

# Fluoxetine and Extrapyrimal Side Effects

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**Objective:** The authors' goal was to determine whether fluoxetine is associated with extrapyramidal side effects. **Method:** They assessed the notifications of extrapyramidal manifestations in patients given fluoxetine in the New Zealand Intensive Medicines Monitoring Programme, a national system that monitored adverse reactions associated with fluoxetine over a 4-year period, and determined whether these adverse reactions were causally related to fluoxetine. **Results:** In reports of adverse reactions in 5,555 patients given fluoxetine throughout New Zealand, there were 15 notifications of extrapyramidal events probably or possibly caused by fluoxetine. Fluoxetine was the only psychotropic agent used for seven of the 15 patients; two patients were also taking lithium, four were taking neuroleptics, two were taking tricyclic antidepressants, and one was taking metoclopramide. **Conclusions:** The authors conclude that fluoxetine may be associated with extrapyramidal reactions. These may occur with fluoxetine alone or fluoxetine may facilitate the reaction in patients receiving psychotropic medication or dopamine receptor blocking drugs.

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There is a growing number of case reports of extrapyramidal side effects with the selective serotonin reuptake inhibitor fluoxetine. This paper describes the experience of the New Zealand Intensive Medicines Monitoring Programme, a national monitoring system for adverse reactions to selected medications.

## METHOD

Fluoxetine was one of a small number of medications included in the New Zealand Intensive Medicines Monitoring Programme. For the chosen medications, enhanced surveillance is a condition of registration and use. Rates up to 70 times the rate of standard spontaneous reporting of adverse reactions to medication in New Zealand have been achieved in this program. Fluoxetine was monitored over the 4-year period January 1989 to January 1993; notifications of reactions were received for a total of 5,555 patients given fluoxetine

during this time. All notifications of adverse events were sent in by physicians for all patients in New Zealand.

Causality was assessed by a clinician using guidelines set by the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring (1). A probable causal relationship was assigned for an adverse reaction if there was a plausible temporal relationship between administration of the drug and the reaction, the reaction was not likely to have been caused by a concurrent disease or other drugs, and there was improvement in the reaction when the drug was withdrawn. Possible causality was assigned if there was a reasonable temporal relationship but the reaction could have been confounded by concurrent disease or other drugs and information on drug withdrawal was lacking or unclear.

## RESULTS

A probable or possible causal relationship between fluoxetine and extrapyramidal side effects was found for 15 patients. The clinical characteristics of these patients are given in table 1. The causal association was thought to be probable for the first five patients in the table and possible for the remainder. Fluoxetine was prescribed for depression in all cases. Seven of the patients were women and eight were men; their ages ranged from 25 to 88 years. Nine of the 15 patients were older than 65. Eleven patients were receiving 20

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TABLE 1. Description of 15 Patients Who Experienced Extrapyramidal Side Effects After Taking Fluoxetine for Depression

Patient	Age (years)	Sex	Dose of Fluoxetine (mg/day)	Duration of Fluoxetine Therapy	Concomitant Drug	Reaction	Outcome of Fluoxetine Withdrawal	Additional Information
1	88	F	20	13 days	None	Acute dystonia; torticollis	Recovered	
2	32	M	80	7 days	None	Mild dystonia	Recovered after 7 days	
3	81	M	60	1 month	None	Coarse tremor (all limbs)	Recovered	
4	27	F	20	4 months	None	Spasms right leg	Marked improvement	Previous head injury; spastic triplegia sparing right arm
5	71	M	20	1 month	Thyroxine, 0.05 mg/day; ranitidine, 150 mg/day	Opisthotonus; rigidity	Recovered	Hypothyroid
6	73	M	60	4 months	Lithium carbonate, 750 mg/day	Opisthotonus; ataxia	Recovered (symptoms continued when lithium was stopped)	Reaction 2 days after lithium was started
7	29	M	20	7 days	Haloperidol, 100 mg/month i.m. for 4 months	Severe akathisia	Recovered 14 days after fluoxetine was stopped	Schizophrenia
8	74	F	20	14 days	Trifluoperazine, 2 mg/day (long-term)	Trismus	Recovered	
9	49	M	40	3 months	Buspirone	Severe tremor (generalized)	Recovered when doses of both drugs were reduced	
10	78	M	20	6 weeks	Famotidine, 80 mg/day for 8 months; dipyridamole, 50 mg/day for 6 months; aspirin, 150 mg/day for 6 months	Tremor left arm and leg	Fluoxetine continued—no improvement	Reflux oesophagostomiasis; peripheral vascular disease
11	73	F	20	4 months	Digoxin, 0.1875 mg/day for years; furosemide, 20 mg/day for years; allopurinol, 100 mg/day for years; indomethacin, 50 mg/day as required for years	Akathisia; resting tremor	Recovered	Atrial fibrillation; cardiac failure; gout
12	70	F	20	1 month	Metoclopramide, 30 mg/day for 1 month	Dystonia; tremor	Recovered 4–5 days after fluoxetine and metoclopramide were stopped	Metoclopramide for nausea
13	67	F	20	10 months	Carbamazepine, 600 mg/day for 10 months; captopril, 25 mg/day for 2 years; trimipramine, 100 mg/day for 8 years; lithium carbonate, 750 mg/day for 8 years	Dystonia (spasms right side of head)	Fluoxetine continued with careful control of dose; spasms resolved	Hypertension; bipolar depression; excessive drug ingestion suspected (one admission for overdose with loss of consciousness)
14	25	M	20	5 months	Pericyazine for 1 month	Leg spasms worse	Improved	Previous severe head injury
15	47	F	20	6 months	Pimozide, 6 mg/day for 8 months; benztropine, 1 mg/day for 8 months; nortriptyline, 50 mg/day for 8 months	Tardive dyskinesia	Minimal improvement	Pimozide and benztropine were also stopped

mg/day of fluoxetine, one was receiving 40 mg/day, two were receiving 60 mg/day, and one was receiving 80 mg/day. In 12 patients, parkinsonian symptoms began from 7 days to 4 months after the first administration of fluoxetine. The reactions included mild dystonia, tremor, leg spasms, trismus, torticollis, opisthotonus, akathisia, and tardive dyskinesia.

For seven patients, fluoxetine was the only psychotropic agent used. Two patients were also taking lithium, four were also taking neuroleptics, two were also taking tricyclic antidepressants, and one was also taking metoclopramide. In the one patient who had been asymptomatic after taking 60 mg/day of fluoxetine for 4 months, opisthotonus occurred 2 days after lithium

administration was started and persisted after lithium was discontinued until fluoxetine was stopped. There were no adverse effects when lithium was later reintroduced alone. The patient who was receiving haloperidol as well as fluoxetine had been asymptomatic while taking haloperidol alone for 4 months but developed akathisia 7 days after fluoxetine administration started. Patient 8 had tolerated long-term administration of 2 mg/day of trifluoperazine but developed trismus 14 days after the addition of fluoxetine.

In the 12 cases where fluoxetine was withdrawn, there was improvement in the extrapyramidal manifestations, although this was minimal in the patient with tardive dyskinesia. In another two cases, recovery occurred after a reduction in the dose or careful control of the dose. Rechallenge was not performed in any of the cases.

Of all of the patients treated with fluoxetine during the 4-year period whose sex was known, 1,917 were male and 3,539 were female. The rate of fluoxetine-associated reports of extrapyramidal effects was 2.7 (95% confidence interval=1.5–4.4) per 1,000 overall, 4.2 (95% confidence interval=1.8–8.2) for male patients, 2.0 (95% confidence interval=0.8–4.1) for female patients, and 1.3 (95% confidence interval=0.5–2.6) for the patients receiving fluoxetine alone. When the two patients with akathisia, which can be a confusing diagnosis, were excluded, the rate was 2.3 per 1,000 overall. Extrapyramidal reactions were the fifth most frequent type of side effect reported with fluoxetine after psychiatric manifestations (e.g., agitation/anxiety) (rate=5.6 per 1,000), diarrhea (rate=3.2 per 1,000), nausea/vomiting (rate=2.8 per 1,000), and insomnia (2.8 per 1,000).

## DISCUSSION

Fluoxetine has a low side effect profile, and it is perhaps not surprising that extrapyramidal events were among the more common reactions detected with intensive monitoring. These cases illustrate the spectrum of fluoxetine-associated extrapyramidal manifestations. Eleven of the patients in this series were receiving 20 mg/day of fluoxetine, and a dose relationship was not apparent, although patient 2 developed mild dystonia after 7 days of 80 mg/day and acute dystonia and akathisia have been described after an increase in dose (2–4). Nine of 15 patients in this series were older than 65. However, in view of the small number of patients and the fact that many case reports described extrapyramidal symptoms in younger patients (2, 3, 5–10), we are unable to speculate on the influence of age.

In addition to the numerous case reports in the literature, the WHO Collaborating Centre for International Drug Monitoring had received 438 reports of dyskinesia in patients receiving fluoxetine as of December 1992, although the total number of reports is unknown. The Drug Safety Research Unit in Southampton, United Kingdom, has 35 reports of extrapy-

ramidal reactions from reports on 10,635 patients treated with paroxetine (11). Extrapyramidal side effects have also been described with sertraline and fluvoxamine (12–14).

Although a definite association between selective serotonin reuptake inhibitors and extrapyramidal symptoms has not been established, in seven of the 15 patients in the present series fluoxetine was the only psychotropic agent used. Furthermore, there are reported cases where fluoxetine administration alone has been associated with extrapyramidal reactions (2–6), and in one patient acute dystonia occurred on rechallenge (2). The pathogenesis of such adverse reactions, which may be heterogeneous, is unknown, but it has been suggested that they may be caused by serotonergically mediated inhibition of dopaminergic transmission (8). Fluoxetine has been shown to inhibit synthesis of dopa in dopamine-rich areas of the rat forebrain (15). Raised serum prolactin levels (5) and a favorable response to anticholinergic agents (3) are in keeping with decreased dopaminergic activity. Alternative explanations have been proposed to explain extrapyramidal symptoms in patients who were no longer taking neuroleptics. Budman and Bruun (9) suggested that previous exposure to neuroleptics and/or lithium may sensitize nigrostriatal dopaminergic responses to increased serotonergic input from the raphe nuclei. Patients with underlying Parkinson's disease or spasticity are more likely to experience extrapyramidal reactions (5, 7). That extrapyramidal manifestations disappeared or improved in 12 of the patients after withdrawal of fluoxetine is supportive evidence that fluoxetine was causally related.

A pharmacokinetic interaction, however, may account for the extrapyramidal symptoms in the patients in this series who were also taking haloperidol, pericyazine, trifluoperazine, pimozide, trimipramine, nortriptyline, lithium, and carbamazepine. Fluoxetine and norfluoxetine are potent inhibitors of cytochrome P450 2D6 activity (16, 17), and such inhibition may contribute to elevated plasma levels and side effects of antidepressants and antipsychotics (18). There are numerous reports of elevated cyclic antidepressant levels (18–21), and extrapyramidal reactions have been reported with antipsychotic agents, including haloperidol and pimozide, when administered with fluoxetine (6, 22, 23). Similarly, lithium toxicity (24) and increased carbamazepine plasma concentrations (25) have been described in patients treated with fluoxetine as well, as has parkinsonism with carbamazepine (26), lithium (9), and the dopamine antagonist metoclopramide (10).

From reports in the literature and the cases in this series, it appears that fluoxetine alone may be associated with extrapyramidal reactions. Furthermore, because of its potent inhibitory effect on hepatic oxidative metabolism, the potential for increased levels of concomitant psychotropic medicines and increased side effects, which may include extrapyramidal symptoms, should be borne in mind.

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