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Withdrawal reactions with selective serotonin re-uptake inhibitors as reported to the WHO system

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Abstract *Objective*: The present study was performed both to investigate whether there might be a difference between the selective serotonin re-uptake inhibitors, (SSRIs) with regard to the incidence of withdrawal reactions, and to describe the associated symptoms. From the WHO database, therefore, all case reports from the year of introduction for each of the SSRIs, fluoxetine, paroxetine and sertraline, were retrieved. Sales figures were obtained from Intercontinental Medical Statistics International. The reporting rates were calculated as the number of reports per million defined daily doses (DDDs) sold per year.
Results: The reporting rate of withdrawal reactions for paroxetine was found to be higher than that for sertraline and fluoxetine in each of the countries selected for detailed analyses (US, UK and Australia), as well as for all 16 countries combined. Moreover, using the WHO system of organ classification, the ratio of central nervous system to psychiatric withdrawal symptoms was 1.9 and 2.1 for paroxetine and sertraline, respectively, whereas that for fluoxetine was 0.48, indicating a possible qualitative difference between the SSRIs with respect to the nature of the withdrawal syndrome.

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Introduction

Withdrawal reactions appear following cessation of a drug, are different from the patient's underlying disorder, show a specific time course, resolve on readministration of the drug and subside without specific treatment. Withdrawal reactions following discontinuation of tricyclic antidepressant drugs are well known, the most frequent symptoms being influenza-like symptoms and sleep disturbances, such as middle and initial insomnia, vivid dreams and nightmares, whereas movement and affective disorders seem rare [1]. A cholinergic rebound may be the most likely underlying mechanism, but effects on noradrenergic and dopaminergic systems have also been discussed [1]. The newer second-generation antidepressant drugs, the selective serotonin re-uptake inhibitors (SSRIs), are weaker than the older compounds at blocking muscarinic and α-adrenergic receptors [2]. However, case reports on withdrawal reactions, such as dizziness, nausea, influenza-like symptoms or neurological symptoms with the SSRIs, especially paroxetine [3–13], but also fluoxetine [14–17], sertraline [7, 9, 18–21] and fluvoxamine [22, 23], have been published over the past few years.

The present database study was initiated both to investigate possible differences between fluoxetine, paroxetine and sertraline with regard to the incidence of withdrawal reactions and to describe the symptoms associated with the withdrawal reactions.

Material and methods

The WHO database

Spontaneously reported cases of suspected adverse drug reactions (ADRs) are forwarded from national centres in 47 countries to the

WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden. The case reports, recorded using a common format, are processed and stored in the 1.6 million case-record database, maintained by the collaborating centre, which provides a unique source of international ADR information.

The information in a WHO case report consists of administrative data (source and type of report), patient data, ADR data and medication data. The minimum information required for acceptance of a report is the reporting country and ID, an ADR and the name of the medication. All ADRs are coded according to the WHO Adverse Reaction Terminology. This is a hierarchical classification which includes medical terms, grouped into broad body-system organ classes. Medicines can be listed as being suspected of having caused the reaction, as interacting or as "other" (concomitant medication). Provision is made for the result of a causality assessment by the national centres, though this facility is not universally used.

The Intercontinental Medical Statistics database

Drug utilisation data were obtained from Intercontinental Medical Statistics (IMS) International. This organisation has been collecting data on drug use for many years in the major markets of the world and its database contains the only internationally comparable denominator data, except for ex-manufacturer sales. The data collected by IMS includes hospital and pharmacy drug sales and medical-audits data, based on the records of practising physicians.

Data retrieved

From the WHO database, all case reports mentioning paroxetine, fluoxetine or sertraline as a "suspected" drug were incorporated into a search. The search included data from the year of introduction of the respective drug until 1995 inclusive. The three SSRIs were chosen because they had the widest international use. For the purpose of this analysis, no attempt was made to confirm the clinical details of the cases reported, and total validity in attribution was assumed.

From the IMS database, total drug sales in kilograms for paroxetine, fluoxetine and sertraline were retrieved for the world's largest pharmaceutical markets. The sales figures were broken down into country and year and, for comparability, expressed per million defined daily doses (DDDs) sold; the term DDD was assigned by the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway. To obtain these figures, the total sales in kilograms from the IMS database were divided by the DDD value for each drug. The DDD used for fluoxetine was 20 mg and for paroxetine and sertraline 20 mg and 50 mg, respectively. The sales data were used as the denominator in the calculations of reporting rates for the three drugs.

The IMS medical data are obtained from a rolling panel of doctors, selected to be representative of medical practice in each country. The doctors record all data on prescriptions (including patient data, diagnoses and prescribed products) for a specified period (usually 5–7 days). The data are then analysed and statistically projected to reflect the total relevant doctor and patient populations at the lowest level of stratification possible. This type of data was used for estimating reporting rates by age (grouped into decade age bands) and gender.

An evaluation was made of data from the 16 countries, which together accounted for more than 80% of global sales and 99% of the ADR reports. The highest number of reports were from the US, UK and Australia. These countries were selected for individual analyses in addition to the overall international data.

In our analyses, a withdrawal case report was one which contained the WHO ADR terms "withdrawal syndrome", "withdrawal headache" or "withdrawal convulsions". Because time from discontinuation of the SSRI to appearance of the withdrawal reaction (e.g. due to half-life of the drug) may influence the likelihood of detecting, diagnosing and consequently reporting a drug-related withdrawal syndrome, these data were also obtained from the WHO database.

Results

Of a total of 49 393 case reports retrieved, 33 776 referred to fluoxetine, 10 030 to paroxetine and 5641 to sertraline. The reports were received from 23 countries. Sales data were available for 16 of these countries. Thus, data from 16 countries, accounting for 49 335 reports, were analysed. A small number of reports (58) from seven countries were, therefore, excluded from further analysis.

For the 16 countries over the whole time period, there were 947 (of a total of 10 020) withdrawal case reports for paroxetine, 271 (of 33 731) for fluoxetine and 170 (of 5638) for sertraline. In the US, the total numbers of withdrawal reports were 279, 223 and 130 for paroxetine, fluoxetine and sertraline, respectively. In the UK, the corresponding numbers were 618, 35 and 33, respectively and in Australia, 21, 4 and 7 repectively. The withdrawal resporting rates per year, expressed as the number of withdrawal reports per million DDDs sold per year for paroxetine, fluoxetine and sertraline in the selected countries, US, UK, and Australia, as well as for all countries combined are shown in the left column of Fig. 1. The non-withdrawal ADR reporting rates per year for paroxetine, fluoxetine and sertraline in the selected countries, US, UK and Australia, and for all countries combined are shown in the right column of Fig. 1.

The most frequent withdrawal symptoms for paroxetine, fluoxetine and sertraline, considering data from all countries, are illustrated in Table 1. It should be pointed out that only in some of the withdrawal reports were the symptoms actually specified. Thus, for paroxetine, 414 of a total of 947 withdrawal reports (44%) were accompanied by a symptom description. For fluoxetine and sertraline, the corresponding percentages were 83% and 80%, respectively. The relative preponderance of withdrawal symptoms assigned to the central nervous system (CNS) organ class compared with psychiatric symptoms is clearly seen for paroxetine and sertraline (Table 1). The reverse pattern is evident for fluoxetine.

When all withdrawal symptoms, including the most frequent, seen in Table 1, were included, the proportion of CNS/all withdrawal symptoms was 43% and 47% for paroxetine and sertraline, respectively. The proportion of psychiatric/all withdrawal symptoms was 23% and

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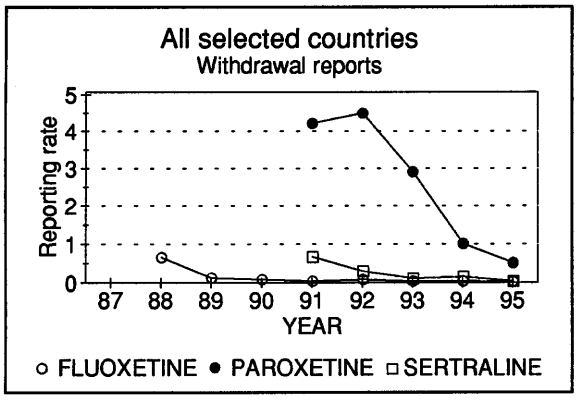
Fig. 1 Reporting rates expressed as the number of withdrawal repors per million defined daily doses (DDDs) sold per year for paroxetine, fluoxetine and sertraline, in the selected countries, US, UK and Australia, and for all 16 countries combined (*left column*). The number of reports obtained from the WHO database and sales data was provided by IMS International. For comparison, the corresponding rates for all adverse drug reactions (excluding reports on withdrawal) are shown in the *right column*


All selected countries
Withdrawal reports
Reporting rate
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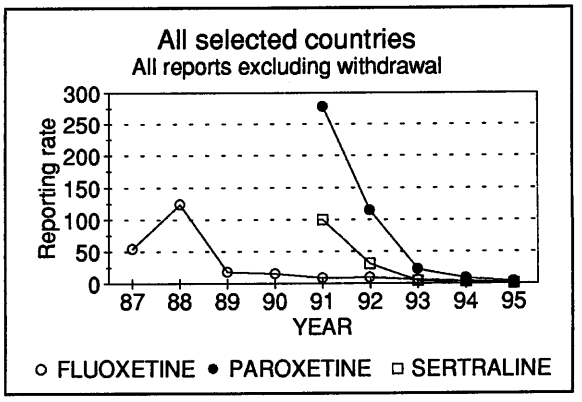
87 88 89 90 91 92 93 94 95
YEAR
o FLUOXETINE • PAROXETINE □ SERTRALINE


All selected countries
All reports excluding withdrawal
Reporting rate
0
50
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150
200
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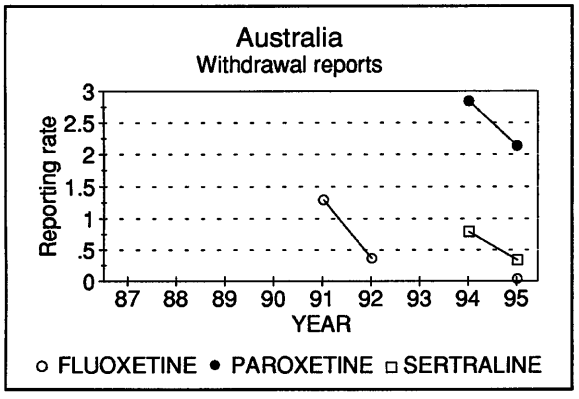
Australia
Withdrawal reports
Reporting rate
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YEAR
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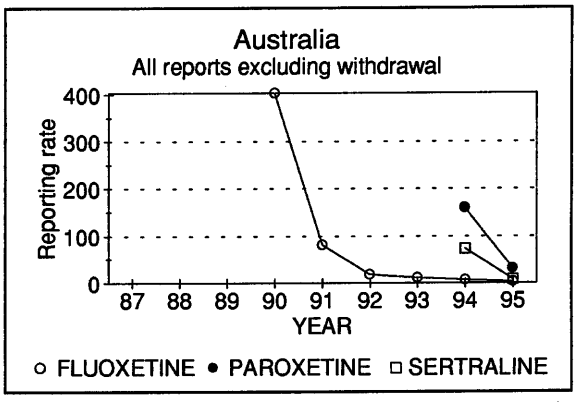
Australia
All reports excluding withdrawal
Reporting rate
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YEAR
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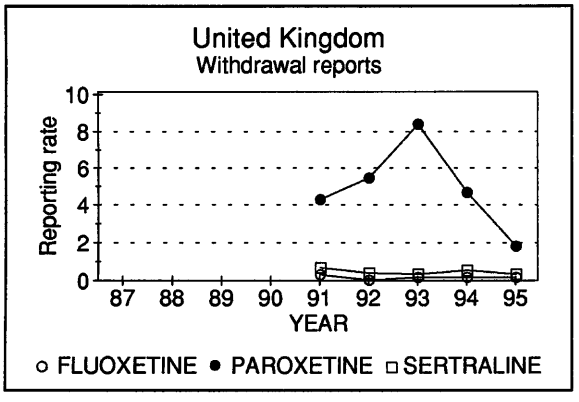
United Kingdom
Withdrawal reports
Reporting rate
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2
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YEAR
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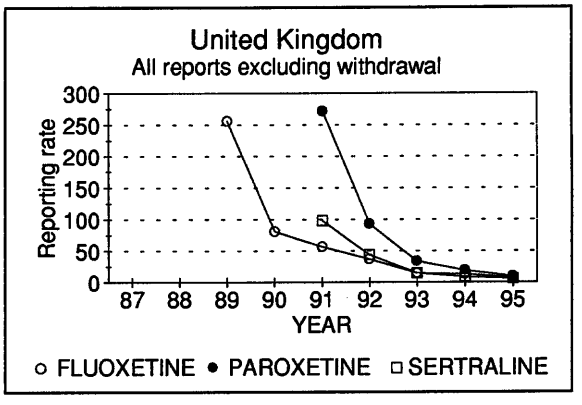
United Kingdom
All reports excluding withdrawal
Reporting rate
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YEAR
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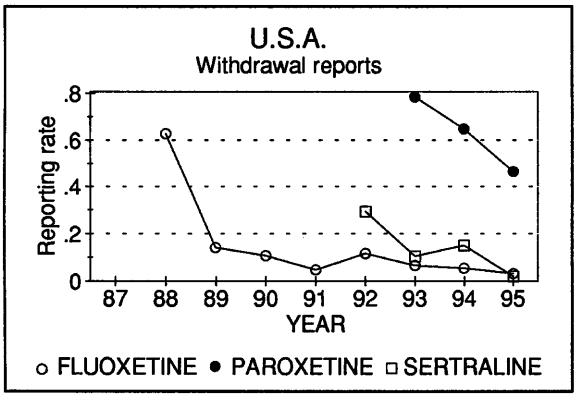
U.S.A.
Withdrawal reports
Reporting rate
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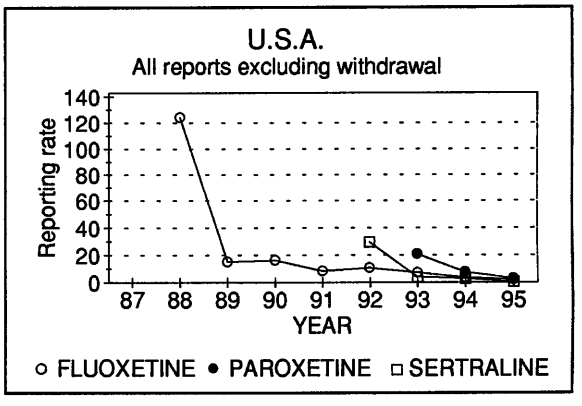
U.S.A.
All reports excluding withdrawal
Reporting rate
0
20
40
60
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87 88 89 90 91 92 93 94 95
YEAR
o FLUOXETINE • PAROXETINE □ SERTRALINE

Table 1 The most frequent symptoms/adverse reactions reported in connection with drug withdrawal, together with their corresponding system organ class. Of the fluoxetine reports, 83% contained a specification of the withdrawal symptoms. For paroxetine and sertraline the proportions were 44% and 80%, respectively

Drug	Adverse reaction		No. of reactions
Fluoxetine		(271 reports)	
	Dizziness	CNS	24
	Nervousness	Psychiatric	24
	Anxiety	Psychiatric	21
	Depression	Psychiatric	19
	Suicide attempt	Psychiatric	17
	Depression psychotic	Psychiatric	15
	Headache	CNS	15
	Convulsions	CNS	13
	Aggressive reaction	Psychiatric	9
	Agitation	Psychiatric	9
(Total no. of reactions 431; total no. of CNS reactions 96; total no. of psychiatric reactions 200)			
Paroxetine		(947 reports)	
	Dizziness	CNS	142
	Nausea	G-I	63
	Paraesthesia	CNS	55
	Headache	CNS	53
	Vertigo	CNS	35
	Sweating increased	Skin	29
	Agitation	Psychiatric	25
	Tremor	CNS	25
	Fatigue	General	24
	Anxiety	Psychiatric	22
(Total no. of reactions 898; total no. of CNS reactions 382; total no. of psychiatric reactions 204)			
Sertraline		(170 reports)	
	Dizziness	CNS	52
	Paraesthesia	CNS	24
	Headache	CNS	22
	Nausea	G-I	21
	Vertigo	CNS	14
	Agitation	Psychiatric	10
	Tremor	CNS	9
	Nervousness	Psychiatric	8
	Anxiety	Psychiatric	6
	Depression	Psychiatric	6
(Total no. of reactions 305; total no. of CNS reactions 143; total no. of psychiatric reactions 66)			

22% for the same drugs, respectively. The ratio of CNS/psychiatric withdrawal symptoms, therefore, was 1.9 and 2.1 with paroxetine and sertraline, respectively. For fluoxetine, the proportion of CNS/all withdrawal symptoms was 22% and psychiatric/all withdrawal symptoms was 46% and, consequently, the ratio CNS/psychiatric withdrawal symptoms was 0.48, i.e. the inverse of that seen for paroxetine and sertraline. When other non-psychiatric (i.e. physical) withdrawal symptoms were added to the CNS symptoms, the proportion of non-psychiatric/all withdrawal symptoms with paroxetine and sertraline was 77% and 78%, respectively, whereas that for fluoxetine was 54%.

The ratio of female/male withdrawal reporting rates for paroxetine was 1.40 and 1.31 in the US and UK, respectively, and for fluoxetine, 0.72 and 0.73, respectively. For sertraline, the ratio was 1.18 and 1.60, respectively. The corresponding ratio for all ADR reports was 0.92–0.99 (range) for paroxetine and fluoxetine in the US and UK. For sertraline, this ratio was 0.79 and 1.14 in the US and UK, respectively.

The calculated reporting rates by decade age groups showed no major differences in pattern between withdrawal reports or all ADRs and no further evaluation was made of these data.

A considerable amount of data were missing on time from discontinuation of the SSRI to the detection of the withdrawal reaction. In 572 withdrawal reports on paroxetine, no such data were available and, in 47 reports, the time interval obtained was negative, indicating an onset of the reaction before treatment was interrupted, but clarifying details were not available in those reports. For fluoxetine, the corresponding numbers were 222 and 9, respectively, and for sertraline, 108 and 15, respectively. Thus, 328 withdrawal reports on paroxetine, 40 on fluoxetine and 47 on sertraline remained. Based on these reports, the mean time from discontinuation of drug to appearance of the withdrawal reaction was 9.5 days with paroxetine, 24 days with fluoxetine and 6.6 days with sertraline, and the median times were 2, 3, and 2 days, respectively, indicating that the distribution was skewed. Further analysis of these data was not considered justifiable.

Discussion

The present analysis showed a considerably higher withdrawal reporting rate (expressed as the number of reports per million DDDs sold per year) for paroxetine

in comparison with sertraline or fluoxetine. This result was found for all countries combined as well as for each separate country (US, UK and Australia) (Fig. 1, left column). Furthermore, a predominance of physical withdrawal symptoms, especially symptoms assigned to the system organ class "CNS", was seen for paroxetine and sertraline, whereas for fluoxetine, psychiatric symptoms were more prevalent (Table 1). The same tendency was seen in the US, which was the only country that had a substantial number of reports on all three drugs (data not shown). Thus, the above findings not only indicate that withdrawal reactions can occur upon cessation of SSRIs, as illustrated by a number of published case reports reviewed below, but also point to the possibility of there being a difference between the studied SSRIs with respect to the incidence and type of withdrawal reactions. In addition, our data suggest that there may be a gender difference with respect to the withdrawal reporting rates for paroxetine and sertraline in comparison with fluoxetine.

The CSM (Committee on Safety of Medicines) and MCA (Medicines Control Agency) highlighted, in 1993, the frequent reporting of withdrawal reactions with paroxetine in the UK [24]. This attention may have further increased the reporting of withdrawal reactions for paroxetine in the UK, as evidenced by the peak in reporting rate observed in Fig. 1, thereby creating a differential under-reporting of fluoxetine and sertraline withdrawal reactions. However, it is doubtful whether this could explain the higher reporting rate for paroxetine compared with fluoxetine and sertraline found in our material, because the rate for paroxetine was also high in the US and in Australia. Interestingly, there was no parallel increase in the reporting of other ADRs (excluding withdrawal reactions) with paroxetine in the UK, nor of withdrawal reactions with other SSRIs in that country (Fig. 1, right column). Moreover, despite the fact that reports of withdrawal reactions started to appear in the UK in the same year for all three SSRIs (1991, the year of introduction to the market of paroxetine and sertraline in the UK; fluoxetine was introduced in 1989, but there were no withdrawal reports until 1991), there was no substantial increase in the reporting rate for fluoxetine and sertraline, whereas for paroxetine the rate at that time was already 6 and 13 times higher than that for sertraline and fluoxetine, respectively (Fig. 1, left column). Therefore, it seems unlikely that the difference between paroxetine and the other SSRIs studied would be due to a higher reporting rate immediately following approval of the drug (the so-called Weber effect), although after 1993 a decrease in the withdrawal reporting rate was seen for paroxetine (Fig. 1, left column).

The indications for prescribing SSRIs and the severity of disease in the patients considered for treatment might differ between Europe and the US, in particular, and there have been articles addressing this issue [25]. In our analysis, sufficient data on indications were not available from the WHO case reports. Therefore, the question of whether the WHO withdrawal reports on paroxetine constitute a special subgroup of patients cannot be resolved. However, the indications for use of SSRIs, in general, were examined for the US and UK, where prescription data from IMS were available. Thus, in a compilation of the 10 most common indications, constituting more than 80% of all prescriptions for each SSRI per country, the main diagnoses were depressive disorder and manic-depressive psychosis. In the UK, the percentages of total usage for these diagnoses combined were 50% for fluoxetine, 48% for paroxetine and 48% for sertraline. In the US, the corresponding figures were 68, 70 and 69%, respectively; the minor difference between the UK and the US was due mainly to a higher percentage of patients with depressive disorder in the US. In neither country did any of the other diagnostic groups exceed 10% of the total for any of the SSRIs. These data indicate that there was no substantial difference in the indications of usage between these SSRIs in the respective country, or between countries. Furthermore, in the present material, the higher reporting rate with paroxetine was observed in all selected countries, and with regard to the relative reporting rates of non-withdrawal ADRs, there was little difference between the countries (Fig. 1, right column). A change in patient population over time, possibly due to a change in treatment indication, to include subjects less prone to develop withdrawal reactions with SSRIs, especially paroxetine, could theoretically explain a decrease in reporting rate. However, we have not found any data to support this, and further it is not possible to separate this from the Weber effect.

It seems logical to assume that the shorter the time from discontinuation of a drug to the appearance of withdrawal symptoms, the easier would be the detection of withdrawal symptoms and, consequently, the reporting rate would increase. However, only a limited amount of data was available for our analysis of time from interruption of the drug to onset of the withdrawal reaction. This did not permit an analysis of correlation with half-life. Therefore, it cannot be excluded that under-reporting of late withdrawal reactions with fluoxetine (long half-life) might have biased our results.

There exist several case reports on withdrawal reactions with paroxetine [3–13] describing a syndrome consisting of physical symptoms, usually occurring within 1 week after interrupting paroxetine and generally subsiding within 2–3 weeks after symptoms start; however, withdrawal symptoms persisting for 2 months or more post-cessation have been reported [3]. The withdrawal syndrome described for paroxetine in these reports is rather uniform, the most frequent symptoms being nausea; dizziness; vertigo; lightheadedness; fatigue/lethargy; headache; sometimes influenza-like symptoms, such as myalgia/muscle aches, shaking chill, diarrhoea, abdominal discomfort and rhinorrhoea; CNS-related symptoms (gait instability/dyscoordination/ataxia, tremor, psychomotor agitation, initial and middle insomnia, paraesthesia); and eye-related symptoms, such as migraine-

like visual phenomena, blurred vision and diplopia. Withdrawal syndromes including sensations like "electric shocks" or "electricity" have also been described for paroxetine [9, 10]. Only two reports were found on distinct psychiatric symptoms, such as hypomania, aggression and behavioural dyscontrol, following the withdrawal of paroxetine [8]. One investigator described three patients with crying spells and vivid dreams [10]. Other symptoms were nightmares and a feeling of depersonalisation, in addition to the physical withdrawal symptoms [10]. The indication for use in the above paroxetine reports was usually major depression – in some cases minor depression [8] or obsessive-compulsive disorder [10–12] – and the dose was 20–60 mg daily, being tapered or stopped abruptly. Singular cases indicate that withdrawal symptoms may be more prolonged with fluoxetine than with other SSRIs [14].

In the above case reports, the withdrawal symptoms resolved on readministration of treatment and recurred on further dose reductions. They were distinctly different from the patient's usual depressive or anxiety symptoms and showed a specific time course. The treatment duration, where stated, was generally less than 6 months. Both cholinergic rebound and disturbances in the serotonergic system were discussed as possible mechanisms in these cases, and the relatively short half-life of paroxetine was considered a likely contributory factor.

There are only a few studies that in some way address the issue of withdrawal symptoms after discontinuation of SSRIs [26–29]. Patients with panic disorder and fluvoxamine [26], major depression and paroxetine [27], and social phobia of the generalised type and paroxetine [28] were included. Qualitatively, the same withdrawal symptoms were observed as described above. However, these studies were not primarily designed to study discontinuation symptoms, and some lacked both placebo control and blinding [26]. Due to the small numbers of patients, reliable incidence rates could not be calculated. In one investigation [29], which was a prescription-event monitoring study, no difference was observed between paroxetine, fluoxetine and fluvoxamine in the rates of various symptoms occurring within 7 days of stopping treatment, but the number of patients with withdrawal symptoms was low.

Non-linear kinetics is known to occur at therapeutic doses with paroxetine and fluoxetine [30] and the plasma levels of the SSRIs at the time of discontinuation might have been of importance for the occurrence of the withdrawal reaction. However, these data were not contained in the WHO reports and are not reported for the published cases.

Paroxetine is unique among the SSRIs because of its appreciable affinity, similar to that for desipramine and imipramine, for muscarinic receptors, being an antagonist at this receptor [31, 32]. The "within-study" affinity of paroxetine for muscarinic receptors has been estimated to be 5–17 times higher than that of fluoxetine or norfluoxetine and the affinity of sertraline for muscarinic receptors may be only slightly higher than that of fluoxetine [31]. The similarity between the withdrawal symptoms with tricyclic antidepressants [1] and those following discontinuation of paroxetine and cholinergic symptoms [33] may speak in favour of a cholinergic overdrive as an underlying mechanism. Both the rank order of withdrawal symptoms (Table 1) and the ratio of the number of reports of each withdrawal symptom to the total number of reported withdrawal reactions were identical for paroxetine and sertraline. This may further argue for a cholinergic mechanism as a cause of the withdrawal syndrome, although sertraline is considerably less active at muscarinic receptors than paroxetine [31]. From the point of view of a possible serotonin withdrawal syndrome, it is interesting to note that paroxetine is much more potent at blocking uptake of serotonin than are sertraline and fluoxetine [2]. Further, it has been suggested that a high potency in 5-HT uptake blockade in synaptosomal preparations, in combination with low potency in dopamine uptake, such as has been found for paroxetine in comparison with sertraline and fluoxetine, would increase the likelihood of adverse serotonergic effects [31, 34, 35].

Both fluoxetine and its active metabolite, norfluoxetine, have fairly long half-lives (2–7 days and 4–15 days for fluoxetine and norfluoxetine, respectively. The observation in our study of a low reporting rate of withdrawal reactions with fluoxetine and the predominance of psychiatric withdrawal symptoms with this drug may therefore indicate, although speculative, that the symptoms described constitute a rebound of the patient's underlying disorder, rather than a "true" withdrawal reaction. The half-lives of sertraline and paroxetine are similar and are around 24 h or less and the metabolite of sertraline, desmethylsertraline, though eliminated slowly with a half-life of 60–70 hours, appears to contribute limited pharmacological activity [36]. Nevertheless, it is possible that desmethylsertraline, by preventing the occurrence of withdrawal reactions, may explain the lower rate of withdrawal reactions with sertraline in the present study.

Randomised, controlled and comparative, clinical trials, specifically designed to detect withdrawal symptoms, are necessary to test the hypotheses generated and further studies to elucidate the underlying mechanisms are needed to be able to more fully assess the risk/benefit ratio for each of the SSRIs now in widespread use.

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