Treatment of Bipolar Depression with Twice-Weekly Fluoxetine: Management of Antidepressant-Induced Mania

James L Megna and Patrick J Devitt

OBJECTIVE: To report a case of treatment of bipolar depression and management of antidepressant-induced mania with a low-dose fluoxetine regimen.

CASE SUMMARY: A 59-year-old white woman was admitted involuntarily to a New York State psychiatric center with a diagnosis of bipolar (type I) disorder, mixed, with psychotic features. Initial treatment with lithium, olanzapine, and clonazepam produced a remission of manic and psychotic symptoms. However, the patient remained clinically depressed. Addition of oral fluoxetine 10 mg every morning to her medication regimen was followed 22 days later by the development of a manic state. Reduction of the fluoxetine dosage to 10 mg twice weekly was associated with the attainment of euthymia in 18 days. Thirteen days after the fluoxetine dosage reduction, the patient's fluoxetine blood concentration was 20 µg/L and the norfluoxetine concentration was reported as 53 µg/L.

DISCUSSION: To our knowledge, this is the first published case that describes the association between a low-dose fluoxetine regimen and the evolution of a bipolar affective state from depression to euthymia via manic switching. The temporal synchrony of this switching with initial implementation of fluoxetine 10 mg every morning, followed by a dose reduction to 10 mg twice weekly, suggests that bipolar depressed patients are extremely sensitive to low doses of antidepressants and to incremental changes in these doses. However, it also suggests that they can respond clinically to such treatment. Furthermore, our laboratory data indicate that antidepressant blood concentrations may play a contributory role in maintaining the balance between euthymia and mania in these patients.

CONCLUSIONS: Manic switching is always a concern when treating a bipolar depressed patient. Utilization of a low-dose antidepressant drug regimen may be a clinically prudent approach in such an individual.

KEY WORDS: bipolar depression, fluoxetine, mania.

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The treatment of bipolar depression has not been well studied systematically. This is of profound clinical importance given the 15% prevalence of suicide in bipolar disorder.[1] Furthermore, there are the attendant risks such as manic switching and increased cycling rate.[2] Sachs[3] has presented a comprehensive review of treatment of bipolar depression in which recommendations are made for maintaining mood-stabilizing therapy while treating the depressed phase. We present a case in which bipolar depression and antidepressant-induced mania were managed with a unique fluoxetine dosing regimen while adhering to Sachs's general recommendations. This case illustrates that antidepressant blood concentrations may play a contributory role in maintaining the balance between euthymia and mania in bipolar depressed patients.

CASE REPORT

A 59-year-old single white woman was admitted involuntarily to a New York State psychiatric center on the certification of two physicians. Over a period of several months, she had been sporadically compliant with her medications and had required respite at a state-operated crisis residence on a number of occasions. On the evening before her admission, at the crisis residence, she became suddenly agitated, hitting herself and yelling that she did not "want to be like Satan…I'm Satan, I'm part man and woman." Her speech was reported as disorganized and loose. She ran away from the residence, was later found by police, and was taken to the local comprehensive psychiatric emergency program (CPEP).

The clinical notation at CPEP reported that she was agitated, tangential, loud, not sleeping well, verbalized very sporadic racing thoughts, was unable to sit still, but did not appear suicidal. Her mood was described as fluctuating and angry, with poor concentration. In addition, she was reported saying that the television was sending her special messages and that she was seeing "Mary in a carriage across the sky." She had been eating poorly and had increased energy. This was her second admission to CPEP in two days. At CPEP, she was treated with perphenazine 8 mg and clonazepam 0.75 mg, both orally. Previously, she had been prescribed lithium 600 mg twice daily and trazodone 50 mg at night. A lithium concentration at CPEP was 0.53 mEq/L.

On admission to the psychiatric center, she was noted to be labile and religiously preoccupied, saying "I walked around the world, literally. It took only 25 hours to do it, and on the way I found my Father and Holy Ghost." After haloperidol and lorazepam were administered as needed and compliance was achieved with her medication regimen (lithium 600 mg po bid, olanzapine

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5 mg po hs, clonazepam 0.5 mg bid), the patient became more calm, less delusional, and less agitated over the next three to four days. At that point, she was able to converse rationally and stated that she had not been taking her medications as an outpatient. She reported that she had been depressed. Her brother confirmed that she had appeared depressed to him for the past two years. He described a gradual decline in her interests and activities.

The patient was diagnosed with bipolar I disorder, mixed, with psychotic features. On hospital day 12, she was started on oral fluoxetine 10 mg each morning and continued on her other medications, except that the clonazepam dosage was changed to 1 mg at bedtime. The patient's lithium blood concentration was 1.12 mEq/L. She was by now participating actively in unit programs, and three days later a nursing report stated that she was "in a great mood." The next day, she was reported as "cheerful." Nine days after initiation of fluoxetine she was reported as "hyper" and was noted to be awake from 0200. The next day, her brother reported that from a telephone conversation with her, he believed that she was "too high." Twenty-two days after starting fluoxetine therapy, the attending psychiatrist diagnosed her as manic, and the dosage of fluoxetine was reduced to 10 mg twice weekly, on Mondays and Thursdays. She reported that she had felt well when receiving the daily fluoxetine and was concerned with the reduction to twice weekly. However, her manic symptoms rapidly subsided. She remained euthymic, participated appropriately in unit activities and programs, and had a series of increasingly more autonomous, successful community passes. On hospital day 40, the patient's lithium blood concentration was 0.92 mEq/L, and 13 days after the reduction of the fluoxetine her fluoxetine blood concentration was <20 µg/L; norfluoxetine was reported as 53 µg/L. Her condition continued to improve, and she was discharged 60 days after her admission to be followed at a state-operated clinic (Figure 1). Medications on discharge were oral lithium 600 mg twice daily, oral olanzapine 5 mg at bedtime, oral furosemide 20 mg/d (she had developed ankle edema during her stay), oral clonazepam 1 mg at bedtime, guaifenesin 200 mg three times daily, and oral fluoxetine 10 mg every Monday and Thursday. Since her discharge 19 months ago, she has been maintained on this regimen in a euthymic state.

Discussion

Our case illustrates the contributing factors to a mixed state in bipolar disorder and the importance of a rational and systematic approach to treatment of target symptoms. The manic symptoms were controlled with adequate doses of and compliance with the mood stabilizer lithium, whereas the psychotic features were well treated with olanzapine, which may also have had a mood-stabilizing effect,[4] and has little pharmacokinetic interaction with fluoxetine.[5] Having thus isolated and eliminated the manic component, the true nature of the depressive component was revealed.

Although blood concentrations of fluoxetine and norfluoxetine were not available at the time of manic switching, it can be assumed that they were higher than when the dosage was subsequently reduced and the patient achieved a euthymic state three weeks later. As the half-life of fluoxetine is four to six days and that of the active metabolite norfluoxetine is four to 16 days, it would appear that clinical efficacy could be achieved with weekly or twice-weekly dosing. Burke et al.[6] described once-weekly fluoxetine in the treatment of depression, noting no significant treatment differences between patients taking fluoxetine 60 mg/wk and those taking 20 mg/d. Emmanuel et al.[7] observed that fluoxetine appears to be effective when administered once weekly for panic disorder. Bourdeaux et al.[8] reported no correlation between the psychiatric scores of patients reacting positively to fluoxetine treatment and blood concentrations of fluoxetine and norfluoxetine. A similar outcome was obtained by Amsterdam et al.[9] in a large multicenter study. They found that plasma concentrations of fluoxetine and norfluoxetine did not differ between responders and nonresponders with a DSM-IIIR diagnosis of either major depression or bipolar disorder NOS, depressed phase.

Our case, however, suggests that concentrations of fluoxetine and norfluoxetine may play a contributory role in maintaining the balance between euthymia and mania in patients with a diagnosis of bipolar I disorder treated for depression. There is one limitation to consider: fluoxetine had no effect at the low dosage administered and the patient's evolution of mood (including the maintenance of euthymia for 19 mo) was related to the combined effects of her other medications. This, however, appears to be less consistent with the clinical material we present.

Summary

As shown by our case, it may be postulated that mood switching from depression to mania can be regulated on a continuum of antidepressant blood concentrations. This type of manic switching in bipolar disorder in association with antidepressant therapy does not appear to be of the same severity and appears to have different clinical characteristics than spontaneous manic episodes.[10] Furthermore, the low-dose fluoxetine regimen and the attendant low fluoxetine blood concentrations likely contributed to the

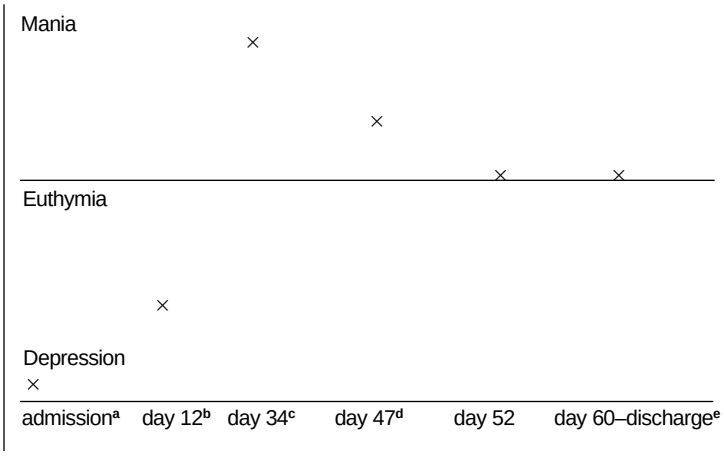

Figure 1. Change in mood as related to fluoxetine dosing.
[a]Lithium 600 mg bid, olanzapine 5 mg hs, clonazepam 0.5 mg bid.
[b]Fluoxetine 10 mg qam, clonazepam 1 mg hs, olanzapine 5 mg hs, lithium 600 mg bid (concentration 1.12 mEq/L).
[c]Fluoxetine 10 mg Monday and Thursday.
[d]Fluoxetine concentration, 20 µg/L (norfluoxetine 53 µg/L).
[e]Lithium 600 mg bid, olanzapine 5 mg hs, clonazepam 1 mg hs, fluoxetine 10 mg Monday and Thursday.

restoration of a euthymic state (although the presence of slow CYP2D6 metabolism in this patient cannot be excluded as a factor). Judged by the Naranjo probability scale[11] these events scored a possible for the association with fluoxetine. With respect to spontaneous switching, we think that an all-or-none phenomenon produced by kindling creates a robust and rapidly developing manic syndrome, which occurs especially in the latter stages of bipolar illness when malignant transformation contributes to treatment nonresponsiveness.[12] There is anecdotal evidence at our facility supporting the above hypothesis, although little support for it exists in the literature. Therefore, more controlled, prospective studies are needed to elucidate the relationship between antidepressant blood concentrations and mood in bipolar I disorder to advance our understanding and treatment of the disease.

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EXTRACTO

OBJETIVO: Informar el caso de una paciente tratada para la depresión bipolar y el manejo de manía inducida por antidepresivos debido a un régimen de fluoxetina en dosis bajas.

RESUMEN DEL CASO: Una mujer de 59 años de edad fue admitida al centro siquiátrico del estado de Nueva York con un diagnóstico de desorden bipolar tipo I, mixto con rasgos sicóticos. Su tratamiento inicial incluyó litio, olanzapina, y clonazepam. Esto produjo remisión de los síntomas mánicos y sicóticos. Sin embargo, la paciente continuó clínicamente depresiva por lo que se le añadió fluoxetina 10 mg diarios. Veintidos días después de la reducción de la dosis del antidepresivo, la paciente pudo llegar a eutimia. A los trece días después de la reducción en dosis de fluoxetina se obtuvo niveles séricos de fluoxetina y su metabolito activo norfluoxetina, los cuales fueron 20 µg/L y 53 µg/L, respectivamente.

DISCUSIÓN: De acuerdo a los autores, éste es el primer caso presentado para publicación que describe la asociación entre un régimen de dosis bajas de fluoxetina con la evolución del estado afectivo de depresión a eutimia después de un cambio en manía. Tales cambios en el estado afectivo con el inicio de fluoxetina 10 mg/día seguido por una reducción a 10 mg dos veces en semana sugiere que los pacientes con depresión bipolar son extremadamente sensitivos a dosis bajas de antidepresivos y a los cambios incrementales de estas dosis. Los hallazgos de laboratorio indican que los niveles séricos de antidepresivcos pueden contribuir a mantener el balance entre eutimia y manía en estos pacientes.

CONCLUSIONES: El potencial de cambiar a manía que tienen los antidepresivos en los pacientes con depresión bipolar es siempre motivo de preocupación. La utilización de dosis bajas de un régimen antidepresivo podría ser una forma prudente para tratar a estos pacientes.

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RÉSUMÉ

OBJECTIF: Décrire un cas de dépression bipolaire et de manie induite par un antidépresseur traitée par la fluoxétine à faible posologie.

RÉSUMÉ DU CAS: Une femme de 59 ans, d'origine caucasienne, a été admise contre son gré dans un centre psychiatrique de l'état de New York avec un diagnostic de trouble bipolaire (de type I) mixte avec troubles psychotiques associés. Le traitement initial par le lithium, l'olanzapine et le clonazépam a produit une rémission des symptômes maniaques et psychotiques; cependant, la personne est demeurée cliniquement déprimée. L'ajout de fluoxétine à la posologie de 10 mg le matin à sa thérapie médicamenteuse a provoqué, 22 jours plus tard, l'apparition d'une phase maniaque. La diminution de la posologie de la fluoxétine à 10 mg deux fois par semaine a permis l'atteinte de l'euthymie 18 jours plus tard. Treize jours après la diminution de la posologie de la fluoxétine, la concentration sanguine de ce médicament était de 20 µg/L alors que celle de la norfluoxétine était de 53 µg/L.

DISCUSSION: Selon les auteurs, ceci est le premier cas qui décrit une association entre un traitement par la fluoxétine à faible posologie et l'évolution d'un état affectif bipolaire qui est passé de la dépression à l'euthymie via le passage par une phase maniaque. Ceci a évolué dans un synchronisme temporel avec l'initiation de la fluoxétine à raison de 10 mg chaque matin, suivie d'une réduction de la posologie à 10 mg deux fois par semaine, suggérant que les patients déprimés et présentant un trouble bipolaire sont extrêmement sensibles à de faibles doses d'antidépresseurs et à toute augmentation de cette posologie. Cependant, ce cas suggère que ces patients peuvent répondre cliniquement à un tel traitement. De plus, les tests de laboratoire indiquent que les concentrations sanguines de cet antidépresseur peuvent jouer un rôle contributoire dans le maintien de l'équilibre entre l'euthymie et la manie chez ces patients.

CONCLUSIONS: Le passage par une phase maniaque est toujours une préoccupation lorsque l'on traite un patient déprimé porteur d'un trouble bipolaire. L'emploi d'un traitement par un antidépresseur à faible posologie peut être une approche prudente chez ces individus.

Denyse Demers