Movement Disorders Associated With the Serotonin Selective Reuptake Inhibitors

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Background: To review the case reports and case series of movement disorders ascribed to the use of serotonin selective reuptake inhibitors (SSRIs).

Method: Reports of SSRI-induced extrapyramidal symptoms (EPS) in the literature were located using a MEDLINE search and review of bibliographies.

Results: Among the 71 cases of SSRI-induced EPS reported in the literature, the most common side effect was akathisia (45.1%), followed by dystonia (28.2%), parkinsonism (14.1%), and tardive dyskinesia-like states (11.3%). Among patients with Parkinson's disease treated with SSRIs, there were 16 cases of worsening parkinsonism. Patients who developed dystonia, parkinsonism, or tardive dyskinesia were older on average than patients with akathisia; 67.6% of affected patients were females. Fluoxetine, the most commonly prescribed SSRI to date, was implicated in 53 (74.6%) of cases of SSRI-induced EPS. Several reports (57.7%) were confounded by the concomitant use of other medications that can contribute to the development of EPS.

Conclusion: SSRI-induced EPS are probably related to agonism of serotonergic input to dopaminergic pathways within the CNS. Several patient-dependent and pharmacokinetic variables may determine the likelihood that EPS will emerge. Although these side effects are infrequent, clinicians should be alert to the possibility of their occurrence.

(J Clin Psychiatry 1996;57:449–454)

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The author thanks Seymour Axelrod, Ph.D., and Cynthia Pristach, M.D., for valuable comments on the manuscript.

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With generally fewer side effects than the tricyclics and monoamine oxidase inhibitors, the serotonin selective reuptake inhibitors (SSRIs) have become the most widely prescribed antidepressants in the United States. Owing to the popularity of these agents, increasing attention has been directed at adverse drug events associated with their use, the severity of which had been unappreciated in premarketing clinical trials. For example, a growing body of case reports and reviews on SSRI-induced sexual dysfunction has recently emerged.[1–4] This article addresses a previously underrecognized but clinically significant consequence of SSRI use, namely, the development of movement disorders, i.e., extrapyramidal symptoms (EPS) and tardive dyskinesia. These disorders can be uncomfortable for patients, influence compliance, and contribute to significant psychosocial and occupational impairments.

THE ASSOCIATION OF SSRI USE AND EPS

Medication-induced movement disorders are now included in the appendix of DSM-IV, to be listed, whenever appropriate, on Axis I.[5] These disorders include EPS related to neuroleptic use, i.e., dystonia, akathisia, and parkinsonism. Separate diagnostic criteria are also included for medication-induced tardive dyskinesia and postural tremor. The inclusion of these iatrogenic disorders acknowledges the potential untoward influences of prescribed medications contributing to noncompliance and emphasizes the importance of considering measures to prevent and/or treat such disorders. The addition of the category, Medication-Induced Movement Disorder Not Otherwise Specified, acknowledges that agents other than neuroleptics, e.g., antidepressants, can result in the development of comparable movement disorders.[6–11]

As regards SSRI-induced EPS, product literature provided by Eli Lilly and Company indicates 375 cases of akathisia, 218 cases of dystonia, and 76 cases of tardive dyskinesia associated with fluoxetine use as of December 31, 1995 (data on file, Lilly Research Laboratories, Indianapolis, Ind.). Similarly, the World Health Organization Collaborating Centre for International Drug Monitoring has 438 reports of motoric side effects associated with fluoxetine.[12] The Drug Safety Research Unit in Southampton, United Kingdom, received 35 reports of EPS associated with paroxetine.[13] Because the aforementioned reports largely consist of spontaneously generated, i.e., unsolicited, reports, inferences regarding the prevalence of SSRI-associated motoric side effects cannot be generated from these data. No data are currently available

about individuals who may have experienced comparable side effects but did not report them. It is reasonable to speculate that the symptoms had to be quite severe for patients to report them without solicitation.

This paper presents an analysis of case reports and case series indicating the association of movement disorders and SSRI use. Attempts are made to describe possible mechanisms for the emergence of these disorders and to address the clinical issues of prevention and treatment.

METHOD

Case reports and case series reporting movement disorders and SSRI use were generated by a MEDLINE search and review of bibliographies from each article retrieved. MEDLINE was searched from January 1979 to March 1996, and the terms *extrapyramidal symptoms, dystonia, parkinsonism, drug-induced akathisia,* and *drug-induced dyskinesia* were cross-referenced with each of the following: *antidepressants, serotonin uptake inhibitors, fluoxetine, sertraline, paroxetine,* and *fluvoxamine*. The individual cases were then categorized by type of motoric side effect; categorization was based on the most salient symptoms described in the published report. Case summaries that described torticollis, muscle spasm, opisthotonos, dystonia, blepharospasm, trismus, jaw tightness, or tongue protrusion were categorized as dystonic reactions. Those describing pacing, restlessness, or an inability to remain still were classed as akathisia. Reports categorized as involving parkinsonism described two or more cardinal signs, e.g., cogwheel or lead-pipe rigidity, bradykinesia, resting tremor, masklike facies, gait disturbances, and impaired postural reflexes. Case summaries classified as involving tardive dyskinesia typically reported choreoathetotic movements affecting the face, limbs, or trunk. Documents and articles reporting numbers of cases of motoric side effects associated with the use of an SSRI, but lacking descriptions of motor symptoms or patient data, were not included. In particular, the product information provided by Eli Lilly and the paper by Choo[13] could not be included in the analyses that follow.

RESULTS

Forty-two articles were obtained,[12,14–54] reporting 71 cases of de novo motor symptoms after SSRI use. Akathisia* was reported in 32 cases (45.1%); dystonia† in 20 cases (28.2%); parkinsonism[14–16,18,19,25,32,51] in 10 (14.1%); tardive dyskinesia-like movements[12,22,27,30,34,44,48,54] in 8 (11.3%), and tremors[12,28,42] in 7 (9.9%). Patients could not always be categorized in mutually exclusive groupings, e.g., two patients had both akathisia and dystonia[46,50] and four patients had tremor in addition to another motoric side effect.[12,28,42] Two findings were unexpected. Curiously, one of the cases of dystonia occurred upon abrupt *discontinuation* of fluoxetine.[28] In addition, the fact that only seven cases of tremor were reported is less than would be expected given prior estimates of new-onset tremor arising in 5% to 16% of SSRI-treated patients.[55–57] It is possible that the development of an isolated tremor in SSRI-treated patients is not of clinical significance to warrant publication as a case report or case series.

The mean ± SD age for patients experiencing tardive dyskinesia was 55.4 ± 22.2 years; for patients with parkinsonism, 53.9 ± 18.1 years; for patients with dystonia, 49.7 ± 20.0 years; and for patients with akathisia, 37.8 ± 13.7 years. The patients who had both akathisia and dystonia were not included in this analysis. The four groups differed significantly for age, $F = 3.96$, $df = 3,62$; $p < .01$. Two-way comparisons revealed that patients developing tardive dyskinesia, parkinsonism, or dystonia were significantly older than those developing akathisia.

Of the 71 cases, 23 (32.4%) were males.[12,17,26–29,34,42,43] A binomial test of the hypothesis of a male:female ratio of 50:50 revealed a probability of 0.002 of obtaining 23 or fewer males in a sample of 71 cases. The numbers of males in each of the movement disorder categories were 9/18 (50%) for dystonia; 3/30 (10%) for akathisia; 1/2 for combined dystonia and akathisia; 3/10 (30%) for parkinsonism; and 2/8 (25%) for tardive dyskinesia.

In 53 cases (74.6%), the implicated drug was fluoxetine.‡ More recent reports have emerged demonstrating comparable side effects resulting from sertraline (8 cases, 11.3%)[37,38,40,41,45,46,50]; fluvoxamine (6 cases, 8.5%)[21,32,34,35,49,52]; and paroxetine (4 cases, 5.6%)[47,48,53] use.

The mean dose of fluoxetine employed in those cases (N = 15) resulting in dystonia was 40 mg/day (range, 20–80 mg/day); for akathisia (N = 20), the mean dose was 42 mg/day (range, 5–140 mg/day); for parkinsonism (N = 9), the mean dose was 36.3 mg/day (range, 15–80 mg/day); and for tardive dyskinesia (N = 6), the mean dose was 33 mg/day (range, 20–80 mg/day). In the six cases of sertraline-induced akathisia, the mean dose was 67.9 mg/day (range, 25–200 mg/day); there were two reports of combined dystonia and akathisia (100 mg/day and 200 mg/day, respectively) and no reports of parkinsonism associated with sertraline use. For fluvoxamine, there was one case each of tardive dyskinesia and parkinsonism; the doses were 100 mg/day and 200 mg/day, respectively. The doses of fluvoxamine in the cases resulting in akathisia were 200 mg/day and 300 mg/day, respectively, and for the two cases resulting in dystonia, 100 mg/day and 200

*References 12, 17, 21, 23, 24, 26, 31, 33, 37–39, 47, 52, 53.
†References 12, 20, 28, 29, 35, 36, 42, 43, 48, 49.
‡References 12, 14–31, 33, 36, 39, 42–44, 51, 54.

mg/day, respectively. For paroxetine, there was one case each of dystonia and tardive dyskinesia and two cases of akathisia; the dose in all four cases was 20 mg/day. The interval between treatment initiation or dose change and onset of side effects was variable. For dystonia, the range extended from 3 days[46] to 14 months[43]; for akathisia, 12 hours[17] to 4 months[12]; for parkinsonism, 4 days[14,16] to 1 year[51]; and for tardive dyskinesia-like movements, 3 days[22] to 1 year.[54]

In 41 cases (57.7%), patients had been concurrently treated with other medications. Five (7.0%) patients were treated with lithium,[12,19,22,45] 11 (15.5%) with neuroleptics,* four (5.6%) with carbamazepine,[12,25,33] two (2.8%) with metoclopramide,[12,23] and 19 (26.8%) with miscellaneous medications including benzodiazepines,[17,26,39] buspirone,[12] thyroxine,[12,20,33] or other antidepressants.[12,26,41]

With regard to treatment, anticholinergic agents were employed to reverse SSRI-induced dystonia in five cases,[29,35,36,42,46] but none had been used to treat those cases in which parkinsonism emerged. One patient with parkinsonism responded to low-dose treatment with carbidopa/levodopa.[51] β-Blockers were employed in 10 cases of akathisia[17,24,26,33,37,53]: seven cases were treated with benzodiazepines,[33,38–41,45] two cases were treated with both β-blockers and benzodiazepines,[23,47] and one case was successfully treated with a serotonin antagonist.[52] Eleven patients who developed akathisia experienced an improvement in their symptoms with dose reductions or drug cessation.[21,26,31,33,37,39,50] Complete remission of tardive dyskinesia occurred in three SSRI-treated patients after drug cessation[30,44,54]; however, symptoms persisted in the other five patients despite drug cessation.[12,22,27,34,48]

Seven articles[48,58–63] reported 16 cases of patients with preexisting parkinsonism worsened by the use of SSRIs. Fluoxetine was implicated in 12[58–61] cases; fluvoxamine[63] and paroxetine[48,62] were each implicated in two cases. The mean fluoxetine dose employed in these cases was 16.9 mg/day (range, 20 mg every 4 days to 20 mg/day). The mean fluvoxamine dose employed was 125 mg/day (range, 100–150 mg/day); the paroxetine was administered at 20 mg/day in both cases. Information on patient age and gender, duration of treatment, and coadministered drugs was often omitted for these 16 cases.

DISCUSSION

One of the difficulties encountered in this retrospective review is that the data reflect only published cases or case series. Little is known about others who may have experienced comparable symptoms while treated with SSRIs but whose cases have not been published. There is a lack of well-controlled epidemiologic research focusing on SSRI-induced movement disorders. The precise measures of the prevalence rates of SSRI-induced dyskinesias are lacking at this time, however, the rates are thought to be low.

A retrospective review such as this is limited by a lack of a uniform approach to the assessment and description of movement disorders. Distinguishing movement disorders from other syndromes can be difficult,[53] e.g., differentiating akathisia from agitated affective states or anxiety. Terms such as *restlessness* or *akathisia* may have been used quite variably by different authors.[56] One study of fluoxetine-treated patients revealed that 30% experienced "jitteriness," which encompassed a wide range of reactions including mild anxiety, nervousness, and akathisia.[64] By contrast, some authors made a point of describing the severity of the akathisia, making it clear that they were not merely reporting nervousness.[17,31,33,52] It is possible that, as with akathisia, the terms *dystonia* and *parkinsonism* have been variably applied by different authors. In addition, distinguishing movement disorders from each other can be difficult.[53] For example, akathisia may be difficult to differentiate from tardive dyskinesia. It is possible that tremor might be misperceived as anxiety or akathisia[56] and that this might account for underreporting of this side effect in case studies.

The pathophysiologic mechanisms for drug-induced movement disorders are poorly understood. Blockade of dopamine (D_2) receptors in the basal ganglia and dopaminergic tracts has been implicated in neuroleptic-induced EPS. It seems likely that SSRI-induced EPS result from some interaction between serotonergic and dopaminergic pathways.

There are diffuse interconnections between serotonergic and dopaminergic nuclei.[65,66] The serotonergic input to dopaminergic systems appears to be inhibitory.[67] In rats, fluoxetine was shown to inhibit the synthesis of catecholamines in dopamine-rich areas of the forebrain, hippocampus, and extrapyramidal regions. Neurophysiologic and electric stimulation studies[68] have demonstrated the inhibitory effects of raphe fibers on extrapyramidal neurons and reversal of the inhibition by serotonin antagonists.

The mechanisms underlying SSRI-induced EPS are likely to be more complex than has been suggested by the animal models above. For example, the case of the occurrence of dystonia upon fluoxetine withdrawal[28] is inconsistent with the aforementioned models. Further, serotonin and its agonists have been reported to *improve* symptoms of parkinsonism[69–71] and dystonic symptoms, e.g., blepharospasm.[72] It is possible that serotonergic innervations also influence GABA and cholinergic pathways[65,73] and thereby contribute to the development of EPS. Just how the SSRIs induce EPS in some patients, but improve parkinsonism or dystonia in others, may be clarified by a better understanding of these interconnections.

*References 12, 16, 18, 27, 33, 36, 38, 43, 45.

Hypersensitivity of postsynaptic dopamine receptors has been offered as the underlying mechanism of neuroleptic-induced tardive dyskinesia, whereas tricyclic-induced tardive dyskinesia is thought to involve noradrenergic hypersensitivity and increased anticholinergic activity.[7] The mechanism of SSRI-induced tardive dyskinesia is less clear, as all but three patients who developed it had prior or current neuroleptic exposure.[12,22,27,44]

As with neuroleptic-induced EPS, SSRI-associated movement disorders have a tendency to be elicited idiosyncratically by any of a number of agents of the same class. The majority of cases (74.6%) involved an association between fluoxetine and EPS. Presumably, this dramatic preponderance is attributable to the fact that fluoxetine was the first of the SSRIs and the most often prescribed; however, pharmacologic differences among the SSRIs may be involved. For example, SSRIs with longer half-lives, e.g., fluoxetine, would be expected to exert a more enduring inhibition of central dopaminergic systems. The dosages and duration of treatment were variable, precluding making statements regarding dose relationships. Some cases displayed the rapid onset of symptoms characteristic of neuroleptic-induced EPS.[74] Curiously, in one of the eight cases in which tardive dyskinesia-like movements developed, the latency occurred after 3 days.[22]

Another pharmacologic difference among the SSRIs of potential import on the development of EPS is dopamine reuptake inhibition. Sertraline has been noted to exhibit a direct augmenting effect on dopamine reuptake inhibition[75–77]; inhibitory serotonergic input to dopaminergic systems would be mitigated by such direct augmentation. Paroxetine, fluvoxamine, and fluoxetine have lower potencies than sertraline for dopamine reuptake inhibition in vitro.[77,78] In vitro activity need not necessarily reflect what happens in vivo; nevertheless, these differences in dopamine agonism may contribute to a lesser risk of EPS occurring with sertraline.

In a number of the cases (57.7%), the concomitant use of other medications that can produce EPS, e.g., neuroleptics or metoclopramide, has the potential to confound. It is possible that pharmacokinetic interactions occurred, leading to increased availability of the SSRI, the concurrently administered drug, or both. For example, fluoxetine has been reported to increase serum levels of haloperidol,[79] pimozide,[80] and carbamazepine.[81,82] Such drug combinations might increase the likelihood of EPS.

Alternatively, medications that normally do not produce EPS may, when combined with an SSRI, predispose a patient to EPS. Several commonly prescribed drugs can inhibit the cytochrome P450 enzymes, interfering with SSRI metabolism and thereby increasing SSRI availability.[83] One patient who had taken fluoxetine 60 mg/day uneventfully for 1 year developed parkinsonism after the addition of cimetidine.[51] Several other cases of EPS were also prescribed drugs dependent on the P450 enzyme system for metabolism, e.g., cimetidine,[38] ranitidine.[12,38]

It is possible that some patients are more vulnerable than others to SSRI-induced EPS.[14] Included are (1) elderly patients whose vulnerability may be related to neuronal loss[32,43]; (2) patients in whom circulating levels of an SSRI are particularly high, either because of high doses or reduced hepatic clearance; (3) patients with current or prior neuroleptic exposure[44]; and (4) patients with compromised nigrostriatal functioning.[48,58–63] These determinants need not be mutually exclusive. Thus, advancing age may lead to both neuronal loss and reduced hepatic functioning. Like neuroleptic-induced EPS, parkinsonism tended to occur in older patients. In contrast to neuroleptic-induced dystonia, SSRI-induced dystonia tended to occur in older patients as well. However, because of the limitations cited previously, it is impossible to speculate on the influence of age in the development of these side effects. Further, the rate of spontaneously occurring dyskinesias increases with advancing age. Controlled studies comparing movement disorders among SSRI- and placebo-treated patients are required.

Similarly, one can only speculate on the influence of gender. In the cases reviewed here, females were represented significantly more often than males. While females may be more vulnerable to EPS, there is a potential confound in that the prevalence of depression is greater among females[5] and more females seek treatment for depression than do males.[84] The gender differences observed in the cases reviewed here may simply reflect these epidemiologic differences.

On the other hand, it is possible that males are more susceptible to SSRI-induced EPS than females. Among SSRI-treated patients involved in the New Zealand Intensive Medicines Monitoring Programme, females (N = 3539) exceeded males (N = 1917) by a significant margin.[12] Nevertheless, the number of males who developed movement disorders (N = 8) was approximately equal to the number of females (N = 7) who did so.

Similar to neuroleptic-related disorders, SSRI-induced akathisia and parkinsonism was found by the present review to occur more frequently in females than in males. However, unlike neuroleptic-induced dystonia that affects males more frequently, the number of cases of SSRI-induced dystonia was equal among males and females. Large scale, prospective studies are required to assess the determinants of any gender differences.

Patients with idiopathic Parkinson's disease often suffer from comorbid depression.[85] There is a possibility of exacerbation of parkinsonism with SSRI use. It has been suggested that worsening of parkinsonism by SSRIs is unlikely; otherwise, one would encounter numerous cases in the literature[58,86]; however, patients with Parkinson's disease have often concurrently been treated with antiparkinsonian medications that may have miti-

gated the potential aggravation of parkinsonism by the SSRIs.

Treatments for SSRI-induced movement disorders were comparable with those of neuroleptic-related disorders. Three reports have indicated the efficacy of anticholinergic agents in reversing SSRI-induced dystonia.[36,42,46] It is impossible to make generalizations based on a few case reports, nevertheless, because of the discomfort associated with acute dystonia, a trial of an intramuscular anticholinergic may be considered. Regarding akathisia, β-blockers[17,24,26,37,47,53] and benzodiazepines[40,45,47,64] have been demonstrated to reduce or eliminate the restlessness associated with SSRI use. While dose reduction has been associated with an improvement of symptoms,[21,33,37,39] most patients appear to have done best with drug cessation[12,26,31,33,40,41,50] or use of an alternate antidepressant.[19,31,33,41,50] If parkinsonism develops, the offending agent should be discontinued or the dose lowered. Parkinsonism may emerge only when another agent (an antipsychotic or medication interfering with SSRI metabolism) is introduced[51]; in such cases, symptoms may be ameliorated by merely removing the coadministered drug or by use of an alternate antidepressant. No cases in which anticholinergic supplementation was employed to treat the parkinsonism were found, but this is a possible option. Little can be said about the treatment of SSRI-induced tardive dyskinesia in view of the limited number of cases in which it was reported. In most instances, symptoms did not improve with drug cessation.[12,22,27,34,48] Thus, prevention appears to be of prime importance.

SUMMARY

For most patients, the benefits of SSRI use far outweigh the potential problems of an SSRI-induced movement disorder. Nonetheless, EPS can occur consequent to SSRI use, presumably because of an increase in serotonin's inhibitory influences on dopaminergic pathways. Although this occurs quite infrequently, certain patients appear to be at increased risk, e.g., the elderly, patients with Parkinson's disease, and patients concurrently treated with other medications.

Drug names: buspirone (BuSpar), carbamazepine (Tegretol and others), carbidopa-levodopa (Sinemet), cimetidine (Tagamet), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), metoclopramide (Reglan and others), paroxetine (Paxil), pimozide (Orap), ranitidine (Zantac), sertraline (Zoloft).

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