

Extrapyramidal symptoms associated with antidepressants—A review of the literature and an analysis of spontaneous reports

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BACKGROUND: Antidepressant-induced extrapyramidal symptoms (EPS) represent an underrecognized but important clinical entity. We reviewed the literature on new antidepressants and conducted an analysis of cases from the FDA Adverse Event Reporting System (AERS), which has not been published before.

METHODS: A literature review was conducted using PubMed, Ovid, MEDLINE, PsycINFO, and the Cochrane Database. Search terms used were *extrapyramidal*, *antidepressants*, *selective serotonin reuptake inhibitors (SSRIs)*, *tricyclic antidepressants (TCAs)*, *serotonin-norepinephrine reuptake inhibitors (SNRIs)*, *norepinephrine-dopamine reuptake inhibitors (NDRIs)*, *miscellaneous antidepressants*, and *monoamine oxidase inhibitors (MAOIs)*. Inclusion criteria for the FDA AERS analysis were cases of EPS reported by physicians, cases where patients were on one antidepressant, and cases reported between July 2005 and March 2008. Reports of patients who were on concurrent psychotropics were excluded.

RESULTS: Our literature review revealed 1 report each of EPS for duloxetine, nefazodone, and bupropion, 3 for escitalopram, and 4 for citalopram. For the FDA AERS analysis, 89 cases met our inclusion criteria: duloxetine was implicated in 66% of cases, sertraline in 10%, escitalopram in 7%, and bupropion in 6%.

CONCLUSIONS: EPS have been reported with different classes of antidepressants, are not dose related, and can develop with short-term or long-term use. In view of the risk for significant morbidity and decreased quality of life, clinicians must be aware of the potential for any class of antidepressants to cause these adverse effects.

KEYWORDS: EPS, antidepressant, literature review, spontaneous reports

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INTRODUCTION

The issue of drug-induced extrapyramidal symptoms (EPS) followed the discovery of chlorpromazine in 1952 by Delay and Deniker.¹ The neuroanatomic, neurophysiologic, and neurochemical mechanisms underlying neuroleptic-induced EPS have been well researched. However, EPS associated with antidepressants are underrecognized. The earliest report of EPS secondary to antidepressants was published in 1959,² but until the introduction of selective serotonin reuptake inhibitors (SSRIs) in the 1980s and the widespread use of fluoxetine, no significant studies addressed this topic. There are now more than 100 published reports of SSRI-induced EPS. From 1996 to 2002, there were 4 major published studies in this area.³⁻⁶

However in the past 10 to 15 years, several new antidepressants have been marketed in the United States, including duloxetine, escitalopram, nefazodone, bupropion, and citalopram. The scope of indications for antidepressants has also widened. We have not come across any analysis of the adverse drug reactions (ADRs) from the FDA regarding EPS associated with antidepressants.

In our study, we attempted to focus on published literature regarding EPS associated with the relatively newer antidepressants in the United States and to analyze the ADRs from the FDA regarding EPS and antidepressants for the period July 2005 through the first quarter of 2008. We chose this period because the country of origin of the report in the FDA database was available only from July 2005 forward.

METHODS

We reviewed pertinent English-language literature on antidepressants and EPS, including studies and case reports of patients who developed EPS during treatment with antidepressants. Because there have been several published studies on SSRIs, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and miscellaneous antidepressants,³⁻⁶ we focused our review on antidepressants that have not been covered adequately in the previous studies. These antidepressants include duloxetine, escitalopram, nefazodone, bupropion, and citalopram.

Relevant articles were obtained by a search of PubMed, Ovid, MEDLINE, PsycINFO, and the Cochrane Database, using the following search terms: *extrapy-*

ramidal, antidepressants, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), miscellaneous antidepressants, and monoamine oxidase inhibitors (MAOIs). These terms were cross-referenced with EPS, as follows: *akathisia, akinesia, ataxia, athetosis, abnormal coordination, abnormal gait, bradykinesia, buccoglossal syndrome, bruxism, chorea, choreoathetosis, dyskinesia, dystonic reactions, fasciculation, hypertonia, hypokinesia, masklike facies, movement disorder, myoclonus, oculogyric crisis, parkinsonism, rigidity, tardive dyskinesia, tics, torticollis, tremor, and twitching.*

In addition, we obtained data regarding these adverse effects from the AERS, a computerized information database designed to support the FDA's postmarketing safety surveillance program for all approved drugs and therapeutic biologic products. We reviewed the data from the third quarter of 2005 to the first quarter of 2008, because the information regarding the reporting country became available only as of July 2005.

FDA AERS reports

Inclusion criteria. The inclusion criteria for this analysis were cases of EPS reported by physicians only, cases in which patients were taking only one antidepressant at the time the adverse effect occurred, and cases that were reported between July 2005 and March 2008.

Exclusion criteria. Not included in this analysis were reports of patients on concurrent psychotropics.

We reviewed the occurrence of different types of EPS associated with the particular antidepressant drug, the patient's gender and age, the mean dosage, and the duration of treatment.

Literature review

TCAs and EPS. The first published case reports linking antidepressants to possible extrapyramidal adverse effects date back to the 1950s. In 1959, Foster and Lancaster reported a few cases of patients being treated with imipramine presenting with a coarse tremor. They acknowledged that the adverse effect observed could be a "manifestation of the dystonic type of motor disturbance" already described for perphenazine by Montgomery and Sutherland in 1959.²

During the 1970s, a variety of EPS resulting from TCA treatment were reported.^{5,7,8} The review of literature describing the TCA-related EPS suggests that these are infrequent.⁵

TABLE 1
Selected antidepressant-induced EPS—Published reports

Antidepressant	Total reports	Bruxism	Oculogyric dystonic reaction	Dystonia	Dyskinesia	Rabbit syndrome
Duloxetine ⁴¹	1	0	0	0	1	0
Nefazodone ³⁶	1	0	0	1	0	0
Escitalopram ⁵²⁻⁵⁴	3	0	1	1	0	1
Citalopram ^{6,55-59}	4	1	0	1	1	1
Bupropion ³⁷	1	0	0	0	1	0

EPS: extrapyramidal symptoms.

The EPS reported with TCA monotherapy include dyskinesia,⁷⁻¹¹ akathisia,^{9,12,13} rabbit syndrome,¹⁴ and dystonia.^{2,15-17} These symptoms appear to be unrelated to age but often are dose related.⁵ Other risk factors include prior exposure to neuroleptics and/or lithium or estrogens. In some cases, these EPS resolved without any reduction of the TCA dose.⁵

MAOIs and EPS. Reports of EPS associated with MAOIs are not as frequent as with other classes of antidepressants.⁵ The main types of EPS reported with MAOIs are akathisia,¹² acute truncal dystonia,¹⁸ parkinsonism,^{19,20} and buccolingual-masticatory syndrome.²¹

Phenelzine is the only MAOI reported to be associated with the development of an acute parkinsonian syndrome.^{19,20} There are more published reports of EPS associated with MAOIs for tranlycypromine.⁵

Miscellaneous antidepressants and EPS. Trazodone has been implicated in cases of akathisia,³ dystonic reaction,²² parkinsonism,²³ and chorea.²⁴ There are numerous reports of amoxapine-induced EPS, including akathisia,²⁵⁻²⁹ neck stiffness, spasmodic torticollis, and oculogyric crisis.³⁰⁻³⁴ The higher frequency of EPS seen with amoxapine may be related to the fact that it belongs to the dibenzoxazepine group.

Nefazodone was found to have a protective effect on neuroleptic-induced EPS.³⁵ Burda et al reported a case of nefazodone-induced acute dystonic reaction.³⁶ Gardos reported a case of reversible dyskinesia during bupropion therapy.³⁷ Bupropion discontinuation has been implicated in acute dystonia.³⁸ Ozalp et al have found that bupropion was useful in SSRI-induced EPS.³⁹

SNRI antidepressants and EPS. There is paucity of literature on EPS induced by SNRIs. Conforti et al reported EPS with adjunct therapy of nortriptyline to a venlafaxine and valproic acid combination.⁴⁰ Wang reported a case of acute dystonia resulting from abrupt

bupropion discontinuation when the medication was changed to duloxetine. However, the adverse effect was largely attributed to the bupropion discontinuation.³⁸ We found only one report of dyskinesia induced by duloxetine in the literature.⁴¹

SSRIs and EPS. In 1979, Meltzer et al published one of the earlier reports linking EPS to SSRIs. They reported a case of fluoxetine-induced dystonic reaction and parkinsonian rigidity. They postulated that the increase in 5-hydroxytryptamine (5-HT) activity resulting from 5-HT reuptake blockade by fluoxetine inhibited both the nigrostriatal and tuberoinfundibular dopaminergic neurons.⁴² Studies by Kapur and Remington have supported this hypothesis.⁴³

Although the data are not sufficient to make definitive pharmacoepidemiologic conclusions, it appears that the SSRIs are more frequently associated with these adverse effects than are other antidepressants.^{5,6} Interestingly, Gony et al have found that there is no significant difference in the occurrence of serious EPS among patients with Parkinson's disease being treated with dopaminergic antiparkinsonian drugs and different classes of antidepressants.⁴⁴ Dell'Agnello et al have found that SSRIs do not worsen Parkinson's disease.⁴⁵

Several reviews of case reports of EPS ascribed to the use of SSRIs found that the most common type of EPS was akathisia,^{3,4} followed by dystonic reactions, parkinsonism, and tardive dyskinesia-like states.^{3,4} Patients who developed dystonia, parkinsonism, or tardive dyskinesia were older than patients who developed akathisia³; and the majority of affected patients were female.^{3,4} Fluoxetine, the most commonly prescribed SSRI during the early 1990s, was implicated in the majority of cases of SSRI-induced EPS.³⁻⁵

As of December 12, 1995, Eli Lilly and Company, the original manufacturer of fluoxetine, had in their database 375 cases of akathisia, 218 cases of dystonia, and 7 cases of

TABLE 2
FDA AERS demographic characteristics of EPS (N = 89)*

Characteristics	Tremor	Akathisia	Dystonia	Dyskinesia	Tardive dyskinesia
Cases, n (%) ^a	40 (44.9%)	13 (14.6%)	12 (13.5%) ^b	11 (12.3%)	7 (7.9%)
Female, n (%)	28 (70%)	9 (69%)	6 (50%)	7 (64%)	5 (71%)
Male, n (%)	12 (30%)	4 (31%)	4 (33%)	4 (36%)	2 (29%)
Age, y (mean) ^c	14 to 87 (51)	38 to 55 (47)	39 to 60 (49)	35 to 84 (56)	75 ^d
Female, y (mean)	17 to 87 (56)	40 to 55 (45)	45 to 60 (55)	35 to 84 (50)	70 to 80 (75)
Male, y (mean)	14 to 76 (44)	38 to 55 (49)	39 to 46 (44)	40 to 71 (62)	75

AERS: Adverse Event Reporting System; EPS: extrapyramidal symptoms.

*Table reflects information about side effects of drugs with >7 reports.

^aA single case can have multiple side effects.

^bGender was not reported in 2 cases.

^cAge was not reported for 28 females and 9 males.

^dAge was reported only in 2 out of 7 cases with age 75.

tardive dyskinesia associated with fluoxetine.³ Although fluoxetine has been linked to more cases of EPS in the literature, other SSRIs such as paroxetine,³ fluvoxamine,^{3,46} and sertraline⁴⁷⁻⁵⁰ have also been known to cause several types of movement disorder. The most common type of EPS associated with sertraline was akathisia, but other EPS types were also reported.⁴⁸⁻⁵⁰ We have in the past reported a case of reversible choreiform dyskinesia and EPS in a patient treated with sertraline.⁵¹

The data for escitalopram and citalopram are limited. Escitalopram has been implicated in a few cases of EPS, such as oculogyric dystonic reaction and rabbit syndrome.⁵² Rosenhagen et al reported that the combination of lamotrigine and escitalopram may cause myoclonus.⁵³ Garcia Ruiz reported a case of escitalopram-induced paroxysmal dystonia.⁵⁴ Muldoon asserted in 1996 that citalopram had a low potential to induce EPS.⁵⁵ However, citalopram has been reported to cause dystonia,⁵⁶ bruxism,⁵⁷ rabbit syndrome,⁵⁸ and reemergence of antipsychotic-induced dyskinesia.⁵⁹ Kwon and Lefkowitz reported a case of neonatal EPS associated with withdrawal from maternal citalopram use.⁶⁰

In 1996, Vandell et al hypothesized a link between antidepressant-induced EPS and the CYP2D6 phenotype.⁶¹ This hypothesis was further supported by Garcia-Parajuá et al, who demonstrated some evidence of an in vivo inhibition of the CYP2D6 isoenzyme and antidepressant-induced EPS in the elderly.⁶²

In 2006, Hendenmalm et al in Sweden analyzed the risk factors for EPS during treatment with SSRIs, includ-

ing the cytochrome P450 enzyme, and serotonin and dopamine transporter and receptor polymorphisms. They found that the risk of EPS with SSRIs seemed to increase with advanced age and the presence of the A1 allele of the dopamine D2 receptor (DRD2) gene Taq1A polymorphism.⁶³

Results of published reports of selected EPS associated with duloxetine, nefazodone, escitalopram, citalopram, and bupropion are shown in TABLE 1.

Results of the FDA AERS review

Only 89 cases met our inclusion criteria (TABLE 2). Of the 89 cases, 53 (60%) were females, 33 (37%) males, and 3 (3%) were not identified as female or male.

Tremor was reported in 40 cases (45%), akathisia in 13 (15%); dystonia in 12 (13%), dyskinesia in 11 (12%), and tardive dyskinesia in 7 cases (8%).

The number of females in each EPS category was as follows: 28/40 (70%) for tremor; 9/13 (69%) for akathisia; 6/12 (50%) for dystonia; 7/11 (64%) for dyskinesia, and 5/7 (71%) for tardive dyskinesia.

The mean age of patients who reported EPS was 50 years (range, 14 to 87 years). Females were slightly older (mean age, 51; range, 17 to 87 years) than males (mean age, 48; range, 14 to 80 years). (Data not shown.) Age was not reported for 28 females and 9 males.

Patients who were reported to have tremor, akathisia, and dystonia were younger (mean age 51, 47, and 49 years, respectively) than patients who had dyskinesia and tardive dyskinesia (mean age, 56 and 75 years, respectively).

TABLE 3
FDA antidepressant-induced EPS (N = 89)*

Antidepressant/ Time to onset of symptoms	Dose, mg/d (mean)	Total cases, n ^a	Tremor, n (%) ^b	Akathisia, n (%) ^b	Dystonia, n (%) ^b	Dyskinesia, n (%) ^b	Tardive dyskinesia, n (%) ^b
Duloxetine ^c	20 to 90 (46)	59 (66%)	27 (34%)	11 (14%)	6 (8%)	10 (13%)	6 (8%)
Sertraline	50 to 150 (121)	9 (10%)	3 (28%)	1 (9%)	2 (18%)	0	0
Escitalopram	10	6 (7%)	3 (50%)	0	2 (33.3%)	0	1 (16.7%)
Fluoxetine	5 to 20 (15)	3 (3%)	3 (60%)	1 (20%)	0	1 (20%)	0
Bupropion	300 to 800 (425)	5 (6%)	1 (20%)	2 (40%)	2 (40%)	0	0
Time to onset of symptoms, d (mean)	—	—	1 to 181 (38)	8 to 42 (27)	6 to 91 (30)	1 to 88 (40)	NA

AERS: Adverse Event Reporting System; EPS: extrapyramidal symptoms; NA: not available.

*Table reflects information only about side effects for duloxetine, sertraline, escitalopram, fluoxetine, and bupropion.

^a7 cases of nortriptyline, selegiline, citalopram, and paroxetine are not included.

^bPercentage based on the number of cases for this particular side effect.

^cTwo patients reported >1 adverse event.

In 59 of the 89 cases (66%), the drug implicated was duloxetine; in 9 (10%), sertraline; in 6 (7%), escitalopram; and in 5 (6%), bupropion (TABLE 3). It is interesting to note that among all of the cases reported to the FDA AERS by US physicians,⁶⁴ the rate of EPS reports for both duloxetine and escitalopram was 12% (TABLE 4).

The mean dose of duloxetine in the reported cases was 46 mg/d (range, 20 to 90 mg/d); sertraline, 121 mg/d (range, 50 to 150 mg/d); escitalopram, 10 mg/d; fluoxetine, 15 mg/d (range, 5 to 20 mg/d); and bupropion, 425 mg/d (range, 300 to 800 mg/d).

The duration of treatment prior to the onset of EPS was as follows: 33% of cases, 0 to 6 days; 28%, 7 to 31 days; 23%, 32 to 90 days; and 15%, more than 91 days. Review of the challenge codes (if the reaction abated when drug therapy stopped) showed improvement of EPS symptoms in 86% of cases after discontinuation of treatment. A summary of all cases reported to the AERS from July 2005 to March 2008 for the United States, Japan, the United Kingdom, France, and Germany is presented in TABLE 5.

DISCUSSION

The exact frequency of occurrence of EPS with antidepressants is unclear, but the estimated incidence is 1 per 1000 or less in users of SSRIs.^{65,66} Calculating this frequency poses many difficulties. Published reports represent only a very small number of actual occurrences. The spontaneous reporting system, because it is voluntary, does not represent the total number of occur-

rences. A cohort study would require more than 100,000 users of antidepressants to detect a 2-fold increase in EPS with SSRIs relative to other antidepressants.^{6,67} As stated, there have been more published studies regarding SSRIs in this connection.

In 1996, Leo³ reported 71 cases of SSRI-induced EPS from published literature. The most common adverse effect was akathisia (45%), followed by dystonia (28%), parkinsonism (14%), and tardive dyskinesia-like states (11%). Fluoxetine, the most commonly prescribed antidepressant during the 1980s and 1990s, was implicated in 75% of cases. However, in 58% of the cases in Leo's report, patients were on concurrent medications that could contribute to the development of EPS. The agonism of serotonergic input to dopaminergic pathways within the CNS was considered a probable cause for the SSRI-induced EPS.³

In the database of published reports, the 1998 study by Gerber and Lynd⁴ included reports from manufacturers of these drugs and the Canadian regulatory agency. Because the standards of reporting are different, this poses a problem in the analysis of the results. However, the number of cases included was large enough to come to certain conclusions. Out of 127 published reports of SSRI-induced movement disorders, akathisia was noted in 38%, dystonia in 24%, dyskinesia in 15%, tardive dyskinesia in 8%, parkinsonism in 32%, and mixed disorders in 19% of cases. They concluded that SSRI use appeared to be associated with the development of movement disorders, either as a direct result of the drug or due to exacerbation of an underlying condition.⁴ The confounding

TABLE 4

**Summary of all cases for selected antidepressants reported by US physicians—
July 2005 to March 2008**

Adverse events	Total	Duloxetine	Sertraline	Escitalopram	Paroxetine	Fluoxetine	Bupropion	Citalopram
All reported adverse events	23,342	4,025	3,151	2,832	2,140	2,017	1,996	1,502
EPS with concurrent psychotropic medication	2,527	294	280	305	262	214	225	141
EPS with no concurrent psychotropic medication ^a	89	59	9	6	2	3	5	2

EPS: extrapyramidal symptoms.

^aOne case each was reported for nortriptyline, amitriptyline, and selegiline.

factors of concurrent medications and underlying medical illnesses and previous exposure to neuroleptics limit interpretation of this study.

In 1997, Gill et al⁵ reviewed EPS associated with cyclic antidepressants and attempted to consolidate the hypothesis regarding causation of these adverse effects. They found that TCAs, miscellaneous agents, MAOIs, and SSRIs were associated, respectively, with parkinsonism, 0%, 14%, 33%, and 19%; akathisia, 26%, 34%, 17%, and 39%; dystonia, 17%, 17%, 17%, and 32%; reversible dyskinesia, 52%, 20%, 33%, and 10%; and neuroleptic malignant syndrome (NMS), 4%, 14%, 0%, and 10%. Among SSRIs, fluoxetine was associated with the highest number of EPS reports (63%). The authors concluded that the SSRIs may be more common offenders in producing these adverse effects and that the final common pathway for production of EPS appeared to be caused by indirect modulation of dopaminergic functions by serotonin/norepinephrine.⁵

In 2002, Schillevoort et al⁶ conducted a case-control study using spontaneous reports collected by the Netherlands Pharmacovigilance Foundation Lareb for the period 1985-1999. From a total of 24,263 reports, 61 were reports of EPS associated with antidepressants. The SSRI and EPS reports were more frequent, compared with EPS associated with other antidepressants. The ADR-reporting odds ratio for SSRI was 2.2 (95% confidence interval [CI], 1.2 to 3.9). In patients using antipsychotic medications concurrently, the risk estimate was higher, at 6.9 (CI, 0.7 to 68.0). The other interesting finding in this study was that paroxetine had the highest number of reports among all antidepressants

(38%) and SSRIs (49%), compared with 23% for all non-SSRI antidepressants.⁶

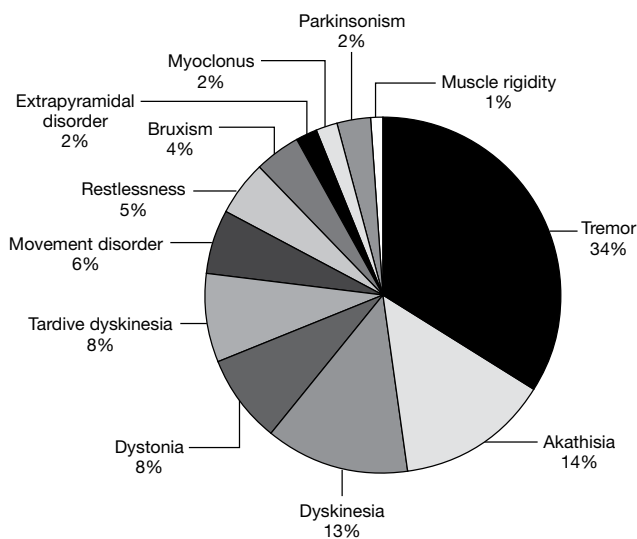
In all other studies we reviewed, fluoxetine had the highest number of reports. The year of fluoxetine's market introduction, which was 1987, did not appear to have any significant relation to the number of reports. However sertraline, venlafaxine, and mirtazapine, which were marketed in 1994 in the Netherlands, had only one report each. This finding might suggest that the inherent pharmacodynamic properties of fluoxetine may be responsible for its EPS potential, rather than the timing of its market introduction or number of years on the market.

In this study, the SSRIs were associated with parkinsonism (49%), akathisia (2%), dystonia (27%), and dyskinesia (20%). The frequency of akathisia reports (2%) was strikingly lower than the previous US and Canadian reports (38% to 45%). This may be related to the definition of akathisia in different countries or the diagnostic expertise of the reporting personnel. Our analysis of the FDA AERS indicates a 15% frequency of akathisia reports.

Our review of the literature identified 1 published report each of EPS with duloxetine, nefazodone, and bupropion, 3 reports with escitalopram, and 4 reports with citalopram. However our FDA analysis indicates about 66% of EPS reports with duloxetine, 9% with sertraline, 7% with escitalopram, and 6% with bupropion monotherapies. For all reports of EPS with antidepressants, escitalopram had 12%; duloxetine, 12%; sertraline, 11%; paroxetine, 10%; and fluoxetine, 8%.

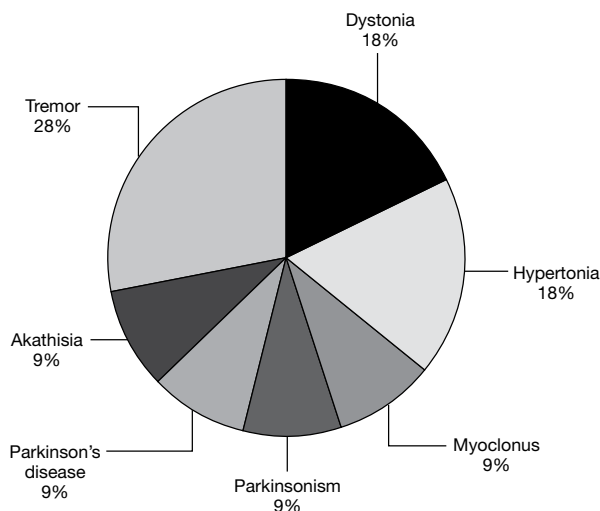
It is intriguing to note that the percentage of EPS reports related to duloxetine monotherapy was signifi-

FIGURE 1
Duloxetine AERS data



AERS: Adverse Event Reporting System.

FIGURE 2
Sertraline AERS data



AERS: Adverse Event Reporting System.

cantly higher than all duloxetine case reports (which may include patients on concurrent medications with a potential to cause EPS). The breakdown of the different types of EPS reports for duloxetine and sertraline are shown in **FIGURES 1** and **2**. Because we included physician-generated reports, and physicians are more likely to report monotherapy cases (because of the cause-effect relationship), this may potentially explain the higher percentage of EPS reports with duloxetine monotherapy compared with all cases. In our analysis, we attempted to eliminate some of the confounding factors, such as use of concurrent psychotropics, and we limited the cases to physician reports in the United States. The AERS provides a valuable tool for monitoring new adverse events that might occur with marketed products. However, not all adverse events are reported, and numerous factors are known to influence the reporting rate, such as the year of introduction of the drug to the market, the extent of use of the drug, and the health professional's attitude toward reporting of adverse events.⁶³ Nevertheless, this does not preclude the possibility that specific pharmacodynamic or pharmacokinetic differences between antidepressants may result in differences in the risk for a particular adverse event.

For patients on antidepressant monotherapy and no concurrent psychotropics at the time of the EPS, duloxetine, sertraline, escitalopram, and bupropion

were the drugs reported most often during the study period. For patients who were on concurrent psychotropics, escitalopram, duloxetine, sertraline, and paroxetine were named most frequently. Finally, for all cases reported by physicians in the United States between July 2005 and March 2008 for any adverse events from antidepressant drugs, duloxetine, sertraline, paroxetine, escitalopram, and fluoxetine were reported more often than other drugs (**TABLE 4**).

Occurrence of EPS with antidepressant treatment and no concurrent medication supports a causal relationship. In addition, improvement of EPS with discontinuation of antidepressant treatment in a majority of cases also indicates a cause-effect relationship. Similar to antipsychotic-induced EPS, antidepressant-induced akathisia and dystonia have been reported more frequently in younger patients than has tardive dyskinesia.⁴

Our results indicate that EPS were more common in females than in males,^{3,4} similar to previous reports.^{3,4} Although females may be more vulnerable to EPS, there is a potential confounding factor in that the prevalence of depression is greater among females and that more females seek treatment for depression than do males.³

The exact mechanism of causation of antidepressant-associated EPS is unknown. Plausible mechanisms include the inhibitory modulation of dopaminergic function in the nigrostriatal pathways; the reciprocal balance

TABLE 5

Summary of all cases reported to AERS from July 2005 to March 2008 by selected countries

Reports	USA	Japan	UK	France	Germany
Total number	650,079	60,195	48,162	45,721	32,655
Total number by physicians	136,451	39,233	12,511	19,250	18,973
Total number for antidepressants	23,342	2,275	1,790	1,026	1,390

AERS: Adverse Event Reporting System.

between dopaminergic, serotonergic, noradrenergic, or cholinergic activity; and CNS synaptic potentiation of serotonin and/or norepinephrine through inhibition of transporters or inhibition of their degradation by monoamine oxidase.^{43,68-71} The striatal inhibition of dopaminergic functions by serotonin,⁴³ the receptor occupancy studies of serotonin,⁶⁹⁻⁷⁰ the receptor polymorphisms, and cytochrome P450 (CYP2D6) phenotypes⁶¹⁻⁶³ all lend credence to the various hypotheses presented.

Advancing age, female sex, pharmacokinetic interaction by CYP2D6 inhibition of concurrent drugs with potential for EPS all appear to be risk factors. The management of antidepressant-associated EPS is essentially not different from that of neuroleptic-induced EPS and consists of dosage reduction, discontinuation or change of medication, and/or use of anticholinergic antiparkinsonian drugs, beta blockers, benzodiazepines, and in some cases, dopamine agonists.³⁻⁶

Limitations of this study include the retrospective nature of reporting, underreporting of adverse events, lack of inclusion of all reports, potential differences in reporting by different personnel, differences in reporting frequency based on timing of market introduction of the drug, unavailability of data regarding total exposures to a particular antidepressant drug, inclusion of cases with

possible concurrent nonpsychotropic medications, and concurrent medical illnesses.

CONCLUSIONS

Although we cannot estimate precisely the frequency of EPS with antidepressants, it is essential to recognize that they have been reported with different classes of antidepressants (SSRIs, SNRIs, NDRIs), are not dose related, and can develop with both short-term and long-term use. Any EPS can interfere with patient compliance, causing significant morbidity and, ultimately, decreased quality of life. Clinicians should be aware of the potential for any class of antidepressants to cause EPS. ■

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