Case Study

Emergence of Self-Destructive Phenomena in Children and Adolescents during Fluoxetine Treatment

ROBERT A. KING, M.D., MARK A. RIDDLE, M.D., PHILLIP B. CHAPPELL, M.D., MAUREEN T. HARDIN, M.S.N., GEORGE M. ANDERSON, PH.D., PAUL LOMBROSO, M.D., AND LARRY SCAHILL, M.S.N., M.P.H.

Abstract. Self-injurious ideation or behavior appeared de novo or intensified during fluoxetine treatment of obsessive-compulsive disorder in six patients, age 10 to 17 years old, who were among 42 young patients receiving fluoxetine for obsessive-compulsive disorder at a university clinical research center. These symptoms required the hospitalization of four patients. Before receiving fluoxetine, four patients had major risk factors for self-destructive behavior including depression or prior suicidal ideation or self-injury. Three hypotheses concerning the apparent association between fluoxetine and these self-injurious phenomena are discussed: (1) coincidence; (2) disorganization of vulnerable individuals secondary to drug-induced activation; and (3) a specific serotonergic-mediated effect on the regulation of aggression. *J. Am. Acad. Child Adolesc. Psychiatry*, 1991, 30, 2:179–186. **Key Words:** children, fluoxetine, obsessive-compulsive disorder, self-injurious behavior, suicide.

Despite the widening use of fluoxetine in children with depression, obsessive-compulsive disorder (OCD), trichotillomania, and other conditions, there are few available data on the behavioral side effects of fluoxetine in this age group. In adults receiving fluoxetine, nervousness, anxiety, akathisia, and insomnia are among the most common side effects. Similar side effects, including increased restlessness, hyperkinetic behavior, insomnia, feelings of excitability, and subtle impulsiveness, have been noted in children and adolescents receiving fluoxetine (Riddle et al., 1990 a,b).

A more worrisome potential complication of fluoxetine administration is the possible emergence of intense suicidal preoccupation reported by Teicher et al. (1990a) in an uncontrolled group of adults receiving fluoxetine for treatment of depression. Given the multiple medications and complex psychopathology of these patients, it is unclear what role, if any, fluoxetine played in the emergence or exacerbation of suicidal phenomena. An earlier report by Gorman et al. (1987) of an open trial of fluoxetine in the treatment of panic attacks noted that two nonresponders who dropped out of the study because of adverse side effects became depressed and developed suicidal ideation while taking fluoxetine; only one of the two had a history of depression. To the authors' knowledge, there are no published reports of these phenomena in children or adolescents beyond Teicher and colleague's (1990b) mention of a 15-year-old male without a prior history of depression who hung himself 2 weeks after initiation of fluoxetine for the treatment of OCD.

The current report describes the development of intense self-injurious ideation and/or behavior in six children or adolescents who received fluoxetine for treatment of OCD.

Method

Subjects

The six subjects described in this report are among the 42 children, age 8 to 17 years old, who received fluoxetine alone or in combination with another medication at the Yale Child Study Center between April 1, 1988, and November 15, 1990, for the treatment of primary diagnoses of Tourette's syndrome (TS) without OCD (N = 3), OCD without TS (N = 24), TS with OCD (N = 10), major depressive disorder (N = 3), or trichotillomania (N = 2). One child (Case 2) was among the first 20 subjects enrolled in an ongoing double-blind, placebo-controlled crossover study of fluoxetine (20 mg/day) in children and adolescents with OCD and/or TS. Four subjects were among 22 other children who received fluoxetine for these disorders in an open trial in the Tic Disorders Clinic or Obsessive-Compulsive Disorder Clinic of the Yale Child Study Center or on the Children's Psychiatric Inpatient Service, Yale-New Haven Hospital. One additional child (Case 1) completed the double-blind placebo-controlled trial of fluoxetine with no self-destructive concerns reported during the initial fluoxetine phase of the study; however, obsessional thoughts of self-injury emerged after she was restarted on fluoxetine in an open treatment protocol. The nonsuicidal behavioral side

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From the Yale Child Study Center, Yale University School of Medicine, New Haven, CT.

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Reprint requests to Dr. King, Yale Child Study Center, P.O. Box 3333, New Haven, CT 06510-8009.

effects of fluoxetine in some of these children are described elsewhere (Riddle et al., 1990a,b). The acute medical aspects of Case 4's massive overdose of fluoxetine have been previously reported (Riddle et al., 1989).

Data collection and symptom surveillance varied with the context in which each child was treated.

Case Reports

Case 1

F., a 12-year-old male seventh grader, entered a double-blind, placebo-controlled fluoxetine protocol for treatment of long-standing obsessions and compulsions that included compulsive checking, washing, and arranging of his room and obsessional preoccupations with germs, dirt, and video games. F. was a successful but perfectionistic and socially isolated student who avoided the rough play of peers. Chronic separation anxiety and intermittent school refusal had been present for several years. He was depressed with occasional nonspecific suicidal thoughts, such as that his parents would be better off without him and that life was not worth living. Frequent nightmares, sleepwalking, and night terrors began at age 2 and persisted for several years; these symptoms had not recurred in recent years. At the beginning of the fluoxetine protocol, he was diagnosed as having OCD, separation anxiety disorder, overanxious disorder, and probable dysthymic disorder. The family history was noteworthy for mother's postpartum depression after his birth, the suicides of two second-degree relatives, and compulsive symptoms in several relatives.

Over the first month of the protocol, F. showed a marked clinical improvement in mood as reflected in his Children's Depression Inventory (CDI) (Smucker et al., 1986) score that fell from an initial 30 to 11 (with denial of suicidal thoughts). He became less easily upset and less resistant to attending school. Improved functioning was reflected in his Children's Global Assessment Scale (CGAS) (Bird et al., 1987) score that rose from 40 to 60. However, his OCD symptoms were only slightly improved. He reported feeling "high" since beginning the medication and had increased difficulty falling asleep.

Thirty-eight days after beginning the protocol, F. experienced a violent nightmare about killing his classmates until he himself was shot. He awakened from it only with difficulty, and the dream continued to feel "very real." He reported having had several days of increasingly vivid "bad dreams" before this episode; these included images of killing himself and of his parents dying. When he was seen later that day he was agitated and anxious, refused to go to school, and reported marked suicidal ideation that made him feel unsafe at home as well. The protocol was interrupted, revealing that he had been on fluoxetine, 20 mg q.d. (0.57 mg/kg), since the beginning of the protocol. The medication was discontinued. Examination of his laboratory studies revealed that his whole blood serotonin levels had fallen dramatically from 170 ng/ml just before receiving medication to 11.1 ng/ml after 1 month of fluoxetine treatment. F. was hospitalized at a community hospital for 3 days, during which time his suicidal ideation partially abated. However, he became more depressed and obsessional, and, consequently, on the 9th day after stopping fluoxetine, he was again briefly hospitalized for further evaluation. He appeared depressed, with a CDI score of 27 and acknowledged continued suicidal ideation. His OCD symptoms were again moderately severe, and his overall functioning had deteriorated with a CGAS of 43.

Because of persistent obsessive thoughts of hurting himself (cutting himself with a knife), F. was admitted to a children's psychiatric inpatient unit 17 days after the fluoxetine was stopped. Upset over being hospitalized, he continued to complain of suicidal ideation and threatened to run away or hurt himself, necessitating his transfer to a locked unit. Gradually, he became more settled in the hospital and no longer reported suicidal ideation. Treatment with desipramine was begun during the second hospital week and increased up to 100 mg q.d. The hospital staff was struck by the prominence of separation anxiety, rather than obsessive-compulsive symptoms. He was discharged after a month's hospitalization.

After his discharge, F.'s OCD symptoms increased in intensity. Desipramine, up to 200 mg per day, had no effect on these symptoms and was discontinued. Three weeks after his discharge, fluoxetine treatment was restarted at 20 mg every other day and increased over a month to 20 mg daily, with only a mild decrease in checking. Seven weeks after his discharge, the addition of one extra 20 mg tablet of fluoxetine resulted in complaints of chest pain and nausea. An EKG was normal, and the patient continued on fluoxetine, 20 mg/day. Two days later, F. again reported suicidal ideation but without a plan, and fluoxetine was discontinued.

One month later, F. was begun on clomipramine, which was gradually increased to 175 mg/day over the next 4 months. With clomipramine treatment, F.'s obsessive-compulsive symptoms gradually remitted, and his social and separation anxiety markedly decreased. At follow-up 1 year after discharge, F. showed dramatic improvement with clomipramine treatment; he was attending school with less anxiety, was socially more outgoing and active, and, despite some residual symptoms, no longer met the criteria for any *DSM-III-R* diagnoses, according to his therapist.

Case 2

C., a 10-year-old girl, entered a double-blind placebo-controlled fluoxetine trial because of long-standing obsessional contamination fears and compulsive washing, checking, pathological doubting, counting, and doing and undoing rituals that had worsened despite individual psychotherapy. A bright and capable student, C. had increasingly constricted her outdoor activities because of contamination fears. She did not appear depressed and had no reported history of self-injurious ideation or behavior. Family history was notable for affective illness on both sides and OCD in one parent.

During the first half of the double-blind trial, C.'s OCD symptoms gradually improved, and she became less anxious and constricted in her activities. Her parents described her as more restless and active, but this did not interfere with

her concentration or disrupt her activities, save for her frequently standing on her head. C. had more bruises on her limbs, which she felt were due to minor bumps and falls, secondary to her increased outdoors activity. The protocol was interrupted 6 weeks after the crossover because of worsening OCD symptoms. When the medication code was broken, it was discovered that she had been receiving fluoxetine, 20 mg/day (0.66 mg/kg), for the first 8 weeks. Her whole blood serotonin levels had fallen from a baseline of 140 ng/ml to 9.3 ng/ml after 8 weeks of treatment with fluoxetine, indicating compliance.

C. was started back on fluoxetine, 20 mg q.d. When she was evaluated 4 weeks later, her OCD symptoms had somewhat improved. However, she revealed that she was having increasing thoughts of wanting to bump into or fall off things in order to hurt herself or to pinch herself to experience pain. These thoughts at times were quite strong, but C. had not actually experienced anything more than slight self-inflicted pain by pinching or bumping into objects. She had a few bruises on her legs. C. did not appear depressed. She also once again experienced mild restlessness but not to the same degree as during the double-blind trial.

Case 3

S., a 14-year-old female eighth grader, began fluoxetine treatment for an exacerbation of longstanding obsessive-compulsive symptoms and perfectionistic tendencies that had begun to interfere with her school work and attendance. Always a model student and musician, S. had begun compulsively rereading homework, with the constant feeling she had not mastered it. As a result, she stayed up studying into the early hours of the morning. In an agitated state, she did poorly on an exam and thereafter felt unable to return to school, despite continued compulsive studying. When she was evaluated before medication, she acknowledged feeling depressed with feelings of self-reproach and increased tearfulness but denied suicidal ideation.

From age 3½ years on, S. had manifested a variety of intermittent ego-dystonic obsessions, compulsions, and anxiety symptoms, including: repetitive checking, counting, praying, and washing; unrealistic obsessional doubts that she might have harmed someone or stolen; and mental counter-rituals. She was generally well behaved, even inhibited, albeit often perfectionistic and prone to be upset by changes.

She begun receiving fluoxetine, 20 mg/day (0.38 mg/kg), but continued to study and reread assignments compulsively and remained unable to return to school. About 3 weeks after beginning fluoxetine, she furtively brought a knife to her room and scratched her wrists. She revealed ruminative suicidal thoughts of 3 to 4 days' duration concerning violent ways of killing herself by cutting, shooting, or hurling herself downstairs. She stated she would not kill herself in these ways, because of physical cowardice, but could not promise to refrain if she could find a painless method.

S. was hospitalized on a children's inpatient psychiatric unit and the fluoxetine was increased by the addition of a second 20 mg tablet on alternate days. The following day, she spoke of wanting to hurt herself and die, drew a picture of a dead person on the ground, and picked and bit at her skin. She was placed on one-to-one supervision and remained so throughout this hospital stay. Over the next 10 days, she appeared increasingly withdrawn, labile, and depressed. She spoke agitatedly of hurting herself and had to be restrained when she slammed her chair on her toes, excoriated her arms, and threw herself on the floor. Ten days after admission, the fluoxetine was stopped temporarily, and over the next 2 weeks, she continued to be preoccupied with death. She banged her head and hands on the quiet room wall, picked at her arms to produce deep excoriations, and attempted to scald her hands, to choke herself, and to make herself vomit. Restraints, mitts, and behavioral techniques did little to relieve this relentless self-destructive preoccupation or her intermittent agitation. Periods of food and fluid refusal began, at times requiring IV rehydration.

During the second month after her admission, S. was withdrawn, apathetic, and intermittently anorexic. Her profound self-destructive preoccupations continued with repetitive attempts to injure herself; she frequently insisted, "I'm just waiting for the opportunity to kill myself," and chanted, "kill, kill, kill; die, die, die; pain, pain, pain" over and over. A 10-day trial of imipramine, 25 to 50 mg q.d. provided no apparent relief and was discontinued because of dehydration due to her food and fluid refusal.

At the beginning of the third hospital month, S. was placed again on fluoxetine treatment, 20 mg q.d. on which she remained until almost the end of her stay. She continued to chant and to attempt to hurt herself. Her behavior became increasingly bizarre, e.g., covering the floor with numbered paper squares. She choked and stamped on her teddy bear and cried out, "Bear wants to die with me, don't you?" As a result, a week after the fluoxetine was restarted, she was begun on trifluoperazine, up to a maximum of 13 mg q.d., and benztropine, 0.5 to 1 mg q.d. The dosage of these additional drugs had to be adjusted because of dystonia, anticholinergic effects, and possible confusion. She began to punch herself in the face and bang her head severely enough to inflict bruises and to require x-rays; she also began to strike out at the staff. Periods of improvement, during which she was able to become more involved in the unit's activities and control her self-injurious impulses, were short-lived.

Because of these unremitting symptoms, S. was transferred 3½ months after admission to a longer-term adolescent psychiatric unit in another state. Five days before her transfer, the fluoxetine and trifluoperazine were discontinued, and S. was treated with perphenazine, 20 mg/day. Diagnoses at transfer were OCD, overanxious disorder, and major depression; the staff was in disagreement about the appropriateness of a diagnosis of borderline personality disorder.

At the second hospital, S. continued to take perphenazine. During her first month after transfer, she continued to have prominent suicidal ideation and self-injurious behavior that frequently required restraints or seclusion. Because of symptoms of major depressive disorder, she was placed on desipramine, 100 mg q.d., which produced a blood level of

207 ng/ml in the therapeutic range. Over the next several weeks, however, this appeared to produce further deterioration of her behavior to the point that she daily required restraints. In addition to frequent periods of agitation and driven self-destructive behavior, she also increasingly directed her physical and verbal assaults toward others and injured several staff members. During the fourth month after transfer, after an unproductive trial of lithium augmentation, the desipramine was discontinued, and she was started on a regimen of chlorpromazine, lorazepam, and lithium. Gradually, over the next several weeks, she became calmer. Her aggressive behavior toward herself and others decreased, and her need for restraints or seclusion diminished. Obsessional symptoms no longer appeared to be as prominent.

Nine months after transfer, S. remains at the second hospital and is being treated with chlorpromazine and lorazepam; she is calmer, more able to participate in the daily life of the ward, and better able to reflect verbally about her feelings.

Case 4

R., a 14-year-old female, was placed on an open trial of fluoxetine, 20 mg/day (0.33 mg/kg) for prominent obsessions and compulsions of at least 2 years' duration. These included sexual and contamination obsessions; cleaning, washing, and checking compulsions; and contamination-related food avoidance. At the time the fluoxetine treatment was begun, she was diagnosed as having OCD, dysthymia secondary to OCD, and possible overanxious disorder. In addition to her obsessions and compulsions, her past history included separation anxiety and an episode of sexual abuse. Obsessional fears of dying, which included intrusive thoughts of being burned to death, had been present for several years. At the age of 12 years, in the context of family difficulties, she had recurrent thoughts of killing herself. Over the next year, in the course of psychotherapy, these suicidal thoughts had gradually abated but were replaced by a germ phobia with attendant compulsive washing.

At the onset of fluoxetine treatment, R.'s score on the Hamilton Depression Scale (Hamilton, 1967) was 21, but she denied suicidal ideation. Her score on the Hamilton Anxiety Scale (Hamilton, 1959) was 19. Over the next 2 months on fluoxetine, 20 mg, she showed a dramatic improvement in her obsessions, compulsions, anxiety, and depression. Her Hamilton Anxiety and Depression Scale scores both fell to one. Despite 10 days of missed medication, these improvements were maintained during the third month on medication.

By the fourth month, however, R. experienced increasing depression, agitation, anger, and guilt, and a mild recrudescence of obsessions and compulsions. She had difficulty concentrating at school, where she was impulsive and provocative with teachers. She had periods of feeling confused and overwhelmed and at times felt life was not worth living and that killing herself would be a solution.

At 5 months, despite apparent good compliance with medication, which continued at the same dosage, and increased frequency of psychotherapy, her Hamilton Anxiety Scale score increased to 9, reflecting feelings of severe tension, moderate anxious mood and restlessness, and mild insomnia and somatic complaints. Her Hamilton Depression Scale score also rose to 10; she continued to have thoughts of killing herself to relieve her obsessions, but had no specific plans and denied any intentions to act on her thoughts. At 6 months, the patient stopped taking fluoxetine because of contamination fears after she dropped the tablets in an airport. Six days later, when returning from a trip, she was overwhelmed with obsessional thoughts, including thoughts of killing herself, and made a suicide attempt with 23 ibuprofen tablets.

R. was admitted to an adolescent inpatient psychiatric unit and restarted on fluoxetine, 20 mg/day, which was increased after 2 weeks to 40 mg q.d. Over the next 2 weeks, R. was noted to be very anxious, pulling out hair, biting her nails, and hitting her legs. Her deliberate attempts to slam her hand on a table and in a door necessitated restraints and x-rays. Because of her agitation, buspirone, 5 mg t.i.d., was started. Two days later, on the 31st hospital day, fluoxetine was discontinued and perphenazine, 8 mg b.i.d., and cogentin, 0.5 mg b.i.d., were begun. Over the next 2 days, R. remained agitated, and her buspirone was increased to 10 mg t.i.d. Her agitation decreased transiently, but 5 days later, she burned her wrist with a lighter and again became more agitated. On the 46th day after her admission, her buspirone was further increased to 20 mg b.i.d. Nonetheless, she continued to be irritable, had difficulty sleeping, had pressured speech, and complained of racing thoughts and distractibility. Because of these apparently hypomanic symptoms, lithium was begun on the 51st hospital day and gradually increased to 600 mg b.i.d. With the initiation of lithium, her behavior and concentration improved markedly. Her OCD symptoms during this difficult time were minimal. Three months after admission, she was discharged to the care of her outpatient therapist on lithium, perphenazine, and buspirone.

R. did well with outpatient treatment, and, over the next 3 months, her medications were gradually discontinued. However, 6 months after discharge, her OCD symptoms recurred, and she was restarted on fluoxetine, 20 mg q.d. Over the next 6 weeks, she faced several major stresses, including the suicide of a hospital friend, the approaching anniversary of her hospitalization, and the impending long vacation of her therapist. A friend she was visiting in another town was hospitalized for suicidal ideation, and R. purposely burned her own hand with a cigarette. On returning home, she felt irritable and depressed. Over the next few days, she felt increasingly "not safe" because of suicidal ideation and the impulse to hurt herself.

R. was readmitted to the hospital where she was noted to have occasional racing thoughts, difficulty concentrating, pressured speech, and dysphoric, anxious, labile affect. Obsessive compulsive symptoms were minimal and fluoxetine was discontinued. R.'s mood stabilized, her suicidal ideation gradually cleared, and she was discharged 2 weeks after admission with a diagnosis of borderline personality disorder, adjustment disorder with depressed mood, and obsessive-compulsive disorder in remission.

Case 5

J., an obese 12-year-old boy, was admitted to a children's inpatient psychiatric unit because of a serious assaultive episode at school. His long history of multiple motor and phonic tics, obsessions and compulsions, attentional difficulties, and impulsive, oppositional behavior had resulted in three previous psychiatric hospitalizations beginning at the age of 6 years. Three years of treatment with haloperidol had reduced tic severity, but the treatment was discontinued because of dyskinesias. A subsequent 18-month trial of clonidine had been discontinued a year before admission because of only minimal improvement in his tics, and no improvement in his obsessions and compulsions. J. had chronic low self-esteem and was sensitive to rejection; prior self-destructive behavior included slamming his hand against a wall and wrist scratching.

At admission, J. was angry and provocative. He reported ideas of reference when angry; obsessive thoughts about death, destruction, and satanic themes; and occasional auditory hallucinations of demon voices. Because of these intrusive thoughts and compulsive touching, checking, and counting rituals, J. began receiving fluoxetine, 20 mg q.d., which was increased 2 weeks later to 40 mg/day (0.52 mg/kg). Mild sedation was noted that improved with a switch to evening administration. J.'s obsessive compulsive symptoms improved over the next 4 weeks, and he was discharged to outpatient care on fluoxetine, 40 mg q.d.

Two weeks after his discharge, J. became upset after a disappointment and impulsively ingested 94 capsules of fluoxetine with the intention of killing himself.

At readmission, J. reported feeling hopeless, helpless, and depressed, with continued suicidal ideation and the thought "I'm going to die soon." He reported that he had had suicidal thoughts intermittently since the age of 4 years. Ideas of reference, occasional auditory hallucinations, and possible delusions were also present. After an extended evaluation, J. was transferred to a long-term psychiatric hospital where he remained over the next year and a half with gradual improvement in his intermittent explosiveness on lithium and propranolol.

Case 6

D. was a 17-year-old honors student with a 10-year history of prominent motor and phonic tics and a more recent onset of OCD. In addition to many simple and complex motor and vocal tics, which were only partially controlled on clonidine, 0.2 mg q.d., D. had compulsive touching, washing, counting, and needed to perform complex mathematical calculations in his head. Despite these dramatic symptoms, D. functioned well academically, socially, and at home. Fluoxetine was begun at 20 mg q.d. and was increased 5 months later to 40 mg, producing a substantial improvement in his OCD symptoms. About 7 months after his fluoxetine dose was increased, D. experienced an exacerbation of OCD symptoms. Facing the prospect of an important exam, D. took, on his own initiative, an extra 20 mg tablet on each of the three mornings before the exam, yielding a maximum dose of 60 mg daily (0.73 mg/kg), then resumed his regular dose of 40 mg q.d. He felt he did extremely well on the exam.

Two weeks later, D. unexpectedly called home from school in a state of extreme agitation, terrified by intense, ego-dystonic, obsessional suicidal ideation that had increased in intensity over the preceding week, coinciding with his honors French class reading Madame Bovary and Camus. When interviewed later that day, D. was distraught, frightened, and tearful. He described intense suicidal obsessions, including the powerful urge that morning to throw himself in front of a car. He denied feeling depressed and emphasized the intrusive, ego-dystonic, obsessional nature of his suicidal ideation. Although in the past, like many patients with Tourette's syndrome, obsessional concerns had become "stuck in his head," these had never before included self-destructive or suicidal impulses. Indeed, D. felt life had been going generally well for him. One significant stressor was the deteriorating health of his sister, who had a chronic, potentially fatal illness. However, D. was insistent that her ill health did not make him feel suicidal but rather "just the opposite"—all the more eager to live.

Fluoxetine was discontinued, and a change in curriculum was arranged. Although hospitalization was initially contemplated, D. remained at home, and the driven suicidal ideation disappeared over the next 2 to 3 days. Five days later, his mother noted that, compared with recent weeks, D. appeared calmer with less pressured speech and less troubled by recent uncharacteristic absentmindedness.

Discussion

Three boys and three girls, age 10 to 17 years old, developed intense self-injurious ideation or behavior while receiving fluoxetine for treatment of obsessive-compulsive disorder. Comorbid diagnoses at the initiation of fluoxetine treatment included: Tourette's syndrome (two cases); oppositional disorder (one case); obsessive compulsive personality (one case); social and separation anxiety (one case); and probable dysthymic disorder (three cases). A history of prior suicidal ideation was obtained in three subjects, one of whom also had a history of self-injurious behavior.

While receiving fluoxetine, 20 to 60 mg/day (corresponding to 0.33 to 0.73 mg/kg), de novo or intensified self-injurious ideation or behavior emerged that was severe enough to require psychiatric hospitalization in four cases. The interval between the initiation of fluoxetine and the appearance of these symptoms was 1 month or less (N = 3), 2 months (N = 1) and 6 months or more (N = 2). One patient (Case 6), who developed suicidal ideation about a week after increasing his fluoxetine to 60 mg/day, had tolerated lower doses for almost a year without such symptoms. One patient (Case 2) developed obsessional thoughts and impulses about injuring herself 3 to 4 weeks after beginning an open trial of fluoxetine, 20 mg q.d. but had not reported such symptoms during an earlier 8-week double-blind trial of the drug at the same dosage. In two other cases, recrudescent OCD symptoms led to a second trial of fluoxetine that was followed by the reappearance of suicidal ideation about 7 weeks later (Case 1 and 4).

The relationship of these emergent self-destructive phe-

nomena to the vicissitudes of the subjects' other symptoms was variable. One subject (Case 5) had experienced substantial improvement in his OCD symptoms before his impulsive suicide attempt. Despite insomnia and feeling "high," another subject (Case 3) showed marked improvement while being treated with fluoxetine in his preexisting dysthymia and overall functioning and mild improvement in his OCD symptoms before the sudden onset of violence filled nightmares and intense suicidal ideation. Three patients made suicide gestures or attempts, one of which involved a massive overdose of fluoxetine. Three patients manifested persistent, driven self-injurious behavior and/or ideation that required restraints, seclusion, or one-to-one nursing care. Suicidal ideation or self-injurious behavior persisted up to 1 month after the fluoxetine was discontinued.

There are several possible explanations for the emergence of suicidal ideation and self-destructive behavior in these children and young adolescents during fluoxetine treatment.

First, the self-destructive behavior or ideation observed in this study may be only coincidentally related to fluoxetine. Although the subjects received fluoxetine for symptoms of well-defined OCD, they all had complex, long-standing psychiatric difficulties and had sought treatment in a university-based setting because of increasing distress. Suicidal and self-destructive phenomena are certainly not uncommon in the clinical vicissitudes of such children. Four of the subjects in this study had one or more major (albeit nonspecific) risk factors for suicidal behavior before being treated with fluoxetine, namely depression and/or a history of suicidal ideation or self-destructive behavior. Whether this diverse group of vulnerable children would have been as likely to develop the same self-destructive phenomena in the absence of fluoxetine cannot be definitively answered without data from untreated or alternately treated contrast groups. The variable time interval and, in some cases, the occurrence of significant psychosocial stresses between the initiation of fluoxetine and the appearance of suicidal phenomena make it difficult to conclude with complete confidence that fluoxetine was responsible in all of the cases for these patients' self-destructive symptoms. The individual case histories have been reported here in some detail to illustrate the complexity of making such a determination.

A second possibility is that the emergence of suicidal and/or self-destructive phenomena during fluoxetine treatment was related to or a consequence of medication-induced agitation, disorganization, or mood changes. As the authors have reported, a substantial proportion of children receiving fluoxetine experience motor restlessness, insomnia, social disinhibition, or an internal sense of excitation (Riddle et al., 1990a,b). The self-destructive phenomena described here may, in some cases, represent a response to fluoxetine-induced agitation in otherwise vulnerable children. For example, recent epidemiological data suggest that at least one form of anxiety disorder, panic disorder, is a potent risk factor for suicidality, even in the absence of substantial depression (Weissman et al., 1989). In addition to their obsessive compulsive symptoms, three of the subjects described here had significant histories of general, social, and/or separation anxiety. It is possible that fluoxetine-induced agitation may have had a particularly severe and disorganizing impact on these already anxious children.

Fluoxetine and other antidepressant medications are also associated with other adverse psychological side effects. In clinical trials of the use of fluoxetine in adults, the manufacturer reported mania or hypomania in 0.78% of patients receiving the drug (cited in Sholomskas, 1990). Mania has also been reported in a patient receiving fluoxetine for panic disorder (Sholomskas, 1990). These deleterious psychological side effects are not unique to fluoxetine. Tricyclic antidepressant treatment may also result in mania or hypomania, psychosis or exacerbation of depressive delusions (Nelson et al., 1979); sleep and dream disturbance; paradoxical aggression (Rampling, 1978); or worsening of depressive symptoms (Damluji and Ferguson, 1988) or of borderline personality disorder (Soloff et al., 1986).

The possible precipitation of suicidal ideation may also not be unique to fluoxetine. The four patients whom Damluji and Ferguson (1988) reported as experiencing desipramine-induced exacerbation of major depressive symptomatology all developed suicidal ideation that was not present before treatment. In a survey of 1,017 depressed patients receiving pharmacotherapy at the Massachusetts General Hospital in 1989, Fava and Rosenbaum (1990) found 12 patients who became suicidal only after antidepressant treatment was initiated. They concluded that the frequency of suicidality occurring after fluoxetine given alone ($N = 6$) was not significantly different from the rate for tricyclics given alone or in combination with fluoxetine or lithium. It is of interest, however, that at least one of the subjects in the present study (Case 1), who developed violent dreams, increased anxiety, and persistent suicidal ideation while receiving fluoxetine, subsequently tolerated tricyclic medication without adverse effects and indeed showed a dramatic therapeutic response to clomipramine, a tricyclic serotonin reuptake blocker.

Three subjects (Cases 1, 3, 4) remained agitated with prominent suicidal ideation for 3 or more weeks after a discontinuation of the fluoxetine. In two of these cases, subsequent to their decompensation, the staff considered a diagnosis of borderline personality diagnosis. Once disorganized and regressed, it was difficult for these three children to reconstitute their previous rigid, yet fragile defenses.

Many patients tolerate fluoxetine well with only minor side effects. Indeed, in a double-blind study in depressed adult outpatients, fluoxetine appeared more effective than mianserin or placebo in reducing suicidal feelings (Muijen et al., 1988). If the emergence of self-injurious phenomena is a side effect of fluoxetine, it remains unclear what the biological or psychological risk factors are for these side effects. In terms of baseline symptom severity, comorbidity, or functional impairment, the subjects who developed self-injurious symptoms while receiving fluoxetine did not, as a group, appear to differ substantially from those subjects who did not. All 42 subjects received at least 20 mg q.d. of fluoxetine. Save for Case 6, who transiently took 60 mg (0.73 mg/kg) of fluoxetine for 3 days, the subjects who developed self-injurious symptoms were not on a higher absolute or mg/kg dose of fluoxetine than those who did

not develop such symptoms.

Another unanswered question concerns the broader impact of fluoxetine's antiobsessional action on obsessional children's overall psychological functioning. Although pharmacological treatment of OCD symptoms can be beneficial, dynamic theories of OCD conceptualize these symtoms as binding or defending against other anxieties in complex ways (King and Noshpitz, 1991). Like other groups of children with OCD, the children in this series were diverse in their underlying personalities, which ranged from the compulsive and perfectionistic through the impulsive. The impact of antiobsessional medication on the overall personality functioning of obsessional children deserves further study.

A third and theoretically most intriguing possibility is that the emergence or intensification of self-destructive behavior and ideation during treatment is due to a specific effect of fluoxetine on the regulation of aggression directed either outward or toward the self. Alterations in serotonergic metabolism have been implicated in a variety of violent phenomena, including, in animals, certain types of aggressive behavior (Olivier et al., 1990) and, in humans, completed suicide, suicide attempts, impulsive violent acts, and obsessions of violence (Coccaro, 1989; Brown et al., 1990; Leckman et al., 1990; Roy and Linnoila, 1990).

Preclinical studies have shown that fluoxetine has complex effects on serotonin regulation that vary over time. In rats, although presynaptic serotonin reuptake is promptly blocked by specific reuptake blockers, such as fluoxetine, there is an initial marked *decrease* in the firing activity of serotonergic neurons. It is only with the apparent desensitization of the presynaptic serotonin autoreceptor, which may take at least 2 weeks to develop, that the inhibition of serotonin release decreases, and the neuronal firing rate recovers (Blier et al., 1987, 1988, 1990). Postsynaptic receptor desensitization has not been observed in animal studies. It is thus possible that the net effect of acute fluoxetine administration may to be to depress serotonergic functioning, while continued treatment may enhance serotonergic tone. In addition, fluoxetine may alter the balance between the serotonergic system and related neurotransmitter systems (Baldessarini and Marsh, 1990).

Unfortunately, the time course and diversity of the fluoxetine's action in humans is less well studied. Some effects of the drug, such as insomnia, agitation, and restlessness, seem most prominent when medication is first started. The antidepressant, antiobsessional, and antipanic effects of fluoxetine, however, may require at least 8 weeks to be fully manifested (Gorman et al., 1987; Liebowitz et al., 1989; Schweizer et al., 1990). Thus, some patients may experience the adverse effects of fluoxetine before its therapeutic effects are fully apparent. In addition, some patients are more prone to these adverse effects (Gorman et al., 1987). These data suggest that fluoxetine has diverse neuropharmacological effects that may vary over time and across individuals. Additional complexity is added by the existence of several 5-HT receptor subtypes; whether these diverse receptor subtypes play distinctive roles in specific psychiatric illnesses or the response to fluoxetine remains to be explored (Montgomery and Fineberg, 1989). It is not clear which of fluoxetine's many effects on serotonergic functioning might produce suicidal or perseverative self-destructive symptoms or whether these possible side effects are shared by other serotonin reuptake blockers, such as clomipramine or fluvoxamine.

Distinguishing among these three alternative hypotheses is not possible on the basis of the uncontrolled clinical material presented here. However, the violent nightmares of Case 1 and the initial compulsive self-injurious preoccupations of Cases 2, 3, and perhaps 4 appear to be more than coincidentally related to fluoxetine administration. Additional clinical and neurobiological research is needed to characterize more carefully those children and adults who experience adverse responses to fluoxetine. Imaging studies and assays of platelet receptor functioning, neurotransmitter metabolite levels in cerebrospinal fluid, and response to pharmacological challenge agents would be of particular interest.

Like all psychotropic agents, the behavioral and neuropharmacological effects of fluoxetine are complex and variable. Careful clinical scrutiny of patients both before and during treatment is essential both to understand better the drug's manifold effects and to detect adverse reactions. As fluoxetine and other medications are used in increasing numbers of younger patients with a wide range of psychopathology, vigilance is needed to detect potentially deleterious behavioral side effects.

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