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

Yi-Chun Yao[1], MD; Pi-Hui Chiang[3], MS; Mei-Chun Hsiao[1,4], MD; Chia-Yih Liu[1,2], MD

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 D_2 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

Premenstrual exacerbation (PME) of a variety of related disorders, especially mental disorders, has been demonstrated.[1] Nearly 50% of patients with depressive disorders and anxiety disorders in our previous study might experience PME.[2] Premenstrual phase-related violent criminal acts have also been reported.[3] Possible symptom cluster diversity expressed during the premenstrual phase suggests that similar triggers might cause diversified symptoms, depending on the individual's specific vulnerability.[4]

Serotonergic antidepressants, both continuously used and with increased dosage in the late luteal phase, are believed effective for major depressive disorders with PME.[5] However, adding a second medication for the non-responder is another treatment option.[6]

This paper reports a woman, suffering from major depression with PME of irritability and uncontrollable violence, who failed to respond to a selective serotonin reuptake inhibitor (SSRI) but had a fair response to a combination of an SSRI (paroxetine) and an atypical antipsychotic (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

From the [1]Department of Psychiatry; [2]Neuroscience Research Center, Chang Gung Memorial Hospital, Taipei, Chang Gung University College of Medicine, Taoyuan, Taiwan; [4]School of Traditional Chinese Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan; [3]Family Education Graduate School of Chiayi University, Chiayi, Taiwan.
Received: May 7, 2007; Accepted: Aug. 16, 2007
Correspondence to: Dr. Chia-Yih Liu, Department of Psychiatry, Chang Gung Memorial Hospital. No. 5, Fusing St., Gueishan Township, Taoyuan County 333, Taiwan (R.O.C.) Tel.: 886-3-3281200 ext. 2439; Fax: 886-3-3280267; E-mail: liucy752@cgmh.org.tw

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 ($HAMD_{21}$) 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 $HAMD_{21}$ 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.[7] The whole treatment course is shown in Fig. 1.

DISCUSSION

Agitation and aggression are common disruptive

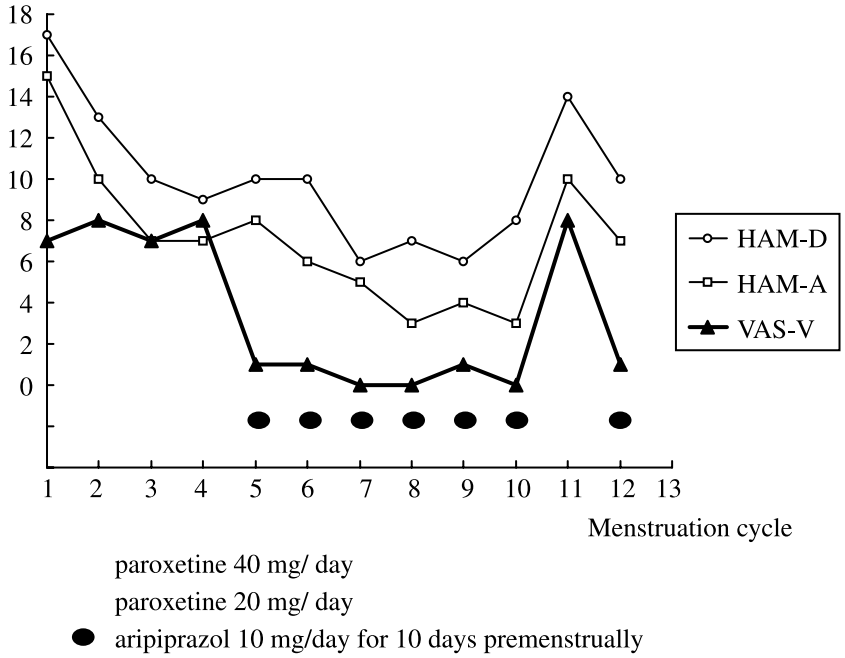

Fig. 1 Premenstrual scores of Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), and Visual Analogue Scale for Violence (VAS-V) during one year follow-up.

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,[8] PME of major depression is a clinically well-recognized phenomenon.[9] Certain study results speculate that PME of major depression is actually two disease processes, major depressive disorder and PMDD.[10]

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.[11] 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.[5]

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 D_2 partial agonist with serotonin 5HT-1A partial agonist, and 5HT-2A and 5HT-7 antagonist activity.[12] 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.[13]

Recent open label studies and retrospective chart reviews report the efficacy of adjunctive aripiprazole for patients with either inadequate response or treatment resistant depression.[14-18] The results from these studies suggest that the serotonergic property of aripiprazole provides a synergic effect to paroxetine for relieving PME of depression.[19] The role of dopamine D_2 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.

Acknowledgements

This paper was supported, in part, by grants from the National Science Council (NSC-90-2314-B-182-054, NSC-91-2314-B-182-049) and Chang Gung Memorial Hospital (CMRP-1267, CMRPG-32106).

REFERENCES

1. Hsiao MC, Liu CY, Chen KC, Hsieh TT. Characteristics of women seeking treatment for premenstrual syndrome in Taiwan. Acta Psychiatr Scand 2002;106:150-5.
2. Hsiao MC, Hsiao CC, Liu CY. Premenstrual symptoms and premenstrual exacerbation in patients with psychiatric disorders. Psychiatry Clin Neurosci 2004;58:186-90.
3. Dalton K. Cyclical criminal acts in premenstrual syndrome. Lancet 1980;2:1070-1.
4. Halbreich U, Monacelli E. Some clues to the etiology of premenstrual syndrome/premenstrual dysphoric disorder. Prim Psychiatry 2004;11:33-40.
5. Steiner M, Pearlstein T, Cohen LS, Endicott J, Kornstein SG, Roberts C, Roberts DL, Yonkers K. Expert guidelines for the treatment of severe PMS, PMDD, and comorbidities: the role of SSRIs. J Womens Health (Larchmt) 2006;15:57-69.
6. Miller MN, Miller BE. Premenstrual exacerbations of mood disorders. Psychopharmacol Bull 2001;35:135-49.
7. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health 1990;13:227-36.
8. Robinson GE. Premenstrual syndrome: current knowledge and management. CMAJ 1989;140:605-11.

9. Pearlstein TB, Frank E, Rivera-Tovar A, Thoft JS, Jacobs E, Mieczkowski TA. Prevalence of axis I and axis II disorders in women with late luteal phase dysphoric disorder. J Affect Disord 1990;20:129-34.
10. Yonkers KA, White K. Premenstrual exacerbation of depression: one process or two? J Clin Psychiatry 1992;53:289-92.
11. Rubinow DR, Schmidt PJ, Roca CA. Estrogen-serotonin interactions: implications for affective regulation. Biol Psychiatry 1998;44:839-50.
12. Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu LX, Sibley DR, Roth BL, Mailman R. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 2003;28:1400-11.
13. Marder SR. A review of agitation in mental illness: treatment guidelines and current therapies. J Clin Psychiatry 2006;67:13-21.
14. Papakostas GI, Petersen TJ, Kinrys G, Burns AM, Worthington JJ, Alpert JE, Fava M, Nierenberg AA. Aripiprazole augmentation of selective serotonin reuptake inhibitors for treatment-resistant major depressive disorder. J Clin Psychiatry 2005;66:1326-30.
15. Patkar AA, Peindl K, Mago R, Mannelli P, Masand PS. An open-label, rater-blinded, augmentation study of aripiprazole in treatment-resistant depression. Prim Care Companion J Clin Psychiatry 2006;8:82-7.
16. Simon JS, Nemeroff CB. Aripiprazole augmentation of antidepressants for the treatment of partially responding and nonresponding patients with major depressive disorder. J Clin Psychiatry 2005;66:1216-20.
17. Adson DE, Kushner MG, Fahnhorst TA. Treatment of residual anxiety symptoms with adjunctive aripiprazole in depressed patients taking selective serotonin reuptake inhibitors. J Affect Disord 2005;86:99-104.
18. Worthington JJ 3rd, Kinrys G, Wygant LE, Pollack MH. Aripiprazole as an augmentor of: 9-11er patients. Int Clin Psychopharmacol 2005 augmentor of selective serotonin reuptake inhibitors in depression and anxiety dselective serotonin reuptake inhibitors in depression and anxiety disorder patients. Int Clin Psychopharmacol 2005;20:9-11.
19. Jordan S, Koprivica V, Chen R, Tottori K, Kikuchi T, Altar CA. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. Eur J Pharmacol 2002;441:137-40.

Aripiprazole 有效治療憂鬱症的月經前暴力

姚怡君[1] 姜丕慧[3] 蕭美君[1,4] 劉嘉逸[1,2]

憂鬱症在月經前的惡化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濾泡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) 出現月經前暴力行爲及憂鬱症狀加劇。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，於是我們使用新一代的抗精神病藥 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得到完全緩解。因此我們認爲新一代的抗精神病藥 aripiprazole 對於憂鬱症的月經前暴力爲一有效治療。(長庚醫誌 2008;31:402-6)

關鍵詞：經前症候群，暴力，aripiprazole

長庚紀念醫院 台北院區 [1]精神科，[2]神經科學研究中心；長庚大學 醫學院 [4]中醫系；[3]國立嘉義大學 家庭教育研究所
受文日期：民國96年5月7日；接受刊載：民國96年8月16日
通訊作者：劉嘉逸醫師，長庚紀念醫院 精神科。桃園縣333龜山鄉復興街5號。Tel.: (03)3281200轉2439;
Fax: (03)3280267; E-mail: liucy752@cgmh.org.tw