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ORIGINAL REPORT

A Comparison of Fluvoxamine, Fluoxetine, Sertraline and Paroxetine Examined by Observational Cohort Studies

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SUMMARY

Objective — To compare the safety and side-effect profiles of the four selective serotonin reuptake inhibitor antidepressants (SSRIs), fluvoxamine, fluoxetine, sertraline and paroxetine.

Methods — The results from four observational cohort studies of the four SSRIs were compared. Each of these studies was conducted by Prescription-Event Monitoring (PEM). The exposure data were derived from general practitioner (GP) prescriptions confidentially supplied by the Prescription Pricing Authority (PPA) in England. Outcome data were obtained from questionnaires (green forms) on which the prescribing doctor recorded event data. The main findings comprised demographic information, including patients' date of birth and sex; the indication for prescribing the monitored drug; the effectiveness of the drug as perceived by the GP; the reasons for stopping treatment and all events recorded during and after treatment.

Results — The final cohort for each of the four SSRIs exceeded 10,000 patients. The sex, age distributions and indications for prescribing the four SSRIs were very similar. Only 36% of the GPs expressing an opinion reported fluvoxamine as effective, compared with approximately 60% for fluoxetine, sertraline and paroxetine. Fluvoxamine was associated with a higher incidence of adverse events than the other three SSRIs. Nausea/vomiting was both the most frequent clinical reason for stopping all four SSRIs and the most frequently reported clinical event. Adverse events reported in patients aged 70 years and over were comparable with the events reported for the total cohorts. Differences were identified between the four SSRIs for less frequently reported adverse events. Withdrawal symptoms were significantly more frequent with paroxetine than the other three SSRIs.

Conclusions — The data from the four studies were comparable in terms of age distribution, sex of patients and indication for prescribing the drugs. Fluvoxamine had a considerably higher incidence of side-effects associated with its use than the other three SSRIs. The side-effect profiles of the four SSRIs were comparable for frequently reported events. Important differences were identified between the four SSRIs in respect of less frequently reported events. This study suggests that fluvoxamine compares unfavourably with fluoxetine, sertraline and paroxetine, both in terms of reported effectiveness and the incidence of adverse events. Biases possibly affecting the comparisons involved in this study are unlikely to account for the observed differences between fluvoxamine and the other three SSRIs. © 1997 John Wiley & Sons, Ltd.

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KEY WORDS — pharmacovigilance; post-marketing surveillance; cohort studies; observational studies; prescription-event monitoring; fluvoxamine; fluoxetine; sertraline; paroxetine

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INTRODUCTION

Fluvoxamine, fluoxetine, sertraline and paroxetine are all selective serotonin reuptake inhibitor (SSRI) antidepressants, used extensively by British doctors. Their efficacy is comparable to that of the older antidepressants.[1] They are marketed as having a favourable side-effect profile compared with previously established antidepressants.[2] Although it has been stated that all the SSRIs have similar unwanted effects,[3] there have been reports of important individual differences. Paroxetine, for example, has been associated with both withdrawal symptoms and dystonia,[4] and sertraline and paroxetine with sexual dysfunction.[3] The SSRIs have been reported as being relatively safe in overdose, because of their lack of anticholinergic and cardiovascular side-effects.[5] The overall rate of suicide in patients treated with SSRIs is similar to the rate of suicide in patients taking tricyclic antidepressants.[6]

This study compares the results of four observational cohort studies of the four SSRIs, fluvoxamine, fluoxetine, sertraline and paroxetine. Each of these studies provides information on over 10,000 patients, and was conducted by Prescription-Event Monitoring (PEM).[7,8]

METHOD

The patients were identified by means of data from the first prescriptions ('FP10s') written by general practitioners (GPs) in England, immediately after release of each drug on the market. The prescription data were provided, in confidence, by the Prescription Pricing Authority (PPA). Simple questionnaires (green forms) were posted to the prescribing doctors at least 6 months following the first prescription received by the Drug Safety Research Unit (DSRU) for each individual patient. The return section of the green form was anonymized and provided the following information: sex; date of birth; indication for prescribing the monitored drug; reason for stopping the monitored drug; effectiveness as perceived by the GP; duration of therapy and events during and after treatment. The term 'event' is defined as any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, or any complaint which was considered of sufficient importance to enter in the patient's notes. Only one green form was sent for each patient and no doctor was sent more than four green forms in any one month.

Thus, the exposure data were derived from the original prescriptions for each drug being monitored and the outcome data were the events recorded by the original prescribers on the green forms.

Events reported on the green forms were coded onto a computer using the DSRU dictionary. The dictionary is arranged in a system–organ classification and the data are retrieved in such a way as to give the number of reports for each event in each separate month of the observation period.

Data analysis

Incidence densities (IDs) have been calculated for events reported during treatment in the first month after the start of therapy for patients for whom either the date of stopping the drug is known or who continue to take the drug. The IDs have been calculated as the rate at which an event occurred in month 1, given the number of reports of the event during month 1 and the number of patient-months of treatment in this time period. The figures were expressed as ID per 1000 patient-months treatment.

$$\mathrm{ID} = \frac{\text{Number of events in month 1 during treatment}}{\text{Patient-months exposure to drug}} \times 1000$$

The denominator was calculated by dividing the total number of days of exposure in month 1 by 30, giving the number of patient-months of exposure.

In some instances the overall ID (ID_A) has been calculated. For each event this has used the total number of reports (not just that in month 1 of treatment) as the numerator and the number of patient-months of exposure throughout the whole period of treatment as the denominator.

Selected events

The green forms for all serious adverse events and selected events of interest were examined by a medical officer. All green forms with events coded as 'not otherwise specified' were also reviewed by a medical officer in order to exclude serious events. Selected events were followed up by contacting the patient's GP or hospital consultant for further information.

Patients aged 70 years and over

Supplementary analyses were carried out for patients aged 70 years and over.

Pregnancies

Pregnancies diagnosed during, or within 3 months of stopping treatment, were followed up by obtaining additional information from the patient's GP.

Deaths

Deaths were, when necessary, followed up by retrieving the life-time general practice records of the patient from the Family Health Service Authority (FHSA) after gaining permission from the patient's GP. Copies of death certificates from the Office for National Statistics were obtained for those cases where notes were unobtainable or the cause of death remained uncertain.

General considerations

Considerable care has been taken to preserve the confidentiality of the data and the computers at the DSRU are fully protected. This study was conducted in accordance with the International Ethical Guidelines for Biochemical Research prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (1993).

Observation period

The prescriptions examined were written between February 1987 and February 1988 for fluvoxamine, March 1989 and March 1990 for fluoxetine, January 1991 and September 1992 for sertraline and March 1991 and March 1992 for paroxetine. The interval between the date of the prescription and the sending of the green form was approximately 6 months in the studies of fluoxetine, sertraline and paroxetine, and 12 months in the study of fluvoxamine.

RESULTS

Size of the cohorts, age and sex characteristics

The numbers of green forms sent, the numbers of the final cohorts, and the age and sex distributions for the four drugs were very similar (Table 1).

Table 1 — Size of the cohorts, age distribution and sex of the patients

	Fluvoxamine	Fluoxetine	Sertraline	Paroxetine
Number of green forms sent out	20504	24738	24632	26194
Number returned	12279	14444	14817	15907
Number void*	1296	1752	2083	2166
Size of final cohort	**10983**	**12692**	**12734**	**13741**
Males				
Number (% of cohort)	3094 (28.2%)	3690 (29.1%)	3910 (30.7%)	4373 (31.8%)
Mean age ± SD (years)	51.0 ± 17.0	50.1 ± 17.0	49.2 ± 17.1	48.6 ± 16.5
Females				
Number (% of cohort)	7694 (70.1%)	8863 (69.8%)	8729 (68.6%)	9279 (67.5%)
Mean age ± SD (years)	51.1 ± 17.9	49.4 ± 18.1	48.1 ± 18.1	48.8 ± 18.0
Sex not specified				
Number (% of cohort)	195 (1.8%)	139 (1.1%)	95 (0.8%)	89 (0.6%)
Age not specified				
Number (% of cohort)	1496 (13.6%)	1306 (10.1%)	1010 (7.9%)	1088 (7.9%)
Age 70 years and over				
Number	1150	1441	1484	1561
Male	294 (25.6%)	366 (25.4%)	434 (29.2%)	416 (26.6%)
Female	839 (73.0%)	1070 (74.3%)	1042 (70.2%)	1139 (73.0%)
(Sex not specified)	(17)	(5)	(8)	(6)

*Includes patients no longer registered with doctor, blank forms, no record of treatment in the notes, patient's doctor moved or retired or died, prescribed drug not taken.

Table 2 — Indications for prescribing the four SSRIs

Indication	Fluvoxamine	Fluoxetine	Sertraline	Paroxetine
Depression	71.2%	71.2%	83.3%	82.4%
Anxiety	6.6%	7.9%	1.5%	3.3%
Not specified	15.2%	15.5%	11.9%	11.1%
Others	7.0%	5.4%	3.3%	3.2%

Table 3 — Effectiveness of the four SSRIs as perceived by GPs

Effective	Fluvoxamine		Fluoxetine		Sertraline		Paroxetine	
	Number	%*	Number	%*	Number	%*	Number	%*
Yes	3030	**35.6**	6063	**57.3**	7071	**63.6**	7375	**62.1**
No	5483	64.4	4516	42.7	4052	36.4	4503	37.9
Not specified	2470	—	2113	—	1611	—	1863	—
Total	10983	100	12692	100	12734	100	13741	100

*Percentage refers to the total number of subjects in which an opinion on effectiveness was expressed. Effectiveness represents the global rating by the GP over the whole period of the patient's treatment.

Indications

As shown in Table 2, the major usage for all four SSRIs was depression.

Effectiveness

The majority of reports included an opinion about the effectiveness of the individual SSRIs (Table 3). There was no significant difference between fluoxetine, sertraline and paroxetine. Only 35.6% of the GPs expressing an opinion reported fluvoxamine to have been effective. The difference between the effectiveness rating of fluvoxamine and the other three SSRIs is both substantial and significant ($P < 0.001$). At the time of the studies, the recommended doses were as follows: *fluvoxamine*: 100–200 mg daily (up to 100 mg as a single dose in the evening), max. 300 mg daily; *fluoxetine*: 20 mg daily; *sertraline*: 50 mg daily, increased if necessary by increments of 50 mg over several weeks to max. 200 mg daily, then reduced to usual maintenance of 50–100 mg daily; *paroxetine*: 20 mg mane, if necessary increased gradually in increments of 10 mg to max. 50 mg daily (elderly, 40 mg daily).[9]

Duration of exposure

Data on the length of exposure to each drug are shown in Fig. 1. A higher proportion of patients received fluvoxamine for 1 month or less than with the other three SSRIs. As a result only a little more than 30% of the fluvoxamine patients were still on therapy at the end of 2 months compared with 55–60% of the patients treated with the other three SSRIs.

Reasons for stopping therapy

The most frequent clinical reason for stopping treatment was nausea/vomiting with all four SSRIs (Table 4).

Incidence densities

Nausea/vomiting was the most frequently reported clinical event in the first month of treatment for all four SSRIs (IDs 26–127 per 1000 patient-months), followed by malaise/lassitude, drowsiness/sedation, dizziness and headache/migraine (Fig. 2). IDs calculated for patients aged 70 years and over showed that the incidence of adverse events in this age group were comparable with those for the entire cohort (Fig. 3). In order to determine whether the results of PEM studies are systematically affected by the sequence in which new drugs within one therapeutic group enter the market, the PEM data arising from studies on four classes of drugs have been reviewed. The classes comprised the non-steroidal anti-inflammatory agents (NSAIDs), angiotension-converting enzyme inhibitors (ACE inhibitors), the proton-pump inhibitors and the SSRIs. Table 5 shows the highest four IDs for the first month of therapy with the first

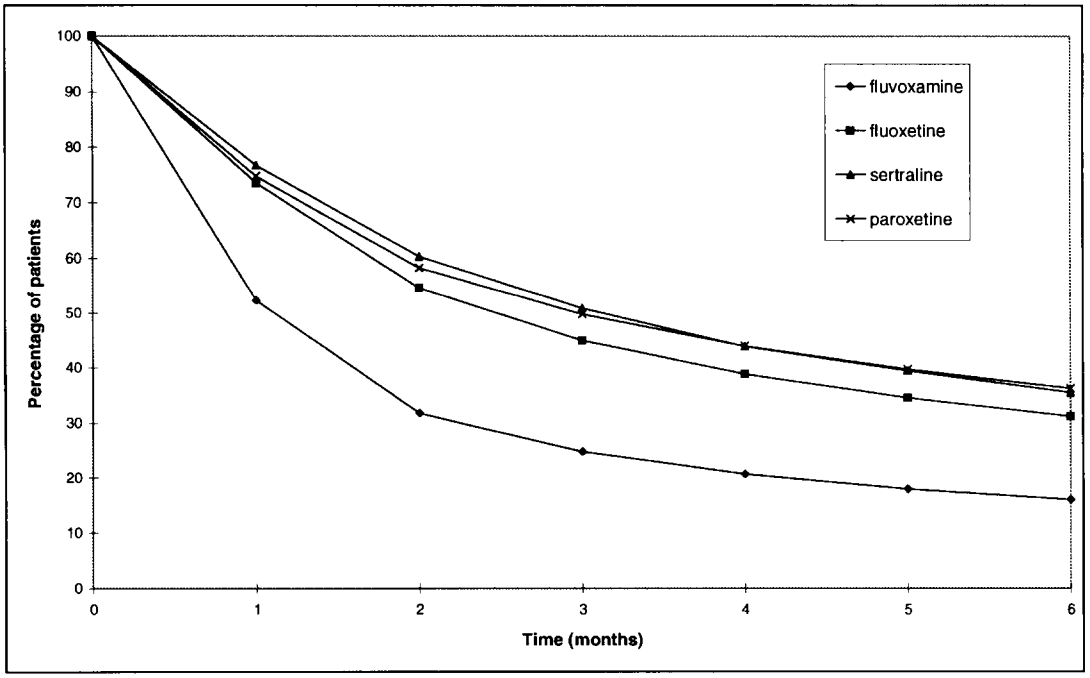

Fig. 1 — Duration of exposure. Figures include patients for whom it was recorded that treatment was continuing or for whom the date of stopping medication was given

drug introduced in each class compared with those of the successive drugs within each class. For each drug given in this comparison the IDs for respiratory tract infection are also given.

Table 6 gives the values for the IDs over the entire treatment period (ID_A).

Selected events

Neurological. Small numbers of cases with involuntary movements (including specified cases of akathisia, choreiform movements and tardive dyskinesia) were reported with all four SSRIs,

Table 4 — Number of patients in whom therapy was stopped due to adverse events (RS)* and incidence densities (ID) of these events per 1000 patient-months in the first month of treatment

Event	Fluvoxamine		Fluoxetine		Sertraline		Paroxetine	
	RS	ID	RS	ID	RS	ID	RS	ID
Nausea/vomiting	811	127.2	193	26.3	281	34.6	459	52.9
Malaise/lassitude	241	41.5	118	16.3	94	12.0	171	17.8
Drowsiness/sedation	162	22.6	71	8.2	78	7.3	183	20.5
Dizziness	147	25.5	59	6.7	67	8.7	107	11.5
Headache/migraine	127	25.1	81	12.5	100	13.1	97	13.1
Diarrhoea	118	23.1	33	7.2	107	11.9	53	7.7
Unspecified	101	14.5	31	2.4	26	2.6	31	2.5
Insomnia	74	15.3	66	9.4	66	7.9	102	13.0
Tremor	69	13.2	36	5.7	48	6.2	104	12.4
Pain — abdomen	60	14.3	23	5.6	31	6.1	20	4.5
Dyspepsia	52	12.0	37	6.5	35	6.2	30	4.6
Agitation	47	9.3	19	5.9	42	4.9	44	5.0
Anxiety	33	9.1	49	8.3	25	2.7	28	4.3

*Excludes: events reported as effective; ineffective; change of indication; hospital admission; pregnancy and electroconvulsive therapy.

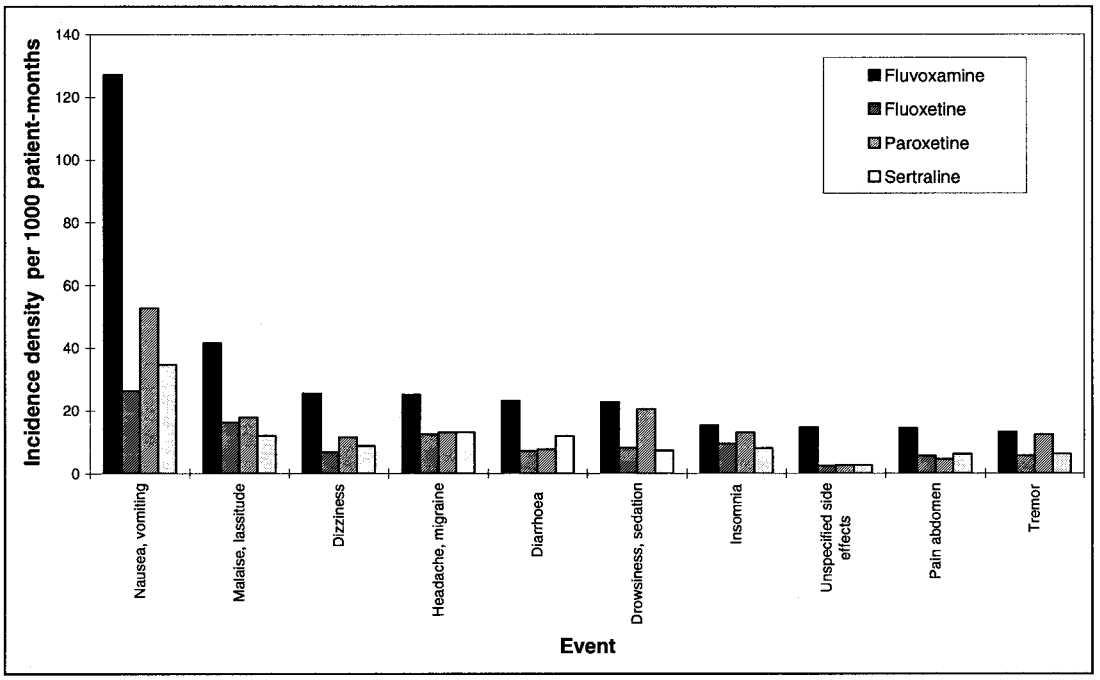

Fig. 2 — Events with the highest incidence densities per 1000 patient-months in month 1

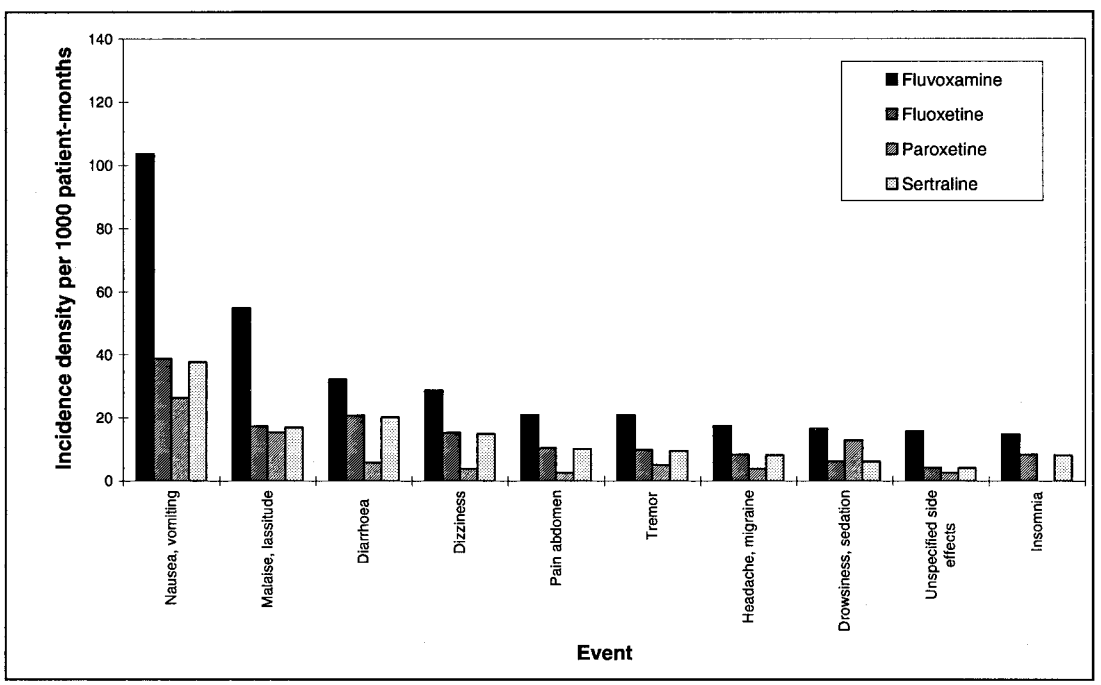

Fig. 3 — Events with the highest incidence densities per 1000 patient-months in month 1 for patients aged 70 years and over

Table 5 — Highest ranking incidence densities for drug series (in order of drug sequence) per 1000 patient-months in month 1

Event				
	Etodolac	Nabumetone	Tenoxicam	
Dyspepsia	24.6	21.8	14.8	
Nausea/vomiting	10.3	11.6	8.9	
Diarrhoea	3.6	8.6	3.0	
Abdominal pain	6.3	6.1	7.7	
Respiratory tract infection	5.2	5.6	7.1	
Mean	10.0	10.7	8.3	
Rank	2	1	3	
	Enalapril	Lisinopril	Ramipril	Perindopril
Malaise/lassitude	12.3	15.8	12.5	6.2
Dizziness	11.4	13.8	7.0	8.2
Nausea/vomiting	7.8	7.9	5.5	5.1
Headache	7.2	15.7	14.1	9.6
Respiratory tract infection	6.8	10.3	8.6	7.3
Mean	9.1	12.7	9.5	7.3
Rank	3	1	2	4
	Omeprazole	Lansoprazole		
Respiratory tract infection	10.7	11.7		
Diarrhoea	9.8	16.5		
Nausea/vomiting	8.6	13.2		
Abdominal pain	7.5	9.7		
Headache/migraine	4.1	8.1		
Mean	8.1	11.8		
Rank	2	1		
	Fluvoxamine	Fluoxetine	Sertraline	Paroxetine
Nausea/vomiting	127.2	26.3	34.6	52.9
Malaise/lassitude	41.5	16.3	12.0	17.8
Dizziness	25.5	6.7	8.7	11.5
Headache/migraine	25.1	12.5	13.1	13.1
Respiratory tract infection	10.4	12.7	9.9	11.7
Mean	45.9	14.9	15.7	21.4
Rank	1	4	3	2

Table 6 — Overall incidence densities with the SSRI agents per 1000 patient-months

Total months on drug	Fluvoxamine 27798		Fluoxetine 47677		Sertraline 63028		Paroxetine 65449	
	Number of reports	ID	Number of reports	ID	Number of reports	ID	Number of reports	ID
Nausea/vomiting	1189	42.8	427	9.0	540	8.6	849	13.0
Malaise/lassitude	422	15.2	263	5.5	233	3.7	342	5.2
Dizziness	266	9.6	131	2.7	177	2.8	259	4.0
Headache/migraine	282	10.1	270	5.7	343	5.4	312	4.8
Respiratory tract infection	283	10.2	576	12.1	670	10.6	734	11.2
Mean		17.6		7.0		6.2		7.6
Rank		1		3		4		2

occasionally necessitating withdrawal of the drugs. Cases of abnormal sensation (including hyperaesthesia, hypoaesthesia and paraesthesia) were also reported with all four SSRIs. Tingling or numbness of the face was an unusual symptom reported with these drugs. Only one case given fluoxetine included a specific reference to hyperventilation.

Drowsiness was reported more often with fluvoxamine and paroxetine (IDs 22.6 and 20.5 per 1000 patient-months) in the first month of treatment than with fluoxetine and sertraline (IDs 8.2 and 7.3 per 1000 patient-months). This difference was statistically significant ($P < 0.001$).

Tremor was reported significantly more often in the first month of treatment with fluvoxamine and paroxetine (IDs 13.2 and 12.4 per 1000 patient-months) than with fluoxetine and sertraline (IDs 5.7 and 6.2 per 1000 patient-months, $P < 0.001$).

Psychiatric. After review of the 100 green forms reporting with hypomania or mania, fluvoxamine was considered possibly related to the event in eight cases, fluoxetine in two cases, sertraline in three cases and paroxetine in eight cases. The differences were not statistically significant.

Cardiovascular. All green forms reporting serious cardiac events, particularly arrhythmias, were reviewed. All cases possibly related to an SSRI were followed up by writing to the patients' GPs. After follow-up it was clear that there were no serious cardiac events associated with any of the SSRIs. There were three cases of bradycardia possibly related to fluvoxamine and one of bradycardia possibly related to paroxetine.

Other selected events. Sweating and impotence/ejaculation failure were both reported significantly more often in the first month after starting therapy with paroxetine than with the other three SSRIs ($P = 0.004$ and $P < 0.001$ respectively). Three patients reporting impotence when taking paroxetine developed impotence again on re-exposure to the drug.

Withdrawal events

After review of green forms reporting withdrawal symptoms, there were 15 cases of withdrawal symptoms after stopping paroxetine and two with each of the other three SSRIs. Two of the patients with withdrawal symptoms from paroxetine had repeated symptoms after re-exposure to the drug. Agitation, anxiety, tremor, dizziness, loss of balance, nausea, vomiting, paraesthesiae and restlessness were all symptoms associated with withdrawal. The timing of the reports of withdrawal symptoms with paroxetine is shown in Fig. 4.

Pregnancy

One hundred and eighty-seven pregnancies were reported among women who had taken one of the SSRIs during the first trimester (Table 7).

Six babies (5.6% of the live births) were born with some form of abnormality.

Fluvoxamine. No abnormalities were reported among the live births exposed to fluvoxamine in the first trimester of pregnancy. One pregnancy was terminated due to 47XXX chromosomal abnormality. The mother had also taken phentermine during the first trimester of pregnancy.

Fluoxetine. Three abnormalities were reported: one baby had a single palmar crease, but no chromosomal abnormality. One baby had spina bifida and hydrocephalus (the mother had epilepsy and also took sodium valproate and carbamazepine

Table 7 — Outcome when drug taken during first trimester of pregnancy

	Number of pregnancies	Live birth	Ectopic	Spontaneous abortion	Termination of pregnancy	Still birth	IUD*	Not known
Fluvoxamine	21	10	1	5	2	0	0	3
Fluoxetine	52	27	2	6	6	0	0	11
Sertraline	51	28	1	2	11	0	1	8
Paroxetine	63	42†	0	8	11	1	1	3
Total	187	107†	4	21	30	1	2	25

*Intrauterine death.

†There were three sets of twins. One of a set of twins was stillborn. The remaining twin was healthy. There were 63 pregnancies exposed to paroxetine in the first trimester, 40 pregnancies resulting in live births and a total of 42 live babies.

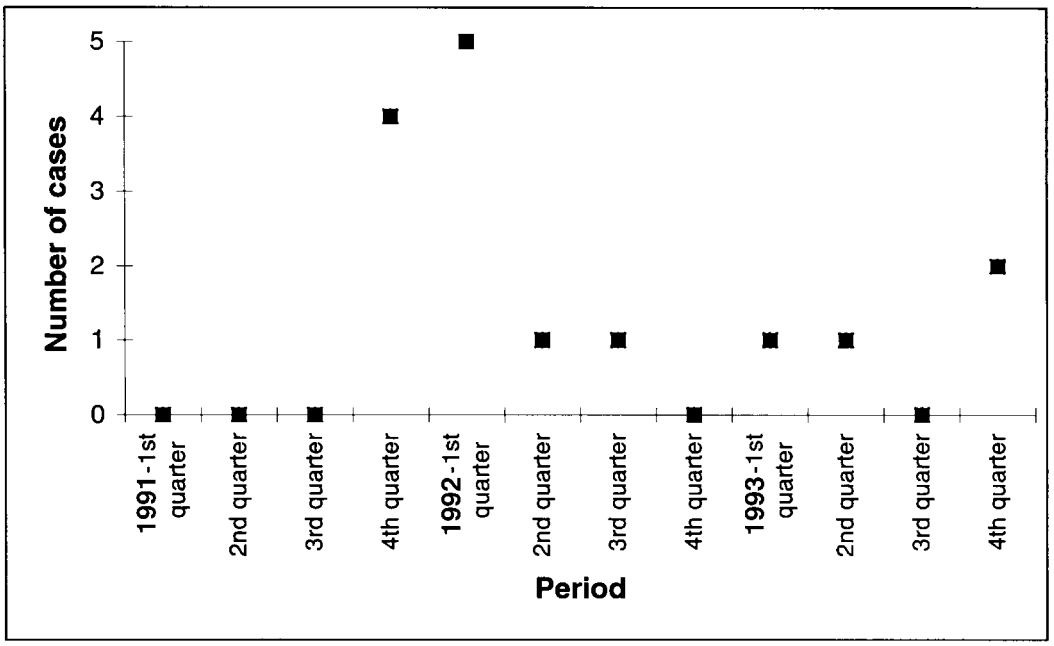

Fig. 4 — Paroxetine and cases of withdrawal

throughout pregnancy). One baby was born with congenital hypothyroidism.

Sertraline. Two abnormalities were reported: one baby had a benign retro-peritoneal cyst. A second baby was born with congenital laryngeal stridor. In addition, there was an intrauterine death at 17 weeks gestation, but post-mortem examination revealed no fetal abnormality.

Paroxetine. One baby was reported to suffer 'jittery episodes ?cause'. There was one stillbirth reported. The baby was one of a set of twins and the remaining twin was normal. The mother had taken paroxetine and no other drug during pregnancy. In addition, there was an intrauterine death at 18 weeks gestation. The mother had idiopathic thrombocytopenic purpura diagnosed during pregnancy.

Deaths and suicide

There were a total of 1547 deaths (3.1% of the total cohorts) reported during these studies and 110 (7.1%) of these were due to suicide (Table 8). The difference between the number of suicides with each of the four SSRIs was not statistically significant. No death in these studies was attributed to an SSRI.

DISCUSSION

The technique, strengths and weaknesses of PEM have been extensively described elsewhere.[10–13] The

Table 8 — Deaths and suicides reported for the SSRIs

	Fluvoxamine	Fluoxetine	Sertraline	Paroxetine	Total
Total deaths (%)*	381† (3.5%)	365‡ (2.9%)	385§ (3.0%)	416‖ (3.0%)	1547
Suicide	20 (0.2%)	31 (0.2%)	22 (0.2%)	37 (0.3%)	110

*Percentage of total cohort.
†Cause of death available in 97% of cases.
‡Cause of death available in 90% of cases.
§Cause of death available in 99% of cases.
‖Cause of death available in 84% of cases.

data from the four studies in this comparison were restricted to experience in general practice. It was not possible to estimate the degree of compliance with the prescribed and dispensed medication. The four SSRIs were introduced onto the British market, in the following order: fluvoxamine (1987), fluoxetine (1989), sertraline (January 1991) and paroxetine (March 1991). This may have affected event reporting. There may also have been selection bias as doctors became accustomed to using the drugs for specific groups of patients. In addition, there may have been publicity bias, as knowledge of the drugs grew over time, e.g. fluoxetine and suicide, paroxetine and withdrawal effects. There may also have been reporting bias, as doctors became more likely to recognize and report adverse events already known to be associated with SSRIs.

An important possible source of bias is the order in which drugs within each therapeutic group, entered the UK market and became available for study. The lower efficacy and higher incidence of adverse events shown with fluvoxamine, compared with the other SSRIs in the present comparisons, may have been due to fluvoxamine having been the first SSRI available for GP use in the UK. Table 5 shows, however, that with the NSAIDs, ACE inhibitors and proton pump inhibitors examined by PEM, the first drug in each therapeutic group is not that which has the highest IDs of the most frequently reported events. Furthermore, the IDs for respiratory tract infection (RTI) do not vary markedly between the four SSRIs. As these RTIs are not clearly related to either the indication for prescribing these drugs or their side-effects, the IDs for these infections can be taken to indicate the 'background noise' in these experiments. That the incidence of RTIs is reasonably constant in the present comparisons argues against fluvoxamine having been subject to differential reporting affecting all event rates. For these reasons we are satisfied that the present findings with fluvoxamine are unlikely to be due to biases arising simply from the fact that it was the first SSRI on the UK market.

Another possible source of bias arises from the inclusion of fluvoxamine, but not the other SSRIs, in a modification of PEM (the 'red alert' experiment) in which doctors were invited to undertake the early reporting of serious adverse drug reactions without waiting the interval of time at which the usual green form would have been sent. This could have led to the earlier receipt of a report by the DSRU but, as the date of each individual event was recorded by the GP, this would not have affected the ID for month 1 of therapy. Nor would it have affected the ID for the whole period of treatment. The relevant values for the overall IDs are given in Table 6, which confirms that the incidence of adverse effects with the highest ID values is far higher with fluvoxamine than for fluoxetine, paroxetine or sertraline, even when the values for respiratory tract infections remain fairly constant.

The sex and age distributions of the cohorts and indications for prescribing the four SSRIs were remarkably similar and this suggests that the patient populations treated with these four drugs were similar.

Effectiveness

The four studies did not provide a formal assessment of efficacy. Side-effects causing cessation of therapy could have prevented patients achieving therapeutic doses. Fluvoxamine was reported (by those GPs who expressed an opinion) to be considerably less effective than the other three SSRIs. This difference was statistically significant.

The events

Fluvoxamine was associated with a higher incidence of adverse events than the other three SSRIs. Nausea/vomiting and malaise/lassitude were, in order of incidence, the most frequently reported events. The most frequent clinical reasons for stopping therapy were often those events with the highest IDs per 1000 patient-months in the first month of treatment (Table 4). These events are likely to be drug-related.

In addition to potentially altered drug distribution and metabolism, the elderly often have a marked reduction in renal clearance. In this study, the frequency and nature of events reported in the first month of treatment for patients aged 70 years and over were comparable with the events reported for the entire cohort.

Differences were identified between the event profiles of the four drugs. Fluvoxamine and paroxetine were significantly more sedative than fluoxetine and sertraline. Tremor was reported significantly more often with fluvoxamine and paroxetine than fluoxetine and sertraline. Sweating and impotence/ejaculation failure were reported significantly more often with paroxetine than the other three SSRIs.

Selected events

A number of reports have suggested a link between fluoxetine and precipitation of manic/hypomanic episodes.[14,15] We found no significant difference between the number of cases possibly related to each of the four SSRIs.

Tricyclic antidepressants are associated with cardiotoxicity. SSRI antidepressants may have been prescribed preferentially to patients with cardiac problems (selection bias). No serious cardiac event in this study was attributed to an SSRI.

There was no statistical significance between the number of suicides and the SSRI taken. It has been suggested that fluoxetine might promote suicidal ideation.[16] Our data do not support this view.

Withdrawal symptoms

There has been publicity over paroxetine and a withdrawal syndrome.[4] The Committee on Safety of Medicines (CSM) circulated a relevant warning which coincided with the final posting of green forms for paroxetine (February 1993). Reports of withdrawal were therefore examined for clustering of relevant events in the months following the publication. Publicity bias was excluded (Fig. 4). Reports of withdrawal symptoms were significantly more frequent with paroxetine than with the other three SSRIs and we do not consider that this difference was due to publicity bias following the CSM warning.

CONCLUSIONS

In these large studies fluvoxamine has shown a considerably higher incidence of side-effects associated with its use than the other three SSRIs. The side-effect profiles of fluoxetine, sertraline and paroxetine have been found to be comparable in terms of frequently reported events. These studies have identified important differences between the four SSRIs in respect of less frequent adverse events. Fluvoxamine and paroxetine are more sedative than fluoxetine and sertraline. Withdrawal symptoms were reported rarely with all four SSRIs but were significantly more frequent with paroxetine. There were more reports of male sexual dysfunction with paroxetine than the other three SSRIs. Fluvoxamine was reported (by those prescribing doctors who expressed an opinion) to be less frequently effective than the other three SSRIs. These studies suggest that fluvoxamine compares unfavourably with fluoxetine, sertraline and paroxetine, both in terms of reported effectiveness and the incidence of adverse events. This difference seems unlikely to be due to bias.

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