

### Violent acts associated with fluvoxamine treatment

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine have been associated with suicide attempts and violent acts.<sup>1,2</sup> We report 3 female patients with refractory panic disorder who, during fluvoxamine treatment, impulsively hit family members.

#### Case 1

A 32-year-old woman experienced abrupt onsets of palpitations and shortness of breath during the last 9 years. She could not enter reinforced concrete buildings or ride on elevators because she had a fear of closed spaces, and she could not go out alone because of anxiety regarding her next attack. This concern was associated with the development of avoidant behaviour. She was diagnosed with panic disorder with agoraphobia and was first treated, unsatisfactorily, with 25–75 mg of clomipramine and several anxiolytics daily because of anticholinergic side effects.

The woman gradually became depressed and was administered 20 mg of fluoxetine and 5 mg of bromazepam daily for 2 months; her medication was then changed to 40 mg of fluoxetine and 1.5 mg of lorazepam daily for about 6 months. However, this medication regimen did not completely suppress her panic attacks or ameliorate her depressive symptoms. The woman was then prescribed 50 mg of fluvoxamine and 2 mg of ethyl loflazepate daily for 1 week, and the fluvoxamine dosage was increased weekly to 150 mg/day. Six

weeks after the initiation of fluvoxamine, the woman became irritable and aggressive, and she expressed impulsive violence during disagreements with her husband and mother. Two days after the fluvoxamine dosage was decreased by half (to 75 mg/day) and coadministered with 20 mg of fluoxetine, the abnormal behaviour stopped.

#### Case 2

A 29-year-old woman began to experience sudden palpitations and shortness of breath when she cleared snow from the front of her house 3 years previously. She sometimes had to be taken to hospital by ambulance when she had a panic attack and would not go out alone because of her fear of the next attack. She was diagnosed with panic disorder with agoraphobia, which was unsatisfactorily treated with 50–75 mg of amoxapine, 25 mg of trazodone and 2–3 mg of ethyl loflazepate, daily, for 6 months. She gradually became depressed and was prescribed a regimen of fluvoxamine (up to 150 mg/day) with coadministration of amoxapine and ethyl loflazepate. After 2 months of treatment, her panic attacks had been, to a large extent, alleviated. She could even ride on the subway alone. However, she gradually began to exhibit signs of irritability and nervousness; she became easily excited when she argued with her husband and was impulsively violent with him. The woman was admitted to a psychiatric hospital for 1 week. Fluvoxamine was discontinued, and 75 mg of amoxapine, 200 mg of sulphiride, 3 mg of ethyl loflazepate and 5 mg of bromaz-

epam was initiated. With this change, the woman's irritability was alleviated and the violence stopped.

#### Case 3

A 28-year-old divorced woman with a 10-year history of episodic obsessive-compulsive disorder (OCD) had been experiencing palpitations and shortness of breath since she was 23 years old. A recurrent fear of an explosion forced her, when outside, to walk in the centre of the street. She was diagnosed with OCD and panic disorder with agoraphobia, which was unsatisfactorily treated with 100 mg of sulphiride, 20 mg of amoxapine and 0.8 mg of alprazolam or with 50 mg of doxepin, 10 mg of prazepam and 2 mg of ethyl loflazepate for about 6 months. When the woman became depressed, she was given 50 mg of fluvoxamine daily, with coadministration of 30 mg of amoxapine and 2 mg of ethyl loflazepate. Fluvoxamine dosage was increased weekly up to a maximum of 150 mg/day. After a month on this regimen, she exhibited signs of irritability and aggressive behaviour, expressing impulsive violence toward her mother. Fluvoxamine treatment was discontinued; sulphiride, mianserin and bromazepam were initiated, and the woman's abnormal behaviour ceased.

#### Discussion

All 3 cases of refractory panic disorder were associated with depressive symptoms. Tricyclic antidepressant treatment was unsatisfactory because of anticholinergic

side effects, but it ameliorated the patients' symptoms to a certain extent. When fluvoxamine was coadministered with ethyl loflazepate or small doses of amoxapine for 1–2 months, patients exhibited signs of irritability and impulsive aggressive behaviour. No other antidepressants used in these cases induced such behaviour. Prompt discontinuation of fluvoxamine in cases 2 and 3 and the reduction of fluvoxamine by half and coadministration of fluoxetine in case 1 reversed the symptoms. In case 1, fluoxetine treatment did not elicit the aggressive behaviour that treatment with fluvoxamine did.

Serotonergic abnormalities have been proposed as a neurobiological basis for aggression and impulsivity.<sup>3</sup> The aggressive behaviour in these cases may be related to the fact that fluvoxamine is a more selective serotonin reuptake inhibitor than fluoxetine.<sup>4</sup> Some reports have described the beneficial effect of SSRIs on impulsivity and aggression.<sup>5,6</sup> However, we wish to draw attention to the emergence of paradoxical effects such as impulsivity and aggressive behaviour induced by fluvoxamine treatment.

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### Long-term treatment with clozapine in an adult with autistic disorder accompanied by aggressive behaviour

Recent clinical studies have reported beneficial effects of risperidone and olanzapine in autism and other pervasive developmental disorders,<sup>1,2</sup> but clozapine has received little attention.<sup>3</sup> We describe the effects of clozapine in an adult with autistic disorder accompanied by disruptive behaviour.

E.B., a 32-year-old man, was diagnosed with autism at the age of 2. Deficit of development of spoken language and profound mental retardation (IQ = 20) were observed, and managing temper tantrums, impulsive behaviour and self- and others-directed aggressiveness became impossible by the age of 18. The patient was admitted to hospital frequently for self-inflicted injuries and was repeatedly admitted to various institutions for harming his parents and destroying household items. Pharmacological mono- or multitherapy was unsatisfactory due to poor clinical efficacy and the emergence of extrapyramidal side effects, including severe dystonia. Drugs used for several months during the

course of treatment included haloperidol (up to 50 mg/day), thioridazine (up to 600 mg/day) and clotiapine (40 mg/day), and diazepam (up to 15 mg/day) for several years.

At the time of initial observation, when he was 27, Clinical Global Impression (CGI) rating was 7 and clinician-rated Visual Analog Scale (VAS) scores were 95 for aggressiveness, 15 and 10 for social and eye contact, respectively, 82 for irritability and 12 for talkativeness.<sup>2</sup> Treatment with clozapine was initiated after routine ECG, EEG and blood tests, and was progressively increased, reaching the maintenance dose of 300 mg/day (100 mg at 8 am, 12 noon and 4 pm) within 6 weeks. Treatment continued throughout the 5-year period (age 27 to 32), during which time regular blood testing was done.

Clinical improvement was evident after 2 months of therapy. After 5 years of therapy, the patient showed marked improvement of aggressiveness and social interaction, and VAS scores were 15 for aggressiveness, 40 and 55 for social and eye contact, respectively, 35 for irritability and 45 for talkativeness. His CGI score was 4. Extrapyramidal side effects, white blood cell count changes, significant sedation or delayed reaction time were not observed. Self- and others-directed aggressiveness and temper tantrums are no longer observed. The patient's social skills, in terms of group interaction, meeting with unfamiliar people and simple monosyllabic dialog, have dramatically improved. Ritualistic behaviour is also moderately reduced (Yale-Brown obsessive-compulsive scale score was 11 compared with 17 before therapy).