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CASE REPORT
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Low-Dose Acetazolamide in the Treatment of Premenstrual Dysphoric Disorder: A Case Series

Gabriele Sani[1,2] ✉, Georgios D. Kotzalidis[1], Isabella Panaccione[1,3], Alessio Simonetti[1,2], Lavinia De Chiara[1,2], Antonio Del Casale[1], Elisa Ambrosi[1], Flavia Napoletano[1,2], Delfina Janiri[1], Emanuela Danese[1], Nicoletta Girardi[1], Chiara Rapinesi[1], Daniele Serata[1], Giovanni Manfredi[1,2], Alexia E. Koukopoulos[1,2], Gloria Angeletti[1,2], Ferdinando Nicoletti[3,4], and Paolo Girardi[1,2,5]

[1]NESMOS Department (Neuroscience, Mental Health, and Sensory Organs), Sapienza University, School of Medicine and Psychology, Sant'Andrea Hospital, Rome, Italy
[2]Centro Lucio Bini, Rome, Italy
[3]IRCSS NEUROMED, Pozzilli, Isernia, Italy
[4]Department of Physiology and Pharmacology "Vittorio Erspamer", Sapienza University, School of Medicine and Psychology, Rome, Italy
[5]Clinica Neuropsichiatrica Villa Rosa, Suore Ospedaliere del Sacro Cuore di Gesù, Viterbo, Italy

The treatment of premenstrual dysphoric disorder (PMDD) is far from satisfactory, as there is a high proportion of patients who do not respond to conventional treatment. The antidiuretic sulfonamide, acetazolamide, inhibits carbonic anhydrase and potentiates GABAergic transmission; the latter is putatively involved in PMDD. We therefore tried acetazolamide in a series of women with intractable PMDD. Here, we describe a series of eight women diagnosed with DSM-IV-TR PMDD, five of whom had comorbidity with a mood disorder and one with an anxiety disorder, who were resistant to treatment and responded with symptom disappearance after being added-on 125 mg/day acetazolamide for 7-10 days prior to menses each month. Patients were free from premenstrual symptoms at the 12-month follow-up. We suggest that acetazolamide may be used to improve symptoms of PMDD in cases not responding to other treatments. GABAergic mechanisms may be involved in counteracting PMDD symptoms. **Psychiatry Investig 2014;11:95-101**

Key Words Premenstrual dysphoric disorder, Sulfonamide diuretics, Acetazolamide, GABA transmission.

INTRODUCTION

Experiencing emotional and physical symptoms during the premenstrual phase is common in most women. More than 80% of reproductive-age women suffer from symptoms during the luteal phase of their ovarian cycle.[1,2] Usually these symptoms are mild, however, they can be severe enough to affect social, working and family life in a minority of patients.[2-8]

A premenstrual tension syndrome was recognized in the early '30s[9] and attributed to rejected fantasies of motherhood, but also related to the activity of the corpus luteum.[10] The syndrome concept was further refined and renamed as premenstrual syndrome (PMS) in the early '50s,[11] but despite this, specific diagnostic criteria were lacking.[12] In 1987, the DSM-III-R introduced diagnostic criteria for "late luteal phase dysphoric disorder" and clearly defined the syndrome;[13] this syndrome was re-named as "premenstrual dysphoric disorder" (PMDD) in the DSM-IV.[6] Less rigorous definitions of PMS were provided by the World Health Organization's International Classification of Diseases (ICD-10),[14] the American College of Obstetricians and Gynecologists,[15] and the Royal College of Obstetricians and Gynaecologists.[16] Recently, a consensus group has proposed new criteria, relevant for research purposes.[17]

Differences in classification criteria for PMS led to significant variations in estimated prevalence; using the restrictive criteria of the American College of Obstetricians and Gynecologists,[15] PMDD is considered to affect at least 3-8% of reproductive-age women, whereas using broader criteria, the prevalence of PMS rises to 30-40%.[18]

Despite PMDD treatment includes a wide range of thera-

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✉ **Correspondence:** Gabriele Sani, MD
NESMOS Department (Neuroscience, Mental Health, and Sensory Organs), Sapienza University, School of Medicine and Psychology, UOC Psichiatria, Sant'Andrea Hospital, Via di Grottarossa 1035-1039, 00189 Rome, Italy
Tel: +39-0633775951, **Fax:** +39-0633775342
E-mail: gabriele.sani@uniroma1.it

peutic options, only few of them are backed by clinical evidence. Selective serotonin reuptake inhibitors (SSRIs) proved to be superior to placebo in several studies[19,20] and have a first-line indication, despite recent questioning of their effectiveness.[21] Treatment with nonSSRI antidepressants[22-24] and lithium[25] failed to relieve symptoms. Among anti-anxiety agents, alprazolam obtained inconsistent effects,[26-29] while buspirone showed weak efficacy.[30,31] Suppression of ovulation with oral contraceptives like the drospirenone/ethinylestradiol combination,[32-34] GnRH agonists,[35] the synthetic steroid 17alpha-ethinyl testosterone,[36] or ovariectomy,[37,38] significantly reduces or eliminates symptoms. Other treatments include diuretics, such as spironolactone,[39] and non-steroidal anti-inflammatory drugs (NSAIDs),[40,41] that are shown to reduce symptoms such as bloating, pain and headache. Nonpharmacological treatments, such as dietary supplements, physical exercise,[42] and cognitive-behavior therapy[43,44] may likewise be helpful.

Acetazolamide, like other sulfonamides such as methazolamide, zonisamide and sulthiame, is a potent inhibitor of carbonic anhydrase (CA). CA is an enzyme catalyzing the reversible reaction in which carbon dioxide (CO_2) and water (H_2O) are converted to carbonic acid (H_2CO_3), which in turn dissociates in hydrogen ion (or proton, H^+) and bicarbonate (HCO_3^-). While originally developed as a diuretic drug, acetazolamide has been used to treat seizures since the discovery of the presence in the brain of a specific isoform of carbonic anhydrase, CA VII,[45] which appears to be involved in the regulation of GABAergic transmission.[46] Interestingly, GABAergic dysfunction appears to be involved in animal paradigms of PMDD.[47] Approval for its use in epilepsy dates back to 1953. Acetazolamide is primarily used in combination with other antiepileptic medications and also in refractory absence, partial, myoclonic and primary generalized tonic-clonic seizures.[48] It has also been used to treat catamenial epilepsy.[49]

Acetazolamide has been proved to be effective in the treatment of several other diseases, such as glaucoma,[50] idiopathic intracranial hypertension *(pseudotumor cerebri)*,[51] mountain sickness,[52] central sleep apnea,[53] hypokalemic periodic paralysis.[54] Interestingly, there are several papers in the literature reporting the efficacy of acetazolamide in the treatment of atypical psychoses,[55] menstrual cycle-related fluctuations in Parkinson's disease,[56] bipolar affective disorders,[57] and acute mania in a patient with bipolar disorder.[58]

On this basis, we tried acetazolamide as an adjunctive medication in women with or without mood disorders suffering from PMDD symptoms.

CASE

All patients were personally treated by one of the authors (G.S.) and were followed for a mean period of 23.1 months (range 10−36, SD 11.24). Six patients had an axis I psychiatric disorder comorbid with DSM-IV-TR Premenstrual Dysphoric Disorder (PMDD), while two had PMDD only. Before making PMDD diagnosis, patients had to fill-out a daily symptom chart[59] for at least four months. We used the Italian version of Temperament Evaluation of Memphis, Pisa, Paris and San Diego-autoquestionnaire version (TEMPS-A).[60] No patient was receiving estrogens or progestins. After specific psychiatric drug treatment, all patients had fully recovered from their comorbid psychiatric disorder, but continued to experience PMDD symptoms before the introduction of acetazolamide. All patients took acetazolamide monthly for a 7-to-10-day period before menses. All patients signed free, informed consent for both treatment and publication of their cases.

Case 1

A 34-year-old single, childless Caucasian woman with a cyclothymic premorbid temperament, suffered from a severe form of PMDD since her adolescence. For more than 10 years she had abused substances (mainly cocaine) and alcohol. Her mood was consistently unstable, with bouts of self-inflicted injuries (self-cutting of the whole body), eating disorder (bulimia with self-induced vomiting) and impulsiveness, meeting DSM-IV-TR criteria for Borderline Personality Disorder. She had voluntarily interrupted a pregnancy when she was 32.

In the last two years, she had stopped drug and alcohol abuse, but her clinical picture remained as before. We instituted therapy with lithium up to 600 mg/day, maintaining lithium blood levels up to 0.6 mEq/L, while slowly titrating lamotrigine up to 200 mg/day.

Her mood stabilized after six months of treatment, with the exception of the period before menses. According to the diary chart, during this period she experienced depressive feelings, severe anxiety, irritability, insomnia, binge eating, desperate crying spells, desire of self-cutting. Her Clinical Global Impressions severity scale score (CGIs) was 6. All symptoms lasted for 7−10 days and disappeared suddenly by the first day of menses. Three months later, we added 125 mg/day acetazolamide, with intermittent monthly intake limited from ten days before the menses to the first day of menses. Since the first month, PMDD symptoms improved significantly (CGIs, 2), while no significant adverse event occurred. However, blood pressure slightly decreased, from 110/80 mm Hg to 100/70 mm Hg. After one year of treatment, the patient continues on add-on acetazolamide and is free from premenstrual symptoms (CGIs=1).

Case 2

A 29-year-old, single, nulliparous Caucasian woman with

cyclothymic premorbid temperament and DSM-IV-TR diagnosis of Bipolar Disorder, type II, had severe PMDD since her teens. The bipolar onset may be traced back to age 15, when she had a first depressive episode. Since then, she had four depressive and three hypomanic episodes. She took several antidepressant drugs with little benefit.

Since the onset of PMDD, she had developed feelings of worthlessness and emptiness, a bleak outlook of future, and an imminent sense of death.

We treated her bipolar disorder with lithium up to 450 mg/day (lithium blood levels, up to 0.7 mEq/L) and oxcarbazepine up to 600 mg/day. Her mood stabilized after four months of treatment. Nevertheless, as emerging from the daily diary, important PMDD symptoms persisted. During the late luteal phase of the menstrual cycle, she was profoundly depressive, hopeless, hypersensitive and emotional, irritable, and unable to make any plan for the future (CGIs, 6). Acetazolamide 125 mg/day was added. The patient took the medication monthly for a 10-day period before menses. PMDD symptoms subsided soon (CGIs, 1). After three months of treatment, the patient stated she was living one more week per month compared to before. No side effects emerged. Improvement still persists at the 12-month follow-up.

Case 3

A 31-year-old, single, nulliparous Caucasian woman with cyclothymic premorbid temperament and DSM-IV-TR Bipolar Disorder, type II, had suffered from PMDD since her adolescence. PMDD was characterized by depressive mood, apathy, hypersomnia, anxiety, severe irritability and inner tension, impossibility to concentrate, fatigue, loss of interest in normal activities, crying, and severe binge eating. Her bipolar onset dates back to her twenties, when she presented with a first hypomanic episode. Since then, she had three depressive and four hypomanic episodes. She sporadically took antidepressant drugs.

We introduced lamotrigine up to 150 mg/day and immediate release quetiapine 100 mg/day to treat her mood disorder. Bipolar symptoms subsided after eight months of treatment, but PMDD persisted. On the diary, she reported that the above described picture of PMDD emerged during the pre-menstrual phase (CGIs, 5) and abruptly disappeared with menses. We added 125 mg/day acetazolamide. After the second month of treatment, PMDD started to improve, and had completely subsided by the fourth month of treatment (CGIs, 1). No side effects were reported.

One year later, the patient was fully asymptomatic. However, when she skipped acetazolamide one month, she re-experienced exactly the same PMDD syndrome as before. The next month, the patient reintroduced treatment, and this was followed by complete symptom resolution.

Case 4

A 30-year-old, single, nulliparous Caucasian woman with hyperthymic premorbid temperament and DSM-IV-TR recurrent major depressive disorder since age 20, had PMDD preceding her mood disorder by two years. A total of four depressive episodes occurred in ten years; these were characterized by depressive mood, initial insomnia, restlessness, and anxiety, but also by mixed features, such as racing and crowded thoughts, increased energy level, goal directedness, and inner tension. She had received trials with selective serotonin reuptake inhibitors (SSRIs).

We treated her for her mood disorder with oral amitriptyline, 50 mg/day, and oxcarbazepine, titrated to 600 mg/day. After three months of treatment, her mood stabilized. During the pre-menstrual period, however, she continued to experience low mood, hypersomnia, fatigue, anxiety, irritability, feeling of being overwhelmed, and concentration difficulties (CGIs, 5). We added acetazolamide 125 mg/day, for ten days before menses. After the first month of treatment, PMDD improved, resolving completely by the second month of treatment (CGIs, 1). No side effects occurred. After one-and-a-half year of add-on acetazolamide the patient has no premenstrual symptoms (CGIs=1).

Case 5

A 35-year-old, Caucasian, woman with two children of 9 and 8 years of age, with a cyclothymic temperament and without a DSM-IV-TR axis I diagnosis, had suffered since adolescence from PMDD, characterized by mood swings, severe irritability, desperate crying spells, hopelessness and inner tension during the days immediately preceding menstruation. The patient was psychotropic medication-naïve. PMDD was absent during pregnancies.

The patient filled-out the daily symptom diary for three consecutive months and reported the above-mentioned symptoms during the 10 days before menses (CGIs, 6). Acetazolamide 125 mg/day was added during the critical days. Right after the first month of treatment she no more experienced the usual symptomatology (CGIs, 1), and reported no side effect. When she suspended premenstrual treatment with acetazolamide for two months PMDD reappeared as before. PMDD resolved completely when treatment was initiated again. No side effects occurred. The patient has already completed 14 months with add-on acetazolamide and is fully asymptomatic (CGIs=1).

Case 6

A 43-year-old, single, nulliparous Caucasian woman with

a premorbid cyclothymic temperament developed since early adulthood intermittent periods of unpredictable mood fluctuations, causing her problems in her personal and professional life and leading to severe impairment of the social and work domains. She received DSM-IV-TR diagnosis of Cyclothymic Disorder. Her PMDD had its onset at early puberty, with depressive mood, inner tension, affective lability, decreased interest in usually pleasurable activities, irritability, and sense of being out of control. Symptoms occurred during the luteal phase, some days after ovulation, and ended few days after onset of menses. She described this intense and painful state as "the worst pain ever experienced".

She received gabapentin 600 mg/day. The amplitude of mood swings diminished from the first month, with mood reaching stabilization after five months of treatment. Nevertheless, the diary completed during follow-up showed that treatment was ineffective in reducing the luteal phase symptoms (CGIs, 7). Premenstrual symptom persistence for more than two consecutive cycles allowed us to diagnose PMDD. We added 125 mg/day acetazolamide during the critical days. Symptoms improved quickly during the next month (CGIs, 2), leading to complete remission within three months. No side effects were reported whatsoever, and the patient is still asymptomatic after twelve months of add on acetazolamide (CGIs=1).

Case 7

A 39-year-old, single, nulliparous Caucasian woman, with cyclothymic/anxious temperament, suffered from severe PMDD since the age of 12. The premenstrual syndrome consisted in depressed mood, anxiety, difficulty in concentrating, and decreased interest in usually pleasurable daily activities.

At age 30, she began suffering from episodes of tachycardia, sweating, tremors, feelings of choking, and wheezing. Symptoms recurred frequently through the following years, forcing her to ask for a companion when she had to leave home or for activities like driving a car. This led to impaired social and working life. She received a diagnosis of DSM-IV panic disorder with agoraphobia. She tried several antidepressants, with no apparent benefit. When she came to our attention, we introduced 200 mg/day gabapentin and 0.5 mg/day clonazepam, while gradually discontinuing the SSRI antidepressant she was taking. Frequency and intensity of panic attacks diminished, to disappear completely after four months. Nevertheless, according to the daily diary, symptoms beginning typically few days after ovulation and ending with onset of menses remained unchanged (CGIs, 6). Hence we added during the luteal phase, i.e., 10 days before menses, 125 mg/day acetazolamide. The following month premenstrual symptoms improved (CGIs, 2) and completely disappeared after three months of treatment. She reported no side effects. More than one year after the introduction of add-on acetazolamide, the patient is premenstrual symptom-free (CGIs, 1).

Case 8

A 32-year-old, Caucasian, nulliparous woman, with cyclothymic premorbid temperament and without a DSM-IV-TR axis I diagnosis, had suffered since adolescence from PMDD, characterized by severe irritability, mood swings, inner tension, desire of "being elsewhere", desperate crying during the days immediately preceding the menstruation. The patient was psychotropic medication-naïve.

The patient filled-out the daily symptom diary for three consecutive months and reported the above-mentioned symptoms during the premenstrual phase (CGIs, 6). Acetazolamide 125 mg/day was added during the critical days. Right after the first two months of treatment she no more experienced the usual symptomatology (CGIs, 1), and reported no side effect.

After four months of treatment she stopped taking the medication and she re-experienced exactly the same PMDD syndrome as before. She resumed acetazolamide intake as scheduled before, and symptoms disappeared once more; after further nine months of treatment, the patients manifests no premenstrual symptoms (CGIs, 1).

DISCUSSION

Our observations show dramatic efficacy of low-dose acetazolamide in preventing PMDD symptom onset. The exact mechanism through which acetazolamide exerts this heretofore not described effect is not known; however we can speculate that it might relate to the antiepileptic action of this molecule. Epileptic seizures are caused by abnormal, hypersynchronous neuronal discharges originating in specific group of neurons (focus), usually located in the cerebral cortex, and then spread to other parts of the brain. Despite this phenomenon has been widely studied since long time, the exact neuronal mechanisms by which seizures are initiated are not entirely understood. One of the most common theories is that seizures are due to an excessive excitability of neurons, which is probably caused by ionic imbalance between the concentrations of depolarizing excitatory ions (sodium and calcium influx) and the hyperpolarizing inhibitor ions (chloride influx and potassium efflux). Also, an aberrant regulation of the excitatory (glutamate) and inhibitory (GABA) neurotransmission may contribute to the genesis of this phenomenon. Interestingly, these amino acids show a complex interplay in the central nervous system[61] which is regulated by steroids and are both putatively involved in mood disorders;[62] furthermore, both these mechanisms might be influenced by the action of

CA. In fact, low extracellular concentration of protons is found to be related to high excitatory activity, whereas high concentrations of protons suppress the excitatory activity of the NMDA receptors. CA increases the intracellular concentration of protons by catalyzing the formation of carbonic acid, which in turn dissociates in a proton and carbonic acid; therefore, the inhibition of CA might provide a possible explanation for the anticonvulsant effects of acetazolamide. It should be recalled that premenstrual symptoms often co-occur with bipolar disorder,[63] and that in our sample the most often comorbid condition was bipolar disorder.

It is unclear why our patients all responded to low-dose acetazolamide while not responding to other GABAergic drugs like topiramate and oxcarbazepine. While there is no evidence that oxcarbazepine interferes with CA, topiramate is well-known to inhibit several CA isoenzymes.[64,65] It is unknown whether this has to do with a cyclical pattern of CA concentration, as such pattern has not been found to occur in the erythrocytes of healthy women during their menstrual cycle.[66] However, acetazolamide proved to be effective in catamenial epilepsy, a condition that shares with PMDD its temporal pattern.[49] In this study, many patients improved considerably on acetazolamide, which often was given continuously; the authors argued that a continuous pattern could have induced tolerance to the therapeutic effect of acetazolamide, proposing an administration pattern similar to ours or every other day. In fact, our patients receiving oxcarbazepine did so on a continuous schedule.

Antiepileptic drugs, such as valproic acid, carbamazepine and topiramate are commonly used as mood stabilizers in a variety of psychiatric disorders. It is possible to speculate that the anticonvulsant activity of acetazolamide, like that of other anticonvulsants, has a mood stabilizing effect, even at a subclinical level. We propose premorbid temperament to be important in the pathogenesis of PMDD. According to the DSM-IV criterion C for PMDD, the disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depression disorder, panic disorder, dysthymic disorder or a personality disorder (although it may be superimposed on any of these disorders). All our patients met this criterion.

It could be that both the primary psychiatric disorder and PMDD are rooted in the same constitutional realm, i.e., temperament. Temperament refers to stable behavioral traits with a strong affective hue.

Cyclothymic temperament is the most unstable and the most likely to be involved in cycling course induced by external stimuli[67] and mixed affective states.[68] It was shared by seven out of our eight patients, while only one patient had hyperthymic temperament. We believe that hormonal changes during the luteal phase, which were shown to be associated with PMDD symptoms[69,70] may affect the nervous system of patients with unstable-mood temperaments to a greater extent than other, more stable, temperaments, thus triggering low mood, affective instability, irritability, anxiety, and other PMDD symptoms. Acetazolamide used as monotherapy in milder PMDD forms and as add-on in more severe cases could prevent PMDD symptoms by ameliorating the constitutional and temperamental instability of such patients. This conjecture could provide impetus for future research.

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