

Letters to the Editor

Isotretinoin Treatment of a Woman With Bipolar Disorder

Sir: Lithium is widely believed to contribute to the onset or worsening of acne.^{1,2} This side effect causes concern for many patients who are already at risk for noncompliance due to the nature of their illness. Although the pathophysiology of the dermatologic reactions to lithium is speculative, there is convincing evidence that lithium increases migration of polymorphonuclear leukocytes into skin lesions.³ This direct leukocyte stimulation and the resulting degranulation produces inflammation.⁴ Lithium-related acneiform eruptions are often resistant to usual treatments. No medication for lithium-induced acne is consistently effective, and a reduction in dose or discontinuation of lithium may be required.⁵⁻⁷

Isotretinoin dramatically reduces scarring and cystic acne.⁸ Its use is accompanied by numerous precautions, and it is indicated only for severe forms of acne.⁹ After "isolated reports of depression and very rarely suicide" were associated with isotretinoin,⁹ the Food and Drug Administration (FDA) and the drug manufacturer added an upgraded warning on the drug's packaging. The label now states that "isotretinoin may cause depression, psychosis, and rarely suicidal ideation, suicide attempts and suicide." The FDA and the drug manufacturer have emphasized that there is no definitive causal relationship and that the adolescent age of the patient population and acne itself are risk factors for depression.¹⁰ However, physicians are being encouraged to be alert to the development of additional or new clinical psychiatric symptoms during isotretinoin use and to discontinue treatment when necessary.

Because of these possible side effects, we were concerned when a patient with bipolar disorder who had cystic acne wanted to begin isotretinoin treatment. She agreed to our suggestion of weekly mood monitoring, and we have reported our findings here.

Case report. Ms. A, a 30-year-old white woman, had bipolar I disorder for 11 years. She had past episodes of mania with psychotic features that required hospitalization. Ms. A came under our care as a well-functioning 26-year-old married teacher, stabilized on treatment with lithium, 600 mg/day, who wanted to become pregnant. Her pregnancy was successfully managed on treatment with perphenazine, 4 mg/day. Immediately postpartum, lithium, 900 mg/day, was reintroduced, and Ms. A's bipolar symptoms remained well contained. She elected not to breast-feed. Seven weeks postpartum, she complained that her acne was progressing. She had cystic facial acne with significant scarring, and her dermatologist recommended isotretinoin after unsuccessful therapy with several topical treatments and oral antibiotics.

We replaced lithium with divalproex sodium but noted minimal improvement in acne. We were wary of isotretinoin use in our patient, who had a history of rapid loss of insight during her decompensations. Her psychotic episodes began quickly and involved paranoid ideation about her husband. This rapid loss of insight was our major concern in that behavioral side effects from the isotretinoin would go unreported if left to her discre-

tion. Ms. A's mood was stable for more than 2 months on treatment with divalproex, 500 mg/day (serum level = 50 mg/L, 13 hours postdose), but she still had severe acne and became insistent on isotretinoin therapy.

The weekly monitoring protocol during her isotretinoin therapy involved the Hamilton Rating Scale for Depression (HAM-D), the Global Assessment Scale, and the Mania Rating Scale (derived from the Schedule for Affective Disorders and Schizophrenia). There was no significant change in any of these scales, and Ms. A remained highly functional throughout the treatment. However, 4 weeks after initiation of isotretinoin, 60 mg/day, she became suspicious, preoccupied by a casual comment made by a relative, and was unable to sleep. Prompted by her husband and mother, who recognized these symptoms as early signs of previous decompensations, she immediately contacted the on-call physician, who advised her to restart perphenazine treatment (4 mg) at bedtime. She was able to sleep the next night, and when evaluated the following day, she was insightful about her overreaction although still tearful and suspicious about the relative. We advised Ms. A to continue taking the added perphenazine plus divalproex and remain on treatment with isotretinoin because the improvement in her acne was significant. She recovered fully and experienced no further behavioral symptoms after the addition of perphenazine. Ms. A was extremely pleased with the improved condition of her skin. She took isotretinoin and perphenazine for a period of 6 months, then discontinued both medications and remained stable on divalproex treatment alone.

The clinical effects of a 4- to 6-month course of isotretinoin can produce a complete and prolonged remission of acne.¹¹ However, if her dermatologist recommends that isotretinoin be restarted, Ms. A has decided she will add perphenazine concomitantly to prevent recurrent psychiatric symptoms. Although she was offered atypical antipsychotics, Ms. A feels comfortable with short-term perphenazine because she has invariably had an excellent clinical response to impending psychosis and no side effects.

We are presenting a method to manage patients with mood disorders who take isotretinoin. Our emphasis is on the importance of consistent monitoring and follow-up, especially since the successful management of a psychiatric disorder improves the ability of the patient to adhere to birth control during isotretinoin (which is teratogenic¹¹) therapy. In this particular case, the patient's mood did not change significantly, and her cognitive symptoms would most likely have gone unnoticed under less careful observation. We were able to intervene immediately owing to our monitoring plan with the patient and her family.

Since this is a single case study, we are limited in our conclusions. An argument can be made that isotretinoin treatment was unrelated to destabilization. However, Ms. A had a very long period of full stability (3 years). She had a recent pregnancy and postpartum period during which she remained completely stable. The postpartum period is one of very high risk for decompensation in women.¹² She had no symptoms until 1 month after the introduction of isotretinoin. However, the symptoms

responded fully to the same regimen (mood stabilizer plus perphenazine) to which she had previously responded during decompensations.

Lithium is still a standard treatment for bipolar disorder and is known to cause or exacerbate acne in some patients. Alternate psychotropic medications may not result in resolution of acne. Therefore, knowledge of dermatologic therapies such as isotretinoin is important for psychiatrists. In light of the recent strengthened FDA warning, the use of this drug by patients with mood disorders should be cautiously initiated and managed by the dermatologist and psychiatrist as a team.

REFERENCES

1. Deandra D, Walker N, Mehlmauer M, et al. Dermatological reactions to lithium: a critical review of the literature. *J Clin Psychopharmacol* 1982;2:199-204
2. Sarantis D, Waters B. A review and controlled study of cutaneous conditions associated with lithium carbonate. *Br J Psychiatry* 1983; 143:42-50
3. Rothstein G, Clarkson DR, Larsen W, et al. Effect of lithium on neutrophil mass and production. *N Engl J Med* 1978;298:178-180
4. Bloomfield FJ, Young MM. Enhanced release of inflammatory mediators from lithium-stimulated neutrophils in psoriasis. *Br J Dermatol* 1983;109:9-13
5. Kanzaki T. Acneiform eruption induced by lithium carbonate. *J Dermatol* 1991;18:481-483
6. Okrasinski H. Lithium acne. *Dermatologica* 1977;154:251-253
7. Heng M. Lithium carbonate toxicity. *Arch Dermatol* 1982;118: 246-248
8. Peck GL, Olsen TG, Yoder FW, et al. Prolonged remissions of cystic and conglobate acne with 13-*cis*-retinoic acid. *N Engl J Med* 1979;300:329-333
9. Accutane [package insert]. Nutley, NJ: Roche Laboratories, Inc; 1998
10. Josefson D. Acne drug is linked to severe depression [news]. *BMJ* 1998;316:723
11. Lamberg L. Acne drug depression warnings highlight need for expert care. *JAMA* 1998;279:1057
12. Cohen LS, Sichel DA, Robertson LM, et al. Postpartum prophylaxis for women with bipolar disorder. *Am J Psychiatry* 1995;152: 1641-1645

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Seizures After Discontinuation of Low-Dose Lorazepam From Originally Seizure-Free Clozapine Regimen: Combined Effects?

Sir: Coadministration of benzodiazepines and clozapine has been reported to cause severe adverse events (including respiratory depression, cardiovascular collapse, confusion, and delirium) in a number of patients.¹ Many of these patients also had medical illnesses that might well have been contributory factors.¹ On the other hand, the reactions to the combination of benzodiazepine discontinuation and concomitant clozapine treatment remain unknown. There is evidence that seizures can occur after rapid discontinuation of benzodiazepines, especially when they have been taken in high doses for long periods of time.^{2,3} We here present a clozapine-treated patient who experienced motor convulsions upon withdrawal of a short-term (6-week), low-dose (1.5-mg/day) lorazepam cotreatment. Noteworthy, this patient's clozapine dose was also rather small (200 mg/day), and the patient had been free of seizure activities at this dose previously.

In contrast, when the patient afterward received risperidone (instead of clozapine) therapy, cessation of lorazepam (1.5 mg/day for 6 weeks again) led to no seizures (as determined by both close clinical observation and serial electroencephalogram [EEG] recordings). We hypothesize that this patient's convulsions might result from the combined effects of discontinuation of low-dose lorazepam and an originally seizure-free clozapine regimen.

Case report. Mr. A, a 26-year-old Chinese nonsmoker, had been physically healthy and devoid of any seizure and substance (including alcohol) abuse history. He had recently been hospitalized for treatment-resistant schizophrenia and associated anxious moods. The baseline EEG was unremarkable (and so were his prior EEGs, including those during treatment with typical neuroleptics). Lorazepam (0.5 mg t.i.d.) and clozapine were then started simultaneously; the latter was titrated to 150 mg b.i.d. over 2 weeks. After 1 week, his EEG showed frequent generalized spike-and-wave complexes and intermittent generalized theta waves. Despite no noted clinical ictal manifestation, the clozapine dosage was reduced to 100 mg b.i.d., while lorazepam doses were kept unchanged. The repeat EEGs 1, 2, and 3 weeks later all were unremarkable. Lorazepam was then halted owing to an improvement in Mr. A's anxiety.

About 40 hours after the last dose of lorazepam, Mr. A experienced a witnessed grand mal convulsion lasting 5 minutes; a second convulsion occurred 2 hours later. The EEG on the same day showed diffuse ictal activities and slow waves. Laboratory evaluation, including a head magnetic resonance imaging (MRI), revealed negative findings. Lorazepam (0.5 mg t.i.d.) was immediately reinstated, and clozapine was stopped. Electrical disturbances in the EEG vanished in 7 days. Mr. A refused to take clozapine again; therefore, risperidone (up to 3 mg b.i.d. in 6 days) was added to the lorazepam regimen. Six weeks after its commencement, lorazepam was discontinued again, and risperidone doses were maintained at 6 mg/day. The follow-up EEGs 1, 2, 3, and 7 days and 1, 2, 4, 6, and 8 months later all appeared unremarkable, and Mr. A has experienced no further seizures. No antiseizure medications were added throughout.

Among benzodiazepines, lorazepam and alprazolam are most commonly associated with withdrawal seizures.⁴ Of note, our patient's lorazepam dose approximates the lowest dose (1 mg/day) in earlier reports concerning lorazepam withdrawal seizures.⁴ In cases of abstinence seizures emerging after low-dose therapy, confounding factors (e.g., concomitant medications, physical illness, aging) usually exist.^{2,3} However, it is uncertain whether concurrent epileptogenic agents at seizure-free doses could still raise the potential of this withdrawal reaction. Compared with typical neuroleptics or risperidone,⁵ clozapine is rather seizure-prone. The reported prevalence of seizures with clozapine is 5% for patients treated with 600 to 900 mg/day, 3% to 4% for patients with 300 to 599 mg/day, and 1% to 2% for patients receiving less than 300 mg/day.⁶ The present case may suggest that clozapine at pre-seizure doses still somewhat (albeit subclinically) lowers the seizure threshold, which could be further curtailed by other epileptogenic factors (e.g., benzodiazepine withdrawal).

Another possible explanation for our patient's grand mal seizures is that the combined use of lorazepam (also with anticonvulsant properties⁷) might have masked the underlying epileptic potential from clozapine. The suspension of this benzodiazepine perhaps merely uncovered the ictal activity of clozapine per se.

In the present case, an EEG revealing frequent generalized spike-and-wave complexes appeared at a clozapine dose of 300 mg/day, which, in general, is not commonly related to seizures.⁶

However, plasma concentration from a given clozapine dose varies broadly.^{8,9} In addition, the mean plasma clozapine concentration is 20% higher in nonsmokers than in smokers.^{8,9} Finally, Chinese patients have been reported to have 30% to 50% higher plasma levels of clozapine in comparison with white subjects.⁹ Our patient, a Chinese nonsmoker, might thus have higher plasma clozapine concentrations than a white individual (especially a smoker). This possible factor might increase our patient's clozapine-related seizure risk, even at such a low dose. Unfortunately, blood levels of neither clozapine nor lorazepam were available in this patient. Blood benzodiazepine levels, however, have not been found to be useful owing to lack of studies regarding concentration-response relationships.

The above observations and hypotheses are indeed preliminary. Further studies are warranted. Nevertheless, at present, when clozapine is coexistent, very slow tapering of benzodiazepines (even at low doses) is suggested. Clozapine, even at doses originally unrelated with seizures or EEG changes, could still elevate the seizure risk of benzodiazepine withdrawal (or, perhaps, other epileptogenic factors). Moreover, this case also supports the recommendation that the combined use of clozapine and benzodiazepines should be discouraged.¹

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REFERENCES

1. Faisal I, Lindenmayer JP, Taintor Z, et al. Clozapine-benzodiazepine interactions [letter]. *J Clin Psychiatry* 1997;58:547-548
2. Einarson TR. Lorazepam withdrawal seizures [letter]. *Lancet* 1980;1:151
3. Soni SD, Smith ED, Shah A, et al. Lorazepam withdrawal seizures: role of predisposition and multi-drug therapies. *Int Clin Psychopharmacol* 1986;1:165-169
4. Martinez-Cano H, Vela-Bueno A, de Iceta M, et al. Benzodiazepine withdrawal syndrome seizures. *Pharmacopsychiatry* 1995;28:257-262
5. Lane HY, Chang WH, Chou JCY. Seizure during risperidone treatment in an elderly woman with concomitant medications [letter]. *J Clin Psychiatry* 1998;59:81-82
6. Haller E, Binder RL. Clozapine and seizures. *Am J Psychiatry* 1990;147:1069-1071
7. Homan RW, Treiman DM. Benzodiazepines: lorazepam. In: Levy RH, Mattson RH, Meldrum BS, eds. *Antiepileptic Drugs*. 4th ed. New York, NY: Raven Press; 1995:779-790
8. Jann MW, Grimsley SR, Gray EC, et al. Pharmacokinetics and pharmacodynamics of clozapine. *Clin Pharmacokinet* 1993;24:161-176
9. Lane HY, Chang YC, Chang WH, et al. Effects of gender and age on plasma levels of clozapine and its metabolites: analyzed by critical statistics. *J Clin Psychiatry* 1999;60:36-40

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Bipolar II Disorder vs. Premenstrual Dysphoric Disorder

Sir: Hendrick and Altshuler have helpfully highlighted the need for further research into the relationship between bipolar II disorder and premenstrual dysphoric disorder (PMDD) with a case report of a patient who showed significant mood variability closely linked to her menstrual cycle.¹ Their patient had a family history of lithium-responsive bipolar disorder and had experienced a major depressive episode in the past as well as premen-

strual dysphoria and spells of relative well-being in the postmenstrual phase of her cycle.

On the basis of the close relationship of her symptomatic depressive episodes to her menstrual cycle, her response to sertraline, and lack of therapeutic response to lithium monotherapy and a later combination of valproate and bupropion, they reasonably prefer a diagnosis of PMDD to bipolar II disorder for their patient.

From this patient's failure to respond to mood-stabilizing agents and bupropion, they draw the conclusion that care should be taken in making the diagnosis of bipolar II disorder in women of reproductive age who show monthly mood cycles. The case they describe highlights the importance of assessment of hypomanic episodes in this context. The diagnosis of hypomanic episodes in bipolar II disorder is primarily a clinical diagnosis, and variability in definitions of hypomanic episodes may have led to heterogeneity in samples of bipolar II patients already assessed for research purposes.²⁻⁴

Premenstrual dysphoria is common in women with both bipolar I and II disorders, perhaps more so in bipolar II disorder.⁵ To assess the relationship between mood cyclicality and the menstrual cycle, patients referred to 2 regional premenstrual syndrome clinics are routinely prospectively assessed using the Calendar of Premenstrual Experiences (COPE)⁶ and the Bipolar Mood Diary.⁷ The Bipolar Mood Diary is a simple mood record, derived from the COPE, which allows accurate assessment of the intensity and degree of functional incapacity associated with manic, hypomanic, and depressive symptoms on a daily basis. Symptomatic criteria from DSM-IV⁸ are rated separately, along with daily medications, both prescribed and nonprescribed, that have been administered.

In addition to information from an informant, we find prospective self-monitoring of symptoms useful in differentiating between PMDD and bipolar II disorder. The Bipolar Mood Diary is easy for patients to use and appears useful in helping to determine whether hypomanic episodes reach DSM-IV diagnostic criteria, although these criteria have been questioned.⁹

We would conclude that patients who present with any form of recurrent depressive episodes, including premenstrual dysphoric episodes, should be carefully examined, with the help of an informant if at all possible, for the presence of hypomanic episodes so that a bipolar II diagnosis is not missed, given that, as Hendrick and Altshuler point out, a bipolar II diagnosis carries implications for treatment.

REFERENCES

1. Hendrick V, Altshuler LL. Recurrent mood shifts of premenstrual dysphoric disorder can be mistaken for rapid-cycling bipolar II disorder [letter]. *J Clin Psychiatry* 1998;59:479-480
2. Dunner DL, Tay LK. Diagnostic reliability of the history of hypomania in bipolar II patients and patients with major depression. *Compr Psychiatry* 1993;34:303-307
3. Endicott J, Nee J, Andreasen N, et al. Bipolar II: combine or keep separate? *J Affect Disord* 1985;8:17-28
4. Coryell W. Bipolar II disorder: a progress report. *J Affect Disord* 1996;41:159-162
5. Winokur G, Coryell W, Keller M, et al. A prospective follow-up of patients with bipolar and primary unipolar affective disorder. *Arch Gen Psychiatry* 1993;50:457-465
6. Mortola JF, Girton L, Beck L, et al. Diagnosis of premenstrual syndrome by a simple, prospective and reliable instrument: The Calendar of Premenstrual Experiences. *Obstet Gynecol* 1990;76:302-307
7. Macmillan IC, Palmer A, Williams H, et al. *The Bipolar Mood Diary: Proceedings of the Stanley Foundation European Bipolar Symposium*; Sept 1998; London, England
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American

Psychiatric Association; 1994

9. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. *J Clin Psychopharmacol* 1996;16(2, suppl 1):4S-14S

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SSRI-Induced Parkinsonism May Be an Early Sign of Future Parkinson's Disease

Sir: In recent years, there have been several case reports of extrapyramidal symptoms as a result of treatment with selective serotonin reuptake inhibitors (SSRIs).¹⁻⁴ These symptoms include dystonia, akathisia, and parkinsonism. In most previously reported cases, the patients had preexisting brain diseases, but some movement disorders developed after initiation of SSRI treatment in both young healthy and vulnerable old patients.^{2,3,5} Furthermore, SSRIs might change the symptom profile of preexisting idiopathic Parkinson's disease.⁶ There are reports of deterioration of parkinsonian patients taking SSRIs.⁷ The literature on this subject was recently reviewed by Caley.⁸

We report a case of a geriatric patient with depression who developed reversible SSRI-associated parkinsonism and was later diagnosed as having Parkinson's disease.

Case report. Ms. A, a 67-year-old woman with no previous psychiatric history, presented with major depressive disorder 2 years prior to the time of this report. She complained of sadness, initial insomnia, anhedonia, and feelings of hopelessness and helplessness that had begun 2 months before she sought treatment. She had been taking amlodipine besylate, 5 mg/day p.o., for hypertension for 1 year up to the time she presented with depression. She was started on treatment with fluvoxamine, 50 mg b.i.d., which was gradually increased over a 2-week period to 100 mg b.i.d. After 6 days on this dose, Ms. A developed a pill-rolling tremor, masked facies, bradykinesia, and a festinating gait with tendency to retropulse. Her family reported that she had fallen once while on this dose. Results of a cranial magnetic resonance imaging (MRI) scan were normal. The fluvoxamine treatment was discontinued 18 days after it was initiated, and Ms. A began treatment with maprotiline, 75 mg/day. All signs of

parkinsonism resolved within 2 weeks. Her depressive symptoms decreased gradually. She stopped taking her drug by herself after 6 months. The onset of parkinsonian symptoms after fluvoxamine initiation and their rapid resolution after discontinuation of fluvoxamine were thought to be a medication-induced syndrome.

After an 11-month symptom-free period, Ms. A recently came to our neurology department with pill-rolling tremor, asymmetrical cogwheel rigidity, and bradykinesia. She was diagnosed as having Parkinson's disease; no depressive symptom had been detected. Selegiline was chosen for treatment.

Serotonin modulates dopamine in basal ganglia by inhibiting its production and release.⁸ Thus, increase in serotonergic transmission may cause parkinsonian symptoms in geriatric patients who may have less dopamine available in their nigrostriatal tract. Furthermore, SSRIs may worsen the symptoms of preexisting Parkinson's disease or depressive symptoms of anhedonia and social isolation. To our knowledge, this is the first case report of a patient with reversible SSRI-associated parkinsonian symptoms who developed Parkinson's disease in 2 years' time. If this finding is confirmed by further clinical observations, SSRI-induced parkinsonism may be an early sign of Parkinson's disease in vulnerable geriatric patients.

REFERENCES

1. Klee B, Kronig MH. Case report of probable sertraline-induced akathisia [letter]. *Am J Psychiatry* 1993;150:986-987
2. Reccoppa L, Welch WA, Ware MR. Acute dystonia and fluoxetine [letter]. *J Clin Psychiatry* 1990;51:487
3. Brod TM. Fluoxetine and extrapyramidal side effects [letter]. *Am J Psychiatry* 1989;146:1353-1354
4. Wils V. Extrapyramidal symptoms in a patient treated with fluvoxamine [letter]. *J Neurol Neurosurg Psychiatry* 1992;55:330-331
5. Schechter DS, Nunes EV. Reversible parkinsonism in a 90-year-old man taking sertraline [letter]. *J Clin Psychiatry* 1997;58:275
6. Jiménez-Jiménez FJ, Tejero J, Martínez-Junguera G, et al. Parkinsonism exacerbated by paroxetine [letter]. *Neurology* 1994;44:2406
7. Chouinard G, Sultan S. A case of Parkinson's disease exacerbated by fluoxetine. *Hum Psychopharmacol* 1992;7:63-66
8. Caley CF. Extrapyramidal reactions and the selective serotonin-reuptake inhibitors. *Ann Pharmacother* 1997;31:1481-1489

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