Reexposure to Fluoxetine After Serious Suicide Attempts by Three Patients: The Role of Akathisia

Anthony J. Rothschild, M.D., and Carol A. Locke, M.D.

Considerable controversy exists regarding the relationship between fluoxetine and the emergence of suicidal ideation. Three cases are presented of patients who were reexposed to fluoxetine after having previously made a serious suicide attempt during fluoxetine treatment. All three patients developed severe akathisia during retreatment with fluoxetine and stated that the development of the akathisia made them feel suicidal and that it had precipitated their prior suicide attempts. The akathisia and suicidal thinking abated upon the discontinuation of the fluoxetine or the addition of propranolol. The emergence of suicidal ideation during treatment with fluoxetine may be secondary to the development of akathisia. Gradual increments of fluoxetine dose and the prompt recognition and treatment of akathisia may reduce further the rare occurrence of suicidal ideation during fluoxetine treatment.

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Reprint requests to: Anthony J. Rothschild, M.D., McLean Hospital, 115 Mill Street, Belmont, MA 02178.

In the past 18 months, there has been considerable controversy regarding the relationship between fluoxetine, a potent serotonin reuptake blocker, and the emergence of suicidal ideation. Teicher and colleagues[1] described six depressed patients who experienced intense, violent suicidal preoccupation after 2–7 weeks of fluoxetine treatment. Since that initial report, there have been several other anecdotal case reports[2-4] describing similar phenomena, although on follow-up of one patient,[5] suicidal ideation later emerged with imipramine. A recent retrospective study[6] found no difference between fluoxetine and other antidepressants in the incidence of suicidal ideation occurring after initiation of treatment.

In this report, we describe three patients referred to our center who had previously made serious suicide attempts while taking fluoxetine. The patients again took fluoxetine (for clinical reasons described below and with informed consent) and were closely monitored for the reemergence of suicidal ideation. We describe a syndrome of emergent akathisia in patients with a past history of suicidal ideation, in which the patients reported the akathisia as the primary cause of their previous desire to commit suicide.

CASE REPORTS

Case 1

Ms. A, a 25-year-old woman, had a 3-year history of major depression with melancholia. She had had two unsuccessful trials of tricyclic antidepressants with adequate dosage and plasma levels. She began having suicidal thoughts and planned to kill herself by jumping off a tall building. She was admitted to a psychiatric facility and began receiving fluoxetine 20 mg/day along with trazodone 25 mg at bedtime for sleep. When she failed to respond, the dosage was raised to 40 mg/day of fluoxetine on the 13th day of hospitalization. At that time, Ms. A remembers becoming increasingly anxious and restless without any change in her depressed mood. Her restlessness was only partly relieved by pacing or by crossing and uncrossing her legs while sitting. Family members confirmed that Ms. A would phone them frequently complaining of anxiety. On Hospital Day 16, Ms. A escaped from the hospital and attempted suicide by jumping off the roof of a building. She hit a landing and sustained a subdural hematoma and compound fractures of her arms and legs. After a 1-month stay in a general hospital, she was transferred to McLean Hospital for further evaluation.

On arrival at McLean Hospital, Ms. A was on a regimen of clonazepam, oxycodone, and acetaminophen. We initially recommended electroconvulsive therapy (ECT), but Ms. A and her family refused. She was begun on a trial of bupropion but was unable to tolerate it secondary to severe gastrointestinal side effects. Monoamine oxidase (MAO) inhibitors were contraindicated because of her potential need for pain medications. Ms. A requested another trial of fluoxetine since she felt that she had not been taking it long enough to see a response. Since she was confined to a wheelchair and we were able to monitor her closely, we started fluoxetine at a dose of 20 mg/day (with informed consent) while continuing the clonazepam, oxycodone, and acetaminophen.

For 4 days, Ms. A received a fluoxetine dose of 20 mg/day, and then the dose was raised to 40 mg/day on Day 5. On Day 11, Ms. A began to complain of severe anxiety, restlessness, and an inability to sit still. Her depression was unchanged, but she stated that the marked anxiety was making her feel more hopeless than ever. She recognized the symptoms as being identical to those she felt at the other hospital prior to her suicide attempt. She stated that "I tried to kill myself because of these anxiety symptoms. It was not so much the depression." The fluoxetine was discontinued on Day 14, and the restlessness and suicidal ideation remitted within 72 hours. Ms. A then agreed to and received a course of nine unilateral ECT treatments and experienced a complete remission of her depressive symptomatology.

Case 2

Mr. B, a 47-year-old man with an 8-year history of recurrent major depression and two prior suicide attempts, began outpatient treatment with fluoxetine, achieving a dose of 60 mg/day by the end of the first week. Four days later, he reported severe anxiety and restlessness. The severe anxiety, coupled with his depressive symptoms, made him feel that "death would be a relief." He felt like he was "jumping out of his skin" and began planning to commit suicide. He jumped from a cliff, but his fall was broken by a tree and he sustained only minor contusions. He was then referred to McLean Hospital for further evaluation.

Mr. B had not benefited from previous treatment trials that had included tricyclic antidepressants, phenelzine, tranylcypromine, carbamazepine, lithium carbonate, and ECT. A trial of bupropion was aborted because of an allergic reaction, and a trial of trazodone was discontinued because of severe side effects. Given our experience with Case 1 and Mr. B's past failure to respond to or tolerate other antidepressant modalities, we again tried fluoxetine (with informed consent), carefully monitoring him for symptoms of akathisia or signs of suicidal ideation. Mr. B was not taking any other medications besides fluoxetine.

Since he did not respond after taking 20 mg/day of fluoxetine for 2 weeks, the dose was raised to 40 mg/day. Five days later, Mr. B reported severe anxiety and restlessness. He paced the floor throughout the day and had difficulty sleeping at night, moving constantly in his bed. He told us that "this is exactly what happened the last time I was on fluoxetine, and I feel like jumping off a cliff again." The addition of propranolol 60 mg/day to his regimen led to the complete disappearance within 24 hours of the restlessness, the anxiety, and the desire to jump off a cliff. He continued to take 40 mg/day of fluoxetine and 60 mg/day of propranolol and his depressive symptoms remitted within 5 weeks.

Case 3

Ms. C, a 34-year-old woman, had a 14-year history of recurrent major depression with two previous suicide attempts. Her first suicide attempt (aspirin overdose) at age 20 had occurred prior to any psychiatric treatment. The second suicide attempt occurred while she was taking fluoxetine; she jumped off the roof of a tall building but landed on a balcony several floors below sustaining only a fracture of her femur. The suicide attempt occurred approximately 1 week after her dose of fluoxetine had been increased from 40 mg/day to 60 mg/day. Previous trials of imipramine, nortriptyline, trazodone, phenelzine, isocarboxazid, bupropion, and amoxapine had been unsuccessful in alleviating her symptomatology. Ms. C and her family consistently refused ECT and were of the opinion that the fluoxetine had little to do with her suicide attempt. Given her past poor response to other antidepressant modalities and our experience with Cases 1 and 2, Ms. C was started on fluoxetine (with informed consent) and monitored on a daily basis for signs or symptoms of suicidal ideation. She was taking no other medications besides fluoxetine.

Since she had had no response after taking 20 mg/day of fluoxetine for 2 weeks, her dose was raised to 40 mg/day. Two days after the increase to 40 mg/day, Ms. C began complaining that she had to move her legs back and forth and pace constantly to relieve anxiety. On examination, she constantly shifted her legs while seated and would get up from the chair many times to walk around the office. She stated that this restlessness was driving her "crazy" and that she was feeling like she did during her last suicide attempt. The addition of propranolol 60 mg/day to the regimen led to a complete remission of the restlessness, anxiety, and suicidal feelings. Ms. C continued on the dose of 40 mg/day of fluoxetine and 60 mg/day of propranolol and had a remission of her depressive symptomatology within the next 4 weeks.

DISCUSSION

Three depressed inpatients, 25–47 years of age, were reexposed to fluoxetine after having previously made a serious suicide attempt while taking the drug. This is the first report, to our knowledge, of patients restarted on fluoxetine after a previous suicide attempt during fluoxetine treatment. We observed that all three patients developed severe akathisia while taking fluoxetine, and they stated that the development of this syndrome, in the context of their depressive episode, is what precipitated their prior suicide attempts. When reexposed to fluoxetine, the patients again developed akathisia and suicidal ideation. The suicidal feelings abated when the akathisia was treated by the discontinuation of the fluoxetine or the addition of propranolol.

Fluoxetine-induced akathisia was first reported by Lipinski and colleagues[7] who estimated its incidence to be between 9.8% and 25%. They did not report the development of suicidal thinking in their five patients; however, the akathisia was rapidly treated with propranolol 30–90 mg/day.

Akathisia has been implicated in the development of suicidal ideation, homicidal ideation, and violence. Drake and Ehrlich[8] reported impulsive suicide attempts associated with akathisia secondary to neuroleptic treatment in two patients with no previous history of suicidal ideation despite histories of severe psychosis. In both cases, sui-

cidal ideation appeared suddenly, concurrent with the development of the akathisia, and disappeared when the akathisia was treated. Shaw and colleagues[9] reported a case of suicidal and homicidal ideation and akathisia in a double-blind neuroleptic crossover study. Similar to the three cases described in this report, Shear and colleagues[10] described two patients who successfully killed themselves by jumping after the development of akathisia secondary to depot fluphenazine treatment. Finally, Keckich[11] reported a case of violence as a manifestation of akathisia when a patient with a previous characterological and social predisposition to violence was treated with a combination of imipramine and haloperidol. It remains unclear whether there exists a common pharmacologic basis for akathisia and suicidal ideation or acts, although it has been postulated that suicidal ideation and suicide occur secondary to the emotional distress of akathisia.[8,10,12]

In the first report on the emergence of intense suicidal preoccupation during fluoxetine treatment,[1] four of the six patients described complained of a "disturbing inner restlessness" which may have been a form of akathisia. In addition, similar to the patients described in this report, all had prior histories of suicidal ideation. However, unlike the patients in this report, the fluoxetine dose was not decreased after the development of akathisia.[1] In another study[2] reporting the development of suicidal ideation during fluoxetine treatment, one of the two patients who developed suicidal ideation described the development of akathisia 1 week after a rapid increase of fluoxetine from 20 mg/day to 60 mg/day. Similar to our patients, this patient also fantasized about jumping from a high place.

It is conceivable that the development of akathisia in patients with a past history of suicidal or homicidal ideation is particularly problematic. Consequently, clinicians should remain alert to the development of akathisia in patients taking fluoxetine and to the fact that patients are often unable to distinguish akathisia from the ongoing symptoms of their psychiatric illness. Patients need to be reassured that the overwhelming symptoms being experienced are the side effects of medication and are treatable. Our patients had concluded their illness had taken such a dramatic turn for the worse that life was no longer worth living.

The cases described in this report suggest that caution should be used when rapidly increasing fluoxetine dosages and that, if akathisia occurs, the dosage of the fluoxetine should be decreased or medications to treat the akathisia should be administered. It is conceivable that the patients described herein may well have responded at a lower daily dose of fluoxetine or that a more gradual increase in dosage would have avoided the distressing side effects that developed. In our experience, fluoxetine is a safe and effective antidepressant. We have observed the emergence of suicidal ideation secondary to akathisia in only 3 of 1500 (0.2%) patients treated with fluoxetine; a rate considerably lower than the 3.5% previously reported.[1] In part, this may be due to our lowering of the fluoxetine dose when side effects develop and the prompt recognition and treatment of akathisia.

Drug names: acetaminophen (Panolol and others), amoxapine (Asendin), bupropion (Wellbutrin), carbamazepine (Tegretol and others), clonazepam (Klonopin), fluoxetine (Prozac), fluphenazine (Prolixin), haloperidol (Haldol and others), imipramine (Tofranil and others), isocarboxazid (Marplan), nortriptyline (Pamelor and others), phenelzine (Nardil), propranolol (Inderal and others), tranylcypromine (Parnate), trazodone (Desyrel and others).

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