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Lithium in the Treatment of Premenstrual Dysphoric Disorder: A Case Report

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ABSTRACT

Premenstrual dysphoric disorder (PDD) is characterized by mental, physical and cognitive symptoms that occurs in the late luteal phase of the menstrual cycle and regresses in the week following menstruation. In PDD, serotonin reuptake inhibitors and combined contraceptives are the primary pharmacologic treatments. In cases where there is a personal or family history of bipolar disorder (BD), the use of antidepressants may pose a risk of inducing manic episodes. The frequent coexistence of BD and PDD, the fact that both diseases are cyclic in nature and that common mechanisms such as hormonal changes play a role in their aetiologies, suggest that lithium might be efficacious in the treatment of PDD. Here, we present a case who didn't have a BD but a family history of BD and was treated with lithium monotherapy for PDD with a successful outcome. In cases where first- and second-line therapies cannot be used or no response is obtained in PDD patients, pharmacological agents that have demonstrated efficacy in preventing mood episodes among first-degree relatives, may present a viable solution.

Keywords: Antidepressive Agents, Drug Therapy, Lithium, Premenstrual Dysphoric Disorder, Premenstrual Syndrome

INTRODUCTION

Premenstrual Dysphoric Disorder (PDD), the severe form of Premenstrual Syndrome (PMS) causing significant impairment in functionality, was first defined in the DSM-IV and classified under the category of mood disorders in the DSM-V. PDD presents during the late luteal phase of the menstrual cycle, regressing in severity in the week following menstruation, with a clinical profile comprising at least one affective (depressive mood/hopelessness, tension, anxiety, emotional lability, irritability/anger) and at least one somatic (decreased interest, difficulty in concentrating, decreased energy, appetite changes, insomnia or excessive sleep, feeling overwhelmed, joint/muscle pain, bloating, sensation of weight gain, breast tenderness) symptom among 11 specified symptoms, with at least 5 being present. Diagnosis of PDD should be confirmed through prospective daily evaluations over a minimum of 2 symptomatic menstrual cycles. Symptoms of PDD are of such intensity as to cause impairment in social relationships and in functionality in occupational/school or family life (American Psychiatric Association 2013).

The prevalence of PDD varies between 3% and 8% (de Carvalho et al. 2018). Although PDD can be seen in women without other psychiatric disorders, 30% to 70% of cases are accompanied by anxiety disorders, major depression and bipolar disorder (BD) (Sepede et al. 2016). Research indicates that women diagnosed with PMS or PDD are more likely to receive a diagnosis of BD-I or BD-II, and women with BD-II are at a higher risk of having PMS or PDD (Cirillo et al. 2012, Slyepchenko et al. 2021).

In patients with PDD without psychiatric comorbidity, selective serotonin reuptake inhibitors (SSRIs) and combined contraceptives are considered primary pharmacological treatments (Carlini and Deligiannidis 2020, Sepede et al. 2016). However, the use of SSRIs in the presence of comorbid BD poses a risk of antidepressant-induced manic shift (Nevatte et al. 2013). In cases of comorbid BD and PDD, the use of mood stabilizers is the initial step to stabilize BD and differentiate whether symptoms are attributable to PDD or to premenstrual exacerbation of BD (Sepede et al. 2020). Karadag et al. (2004) examined menstrual symptom changes in 34

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patients diagnosed with BD who responded to lithium and/or valproate treatment and were in euthymic state, compared to 35 healthy controls, using the Daily Record of Severity of Problems-Short Form and Premenstrual Assessment Form (Karadag et al. 2004). Both retrospective and prospective evaluations indicated that euthymic BD patients experienced fewer mood and behavioral changes during the premenstrual period compared to the control group, suggesting that mood-stabilizing treatment may have a prophylactic effect against premenstrual symptoms (Karadag et al. 2004). D'Mello et al. (1993) reported two cases of premenstrual mania responding to lithium, emphasizing the importance of investigating the link between BD and PDD as it may provide clues to the etiology of both conditions (D'Mello et al. 1993). Studies by Singer et al. (1974) and Steiner et al. (1980) reported that lithium at doses ranging from 600 to 1000 mg per day was ineffective in treating behavioral premenstrual symptoms in the majority of women (Singer et al. 1974, Steiner et al. 1980). However, Sletten and Gershon (1966) reported 8 cases where lithium reduced premenstrual symptoms (Sletten and Gershon 1966). They suggested that some PMS patients benefiting from lithium have first-degree relatives with affective disorders, potentially classifying these patients as "subsyndromal affective disorders" and thus benefiting from lithium (Sletten and Gershon 1966). However, these studies were conducted before the 1980s, when there was no systematic classification for PDD as there is today.

CASE

In this report, a case of PDD who had no accompanying physical or mental illness and who had a family history of BD and was successfully treated with lithium is presented. The patient is a 43-year-old married woman, a university graduate, and a mother of one child. She reported experiencing breast tenderness and irritability during the premenstrual period since her early twenties, with these symptoms subsiding shortly after menstruation. Approximately 15 years ago, during a period of intense life stress, she began experiencing symptoms such as depressed mood, tension, irritability, mood swings, loss of interest, apathy, fatigue, excessive sleepiness, and loss of appetite about one week before menstruation, leading to impairment in performing household chores and caring for her child. She found it increasingly difficult to get out of bed in the morning and eventually became unable to go to work, resulting in obtaining numerous sick leave reports. She reported that her symptoms began to alleviate shortly after menstrual bleeding commenced and disappeared within a week. Subsequently, similar complaints recurred almost every menstrual cycle. After one year, the patient presented to our psychiatric outpatient clinic and was prospectively monitored daily for two consecutive symptomatic cycles, confirming the diagnosis of PDD. In her family history, her father had been diagnosed with BD at the age of 23, with one mixed and one manic episode requiring hospitalization, unresponsive to valproate treatment. For approximately seven years, her father had been regularly using lithium monotherapy at a dose of 1200 mg/day and had been in remission. The patient was initiated on fluoxetine 20 mg/day, which was used for seven weeks with no response observed during two premenstrual cycles. Subsequently, sertraline was started at 50 mg/day, increased to 100 mg/day after four weeks, and the patient was followed for three menstrual cycles without any change in symptoms. Duloxetine was then initiated at 30 mg/day, increased to 60 mg/day during the next menstrual period, and monitored for premenstrual symptoms for eight weeks over two menstrual cycles, but no significant response was obtained. No manic or hypomanic shift was observed in the patient during or after antidepressant treatment. The patient, whose symptoms persisted, was referred to the gynecology and obstetrics outpatient clinic. Combined oral contraceptive therapy was recommended to the patient, but she refused this treatment due to the history of stomach cancer in her mother and colon cancer in her grandfather, considering the possibility of cancer development in herself in the future. The patient, who continued to attend psychiatric outpatient follow-ups and had a positive response history to lithium in her father, was started on lithium treatment. As premenstrual symptoms persisted, a dose increase of 300 mg/day was made during each of the two menstrual cycles, gradually increased to 1200 mg/day, and lithium blood level was measured as 0.8 mEq/L. The patient benefited significantly from lithium treatment at a dose of 1200 mg/day, with premenstrual symptoms decreasing from the first menstrual cycle after reaching this dose and completely disappearing from the third menstrual cycle onwards. One year later, an attempt was made to reduce the lithium dose, however, when the dose was reduced to 600 mg/day and the lithium blood level was measured as 0.4 mEq/L, the patient's symptoms recurred. Premenstrual symptoms receded again from the third menstrual cycle after increasing the dose to 1200 mg/day and restoring the lithium blood level to 0.8 mEq/L. In the following years, lithium dose was attempted to be reduced twice more, however, due to the recurrence of symptoms, the patient insisted on using lithium at a dose of 1200 mg/day. The patient has been using lithium at the same dose for 4 years, and lithium blood level is measured every three months, ranging from 0.7 to 0.9 mEq/L, and the patient is in remission with this treatment. The patient, who had difficulty fulfilling her professional, social, and family responsibilities and was negatively affected in terms of functionality before starting lithium treatment, began to fulfill her responsibilities without difficulty after lithium treatment. No mood attacks or adverse effects related to lithium use developed in the patient during the follow-up period.

DISCUSSION

BD typically manifests in women during adolescence and early adulthood, generally between 15 to 23 years, when hormonal changes mark the onset of reproductive age (Slyepchenko et al. 2021). Rapid cycling, mixed features, and a higher prevalence of BD-II are more commonly observed in women compared to men (Slyepchenko et al. 2021). A significant proportion of women diagnosed with BD experience mood symptoms to varying degrees during the premenstrual period, similar to other periods characterized by hormonal fluctuations such as pregnancy, postpartum, and menopause (Slyepchenko et al. 2021). The symptom cluster resembling mixed features and the rapid cycling nature of PDD share descriptive characteristics with BD, suggesting clinical similarities between the two conditions. The frequent co-occurrence of BD and PDD, the similarity in clinical presentations, and the exacerbation of symptoms during the premenstrual period in some patients with BD raise the possibility of shared etiological factors in these disorders (Sepede et al. 2020).

Although the etiology of PDD has not been fully elucidated, it is thought that the underlying mechanism involves cyclic changes in sex steroids triggering dysregulation of the serotonergic system (Freeman and Sondheimer 2003). It is known that mood disorders such as BD can also be influenced by changes in steroid sex hormones (Teatero et al. 2014). Sensitivity to changes in sex hormones in some women may underlie the mood changes observed in both PDD and BD (Teatero et al. 2014). Additionally, BD, seasonal affective disorder, and PDD have been associated with increased sensitivity to suppression of melatonin induced by light, suggesting the involvement of a common chronobiological mechanism in these disorders (Parry et al. 2010).

It is crucial to differentiate between premenstrual exacerbation of BD and PDD for the management of treatment. The fact that our case's symptoms began only a week before menstruation and subsided in the week following menstruation, the absence of mental symptoms outside these periods, the absence of a history of manic or hypomanic episodes, the absence of manic shift with antidepressant treatment, all distance us from the possibility of premenstrual exacerbation of BD.

Treatment of PDD is challenging and controversial, especially in the presence of a family history of BD, as in our case. While SSRIs are considered first-line agents for PDD treatment, the use of antidepressants in such cases is risky in terms of manic shift and should be used with caution. There is a lack of large, controlled studies for other recommended treatments for PDD when hormonal therapy is contraindicated or refused by the patient. Data on the use of mood stabilizers in PDD treatment is limited, mainly based on case reports (Singer et al. 1974, Sletten and Gershon 1966, Steiner et al. 1980). The frequent co-occurrence of BD and PDD, the cyclical nature of both disorders, and the presence of common mechanisms such as hormonal changes have encouraged us to use lithium in PDD treatment. The primary use of lithium is in recurrent mood disorders, especially bipolar disorder (Pisanu et al. 2022). It is debated whether the efficacy of lithium is specific to the disorder or to the symptoms. Lithium has been suggested to be effective not only in bipolar disorder but also in other episodic conditions (Tupin 1972). Thirty percent of BD patients respond excellently to lithium (Duffy et al. 2007). It has been shown that this subset of patients who benefit from lithium have some phenotypic features such as a family history of BD and a positive response to lithium in the family (Duffy et al. 2007). The clustering of both BD and lithium responses in families indicates the importance of genetics in the onset and treatment response of the disease. Monozygotic and dizygotic twin studies have reported similar responses to lithium in both types of twins (Tomar Bozkurt et al. 2018). Given the inherited aspect of lithium response, increasing number of genetic studies are being conducted in this area (Pisanu et al. 2022). Literature review revealed that pharmacogenetic studies evaluating response to lithium share common gene polymorphisms thought to be involved in the mechanism of action of lithium or the etiopathogenesis of bipolar disorder. These genes include the serotonin transporter gene promoter region (5-HTTLPR), brain-derived neurotrophic factor (BDNF), inositol polyphosphate 1-phosphatase (IPPase), inositol monophosphatase (IMPase), bisphosphate nucleotidase (BPNase), fructose 1,6-bisphosphatase (FBPase), phosphoglucotransferase (PGM), GSK3β, mitochondrial DNA, serotonin receptors (5HT2A and 5HT2C), X-box binding protein 1 (XBP1) (Altınbaş et al. 2018, Seretti et al. 2009, Smith et al. 2010). Our case demonstrated successful treatment of PDD with lithium therapy in the presence of a family history of BD. To our knowledge, this is the first case who had a family history of BD but did not have a mental illness other than PD, and who used lithium monotherapy for the treatment of PD and achieved successful results. Considering a pharmacological agent with a positive response in the family when first and second-line treatments are unavailable or ineffective may be an appropriate solution in patients with PDD. There is limited information in the literature on the effects of lithium use on premenstrual symptoms in patients with a family history of BD or PDD. It is thought that studies comparing the frequency and severity of premenstrual symptoms during periods of mood stabilizer use and non-use in patients with both BD and PDD could contribute to the literature. The need for randomized controlled trials in this regard could contribute to the elucidation of the etiopathogenesis of BD and PDD.

REFERENCES

Altınbaş K, Yeşilbaş D, İnce B et al. (2018) Evaluation of the Association between Lithium Treatment and GSK3β Polymorphism in Bipolar Disorder Patients. Turkish Journal of Psychiatry 29: 73-8.

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders. 5th Ed. American Psychiatric Association, Washington DC.

Carlini SV, Deligiannidis KM (2020) Evidence-Based Treatment of Premenstrual Dysphoric Disorder: A Concise Review. J Clin Psychiatry 81: 19ac13071.

Cirillo PC, Passos RBF, do Bevilaqua MCN et al. (2012) Bipolar disorder and Premenstrual Syndrome or Premenstrual Dysphoric Disorder comorbidity: a systematic review. Braz J Psychiatry 34: 467-79.

de Carvalho AB, Cardoso TA, Mondin TC et al. (2018) Prevalence and factors associated with Premenstrual Dysphoric Disorder: A community sample of young adult women. Psychiatry Res 268: 42-5.

Duffy A, Alda M, Milin R et al. (2007) A consecutive series of treated affected offspring of parents with bipolar disorder: is response associated with the clinical profile? Can J Psychiatry 52: 369-76.

D'Mello DA, Pinheiro AL, Lalinec-Michaud M (1993) Premenstrual mania: two case reports. J Nerv Ment Dis 181: 330-1.

Freeman EW, Sondheimer SJ (2003) Premenstrual Dysphoric Disorder: Recognition and Treatment. Prim Care Companion J Clin Psychiatry 5: 30-9.

Karadag F, Akdeniz F, Erten E et al. (2004) Menstrually related symptom changes in women with treatment-responsive bipolar disorder. Bipolar Disord 6: 253-9.

Nevatte T, O'Brien PMS, Bäckström T et al. (2013) ISPMD consensus on the management of premenstrual disorders. Arch Womens Ment Health 16: 279–91.

Parry BL, Meliska CJ, Sorenson DL et al. (2010) Increased sensitivity to light-induced melatonin suppression in premenstrual dysphoric disorder. Chronobiol Int 27: 1438-53.

Pisanu C, Meloni A, Severino G et al. (2022) Genetic and Epigenetic Markers of Lithium Response. Int J Mol Sci 23: 1555.

Sepede G, Sarchione F, Matarazzo I et al. (2016) Premenstrual dysphoric disorder without comorbid psychiatric conditions: a systematic review of therapeutic options. Clin Neuropharmacol 39: 241–61.

Sepede G, Brunetti M, Di Giannantonio M (2020) Comorbid Premenstrual Dysphoric Disorder in Women with Bipolar Disorder: Management Challenges. Neuropsychiatr Dis Treat 16: 415-26.

Seretti A, Drago A, De Ronchi D (2009) Lithium Pharmacodynamics and Pharmacogenetics: Focus on Inositol Mono Phosphatase (IMPase), Inositol Poliphosphatase (IPPase) and Glycogen Sinthase Kinase 3 Beta (GSK-3 Beta). Curr Med Chem 16: 1917-48.

Singer K, Cheng R, Schou M (1974) A controlled evaluation of lithium in the premenstrual tension syndrome. Br J Psychiatry 124: 50–1.

Sletten IW, Gershon S (1966) The premenstrual syndrome: A discussion of its pathophysiology and treatment with lithium ion. Compr Psychiatry 7: 197-206.

Slyepchenko A, Minuzzi L, Frey BN (2021) Comorbid Premenstrual Dysphoric Disorder and Bipolar Disorder: A Review. Front Psychiatry 12: 719241.

Smith DJ, Evans R, Craddock N (2010) Predicting response to lithium in bipolar disorder: a critical review of pharmacogenetic studies. J Ment Health 19: 142-56.

Steiner M, Haskett RF, Osmun JN et al. (1980) Treatment of premenstrual tension with lithium carbonate: a pilot study. Acta Psychiatr Scand 61: 96–102.

Teatero ML, Mazmanian D, Sharma V (2014) Effects of the menstrual cycle on bipolar disorder. Bipolar Disord 16: 22-36.

Tomar Bozkurt H, Erbasan V, Eğilmez Ü et al. (2018) Clinical, Biological and Genetic Predictors of Lithium Treatment Response. Current Approaches in Psychiatry 10: 405-26.

Tupin J (1972) Lithium use in nonmanic depressive conditions. Compr Psychiatry 13: 209–14.