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Extrapyramidal syndromes associated with selective serotonin reuptake inhibitors: a case–control study using spontaneous reports

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The aim of this study was to assess whether use of selective serotonin reuptake inhibitors (SSRIs) is associated with extrapyramidal syndromes (EPS). We analysed the spontaneous reports of adverse drug reactions (ADRs) collected by The Netherlands Pharmacovigilance Foundation Lareb in the period 1985–99 ($n = 24\,263$). The study population comprised all patients using an antidepressant drug at the time the ADR occurred. We calculated ADR-reporting odds ratios (ADR-OR) to estimate the association between SSRI-use and EPS, relative to other antidepressants. We identified 61 patients with EPS. SSRI-use was associated with spontaneous reporting of EPS compared to other antidepressants (adjusted ADR-OR 2.2; 95% confidence interval 1.2–3.9). This risk estimate appeared to be higher in patients concurrently using antipsychotic medication (6.9, 0.7–68.0), although the confidence interval was very wide. In conclusion, SSRI-use seems only to be moderately associated with EPS compared to other antidepressants. However, those concurrently using antipsychotic drugs or presenting with other risk factors may be more susceptible and should be closely monitored. Int Clin Psychopharmacol 17:75–79 © 2002 Lippincott Williams & Wilkins

Keywords: adverse drug reaction reporting systems, antidepressive agents, extrapyramidal syndromes, serotonin uptake inhibitors

INTRODUCTION

Numerous case reports have described the occurence of extrapyramidal syndromes (EPS) (i.e. parkinsonism, dystonia, akathisia and dyskinesia) in patients using antidepressant drugs (Gill *et al*., 1997). Based on the number of published reports and the antidopaminergic effect of serotonin in the striatum (Kapur and Remington, 1996), selective serotonin reuptake inhibitors (SSRIs) are thought to induce EPS more often than other antidepressant drugs. However, thus far this hypothesis has not been tested in either experimental or observational studies. This may partly be explained by the low frequency of antidepressant-induced EPS. With an estimated incidence of 1 per 1000 users of SSRIs or less (Choo, 1993; Coulter and Pillans, 1995), a cohort study would need to include over 100 000 antidepressant drugs users to detect a two-fold increase in EPS with SSRIs relative to other antidepressant drugs (Fleiss, 1981). Even in a case–control design, the required sample size may be difficult to achieve using classical medical registries.

In many countries, adverse drug reactions (ADRs) are reported by health care professionals to regional or national pharmacovigilance centres. Despite considerable under-reporting (Alvarez-Requejo *et al*., 1998),

this pharmacovigilance data is often used to compare the safety of two drugs from the same pharmacotherapeutic group, especially with regard to new or rare ADRs (Begaud *et al.*, 1991). This is often performed through 'reaction proportion signalling', which assesses whether a drug has a disproportionate share in a certain ADR, relative to all other reported ADRs (Finney, 1974). This methodology has previously been used to study various types of drug-induced morbidity (Stricker and Tijssen, 1992; Egberts *et al.*, 1997; Van Puijenbroek *et al.*, 1999).

In the absence of population-based pharmacoepidemiological studies, we evaluated whether SSRIs were associated with EPS relative to other antidepressants in a database of spontaneously reported adverse drug reactions.

METHODS

Source

Data for this nested case–control study were obtained from the Netherlands Pharmacovigilance Foundation Lareb. From 1985 onwards, Lareb collects reports of adverse drug reactions (ADRs) in The Netherlands. These reports are provided by health care professionals on a voluntary basis through a 'yellow card' system. After being received by Lareb, each report is evaluated by a trained physician and/or pharmacist and filed in a database. Reports contain information about the patient, adverse drug reaction, medication used at the time of the event (both suspected drug and concomitant medication) and indication for use of the suspected drug, as well as the original description of the adverse drug reaction as provided by the reporter. ADRs are coded according to the adverse reaction terminology of the World Health Organization (WHO-ART) (Anonymous, 1995). Between 1 January 1985 and 30 June 1999, Lareb has received 24 263 reports.

Selection of cases and non-cases

The study population comprised all patients for whom an ADR has been reported to Lareb between 1 January 1985 and 30 June 1999 and who were using an antidepressant drug at the time the ADR occurred, either recorded as suspected drug or as concomitant

Table 1. Cases of drug-induced extrapyramidal syndromes (EPS), divided by suspected drug (as indicated by the reporter) and type of disorder

Drug (year of market introduction in The Netherlands)	Any EPS	Parkinsonism[a,b]	Akathisia[c]	Dystonia[d]	Dyskinesia[e]	Unspecified EPS[f]
Any drug	61	36 (30)	1	13	10	2
SSRIs	41*	20 (18)	1	11	8	2
Paroxetine (1991)	23*	9 (8)	–	9	6	–
Fluoxetine (1989)	9	7 (6)	–	1	1	–
Fluvoxamine (1985)	7	3 (3)	–	1	1	2
Citalopram (1997)	1	–	1	–	–	–
Sertraline (1994)	1	1 (1)	–	–	–	–
Other antidepressant drugs	14	11 (8)	–	1	2	–
Amitriptyline (1962)	3	3 (3)	–	–	–	–
Clomipramine (1970)	3	2 (2)	–	–	1	–
Dosulepin (1984)	2	2 (2)	–	–	–	–
Maprotiline (1975)	1	1 (1)	–	–	–	–
Mianserin (1982)	1	–	–	–	1	–
Mirtazapine (1994)	1	–	–	1	–	–
Nefazodone (1997)	2	2 (0)	–	–	–	–
Venlafaxine (1994)	1	1 (0)	–	–	–	–
No antidepressant drug	6	5 (4)	–	1	–	–

EPS, extrapyramidal syndrome; SSRI, selective serotonin reuptake inhibitor. [a]Parkinsonism was identified in reports containing one or more of the following terms in the original text: parkinsonism, masked facies, coghweel rigidity, bradykinesia, shuffling gait, tremor, worsening of pre-existing parkinsonism. [b]The number of reports where tremor was the only sign of parkinsonism are in parentheses. [c]Akathisia was identified in reports containing the term akathisia in the original text. [d]Dystonia was identified in reports containing one or more of the following terms in the original text: dystonia, trismus, jaw spasms, oculogyric spasms, torticollis, opisthotonus. [e]Dyskinesia was identified in reports containing one or more of the following terms in the original text: lingual-facial-buccal dyskinesia, limb-truncal dyskinesia, choreatic movements, athetosis. [f]Unspecified extrapyramidal syndrome was identified in reports containing the term 'extrapyramidal syndrome' in the original text without any specification. *The total number of reports is less than the sum of individual extrapyramidal syndromes, because some reports described more than one different extrapyramidal syndromes.

medication. Subsequently, we identified possible cases of EPS as patients whose ADR was assigned one or more of the following WHO-ART terms: dystonia, torticollis, choreoathetosis, dyskinesia, extrapyramidal disorder, hyperkinesia, hypokinesia, oculogyric crisis, tremor, muscle contractions involuntary, dyskinesia tardive, parkinsonism aggravated or bradykinesia. From this first selection of patients, only those whose original description of the ADR contained one or more terms indicative of EPS (Table 1) were selected as cases. All other patients in the study population (non-cases) were selected as controls.

Statistical analysis

We assessed the use of SSRIs (fluoxetine, paroxetine, sertraline, fluvoxamine and citalopram) and other antidepressant drugs (either recorded as suspected drug or as concomitant medication) among cases of EPS and control patients. To quantify the association between SSRI use and spontaneous reporting of EPS relative to other antidepressants, we calculated the ADR-reporting odds ratio (ADR-OR). The ADR-OR is defined as the ratio of two odds, namely the odds of exposure among reported cases of a certain suspected ADR relative to the odds of exposure among reported non-cases (Stricker and Tijssen, 1992; Egberts *et al.*, 1997). Thus, the numerator of the ADR-OR is calculated by dividing the number of cases (i.e. patients with EPS) where SSRIs are used by the number of cases where other antidepressants were used; the denominator is calculated by dividing the number of controls (i.e. patients with other ADRs) where SSRIs are used by the number of controls where other antidepressants were used.

Crude and adjusted ADR-ORs and their 95% confidence intervals (CI) were calculated using unconditional logistic regression (SPSS for Windows, version 7.5.2; SPSS, Chicago, IL, USA). Odds ratios were adjusted for age and gender of the patient, year and source of the report and the concurrent use of benzodiazepines, antipsychotic drugs and lithium. We also assessed odds ratios within strata of age, gender, calendar year and antipsychotic drug use.

RESULTS

The study population comprised 2476 patients in the Lareb database who were using an antidepressant drug at the time their adverse drug reaction occurred. Sixty-one fulfilled our criteria of EPS and were selected as cases. The remaining 2415 patients were selected as controls. Mean age of cases and controls was comparable (49 versus 51, respectively; $P = 0.33$). Sixty-seven percent of cases and 71% of controls were female ($P = 0.63$). Parkinsonism and dystonia were the most frequently reported extrapyramidal syndrome (59.0% and 21.3%, respectively) (Table 1). However, tremor often was the only sign of parkinsonism (83.3%). Only one report described akathisia.

Table 2. ADR-reporting odds ratios of extrapyramidal syndromes for selective serotonin reuptake inhibitors versus other antidepressant drugs (either suspected drug or concomitant medication

	Cases: reports of EPS (SSRIs/other ADs)[a]	Controls: reports of other ADRs (SSRIs/other ADs)[a]	ADR-reporting OR (crude, 95% CI)	ADR-reporting OR (adjusted, 95% CI)[b]
Overall	41/19	1,264/1,107	1.9 (1.1–3.4)	2.2 (1.2–3.9)
Age				
< 55 years	25/11	919/863	2.1 (1.0–4.6)	2.1 (0.9–4.5)
⩾ 55 years	16/8	345/444	2.6 (1.0–6.6)	2.9 (1.1–7.3)
Gender				
Men	15/5	356/332	2.8 (0.9–8.9)	3.1 (1.0–9.5)
Women	26/14	908/775	1.6 (0.8–3.2)	1.9 (0.9–3.9)
Year of reporting				
1985–90	1/5	50/226	0.9 (0.0–8.3)	1.1 (0.1–10.8)
1991–93	3/3	113/146	1.3 (0.2–9.8)	1.7 (0.3–9.3)
1994–96	16/4	491/288	2.4 (0.7–8.4)	2.7 (0.9–8.2)
1997–99	21/7	610/447	2.2 (0.9–6.2)	2.5 (1.1–6.2)
Concurrent use of antipsychotic drugs				
No	37/18	1,210/1,021	1.7 (1.0–3.2)	2.0 (1.1–3.6)
Yes	4/1	54/86	6.4 (0.6–317)	6.9 (0.7–68.0)

ADR, adverse drug reaction; OR, odds ratio; 95% CI, 95% confidence interval; EPS, extrapyramidal syndromes; SSRI, selective serotonin reuptake inhibitor; AD, antidepressant drug. [a]Excluding patients who used both an SSRI and another antidepressant drug (1 case, 44 controls). [b]Adjusted for age, gender, year or reporting, source and concurrent use of antipsychotic drugs, benzodiazepines or lithium.

In patients with EPS, SSRIs were more often reported as suspected medication than other antidepressants (41 versus 14 times). In six of the patients with EPS, the antidepressant drug that was used was not the suspected medication (Table 1). Not differentiating between suspected and concomitant medication, 41 (67.2%) cases and 1264 (52.3%) control patients were using an SSRI. This yielded crude and adjusted ADR-ORs of 1.9 (95% CI 1.1–3.4) and 2.2 (1.2–3.9), respectively, relative to other antidepressants (Table 2).

The risk estimate was slightly higher for people aged 55 years or older and for male patients. Furthermore, the ADR-OR increased over time. Notably, the association between SSRI use and EPS seemed strongest in those concurrently using antipsychotic medication. However, in many of these subanalyses, confidence intervals were wide (Table 2).

In this study, restless legs was not considered an EPS (Victor and Ropper, 2001). It was reported 14 times. The risk estimate did not change when these reports were included as cases (ADR-OR 2.1, 1.2–3.6). Furthermore, SSRI-use remained significantly associated with EPS when tremor was not regarded a symptom of EPS (ADR-OR 2.8, 1.2–6.7).

DISCUSSION

Our data show that, relative to other antidepressant drugs, the use of SSRIs is associated with a two-fold increase in spontaneous reporting of EPS than in reports of other ADRs. While this might suggest that SSRIs are more likely to cause EPS than other antidepressants, the association is only moderate. Furthermore, several biases have to be considered.

The use of ADR-ORs to estimate relative risks may especially be biased by underreporting of ADRs (Begaud *et al*., 1991). Important factors that can influence reporting include the time a drug has been on the market and recent publications in the medical literature (Schroeder, 1998). The former is unlikely to bias reporting odds ratios. The initial increase and subsequent decrease of the number of ADR reports for a given drug after marketing, known as the 'Weber effect' (Weber, 1984), influences all ADRs of that drug and thus affects the numerator and denominator of the OR to the same extent (Stricker and Tijssen, 1992). However, ORs could be affected by the latter. Case reports of antidepressant-induced EPS published during the study period (most of which involved SSRIs) may have selectively stimulated the reporting of SSRI-induced EPS, thus overestimating the true relative risk. This seems to be supported by the increasing ADR-OR over time. Thus, the overall odds ratio of 2.2 is likely to be an upperbound estimate of the true relative risk.

Based on the antidopaminergic effect of serotonin in the striatum (Kapur and Remington, 1996) and the large number of published case reports of SSRI-induced extrapyramidal symptoms (Gill *et al*., 1997), a much stronger association between SSRI use and the occurrence of EPS might be expected. However, many of the published case reports involved patients who were also carrying other risk factors for EPS, such as advanced age, concomittant use of antipsychotic drugs, previous events of drug-induced EPS or presymptomatic Parkinson's disease. This may suggest that the effect of SSRIs on the development of EPS especially presents in those who are already vulnerable to this side-effect. Indeed, while the number of patients was small, our results suggest that the association between SSRI-use and EPS is strongest in the elderly and in those concurrently using antipsychotic drugs.

In conclusion, our data indicate that SSRIs are only moderately associated with extrapyramidal syndromes relative to other antidepressant drugs. Patients with an already compromised dopaminergic function due to, for example, concurrent treatment with other antidopaminergic drugs or Parkinson's disease may be more susceptible and should be closely monitored.

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