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Adverse Reactions of Selective Serotonin Reuptake Inhibitors

Reports from a Spontaneous Reporting System

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Abstract

Objective: The selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) are extensively used in the treatment of depression, panic disorder and obsessive-compulsive disorder, and are now being evaluated in the treatment of a number of other psychiatric disorders. The aim of this study was to investigate the pattern of adverse reactions reported on SSRIs in Sweden and assess possible risk factors associated with the occurrence of adverse reactions to these agents.

Methods: A survey was made of 1202 reports describing 1861 adverse reactions to SSRIs submitted to the Swedish Adverse Drug Reactions Advisory Committee.

Results: The most often reported adverse reactions were neurological symptoms (22.4%), psychiatric symptoms (19.5%) and gastrointestinal symptoms (18.0%); however, dermatological symptoms (11.4%) and general symptoms (9.8%) were also frequent. Compared with other drugs, gastrointestinal symptoms were more often reported for fluvoxamine, psychiatric symptoms were more often reported for sertraline and dermatological symptoms were more often reported for fluoxetine. In total, the diagnoses most frequently reported were nausea (n = 139), rash (n = 90), anxiety (n = 84), paraesthesias (n = 69), headache (n = 63) and diarrhoea (n = 63).

Parkinsonism, confusion, hallucinations, euphoria, hyponatraemia, bradycardia and hypotension were more often reported in the elderly, whereas urticaria, akathisia, and haematological, endocrinological, sexual and some visual reactions were more often reported in individuals who were younger than average. Dermatological reactions, fatigue, hyponatraemia and cough were more common in women, whereas dyskinesias/akathisia and aggression more often were seen in men.

The median SSRI dosages were above average in patients experiencing seizures, hypomania/mania, personality changes, malaise, bodyweight gain, gynaecomastia and hyperprolactinaemia/galactorrhoea. Severe symptoms, such as seizures, hyponatraemia and the serotonin syndrome, were rarely reported.

Conclusion: Although the design of the study makes it difficult to draw conclusions about causality, a variety of adverse reactions were reported. Therefore,

the awareness that a particular symptom in a patient treated with an SSRI might be an adverse reaction should be high.

The selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) are extensively used in the treatment of depression, panic disorder and obsessive-compulsive disorder, and are now being evaluated in the treatment of a number of other psychiatric disorders. Adverse reactions associated with the SSRIs are less prominent than, and qualitatively different from, those associated with the tricyclic antidepressants.[1,2] Nevertheless, adverse reactions of SSRIs cover a broad spectrum ranging from mild gastrointestinal symptoms to severe, although rare, events, such as seizures,[3] hyponatraemia,[4] and the serotonin syndrome.[5] In view of the increasing use of these drugs, the pattern of adverse reactions reported on SSRIs in Sweden is presented and possible risk factors identified in this study.

Materials and Methods

Since 1965, Sweden has had a system for spontaneous reporting of adverse drug reactions to the Swedish Adverse Drug Reactions Advisory Committee. Since 1975, the reporting of serious or fatal reactions and new reactions has been compulsory. Of the SSRIs available in Sweden, fluvoxamine was approved in June 1990, paroxetine in June 1991, citalopram in October 1992, sertraline in January 1995 and fluoxetine in September 1995.

All reports received up to December 31 1997, were reviewed, but only reactions that were classified as having a possible, probable/likely or certain causal relationship with the drug according to the WHO criteria (table I), and that were reported 3 times or more, were included in this survey. Moreover, reports concerning overdoses and pharmacokinetic interactions which did not cause any adverse reactions were excluded.

The classification of the reports was made by the monitoring centre staff. From each report, the following information was obtained:

- age and gender of the patient
- name and dosage of the suspected, as well as other, drug or drugs
- outcome of dechallenge/rechallenge

Table I. WHO criteria for causality assessment

Certain
A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary

Probable/likely
A clinical event, including laboratory test abnormality, with reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition

Possible
A clinical event, including laboratory test abnormality, with a reasonable test sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear

Unlikely
A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations

Conditional/unclassified
A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination

Unassessible/unclassifiable
A report suggesting an adverse drug reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified

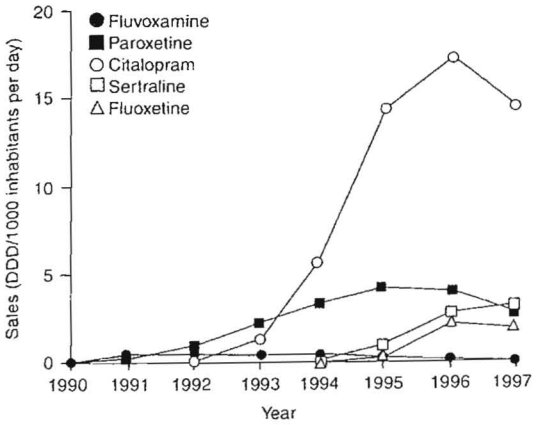

Fig. 1. Sales of selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) in Sweden. Total sales [in defined daily doses (DDD)/1000 inhabitants per day] for the SSRIs were 0.4 in 1991, 1.5 in 1992, 4.3 in 1993, 9.8 in 1994, 20.6 in 1995, 27.3 in 1996, and 23.7 in 1997. The DDDs were 20mg for citalopram, fluoxetine and paroxetine, 50mg for sertraline and 150mg for fluvoxamine.

- other potential risk factors
- time interval between start of the treatment and appearance of the reaction.

Only reports with positive dechallenge, with unknown dechallenge or where drug therapy was not stopped, were included, whereas reports with negative dechallenge were excluded.

Total drug sales statistics in Sweden have been computerised since 1972. These statistics show the total amount of every drug sold from each pharmacy and can be expressed in volume, monetary terms, or in the number of defined daily doses (DDDs). The DDD is the assumed average daily dose of a drug prescribed for its main indication in adults; for SSRIs that is the treatment of moderately severe depression.[6] The number of DDDs sold per 1000 inhabitants per day is thus a useful, although gross, measure of the consumption of a drug in the population. The DDDs for the SSRIs are 20mg for citalopram, fluoxetine and paroxetine, 50mg for sertraline and 150mg for fluvoxamine.[7]

Results

Sales statistics for the SSRIs are presented in figure 1. The total sales from the time of introduction of the agent in question until the end of December 1997 in million DDDs was 183.8 for citalopram, 59.1 for paroxetine, 22.3 for sertraline, 16.9 for fluoxetine and 14.3 for fluvoxamine.

A total of 1202 reports describing 1861 adverse reactions related to SSRI treatment were reviewed. There were no fatal adverse reactions. The number of reports per year is illustrated in figure 2. In total, 67.3% of the reports concerned women and 32.7% concerned men. The median age of the patients was 49 years. For comparison, 66% of the DDDs sold during the years 1994 to 1997 were prescribed to women and 34% to men, and the median age of these patients was 53 years.

The distribution of reports by organ system is presented in table II. Compared with other SSRIs, fluvoxamine was more frequently reported to cause gastrointestinal adverse reactions (26.5% *vs* a mean of 18%), sertraline was more frequently reported to cause psychiatric symptoms (25.5% *vs* a mean of 19.5%) and fluoxetine was more often reported to cause dermatological symptoms (17.4% *vs* a mean of 11.4%).

Neurological Reactions

Neurological adverse reactions reported are presented in table III. The predominating diagno-

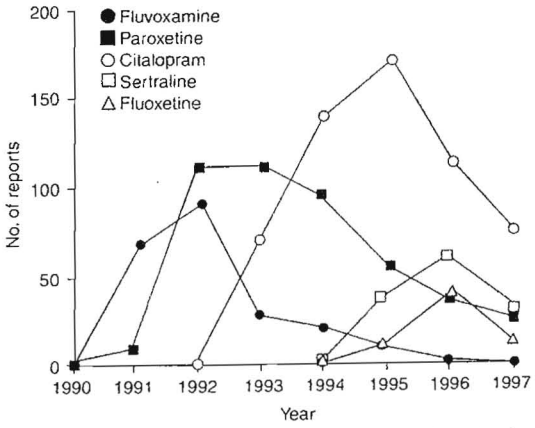

Fig. 2. Annual numbers of adverse reaction reports for selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors in Sweden. In general, reporting is specifically encouraged in the year of approval and the following 2 years.

Table II. Organ groups implicated in 1861 adverse reactions reported in patients receiving selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors. For specific diagnoses within each group, see tables III-VIII

Reaction	No. of reports (%)[a]					
	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Total no. of reports (%)[b]
Neurological	132 (20.6)	22 (23.9)	71 (20.7)	161 (26.0)	30 (18.2)	416 (22.4)
Mental	121 (18.9)	19 (20.7)	67 (19.6)	113 (18.2)	42 (25.5)	362 (19.5)
Gastrointestinal	104 (16.2)	12 (13.0)	91 (26.5)	105 (16.9)	23 (13.9)	336 (18.0)
Dermatological	83 (12.9)	16 (17.4)	32 (9.3)	56 (9.0)	26 (15.8)	213 (11.4)
General	67 (10.5)	9 (9.8)	34 (9.9)	62 (10.0)	11 (6.7)	183 (9.8)
Other	134 (20.9)	14 (15.2)	48 (14.0)	123 (19.8)	33 (20.0)	352 (18.9)
Total	641 (100)	**92 (100)**	**343 (100)**	**620 (99.9)**	**165 (100.1)**	**1861 (100)**

a The percentage value indicates the percentage of the total number of reactions reported for that individual drug.

b The percentage value indicates the percentage of the total number of reactions reported for all drugs.

ses were paraesthesias (n = 69), headache (n = 63), dizziness (n = 60), and tremor (n = 50). Headache was the most typical initial reaction. Other adverse reactions with an early onset were dizziness, muscle weakness, muscle stiffness, increased muscle tone, tremor and paraesthesias. For the extrapyramidal symptoms akathisia and dyskinesias, more than half of the reports concerned men. Patients who developed parkinsonism were older than average, whereas patients with dyskinesias were generally young. Patients experiencing seizures were taking a median daily dose of 1.33 DDDs, whereas patients experiencing other neurological adverse reactions were taking a median daily dose of 1 DDD or less.

Psychiatric Reactions

Psychiatric adverse reactions reported are presented in table IV. The predominating diagnoses were anxiety (n = 84), confusion (n = 32), hallucinations (n = 30) and sleep disturbances (n = 23). Aggression was predominantly reported in men. Patients who developed hypomania/mania had most often been treated with an SSRI for a long period of time. Confusion typically occurred in patients of advanced age. Patients experiencing

Table III. Neurological adverse reactions reported in patients receiving selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors

Reaction	No. of reports	Percentage of reports involving women	Median age in years (range)	Median time interval[a] (range)
Paraesthesias	69	78	60 (23-81)	6 days (0 days-2y)
Headache	63	77	48 (25-88)	2 days (0 days-4wk)
Dizziness	60	77	48 (21-88)	4 days (0 days-3mo)
Tremor	50	77	63 (23-88)	6 days (0 days-3mo)
Seizures	27	71	57 (18-92)	2wk (1 day-2y)
Acute dystonia	14	67	42 (23-80)	6 days (2 days-9mo)
Dyskinesia	14	33	55 (44-84)	2mo (1 day-6mo)
Muscle cramps	12	91	46 (23-77)	13 days (2 days-5mo)
Muscle weakness	10	80	42 (22-74)	1 day (1 day-3mo)
Parkinsonism	8	57	74 (47-87)	2wk (1 day-1 mo)
Muscle stiffness	8	50	54 (19-60)	6 days (1 day-2wk)
Akathisia	7	43	36 (26-57)	4wk (2wk-4mo)
Myoclonus	6	50	50 (24-74)	4wk (1 day-6mo)
Extrapyramidal symptoms	5	80	63 (38-87)	3wk (0 days-6wk)
Increased muscle tone	4	25	51 (31-76)	5 days (3 days-7 days)
Migraine	4	100	51 (25-62)	6wk (1 day-2y)

a Interval between the start of the treatment and the appearance of the adverse reaction.

Table IV. Mental adverse reactions reported in patients receiving selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors

Reaction	No. of reports	Percentage of reports involving women	Median age in years (range)	Median time interval[a] (range)
Anxiety	84	61	47 (22-84)	4 days (0 days-6mo)
Confusion	32	50	74 (26-90)	3wk (0 days-11mo)
Hallucinations	30	76	68 (19-96)	3wk (1 day-11mo)
Sleep disturbances	23	64	42 (22-78)	3 days (0 days-4mo)
Hypomania/mania	21	58	47 (21-85)	2mo (7 days-7mo)
Depersonalisation	15	64	42 (20-74)	8 days (0 days-9mo)
Amnesia	15	54	47 (23-88)	2mo (6wk-3y)
Nightmares	14	86	44 (23-83)	2wk (1 day-8mo)
Aggression	13	38	46 (26-75)	2wk (2 days-4mo)
Insomnia	10	63	55 (29-76)	4 days (0 days-2wk)
Psychosis	10	78	48 (41-85)	2wk (1 day-3mo)
Concentration impaired	9	50	46 (13-58)	2wk (0 days-8mo)
Agitation	7	57	63 (24-86)	3wk (2 days -9mo)
Personality change	6	75	53 (38-63)	2wk (6 days-9mo)
Euphoria	5	60	85 (36-96)	3 days (1 day-7mo)
Pathological inebriation	3	67	36 (32-50)	8mo (7wk-8mo)

a Interval between the start of the treatment and the appearance of the adverse drug reaction.

hypomania/mania were taking a median daily dose of 1.75 DDDs while those with personality change were taking a median daily dose of 1.5 DDDs. Patients experiencing other psychiatric adverse reactions were taking a median daily dose of 1 DDD or less.

Gastrointestinal Reactions

Gastrointestinal adverse reactions reported are presented in table V. The predominating diagnoses were nausea (n = 139) and diarrhoea (n = 63). Patients with constipation were older than average; however, no such age effect was seen in patients with dry mouth. Nausea, vomiting, abdominal pain and dyspepsia mainly occurred early in the course of the treatment. On the other hand, stomatitis, glossitis, parotitis and elevated liver enzyme levels were adverse reactions with a late onset. The liver reactions were mostly of hepatocellular type with elevated serum levels of ALT and AST, but also increased levels of γ-glutamyl transferase, alkaline phosphatase and bilirubin were occasionally reported. Patients experiencing any gastrointestinal adverse reaction were taking a median daily dose of 1 DDD or less.

Dermatological Reactions

Dermatological adverse reactions reported are presented in table VI. The predominating diagnoses were rash (n = 90), urticaria (n = 42) and pruritus (n = 40). Of the rashes, 15% were characterised as maculopapular, 7% as vesicobullous and 5% as erythematous, whereas the nature of the remainder of the rashes was not specified. The proportion of women experiencing all dermatological reactions, but particularly angioedema and photosensitivity, was higher than expected. The median time from the start of treatment until appearance of the reaction was somewhat shorter for rash (5 days) than for urticaria/angioedema (approximately 2 weeks). Patients experiencing any dermatological adverse reaction were taking a median daily dose of 1 DDD or less.

General Reactions

General adverse reactions reported are presented in table VII. The predominating diagnoses were fatigue (n = 42), hyperhidrosis (n = 37) and oedema (n = 33). Also bodyweight gain was reported in several patients. Patients with bodyweight gain were somewhat younger than average and they had been treated with an SSRI for a long

Table V. Gastrointestinal adverse drug reactions reported in patients receiving selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors

Reaction	No. of reports	Percentage of reports involving women	Median age in years (range)	Median time interval[a] (range)
Nausea	139	69	49 (19-86)	5 days (0 days-9mo)
Diarrhoea	63	69	49 (24-87)	10 days (0 days-6mo)
Vomiting	31	72	54 (28-84)	5 days (0 days-4wk)
Hepatic enzymes levels increased	25	58	48 (17-90)	4wk (3 days-9mo)
Mouth dryness	14	64	53 (30-78)	7 days (1 day-5mo)
Abdominal pain	14	75	47 (28-74)	2 days (1 day-6 days)
Dyspepsia	11	40	61 (30-75)	4 days (1 day-1mo)
Constipation	8	63	63 (55-88)	7 days (2 days-1mo)
Stomatitis/glossitis	7	71	55 (46-81)	13 days (7 days-3mo)
Parotitis	4	50	78 (75-84)	12 days (8 days-2wk)

a Interval between the start of the treatment and the appearance of the adverse drug reaction.

period of time. Patients experiencing bodyweight gain were taking a median daily dose of 2 DDDs. Those with malaise were taking a median daily dose of 1.3 DDDs, whereas patients experiencing other general adverse reactions were taking a median daily dose of 1 DDD or less.

Other Reactions

Adverse reactions involving other organ systems are presented in table VIII. Haematological reactions (haematoma, epistaxis and thrombocytopenia) as well as cough and hyperprolactinaemia were reported almost exclusively in women. Among the cardiovascular reactions, palpitations and tachycardia were the predominating diagnoses in younger individuals, whereas bradycardia and hypotension most often were reported in older individuals. Hyperprolactinaemia, galactorrhoea and menstrual disorders were reactions of a late onset that mainly occurred in young individuals. Cough and haematological disorders also had a late onset. In women with galactorrhoea, the highest serum prolactin level measured was 43 µg/L, although many patients had prolactin levels within the normal range. Hyponatraemia and the syndrome of inappropriate antidiuretic secretion, urinary retention and urinary incontinence were more common in women of advanced age. Patients with increased serum creatinine levels were also elderly and they had all complicating diseases such as diabetes mellitus, congestive heart failure or impaired renal function. Patients experiencing gynaecomastia were taking a median daily dose of two DDDs and those experiencing hyperprolactinaemia/galactorrhoea were taking a median daily dose of 1.25 DDDs, whereas the median daily dose was 1 DDDs or lower for patients experiencing the other diagnoses.

Withdrawal symptoms were more often reported in women, in young individuals and in those treated with an SSRI for a long period of time.

Table VI. Dermatological adverse reactions reported in patients receiving selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors

Reaction	No. of reports	Percentage of reports involving women	Median age in years (range)	Median time interval[a] (range)
Rash	90	73	52 (18-88)	5 days (1 day-3y)
Urticaria	42	74	38 (14-77)	2wk (2 days-5mo)
Pruritus	40	76	49 (27-83)	3wk (1 day-15mo)
Angioedema	10	90	37 (24-77)	13 days (1 day-2mo)
Photosensitivity	5	80	44 (27-52)	2mo (3 days-2y)

a Interval between the start of the treatment and the appearance of the adverse drug reaction.

However, there was no indication that the dosages being taken in patients experiencing withdrawal symptoms were above average. The withdrawal symptoms most often reported were dizziness (62%), paraesthesias (41%) and psychiatric symptoms such as anxiety and agitation (31%). In general, the symptoms started 0 to 3 days after SSRI treatment had been stopped and had a duration of 1 to 2 weeks.

Three patients developed the serotonin syndrome. The drug combinations associated with the serotonin syndrome in each patient were: (i) fluoxetine, clomipramine and lithium; (ii) sertraline and mianserin; and, (iii) citalopram and mianserin. All 3 patients recovered spontaneously within a few days after the drug therapy had been stopped. The corresponding symptoms reported in the 3 patients were: (i) confusion, tremor, hyperreflexia and agitation; (ii) confusion, diaphoresis and hyper-reflexia; and, (iii) confusion, fever and myoclonus.

Discussion

Spontaneous reporting of adverse drug reactions represents an important means of detecting infrequent reactions. However, information about the true incidence cannot be obtained by this method, since the events are always under-reported. For example, in epidemiological studies, only 1 to 5% of mild and 10 to 80% of serious adverse drug reactions have been found to be reported.[8,9] Moreover, even though corrected for sales figures, spontaneous reporting cannot be used to investigate whether differences in the occurrence of specific adverse reactions exist between drugs because the extent of under-reporting most probably varies between drugs. The frequency of reports may be influenced by factors such as public knowledge of the uses and adverse effects of a drug, physicians' attention to specific problems, and the year of introduction.[10]

As illustrated in figure 2, most adverse reactions for each SSRI were reported during the first 3 years following approval of the drug. A high initial reporting rate is a well known phenomenon which at least in part is a result of the national recommendations for adverse drug reaction reporting. Due to these factors, and because none of the diagnoses were reported exclusively for 1 drug, the SSRIs have been studied exclusively as a group when the specific diagnoses have been considered.

The observational character of studies using data from spontaneous reporting systems makes it difficult to draw conclusions about causality, although it seems reasonable that the probability of a connection increases with an increasing number of reports. Therefore, diagnoses reported less than 3 times were excluded from the present survey. On

Table VII. General adverse reactions reported in patients receiving selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors

Reaction	No. of reports	Percentage of reports involving women	Median age in years (range)	Median time interval[a] (range)
Fatigue	42	76	48 (23-89)	7 days (0 days-3mo)
Hyperhidrosis	37	67	54 (23-88)	9 days (0 days-4mo)
Oedema	33	72	48 (29-82)	8 days (0 days-3mo)
Bodyweight gain[b]	12	73	39 (21-60)	3mo (12 days-4mo)
Syncope	10	67	38 (25-71)	5 days (1 day-3mo)
Pain	8	57	48 (33-63)	1 day (1 day-5mo)
Fever	7	100	42 (34-48)	3wk (3 days-6wk)
Malaise	5	40	49 (41-43)	2wk (2 days-2mo)
Faintness	4	75	66 (50-79)	7 days (0 days-4mo)
Somnolence	4	100	64 (50-81)	11 days (5 days-7wk)
Anorexia	3	67	44 (28-75)	10 days (not reported)
Chills	3	67	53 (43-65)	7 days (not reported)

a Interval between the start of the treatment and the appearance of the adverse drug reaction.

b Two reports of bodyweight gain due to oedema were excluded.

Table VIII. Other adverse reactions reported in patients receiving selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors

Reaction	No. of reports	Percentage of reports involving women	Median age in years (range)	Median time interval[a] (range)
Haematological				
Haematoma/epistaxis	10	80	37 (23-74)	7wk (3wk-5mo)
Thrombocytopenia	4	100	45 (41-81)	7wk (4wk-3mo)
Cardiovascular				
Palpitations	15	79	50 (22-72)	7 days (1 day-6mo)
Hypotension	8	75	71 (47-85)	1 days (0 days-3 days)
Tachycardia	7	71	52 (31-72)	2 days (1 day-3wk)
Bradycardia	4	67	70 (50-80)	2 days (1 day-2mo)
Endocrinological				
Hyperprolactinaemia/ galactorrhoea	11	100	32 (25-46)	4mo (2mo-11mo)
Menstrual disorder	7	100[b]	39 (20-49)	4wk (3wk-2mo)
Gynaecomastia	6	0[b]	53 (38-57)	9mo (3mo-9mo)
Metabolic				
Hyponatraemia/SIADH	24	79	80 (52-94)	2wk (2 days -1.5y)
Sexual				
Libido decreased	29	52	43 (25-56)	5wk (7 days-4mo)
Ejaculation failure	20	0[b]	44 (22-65)	2wk (0 days-4mo)
Erection disturbance	8	0[b]	43 (28-54)	Not reported
Impotence	7	0[b]	39 (28-71)	10 days (7 days-3wk)
Respiratory				
Cough	10	89	43 (27-69)	6wk (4wk-2mo)
Musculoskeletal				
Myalgia	9	56	41 (32-61)	6wk (3 days-7mo)
Arthralgia	8	75	39 (28-65)	9 days (1 day-1 mo)
Urinary				
Micturition disorder	18	65	39.(22-77)	9 days (1 day-3wk)
Urinary retention	14	77	63 (28-83)	3 days (0 days-3wk)
Urinary incontinence	9	67	62 (24-86)	4 days (0 days-2wk)
Serum creatinine level increased	4	50	84 (65-91)	3mo (5 days-4mo)
Visual				
Vision blurred	10	60	49 (26-82)	10 days (1 day-4mo)
Vision decreased	9	50	61 (38-78)	1mo (8 days-11mo)
Mydriasis	4	75	34 (21-59)	1 day (1 day-1 day)
Accommodation abnormal	3	67	29 (25-37)	4 days (1 day-7 days)
Auditory				
Tinnitus	18	65	46 (30-81)	10 days (1 day-6wk)
Other				
Withdrawal symptoms	29	69	37 (19-71)	8mo (4wk-2y)
Serotonin syndrome	3	0	52 (50-69)	Not reported

a Interval between the start of the treatment and the appearance of the adverse drug reaction.

b Gender-specific diagnosis.

SIADH = syndrome of inappropriate antidiuretic hormone secretion.

the other hand, spontaneous reporting systems are an interesting tool in order to investigate infrequent reactions and to screen whether specific risk factors may exist for the development of various adverse drug reactions. Such potential risk factors are age, gender, treatment with high dosages, long term treatment, the presence of concomitant diseases and concomitant drug treatment. However, it should be emphasised that the estimated distribution of age, gender, dosages and time to onset is uncertain for the reactions for which only a few reports exist. In this study, unexpected adverse reactions were sometimes more often reported than expected adverse reactions. For example, anorexia, which is a common reaction, with SSRIs was infrequently reported compared with the uncommon adverse reaction of bodyweight gain. This apparent inconsistency might be a result of the recommendations from reporting authorities, in which emphasis has been put on the reporting of new and unexpected reactions.

The high frequency of gastrointestinal adverse reactions associated with fluvoxamine in the present study is in accordance with the common belief that this drug causes more such effects than other SSRIs. However, 2 factors need to be taken into account. First, fluvoxamine was [with the exception of zimeldine (zimelidine)] the first SSRI introduced onto the Swedish market and it is a general phenomenon that the most common adverse reactions for a new drug class are more often reported for the first drug marketed in that class, although drugs subsequently marketed in the same class can have the same frequency of these reactions. Secondly, when most reports of adverse reactions were registered, a higher starting dosage than the one currently recommended was being used. In double-blind studies, fluvoxamine at a starting dosage of 50 mg/day has been reported to cause less gastrointestinal adverse reactions than fluoxetine,[11] whereas fluvoxamine at a starting dosage of 100 mg/day has been reported to cause more such reactions than citalopram.[12]

The relatively high frequency of dermatological adverse reactions associated with fluoxetine use seen in the present survey is consistent with the findings of a double-blind study in which fluoxetine was compared with paroxetine.[13] However, as the pattern of differences in the frequency of specific adverse reactions in clinical studies is somewhat inconsistent, there is generally a need for more randomised, double-blind studies, specifically designed to compare adverse reactions between the SSRIs, before firm conclusions can be drawn. For infrequent adverse reactions, epidemiological studies will be more helpful in revealing risk factors.

Most of the adverse reactions identified in this survey have already been reported sporadically in the literature, but comprehensive studies are generally lacking. With the exception of case reports and a few formal studies, adverse reaction data on the SSRIs are most often found in publications not subject to peer review or in drug catalogues based upon data supplied by the manufacturer. In such publications, adverse events with less stringent requirements of causality than in the present study are often presented. This review has generally confirmed the adverse drug reaction profiles of the SSRIs as presented in the data sheets provided by the manufacturers. However, a number of adverse reactions not included in the drug data sheets were identified. For these reports, the clustering in the database suggests a possible causal association.

In addition, some of the adverse reactions seen more frequently in the present study have been only sparsely discussed in the literature earlier. Examples of such reactions are rash, pruritus, urticaria, paraesthesias, oedema and elevated liver enzyme levels. Moreover, several reactions found occasionally in this survey, such as tinnitus, migraine, parotitis/glossitis, cough, fever, syncope, myalgia/arthralgia, pathological inebriation and thrombocytopenia, have not been discussed at all in the literature. In contrast, severe adverse reactions, such as seizures, hyponatraemia and the serotonin syndrome, have been more thoroughly described earlier,[3-5] although drug combinations with mianserin have not previously been reported to cause the serotonin syndrome. This finding is

interesting because mianserin is regularly used as add-on therapy to SSRIs and because both mianserin and its two metabolites desmethyl-mianserin and 8-hydroxy-mianserin exert serotonergic effects.[14]

The withdrawal symptoms reported in the present study are principally the same as those seen in a large survey of cases reported to the WHO database,[15] with dizziness and paraesthesias being the 2 most prominent symptoms. In the same survey,[15] it was also noted that psychiatric symptoms were more common among patients who had been treated with fluoxetine, whereas neurological symptoms were more common among patients who had been treated with paroxetine or sertraline. When considering all adverse reactions reported in the present study, neurological symptoms were more often reported following the withdrawal of paroxetine and psychiatric symptoms were more often reported following the withdrawal of sertraline, whereas there was no clear pattern for fluoxetine.

Most adverse reactions caused by SSRIs can be explained by effects on the serotonergic system. The occurrence of haematomas and epistaxis can be explained by an impairment of blood platelet function caused by SSRIs.[16] Serotonin is involved in the pathophysiology of nausea/vomiting[17] and migraine,[18] and it is an important neurotransmitter for the regulation of body temperature, bodyweight, sexual behaviour, water balance and prolactin secretion. In addition, a high proportion of the neuromuscular, psychiatric and autonomic symptoms seen with the serotonin syndrome in humans are seen animals as well.[5] Although SSRIs have very little or no anticholinergic effects, constipation, dry mouth and urinary retention are not uncommon. For paroxetine, these symptoms can be explained by its weak muscarine receptor blocking properties; for fluvoxamine, it has been suggested that interactions with histamine H_1 and α_1-adrenergic receptors may cause so-called pseudo-anticholinergic effects.[19] However, such pseudo-anticholinergic adverse reactions are reported also for the other SSRIs. The risk for anticholinergic adverse reactions during treatment with tricyclic antidepressants increases with increasing age, and the age distribution for constipation and urinary retention found in the present study indicates that the risk of pseudo-anticholinergic effects with SSRIs might also increase with increasing age.

As most adverse reactions are expected to be dose dependent, they are, in principle, avoidable. However, based on the fact that the majority of adverse reactions reported in this study were observed in patients who had been treated with standard dosages, one may speculate that the dose-effect curve for many of these adverse reactions is close to even or shifted to the left side of the corresponding curve for the antidepressant effect. Alternatively, sudden increases in drug concentration might be a more important factor than the absolute drug concentration for some adverse reactions. The possible development of tolerance might also modify the response of the individual patient to some adverse reactions. Treatment with high dosages might be a risk factor at least for the adverse reactions for which high median dosages were used, such as seizures, hypomania/mania, bodyweight gain, gynaecomastia, personality change, malaise and hyperprolactinaemia/galactorrhoea.

As all SSRIs to a larger or smaller extent are metabolised by the polymorphic cytochrome P450 (CYP) liver enzymes CYP2C19 and/or CYP2D6,[20] individualised drug dosage based on the patient's specific metabolic capacity might reduce the risk of dose-dependent (concentration-dependent) adverse reactions. However, idiosyncratic/immunological reactions such as rash and urticaria can principally not be prevented by optimising the drug dosage.

In conclusion, treatment with SSRIs can give rise to a variety of adverse reactions, mainly of neurological, gastrointestinal and psychiatric nature. Severe symptoms are rarely reported. As more than 90 different adverse reaction diagnoses were reported in this survey, the awareness that a particular symptom in a patient treated with an SSRI might be an adverse reaction, should be high.

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