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Successful Treatment of Fluoxetine-Induced Dystonia With Low-Dose Mianserin

Selective serotonin reuptake inhibitors (SSRI) may cause extrapyramidal side effects (EPS). Akathisia, dystonia, dyskinesia, and parkinsonian symptoms have been reported as a result of treatment with the SSRIs fluvoxamine, sertraline, and paroxetine (1). However, fluoxetine has been implicated in most cases (2–4).

Acute dystonia is an EPS characterized by brief or prolonged muscle contractions that result in abnormal postures or movements (5). Fluoxetine-induced dystonia is apparently more common than previously assumed (4), and a number of recent cases have been successfully treated with anticholinergic compounds and antihistamines (6–9).

Agents with antiserotonergic properties (ritanserin and cyproheptadine) appear to be effective in the treatment of neuroleptic-induced EPS (10,11). Mianserin, an antidepressant with strong central serotonin-blocking activity (12), was found beneficial in a patient with obsessive–compulsive disorder in whom acute akathisia developed during the course of fluvoxamine administration (13). A positive therapeutic effect of mianserin (15 mg/day) also has been noted in lithium-induced akathisia (14) and akathisia-like behavior after electroconvulsive therapy (15). Pharmacologic studies of dopamine–serotonin interactions have shown that serotonin antagonists, including mianserin, reduce haloperidol-induced catalepsy in rats and acute dystonia and parkinsonism in monkeys (16,17). It is assumed that fluoxetine-induced dystonia may be related to the inhibitory effect of serotonin stimulation on dopamine transmission in the nigrostriatal pathway (6,18). We have hypothesized that the administration of an agent with 5-HT2 antagonistic properties, such as mianserin, would alleviate fluoxetine-induced dystonia. We present a case report demonstrating that low-dose mianserin is useful in the treatment of acute fluoxetine-induced dystonia.

Case Report

A 25-year-old technician was admitted to our psychiatric hospital with severe depression with psychotic features. He had a 6-week history of depressed mood, anhedonia, suicidal thoughts, and severe insomnia. Mood-incongruent psychotic features, delusions of persecution, and imperative auditory hallucinations were noted 3 days before hospitalization. The patient had first been admitted to our hospital 2 years earlier at age 23 with symptoms of dysphoric mania and distractive and inappropriate behavior. Treatment with haloperidol (dose range, 10–30 mg/day) ameliorated the symptoms of mania and normalized the disturbed behavior. Subsequently, however, the patient refused a trial with a mood stabilizer and was discharged at his own request. According to his family physician, he displayed only partial remission of symptoms and continued to demonstrate a substantial functional decline. Psychiatric history revealed that the patient's mother had had major depressive disorder and that hyperthymic personality features had been present since his early adolescence.

His medical history was unremarkable, and the patient denied exposure to drugs. Physical examination at this admission was normal, and results of laboratory tests, including blood count, liver and thyroid functions, and urinalysis, were within normal limits. The diagnosis was bipolar disorder, depressive episode with psychotic features; a regimen of fluoxetine (20 mg/day), haloperidol (10 mg/day), and trihexyphenidyl (5 mg/day) was initiated. Within 7 days of the combined treatment, the psychotic component of the syndrome resolved. Two weeks later, the haloperidol and trihexyphenidyl were gradually discontinued, and the patient continued to receive fluoxetine (20

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mg/day). After 6 weeks, the fluoxetine dose was increased to 40 mg/day because of persistent depressive symptoms. Two days later, he complained of stiffness of the neck and trunk and had trismus and sustained muscular contractions of the upper and lower extremities. These motor phenomena were associated with painful sensations, severe anxiety, a sense of desperation, and aggravation of suicidal ideation. The patient claimed that this distressing experience was similar to the one induced by haloperidol at the time of his first hospitalization. We interpreted the state as fluoxetine-induced acute dystonia. Oral administration of trihexyphenidyl (5 mg) failed to alleviate the dystonia, and diphenhydramine (50 mg per os) reduced the anxiety but not the dystonia. On the basis of his partial response to anticholinergic and antihistaminic compounds, we decided to introduce the antiserotonergic agent mianserin (15 mg per os). Twenty minutes after its administration, the trismus and muscle contractions disappeared, as did the painful sensations and the affective component of the dystonia. Four days later, he was seen once again with the clinical picture of acute dystonic reaction. His symptoms did not change after taking a placebo but resolved completely within 30 min after mianserin (15 mg) administration. Because of compliance problems, the fluoxetine treatment was stopped, and the patient continued taking mianserin for the next 3 days. There was no recurrence of dystonia. He was switched to imipramine (≤200 mg/day), and 8 weeks later, when a substantial improvement in depression was noted, the imipramine was gradually discontinued and treatment with a mood stabilizer, carbamazepine, was initiated.

Discussion

Fluoxetine is a widely used SSRI with a generally well tolerated side-effect profile. Coulter and Pilans (4) monitored the adverse reactions to fluoxetine in 5,555 patients over a 4-year period and found that EPS was the fifth most frequent side effect (rate, 2–3/1,000) after agitation/anxiety, diarrhea, nau-

TABLE 1. *Clinical characteristics of reported patients with acute dystonic reaction to fluoxetine (N = 14)*

Reference	Age (yrs)/sex	Dose of fluoxetine (mg/day)	Duration fluoxetine treatment	Concomitant drug	Type of dystonic reaction	Treatment of dystonia	Additional information
Meltzer et al 1979 (6)	25/M	30	4 days	None	Dystonia and parkinsonism	Trihexyphenidyl	
Recoppa et al 1990 (7)	22/F	80	3 mos	Levothyroxine, 0.075 mg/day	Muscle spasms of face and neck	Diphenhydramine, 50 mg/day	Dystonia occurred 10 days after fluoxetine dose was increased from 20 to 80 mg/day
Black & Uhde 1992 (8)	39/M	80	9 mos	None	Dysarthria, tongue stiffness	Benztropine, 1 mg	Dystonia occurred within days after dose was increased from 70 to 80 mg/day
Dave 1994 (9)	54/F	20	4 wks	None	Eye blepharospasm; lip tremor, trunk dystonia	Benztropine	
Coulter & Pillans 1995 (4)	88/F	20	13 days	None	Acute dystonia, torticollis	Fluoxetine withdrawal	
	32/M	80	7 days	None	Mild dystonia		
	71/M	20	1 mo	Thyroxine, 0.05 mg/day; ranitidine, 150 mg/day	Opisthotonus; rigidity		
	73/M	60	4 mos	Lithium carbonate, 750 mg/day	Opisthotonus, ataxia	Fluoxetine withdrawal	Dystonia occurred 2 days after lithium was started
	74/F	20	14 days	Trifluoperazine, 2 mg/day (long-term)	Trismus	Fluoxetine withdrawal	
	70/F	20	1 mo	Metoclopramide, 30 mg/day for 1 mo	Dystonia tremor	Fluoxetine withdrawal	Metoclopramide for nausea
	67/F	20	10 mos	Carbamazepine, 600 mg/day for 10 mos; captopril, 25 mg/day for 2 yrs; trimipramine, 100 mg/day for 8 yrs; lithium carbonate, 750 mg/day for 8 yrs	Dystonia of right side of head	Fluoxetine continued with careful follow-up	
	27/F	20	4 mos	None	Spasms of the right leg	Fluoxetine withdrawal	
Poyurovsky et al (current study)	25/M	40	9 wks	None	Trismus, spasms of extremities	Mianserin, 15 mg/day	

sea/vomiting, and insomnia. Of the 15 patients with EPS, eight had dystonic reactions. Table 1 shows the clinical characteristics of all 14 patients with acute dystonic reactions to fluoxetine reported in the literature. These included seven women and seven men, aged 22–88 years. Doses varied from 20 mg/day fluoxetine to 80 mg/day. For seven patients, the acute dystonic reaction developed within the first 4 weeks of fluoxetine administration. Symptoms included muscle spasms of the face, neck, or extremities; trismus; blepharospasm; torticollis; and opisthotonus. In eight patients, fluoxetine was the only psychotropic compound used. Discontinuation of fluoxetine and administration of an anticholinergic (trihexyphenidyl or benztropine), antihistaminic (diphenhydramine), or, in our case, antiserotonergic agent (mianserin), led to an improvement in the dystonia (Table 1).

The dystonias induced by neuroleptic agents and fluoxetine, or more broadly, the SSRIs, are clinically indistinguishable. Indeed, in our case, the same dystonic reaction was detected during the patient's previous haloperidol exposure. This is also true for neuroleptic- and antidepressant-induced akathisia (13,18).

As in neuroleptic-induced dystonia, the majority of cases of fluoxetine-induced dystonia emerge during the initial period of administration and are related to the recent introduction of the drug or a dose increase. Fluoxetine-induced dystonia also seems to respond to established pharmacologic treatments for neuroleptic-induced dystonia: dose reduction or drug discontinuation with the administration of anticholinergic agents or antihistamines (18).

The pathophysiologic mechanisms of fluoxetine-induced dystonic reactions remain obscure. It seems that some individuals may be more vulnerable to the development of SSRI-induced EPS, especially patients with current or prior neuroleptic exposure or patients with elevated blood levels of SSRIs, particularly fluoxetine, because of rapid dose increase (18). Our patient was exposed to haloperidol before the occurrence of fluoxetine-induced akathisia, an exposure that may contribute to the emergence of iatrogenic EPS. Furthermore, the increase of the fluoxetine dosage (20–40 mg/day) may be an additional contributing factor to the occurrence of fluoxetine-induced dystonia in our patient. Our observation of the beneficial effect of mianserin in the treatment of acute fluoxetine-induced dystonia is consistent with the reported beneficial effects of mianserin in acute fluvoxamine- (13) and neuroleptic-induced (20) akathisia. It is unclear why our patient did not respond to anticholinergic and antihistaminergic agents, which are usually effective in neuroleptic-induced dystonia and have been reported useful in some cases of SSRI-induced dystonia (6,8,9,18). However, it is still possible that in some patients, direct blockade of serotonergic activity is required to alleviate fluoxetine-induced akathisia. Although mianserin has unspecific sedative effects caused by its antihistaminergic activity, it seems unlikely that sedation plays a critical role in the antidystonic activity of mianserin, because the antihistaminergic agent diphenhydramine proved ineffective in our patient. Animal studies have confirmed that mianserin is effective in reducing haloperidol-induced catalepsy, acute dystonia, and parkinsonism (16). However, mianserin had no or a very limited effect on dystonia in monkeys treated over the long term with haloperidol (21) and failed to improve symptoms of chronic neuroleptic-induced parkinsonism in schizophrenic patients (22). Therefore we conclude that serotonin antagonists, particularly mianserin in low doses, may have a beneficial therapeutic effect on acute forms of EPS, whether neuroleptic or SSRI induced, but appeared of limited value for chronic EPS.

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Apraxia of Eyelid Closure Accompanied by Denial of Eye Opening

The inability to close the eyelids voluntarily on command while retaining spontaneous blinking was first described by Roth in 1901 as a "pseudobulbar paralysis" phenomenon (1). In 1907, Lewandowsky was the first to designate this deficit as "Apraxie des Lidschlusses," an apraxia of eyelid closure (2). The loss of voluntary closure of the eyelids has been observed by other investigators, mostly in patients with diffuse, bilateral cerebral abnormalities (3–9).

In this article, we describe the clinical, evoked corneal and blink reflex, and computed tomographic (CT) findings in a patient who exhibited apraxia of eyelid closure. In addition, he also denied that his eyes remained open after attempts to close them. To our knowledge, such a deficit has not been reported before in patients with apraxia of eyelid closure.

Case Report

This 77-year-old right-handed man was admitted to our department because of an acute left-sided hemiplegia that had resulted in postural imbalance that, in turn, had led to a fall and a cerebral concussion with loss of consciousness for ~10 min and posttraumatic amnesia for a few minutes. He had hypertension, diabetes mellitus type II, and Wolf–Parkinson–White syndrome, and had experienced three previous myocardial infarctions and a number of transient ischemic attacks in the vascular area of the carotid artery.

Examination at the time of admission revealed an alert, cooperative, and normotensive man with a regular pulse rate of 75 beats/min. He was fully conscious; was normally oriented in time, place, and person; and exhibited no aphasia. His head and eyes deviated to the right. He was slightly dysarthric and had a left hemianopsia and a slight left-sided central facial paresis. The corneal reflex was normal on both sides. There was a severe left-sided hemiplegia and a left-sided hemianalgesia, of which he was aware. The deep tendon reflexes were all present. The plantar response was flexor on the right side and extensor on the left side. Two days after hospitalization, it was noticed that the patient was unable to close his eyes voluntarily on command, although they continued to blink spontaneously periodically. The corneal reflex was missing on both sides after the left cornea was touched.

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When requested to close his eyes, he contracted the corrugator supercilli muscles on both sides and the procerus muscle. However, clinically there was no sign of contraction of either orbicularis oculi muscle or of relaxation of the levator palpebrae superioris muscles. On command, he was able to wink with the right eye, but not the left. Occasionally, when requested to close both eyes, he would contract either the frontalis muscles, and hence widen the eyes, or the orbicularis oculi muscle on the right side unilaterally, despite our repeated urging. There was no Bell's phenomenon. His visual threat reflex was enhanced on both sides and often resulted in forceful closure of the eyelids. However, this was not a consistent finding. Once the lids were closed passively, the patient was able to keep them closed or to open them without difficulty.

The deviation of the head and eyes was resolved. The blink rate was normal, as were the eye movements and the lid saccades in upward and downward directions. He slept with his eyes closed. His response was normal to other requests, such as opening and closing his mouth, showing his teeth, opening his eyes widely, protruding his tongue, and turning his head. Also, he demonstrated no apraxia of the limbs when following our commands, such as "comb your hair" or "brush your teeth," and his higher cerebral functions were normal.

The patient denied that his eyes remained open after his attempts to close them. Following our request that he close his eyes and the question as to whether he thought the eyes were closed, he answered, "Yes; I think so, yes; they are closed." When asked whether he could see fingers held up in front of him, he answered, "Yes, I can see them." Then, we asked him to close his eyes and to continue trying until he could not see the examiner's fingers. He contracted the same aforementioned muscles and his eyes remained open. To the question of whether his eyes were closed, he answered, "Yes; they are closed." To the question of how many fingers he saw now, he correctly answered, "Two fingers." When we told him that he should not be able to see the fingers if his eyes were actually closed, he reacted as follows: "Yes, that is curious; I cannot close my eyes; how come?" Until then, he was unaware of his inability to close his eyes. He still did not deny his left-sided hemiplegia.

The corneal and blink reflexes were evoked by techniques reported earlier (10). For eliciting the corneal reflex, a small metal sphere connected to an electronic trigger circuit was used. The blink reflex was elicited by electrical stimulation of the supraorbital nerve on both sides. A touch of the right cornea elicited a normal response in the ipsilateral orbicularis oculi muscle with a latency of 37 ms, and in the contralateral orbicularis oculi after a latent period of 43 ms, all within the normal range. To the contrary, no responses could be elicited on either side after the left cornea had been touched (Fig. 1). Stimulation of the right or left supraorbital nerve elicited a normal ipsilateral early response (R1 latency, ±12 ms). However, no ipsilateral or contralateral late response (R2) could be recorded from the orbicularis oculi muscles after stimulation of either the right or left supraorbital nerve.

A CT brain scan performed 1 week after hospitalization showed a large, wedge-shaped infarction in the right parietal lobe, in the vascular area of the posterior branches of the right middle cerebral artery (Fig. 2). The lesion affected the lower two-thirds of the parietal lobe, extended posteriorly to the occipital lobe, and affected anteriorly the lower half of the postcentral gyrus. The frontal and temporal lobes were unaffected.