Emergence of Intense Suicidal Preoccupation During Fluoxetine Treatment

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Six depressed patients free of recent serious suicidal ideation developed intense, violent suicidal preoccupation after 2–7 weeks of fluoxetine treatment. This state persisted for as little as 3 days to as long as 3 months after discontinuation of fluoxetine. None of these patients had ever experienced a similar state during treatment with any other psychotropic drug.

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Antidepressants occasionally promote suicidal actions in severely depressed patients by enhancing drive and counteracting psychomotor retardation (1). However, standard antidepressants are not known to induce severe and persistent suicidal ideation in depressed patients free of such thoughts before treatment. We have recently observed several complex patients who appear to have had serious paradoxical responses to fluoxetine that were characterized by intense, violent suicidal thoughts.

CASE REPORTS

Case 1. Ms. A, a 62-year-old woman, had a 17-year history of major depression with melancholia. Previously she had been cheerful, outgoing, and successful in her profession. She had no evidence of personality disorder but occasionally abused alcohol. Previous treatment trials had included most available tricyclic antidepressants, phenelzine, tranylcypromine, trazodone, alprazolam, carbamazepine, lithium, methylphenidate, and five investigational compounds. Ms. A had had a moderate response to a course of ECT and to a trial of amoxapine, but the benefits were short lived. Her symptoms included fatigue, lethargy, hypersomnia, psychomotor retardation, anhedonia, guilt, and occasional passive suicidal thoughts without any suicide attempts.

Before treatment with fluoxetine, Ms. A had received a second trial of amoxapine, with lorazepam and temazepam available for sedation. After a 4-week medication-free period and with a baseline score on the Hamilton depression rating scale (2) of 23, she was enrolled in a therapeutic study of fluoxetine. She received 20 mg/day in the first week, 40 mg/day on days 8–10, and 60 mg/day thereafter. On day 11 she began to experience forced obsessional suicidal thoughts consisting of intense and incessant wishes to kill herself and described by Ms. A as "uniquely bad." This led to such significant anxiety, fear, and turbulence that she felt "death would be a welcome result." She also felt like "jumping out of her skin" but had no signs of motor restlessness. Her depressive symptoms and Hamilton depression score remained the same, except for these intolerable forced suicidal thoughts. Fluoxetine treatment was discontinued, and after 3 days the intensity and obsessional quality of her suicidal thoughts abated.

Case 2. Mr. B, a 39-year-old successful professional man, had a 21-year history of dysthymia and episodic major depression, but no previous suicidal ideation. He had managed successfully with psychotherapy until 2 years ago, when his depression worsened after a divorce and a medication trial was initiated. Isocarboxazid (50 mg/day) enhanced his energy, mood, and self-confidence and diminished his anger and irritability. Six months later tolerance emerged and Mr. B developed hyperphagia, anergia, poor concentration, diminished libido, and passive suicidal thoughts. After a 2-week washout, fluoxetine was initiated at a dose of 20 mg every other day for 7 days, then daily. One month later his Hamilton depression score was 32 and he had several new complaints, including anxious unproductive energy, nausea, severe loss of appetite, and abulia. Most alarming, however, was the emergence of nearly constant suicidal preoccupation, violent self-destructive fantasies, and Mr. B's resignation to the inevitability of suicide. This was such a dramatic change in his behavior and attitude that both his elderly mother and his former wife made emergency telephone calls to his treaters because they were worried about his risk for suicide. Two weeks of lithium potentiation (600 mg/day) enhanced his energy slightly, but he remained intensely suicidal, so both agents were discontinued. During the next 3 months, trials of imipramine, doxepin, and methylphenidate provided little relief, and Mr. B's intense suicidal thoughts persisted until 2 weeks after treatment with tranylcypromine was initiated. Despite ongoing depression and a Hamilton depression score of 16, all traces of active suicidal ideation vanished

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Case 3. Ms. C, a 19-year-old college freshman, was hospitalized for the first time with symptoms of depression, paranoia, bulimia, agoraphobia, and dissociation. She had a history of mild suicidal gestures that had been managed without hospitalization. Past medications included haloperidol and trifluoperazine, which alleviated the paranoia (but led to substantial extrapyramidal side effects), and imipramine, which relieved her depression.

In the hospital Ms. C experienced occasional suicidal thoughts but had no active plan or intent. Perphenazine (4–12 mg/day) alleviated her paranoia and enabled her to sustain meaningful relationships and to obtain employment after 3 months. However, depression emerged and treatment with tranylcypromine (20–30 mg/day) was initiated, but it was discontinued because of orthostatic hypotension. Passive suicidal ideation reemerged, along with irritability, hopelessness, and increased purging.

Two weeks later, fluoxetine (20 mg/day) was added to the perphenazine (12–20 mg/day). During the next 2 weeks Ms. C became more paranoid, depressed, and irritable, and she developed disturbing self-destructive thoughts but no active suicidality. The fluoxetine dose was increased to 40 mg/day, and the perphenazine dose was lowered from 20 to 16 mg/day because of worsening akathisia. After 3 weeks Ms. C impulsively ran away and superficially scratched her forearms. Over the next week she became more depressed and preoccupied with thoughts of death. After 1 month of treatment, the dose of fluoxetine was increased to 60 mg/day. She then suffered from hypersomnia, poor concentration, diurnal variation, anhedonia, anergy, fatigue, and increased binging and purging. During week 5 she escaped from the hospital and planned to commit suicide, but she was located by hospital security staff. After the fluoxetine dose was increased to 80 mg/day she became violent, banging her head and mutilating herself, and physical restraint was necessary. Although lithium carbonate augmentation was briefly attempted, fluoxetine treatment was discontinued after a total of 6 weeks.

During the next week Ms. C lacerated her forearms and required emergency room treatment. Although less labile, she remained extremely suicidal and required restraint periodically. Her active self-destructive urges abated 1 month after fluoxetine treatment was stopped, although intermittent suicidal ideation persisted. Improvement continued over the next 2 months with perphenazine treatment (32 mg/day), although Ms. C scratched her arms after learning of the sale of her family home. Nortriptyline was added to her regimen, and over the next month she had no further suicidal ideas or intention. Her ability to function markedly improved, and she was discharged 3 months after fluoxetine treatment was discontinued.

Case 4. Ms. D, a 39-year-old former executive, had a history of recurrent major depression, episodic alcohol abuse (in remission), and borderline personality disorder. During the last 8 years she received aggressive pharmacological treatment with little benefit. Trials of monoamine oxidase inhibitors (MAOIs) were moderately successful but were accompanied by intolerable side effects, and ECT produced marked but short-lived improvement. Ms. D had been intermittently suicidal and had taken drug overdoses on three occasions while enraged. However, each suicide attempt, although serious, was a direct request for help, and her suicidal state dissipated rapidly after hospitalization.

Before treatment with fluoxetine, Ms. D had relapsed into major depression after a transient recovery that had followed discontinuation of nortriptyline treatment. Her symptoms included hypersomnia, social withdrawal, irritability, and psychomotor retardation, without suicidal ideation. Fluoxetine treatment was started at a dose of 20 mg/day. Two weeks later, Ms. D was more depressed and was experiencing extreme fatigue, daytime sedation, and persistent negative thoughts that progressed to intense suicidal ideation. For the first time she contemplated obtaining a gun to commit suicide. Her treatment was also complicated by the development of a truncal erythematous pruritic rash, which was initially treated with dexamethasone, then terfenadine. The fluoxetine dose was gradually increased to 60 mg/day over 2 months. She began to think fluoxetine was a "deadly drug," and she developed a strong desire to drink. Despite her poor response, she wished to continue taking fluoxetine, as she knew of other patients who had responded to it only after months of treatment.

By her third month of treatment, at a dose of 80 mg/day, Ms. D remained profoundly depressed. Anger, frustration, and persistent suicidal ideation predominated. After 5 years of sobriety, she drank. Fluoxetine treatment was discontinued, but her symptoms intensified and culminated 2 weeks later in a secret suicide attempt involving diazepam and alcohol. In contrast to her prior attempts, when she had immediately called for help, she was discovered by her sister only when her telephone went unanswered. In the hospital, she disclosed the full extent of her self-destructive thoughts. They included severe suicidal ruminations, dissociative feelings, and the belief that she could not fight or control her suicidal impulses. She believed that fluoxetine would enable her to successfully commit suicide, and she hid this information from others.

In the hospital, Ms. D's profound distress and agitation were partially relieved by chlorprothixene, a neuroleptic with prominent serotonin antagonist effects (3). Her suicidal thoughts diminished over 3 weeks, but profound fatigue and psychomotor retardation returned. Eight weeks after the discontinuation of fluoxetine treatment, tranylcypromine was added to the chlorprothixene, her residual suicidal ideation remitted, and she improved sufficiently to be discharged.

Case 5. Ms. E, a 39-year-old woman with major depression, borderline personality disorder, and temporal lobe epilepsy, had been successfully treated with MAOIs, carbamazepine (1200 mg/day), and clonazepam (0.5 mg every other day). Persistent suicidal thoughts predated pharmacological treatment but had been absent for at least 2 years. She had never made any suicide attempts. Unfortunately, MAOI therapy was complicated by weight gain and virtual anorgasmia. Fluoxetine was substituted for isocarboxazid after a washout period of 2 weeks; the initial dose was 20 mg/day, which was increased after 3 weeks to 40 mg/day. During this time Ms. E was depressed, apathetic, fatigued, and hypersomnolent. Suicidal thoughts reemerged after years of their absence. Pemoline (37.5 mg/day) was added to increase her energy, but the suicidal ideation worsened and she began to fantasize about purchasing a gun for the first time. The fluoxetine dose was increased to 60 mg/day in the sixth week and to 80 mg/day in the eighth week. Ms. E then complained of prominent dissociative symptoms, sedation, and abulia. Fluoxetine treatment was discontinued, and methylphenidate (5 mg/day) was substituted for the pemoline. Although Ms. E felt less depressed, her severe obsessive suicidal thoughts continued. In contrast to her past experience with suicidal feelings, she now embraced these impulses and hid them from the clinicians. She checked the *Physician's Desk Reference* to see if any of her medications were particularly

lethal, and she repeatedly poured out her pills and struggled over taking them. Eleven days after discontinuation of fluoxetine, her suicidal thoughts diminished, but she remained quite depressed. Isocarboxazid treatment was resumed 6 weeks later, and after 1 month her energy, sociability, work performance, and mood were substantially improved and she had no more suicidal thoughts.

Case 6. Ms. F, a 30-year-old woman, had a history of bipolar disorder, multiple personality disorder, pseudotumor cerebri, hypothyroidism secondary to propylthiouracil treatment, and an abnormal EEG. Her history included three significant suicide gestures, the first at age 17 and the last 5 years ago. Intermittent suicidal thoughts had continued during the past 5 years. Past medication trials included tricyclic antidepressants, which were of little benefit, and MAOIs, which led to significant therapeutic responses.

With daily doses of haloperidol (4 mg), carbamazepine (600 mg), clonidine (0.4 mg), thyroxine (150 μg), acetazolamide (750 mg), and diazepam (40 mg), severe anxiety and depression emerged, with self-loathing, anergy, fatigue, hopelessness, suicidal ideation, and social withdrawal. Fluoxetine was added to her complex regimen, and the dose was gradually increased to 40 mg/day over 1 month. After Ms. F developed an erythematous rash, her fluoxetine dose was decreased to 20 mg/day. During this period her condition worsened, with increased feelings of anxiety, dissociation, lethargy, and incapacity. A brief attempt to potentiate treatment by adding pemoline (18.75 mg/day) was unsuccessful. By week 7 she was severely depressed, detached, withdrawn, restless, and agitated; fluoxetine was discontinued. Two days later her internal personalities started shouting at her to commit suicide. During the next 2 weeks she remained depressed and had a Hamilton depression score of 28; hospitalization was recommended, but she declined. Her self-destructiveness continued to intensify; she planned a lethal overdose and put a loaded gun to her head. With family intervention and daily telephone contact, she continued in outpatient treatment. She remained depressed, anxious, and intensely suicidal for 1 month after fluoxetine treatment was abandoned. The severity of her self-destructive thoughts and her need to act on them then abated.

DISCUSSION

Five depressed outpatients and one inpatient, 19–62 years of age, developed intense suicidal thoughts a mean of 26 days (range, 12–50) after initiation of fluoxetine treatment. This state was more intense, obsessive, and violent than anything they previously had experienced. One patient had no prior suicidal ideation (case 2), and only three patients had ever made previous attempts (cases 4 and 6) or gestures (case 3). These intense self-destructive thoughts persisted, and even worsened temporarily, after discontinuation of fluoxetine treatment. They faded in intensity an average of 27 days (range, 3–49) later, but they did not fully abate in most patients until a mean of 87 days (range, 60–106 days) after cessation of treatment.

Four patients received relatively high doses of fluoxetine (60–80 mg/day), but two patients received only 20–40 mg/day. Two patients (cases 1 and 2) developed suicidal ideation while receiving only fluoxetine. The remainder were taking a variety of other medications, which included carbamazepine (cases 5 and 6), neuroleptics (cases 3 and 6), benzodiazepines (cases 5 and 6), and thyroxine (case 6). Three patients also received stimulant trials to combat fluoxetine-induced anergia (cases 4–6), and lithium potentiation was unsuccessful in two patients after suicidal preoccupation had emerged (cases 2 and 3). All patients had previously been treated with MAOIs, and for three (cases 2, 3, and 5), an MAOI had been the last treatment before fluoxetine. Resumption of MAOI treatment (after at least a 6-week fluoxetine washout period) appeared to result in rapid abatement of persistent suicidal ideation in the three cases in which this was tried (cases 2, 4, and 5).

In no case was there evidence that strong preexisting self-destructive urges were activated and energized by fluoxetine. No patient was actively suicidal at the time fluoxetine treatment began. Rather, all were hopeful and optimistic, and the strong obsessive suicidal thoughts apparently emerged de novo after weeks or months of treatment. In four patients (cases 2 and 4–6), these thoughts were accompanied by abject acceptance and detachment. Two patients (cases 4 and 5) tried to conceal their suicidal feelings and impulses and to continue fluoxetine treatment, believing that the drug would eventually enable them to successfully kill themselves!

A great deal has been written on the possible role of serotonin in violence, suicide, and obsessive behavior (4–7), and fluoxetine is known to be a potent and selective serotonergic uptake inhibitor (8, 9). Given this background, we were especially surprised to witness the emergence of intense, obsessive, and violent suicidal thoughts in these patients. Their suicidal thoughts appear to have been obsessive, as they were recurrent, persistent, and intrusive. They emerged without reason but were the patients' own thoughts. It was also remarkable how violent these thoughts were. Two patients fantasized, for the first time, about killing themselves with a gun (cases 4 and 5), and one patient (case 6) actually placed a loaded gun to her head. One patient (case 3) needed to be physically restrained to prevent self-mutilation. Patient 2, who had had no prior suicidal thoughts, fantasized about killing himself in a gas explosion or a car crash. Serotonin may well be related to violent suicidal ideation or action and to obsessional thinking, but the relationship may be complex and fluoxetine may exert a paradoxical response in some patients.

It is always difficult to know whether untoward effects that emerge during pharmacological treatment are a consequence of drug treatment or are coincidental. Alternative explanations should also be considered. Suicidal thoughts may have emerged in these patients because they were not responding to fluoxetine; their underlying depression may have worsened and led to their suicidal states. This is not a compelling argument. Patient 1's Hamilton depression score re-

mained the same, and patient 5 may have had a slight initial antidepressant response. Patients 2 and 4 are presently free from active suicidal ideation even though they are depressed, and all of these patients had been depressed previously but had never been so violently suicidal. Second, it is possible that suicidal thoughts emerged for reasons unrelated to fluoxetine treatment (e.g., loss or abandonment), although no evidence could be found to support this alternative. In fact, no patient was able to articulate a reason for feeling so suicidal. Third, it is possible that other pharmacological factors or interactions may have been involved. Most patients were receiving treatment with other drugs that could have also contributed to this response, although they were free from active suicidal thoughts while taking these drugs before fluoxetine treatment. Fluoxetine can markedly alter the metabolism of concomitantly administered medications (8), and drug interactions may be an important factor. Similarly, their previous histories of treatment with tricyclic antidepressants, MAOIs, or neuroleptics may be relevant risk factors.

There is no simple explanation of why these patients seemed to react so adversely to fluoxetine. It is noteworthy that they all had hypersomnia, fatigue, or psychomotor retardation before or during treatment with fluoxetine. Four patients also complained of a disturbing sense of inner restlessness, and they may have had a form of akathisia (cases 1–3 and 6), which could be a contributing factor. None of the patients had a prominent therapeutic response to fluoxetine, and we have not observed the emergence of suicidal ideation in any patient who was clearly benefiting from this drug.

At the present time we can only state that persistent, obsessive, and violent suicidal thoughts emerged in a small minority of patients treated with fluoxetine. Fluoxetine was the sole pharmacologic agent in only two cases; the other patients were taking a variety of other medications, which may have also contributed to this reaction and thereby complicate interpretation. The purpose of this report is to suggest the surprising possibility that fluoxetine may induce suicidal ideation in some patients. Only additional surveillance will enable us to learn whether this is a widespread or valid concern. In our own experience, this side effect has occurred in 3.5% of patients receiving fluoxetine, which provides an estimated incidence of 1.3%–7.5% with 95% confidence limits. Clinicians should be alert to this possibility and should query patients carefully about suicidal ideation, particularly if they are not responding well to treatment. Recently we have started to inform patients of this risk and have told them that this medication does not always work, that some patients feel worse, and that a few have developed suicidal thoughts. They are instructed to call if they develop side effects or start to feel worse.

At the present time we recommend that this drug be used cautiously and that the practitioner be attentive to the possible emergence of suicidal ideation, even in those patients without a previous history of suicidal thoughts or actions. Patients who have previously been treated with other antidepressants or who develop intense fatigue, hypersomnia, or restlessness while taking fluoxetine may be at risk.

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