian et al., 1987). An increase in fluid retention related to luteal phase might therefore dilute the concentration of drugs lowering their plasma levels. For instance, during pregnancy plasma volume increases by 50% in the third trimester and, consequently, it is recommended to check maternal blood levels of mood stabilizers over the course of pregnancy in order to maintain mood stability (Burt and Rasgon, 2004).

Women have a lower hepatic metabolic rate than men and fluctuations of it might be related to cyclical changes of the reproductive hormones. The peak of hepatic metabolism appears to occur during mid menstrual cycle; it could cause lower levels of plasma drugs in the luteal phase, potentially contributing to premenstrual worsening of mood symptoms. Conversely, a slower rate of metabolism running follicular phase could lead to higher levels of circulating drugs and an increased risk of side effects (Barnes and Mitchell, 2005). It has also been hypothesized that young women may have higher

levels of activity of CYP3A4, CYP2A6, CYP2B6 and CYP2C19 enzymes, such to induce lower plasma concentrations of drugs commonly used for the treatment of mood disorders (Waxman and Holloway, 2009). One of the metabolic pathways of VPA comprises CYP-mediated oxidation, and some studies have reported an effect of CYP2C9/CYP2C19 genotype on pharmacokinetic variability of VPA (Bock et al., 1994, Court et al., 2001). Conversely, some Authors (Smith et al., 2016) found that CYP2C9/2C19 variant genotypes are not relevant for variability in VPA exposure, although the daily VPA dosage in their patients was significantly lower in carriers of reduced-function CYP2C9 variant alleles than in homozygous wild-type carriers. This study has shown that age and gender significantly influence VPA serum concentration; particularly, findings suggest that older female patients would generally require 30–50% lower dosing of VPA compared to younger males (Smith et al., 2016). Although there is evidence that females generally exhibit less uridine diphosphate glucuronosyltransferase enzyme activity than males, little is known about gender-related variability of VPA (Bock et al., 1994, Smith et al., 2016). Some factors taken into consideration include differences in body weight/distribution, bioavailability, and/or drug compliance. As shown by Ibarra et al. (Ibarra et al., 2013), there is an increased reabsorbed fraction and bioavailability of VPA doses in females at level of hepatobiliary output, with higher bioavailability of VPA than in men. Clinical observation was that female, despite receiving lower doses than male, obtained similar absolute VPA concentrations as males and were over-represented among the cases where the measured serum concentration was above the therapeutic reference range.

As concern renal excretion, women have slower elimination than men and that has the potential to prolong the half-life of Li^{++} thus increasing its plasma levels; for this reason, women usually request a lower oral dose than men to obtain the same therapeutic range (Barnes and Mitchell, 2005). A recent study by Tondo et al. (Tondo et al., 2017) evaluating the effects of long-term Li^{++} treatment on Glomerular Filtration Rate (GFR) and other metabolic parameters in a sample of 312 BD patients, showed that lower estimated GFR (eGFR) were significantly associated with female sex. Moreover, the rate of decline of eGFR with age and exposure to lithium was steeper in women than men and

women also had more frequently advanced stages of chronic kidney disease (stage 2, 3,4) than men (stage 1).

Several lines of investigations suggested that Li^{++} ion is handled differently by the cells of patients affected by mood disorders. Specifically, a greater accumulation of Li^{++} ion in erythrocytes (higher erythrocyte lithium ratio) as well as in the total body (greater lithium retention) has been reported in subgroups of patients during manic and depressive episodes (mainly manic), in lithium toxicity (mainly neurotoxicity), and in good lithium responders (Amsterdam et al., 1988). While it is administered as a drug, it can replace the Sodium (Na^+) in the Na^+-Na^+Counter-transport system becoming Li^{++}-Na^+ Counter-transport (LSC). This replacement could reflect the co-transport of the cation in a transport system in which this is not the main function (Birch et al., 1974, Duhm and Becker, 1977). Some studies (Adebayo et al., 1997, Padgham et al., 1994) have analyzed the activity of the LSC in relation to the menstrual cycle, finding a catamenial variation of the maximum speed (Vmax). Adebayo et al. (1997) measured external sodium-stimulated Li^{++} efflux in erythrocytes, blood pressure and estradiol and progesterone plasma levels during menstrual, mid cycle and luteal phases in 22 healthy, non-treated females (30.7±1.8 years) with regular menstrual cycles. Na^+-Li^{++} counter-transport activity (activity in 140 mmol/l external NaCl) in the midcycle phase was lower than in the menstrual ($P<0.030$) and luteal ($P<0.030$) phases. The Vmax of the transporter changed similarly, but the affinity of the transporter for external sodium was unaltered. There was no catamenial correlation between plasma estradiol and LSC activity or Vmax, but plasma progesterone was positively correlated with LSC activity ($r=0.478$, $P<0.025$, $n=22$) and Vmax ($r=0.551$, $P<0.045$, $n=14$) in the luteal phase. Padgham et al. (1994) studied 10 healthy menstruating women and 8 oral contraceptives using (21+7-day regimen); the first group has been studied over at least one cycle. Authors found a correlation ($p<0.02$) between LSC rate and the premenstrual symptoms severity score, but only in the premenstrual phase in healthy women without contraceptive pills. Cyclical fluctuations in both groups were observed in the LSC rate although the groups were too small to show statistical significance.

These evidences underlie the importance of establishing the menstrual cycle phase during the study of the pharmacokinetic properties of psychotropic drugs.

To the best of our knowledge, disruption of Li^{++} steady-state kinetics involved in premenstrual phase is not known and the extent to which such disruption accounts for vulnerability to relapses in bipolar women requires further investigation. Experiencing mood destabilization, especially during premenstrual phase, in BD women could be partly due to reproductive hormones fluctuations and it could represent a marker of a more recurrent and symptomatic course of illness. This is corroborated by a longitudinal study (Dias et al., 2011) that reported premenopausal women with BD to have more premenstrual exacerbation in mood symptoms and more recurrent mood episodes. They had more severe depressive and mood elevation symptoms during follow-up, reflecting greater symptom burden period, and a halved time to relapse defined more broadly as a syndromic or sub syndromic episode.

In conclusion, compelling evidence highlights that some women with mood disorders complain of worsening during the late luteal phase of the menstrual cycle. Since one explanation of symptoms exacerbation might be a fluctuation of Li^{++} and VPA serum levels concurrent with cyclic hormonal fluctuations, clinical studies performing serial assays of these mood stabilizers serum concentrations correlated to psychopathological state throughout the menstrual cycle could be helpful. Moreover, pharmacokinetic gender differences should be assessed to better explain the relationship between catamenial fluctuations and mood changes in some women. Finally, a better understanding in this field could improve the clinical practice adopting new therapeutic strategies to counteract the distress related to premenstrual phase in BD women.

Authors (Year) Country	Study design	Drugs type (oral dosage ranges)	Sample/Menstrual cycle type	Drug levels determination	Results	Limitations
Libusova et al. (1975) Praha	Preliminary report	Li^{++} (600-1500 mg/day; serum Li^{++} levels ranged between 0.5 to 1.0 mEq/L)	35 women with periodic affective psychosis on prophylactic Li^{++} treatment for at least two years: 30 with regular menstrual cycle; 5 in climacteric period; none with OC use. The type of menstrual cycles was studied by measuring basal temperature (ovulational/anovulational cycles).	Serum Li^{++} levels explored twice a week for 3 months; Li^{++}level in blood and urine examined in 7-day intervals in the last 3 months. Blood and urine sampling were done 24-48 hrs before and after the menstruation.	Serum Li^{++} levels significantly decreased 48 and particularly 24 hrs before menstruation ($p=0.01$).	Small sample size
Kukopulos et al. (1985) Berlin	Longitudinal single case study	Li^{++} (600 mg/day)	28-year-old BD woman with a premenstrual (hypo)manic-depressive cycle which improved with menstruation. Regular menstrual cycle. No OC use. Daily determination of sexual hormones (estradiol and progesterone) in serum during the hospitalized periods.	Serial assays for 84 days of Li^{++} concentration on blood (3 blood samples were taken daily, i.e. at 9.00 a.m., between 2.00 and 4.00 p.m., and between 10.30 and 12.00 p.m.), urinary sample and on red blood cells.	Regular and inverse relationship between Li^{++} serum level and mood changes, although the patient received the same dosage of Li^{++}: highest values (1.10 mmol/l) detected at the time of the greatest intensity of depression (the 2 days prior to onset of menstruation); lowest values (0.30 mmol/l) during the time of hypomania (luteal phase).	Single case
Conrad & Hamilton (1986) Washington	Case report	Li^{++} (1500-1800 mg/day)	16-year-old female with BD (mixed episode with psychotic features). Regular menstrual cycles. No OC use.	Blood Li^{++} levels explored during the premenstrual phase (5-10 days preceding the onset of menses).	Serum Li^{++} concentration decreased from the 1.0-1.2 mEq/L maintenance range to 0.6-0.8 mEq/L during premenstrual phase, with concomitant symptom exacerbation. The administration of higher Li^{++} oral doses during the premenstruum (1.4-1.8 times the usual maintenance dose) was well tolerated and blunted symptoms.	Single case
Chamberlain et al. (1990) Canada	Case-control study	Li^{++} (single oral dose 300 mg)	13 healthy women: 6 with regular menstrual cycle; 7 with OC use.	Li^{++} serial assays were dole out before administration of drug and then every half-hour for 4 hours, hourly for the next 8 hours, and 24 hours after ingestion of a single dose of Li^{++}. Women with spontaneous menstrual cycles were studied during the mid-follicular, mid luteal,	Representative curves of Li^{++} serum concentration over time were overlapping independently of the menstrual cycle and the OC interference	Small sample size

				and late luteal phase, while those taking OC in the first and in the third week during active pill, and early in the week of bleeding after withdrawal.		
Herzog et al. (2009) Boston	Cross sectional observational study	VPA	48 epileptic women treated with VPA (24) or LTG (24). 24 women with regular menstrual cycle; 24 with OC (22 monophasic and 2 triphasic). For women with spontaneous menstrual cycle, menstrual phase was determined by reproductive steroid (estradiol and progesterone) levels.	Serum levels assessed twice (between days 20-24 and between days 3-7 of menstrual cycle or during the third week of active pill use and at the end of the week of the inactive pill use)	Women with regular menstrual cycle and without OC showed a not significant decline (8,3%) of VPA level during the mid-luteal phase compared to the early-mid follicular phase.	Small sample size; oral dosages unknown

Table 1 Clinical studies on the relationship between Lithium and Valproate serum levels and menstrual cycle phases

BD = Bipolar Disorder; OC = Oral Contraceptives; VPA = Valproic Acid; LTG = Lamotrigine; Li^{++} = Lithium

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Figure 1

Figure 1-PRISMA flow diagram of the selected and included studies.