Effective Treatment of Premenstrual Violence in Major Depression: Augmentation with Aripiprazole

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Premenstrual exacerbation of major depression is not uncommon. Premenstrual phase-related violence has also been reported. Serotonergic antidepressants, used both continuously and with increased dosage in the late luteal phase, are believed to be effective for major depressive disorder with premenstrual exacerbation. Adding a second medication for non-responder treatment is another treatment option. We present a 38-year-old woman suffering from major depression with premenstrual exacerbation of irritability and uncontrollable violence. The premenstrual exacerbation did not respond to increasing doses of selective serotonin reuptake inhibitor (SSRI) but a combination of an SSRI and late luteal phase aripiprazole was effective for her premenstrual violence. The serotonergic property of aripiprazole provides a synergic effect to SSRI for relieving premenstrual exacerbation of depression. The role of dopamine D₂ as a partial agonist might further add to the effective alleviation of aggression and violence. An antidepressant with aripiprazole augmentation may be a treatment strategy for refractory premenstrual exacerbation and violence. Large-scale double blind placebo-controlled studies to verify efficacy are warranted. (Chang Gung Med J 2008;31:402-6)

Key words: premenstrual syndrome, violence, aripiprazole

CASE REPORT

A 38-year-old married woman, in previous good health, developed depression, energy loss, initial and middle insomnia, poor appetite, indecisiveness and worthlessness four months prior to her first visit to
the psychiatric clinic. She had regular menstruation cycles and no past history of premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) could be traced. She also denied previous suicide or violent acts. A major depressive disorder diagnosis was made in the first interview using a structured clinical interview for DSM-IV-TR axis I disorders (SCID-I). She also scored 17 on the Hamilton Rating Scale for Depression (HAMD21) and 15 on the Hamilton Rating Scale for Anxiety (HAMA). Paroxetine 20 mg per day was prescribed and the patient showed a partial response after eight weeks treatment, with the HAMD21 score decreasing to 10 and the HAMA to 7.

However, the patient reported PME, including decreased ability to concentrate, irritability and uncontrollable violent behavior toward her husband. The above symptoms fully remitted after the onset of the menstruation cycle. We increased the dosage of paroxetine to 40 mg per day for one month but her premenstrual violence did not improve. Therefore, we adjusted the paroxetine dosage back to 20 mg per day and added aripiprazole 10 mg during the last ten days of the luteal phase. This regimen was effective for premenstrual violence, reaching a near complete remission.

The patient discontinued aripiprazole use six months after the late luteal phase combination regimen and the premenstrual violence immediately recurred in the cycle after discontinuation. After the patient resumed aripiprazole use, the premenstrual violence again neared complete remission.

During the treatment course, the patient was asked to rate her violence severity using a Visual Analogue Scale (VAS) in each premenstrual stage. A horizontal line, 100 mm in length, was used. The line was anchored by word descriptors at each end to indicate “not at all” at the left end and “most severe” at the right end. The patient marked on the line the point that represented her perception of her state. The VAS score was determined by measuring in millimeters from the left hand end of the line to the point that the patient marked. The whole treatment course is shown in Fig. 1.

**DISCUSSION**

Agitation and aggression are common disruptive

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Fig. 1 Premenstrual scores of Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), and Visual Analogue Scale for Violence (VAS-V) during one year follow-up.
symptoms in a variety of psychiatric conditions that affect pediatric, adult and elderly patients, and these symptoms are troublesome for both patient and caregiver. Although current studies have not established a cause-effect relationship between premenstrual syndrome or menstruation-related mood changes and aggression, PME of major depression is a clinically well-recognized phenomenon. Certain study results speculate that PME of major depression is actually two disease processes, major depressive disorder and PMDD.

The pathogenesis of PME of major depressive disorder is closely linked to an active hypothalamic-pituitary-gonadal (HPG) axis. Estrogen can up-regulate the expression of the 5HT-1A receptor and estrogen levels decrease during the luteal phase. The combined effects of the premenstrual decrease in estrogen (affecting the 5HT-1 receptor) in a depressive disorder and menstruation-induced elevation of leptin (affecting the serotonin transporters) contribute to worsening premenstrual depression via direct interaction with the serotonin system in the hypothalamus. It is not surprising that an SSRI has become the treatment of choice for improving irritability, depressed mood and dysphoria, as well as improving PME of major depression.

The primary goal when treating PME of major depression is to first treat the major depression continuously with full antidepressant doses. The SSRI dose should be increased for the entire month if PME persists.

For decades, typical antipsychotics and/or benzodiazepines have been the mainstay of treatment for agitation. However, the use of these medications carries the potential for serious and occasionally life-threatening side effects, including extrapyramidal symptoms (EPS), cardiac arrhythmia and neuroleptic malignant syndrome. Aripiprazole is a dopamine D2 partial agonist with serotonin 5HT-1A partial agonist, and 5HT-2A and 5HT-7 antagonist activity. A recently presented analysis of nine U.S. Food and Drug Administration (FDA) registration and post-marketing trials show that aripiprazole is effective for controlling agitation in schizophrenic patients with high baseline levels of agitation, in patients with bipolar mania, and in patients with highly agitated Alzheimer dementia and associated psychosis.

Recent open label studies and retrospective chart reviews report the efficacy of adjunctive aripiprazole for patients with either inadequate response or treatment resistant depression. The results from these studies suggest that the serotonergic property of aripiprazole provides a synergic effect to paroxetine for relieving PME of depression. The role of dopamine D2 as a partial agonist might further add to the effectiveness of alleviating aggression and violence. Therefore, for this patient who did not respond to an increased SSRI dose for menstrual exacerbation, adding aripiprazole, which affects both dopamine and the serotonin system, for late luteal phase augmentation was an effective regimen.

This case report indicates that antidepressants with aripiprazole augmentation may be a treatment strategy for refractory premenstrual violence. Large-scale double blind placebo-controlled studies to verify the efficacy are warranted.

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REFERENCES


Aripiprazole 有效治療憂鬱症的月經前暴力

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憂鬱症的月經前暴力是一個臨床上常見的現象，這樣的惡化是與下視丘-腦下垂體-性腺 (HPG axis) 的週期性波動有關。臨床上也有月經前暴力現象的報告。我們提出一例 38 歲罹患憂鬱症的已婚女性個案，其憂鬱症狀在月經週期的濴期及黃體期前期對抗憂鬱劑 (血清素抑制回收劑) 反應良好，但是仍在月經前 (黃體期後期) 出現月經前暴力行為及憂鬱症狀加劇。我們將血清素抑制回收劑增加，但是對其月經前暴力及月經前憂鬱症狀惡化治療效果不彰，於是我們使用新一陣的抗精神病藥 aripiprazole 於黃體期後期與抗憂鬱劑合併使用。月經前暴力及月經前憂鬱症狀在藥物合併使用後完全緩解。因此我們認爲新一陣的抗精神病藥 aripiprazole 對於憂鬱症的月經前暴力為一有效治療。(長庚醫誌 2008;31:402-6)

關鍵詞：經前症候群，暴力，aripiprazole