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# Drug Safety Monitoring of 12 692 Patients Treated with Fluoxetine

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The safety of new drugs introduced into clinical practice in Britain is assessed by Prescription-Event Monitoring, a system complimentary to that of the Committee on Safety of Medicines. It is independent of studies carried out by the pharmaceutical industry. Data on 12 692 patients treated with fluoxetine under the National Health Service were obtained from family practitioners throughout England. The main outcome measures were the rate of recorded events per 1000 patients during the first month of treatment and the mean rate of events during the following 5 months. The rates were compared with those for other selective serotonin reuptake inhibitors elicited by Prescription-Event Monitoring. Individual events, documented in the literature as unwanted effects of fluoxetine and other antidepressants and reported in the present study, were assessed with the help of information provided by the practitioners. All pregnancies were followed up to determine their outcome. Causes of death were established from patients' medical records and death certificates. Neuropsychiatric symptoms were the most frequently reported events, while the most commonly reported individual event was nausea. The rate of several events increased with increasing age. No hitherto unrecognized severe adverse drug-related events were reported. Fluoxetine was considered to be a safe drug, even when prescribed in family practice for a wide range of patients, many of them treated with other drugs for concomitant diseases. 

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## INTRODUCTION

Prescription-Event Monitoring (PEM) is one of the principal pharmacoepidemiological techniques undertaken in the Drug Safety Research Unit (DSRU), Southampton, UK. PEM, and the spontaneous adverse drug reaction ('yellow card') system of the Committee on Safety of Medicines (CSM), are two complementary national systems of post-marketing drug safety monitoring practised in Britain. The system routinely provides information on over 10 000 patients treated by family practitioners with newly-marketed drugs; that is approximately 10 times the amount of data on volunteers and patients available at the time of the marketing application (Rawlins and Jefferys, 1991). In this paper we report the results of a PEM study of 12 692 patients treated with fluoxetine.

PEM studies are of a non-interventional, observational, cohort design with no doctor being approached before the decision to treat a patient is made; the studies are independent of those set up by pharmaceutical companies.

## METHOD

Patients receiving fluoxetine and the family practitioners who had prescribed it were identified by the Prescription Pricing Authority (PPA). This organization remunerates pharmacists for medicines

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dispensed under the British National Health Service. Copies of prescriptions for fluoxetine were supplied in confidence and legible scripts (the overwhelming majority) were used in the study. The names and addresses of the doctors who wrote the prescriptions were checked against the DSRU register of family practitioners and 24 738 patients who had received one or more prescriptions for fluoxetine between March 1989 and March 1990 were identified. These were among the first patients to receive the drug in general practice after its release for marketing in the UK.

Six months after the first prescription for each patient was written the practitioner was sent a 'green form' questionnaire on which he or she was asked to provide the following information: sex and age of the patient; indication for prescribing fluoxetine; date of starting treatment; date of stopping treatment; reason for stopping; drug(s) substituted; whether or not the treatment was effective; and dates and nature of any events that occurred, regardless of whether or not the treatment was continued. These data were linked with information from the related prescription and processed by the DSRU's technical officers. Questionnaires were not sent to hospital doctors as practically all patients in Britain are assessed by family practitioners before referral to hospital and the hospital then sends a report to the practitioner on each outpatient and inpatient seen.

In PEM, prescribers are asked to record all events and not just suspected adverse drug reactions. An 'event' is defined as any new diagnosis, reason for referral to a consultant or admission to hospital, unexpected deterioration or improvement in a concurrent illness, suspected drug reaction, or symptom, sign or non-medical event that was considered of sufficient importance to be entered into the patient's records. The practitioner is not required to decide if there is a cause-and-effect relationship between any reported event and the drug treatment. Pre-existing diseases are not recorded as events unless an exacerbation occurs. When the same event is reported more than once only the first occurrence is included in the analyses. Symptoms, signs and the results of laboratory tests are analysed as events only if the diagnosis of the disorder or disease responsible is not given. When related events, for example nausea and vomiting, are reported only the more severe is coded. Wherever possible each event is matched with those in an 'event dictionary' (Kubota and Inman, 1994) and then categorized into 'event groups' based on the physiological system they predominantly affect. Further details of the evolution of the methodology of PEM and its application to psychotropic drugs have been reported elsewhere (Inman *et al*., 1986; Rawson *et al*., 1990; Edwards *et al*., 1994; Mann, 1994).

Two methods of assessment were used to examine those events occurring at a rate (number of events/number of patients $\times$ 1000) of one or more per 1000 patients during the first month following the start of treatment ($T_1$). Firstly, a rate ratio $T_1/T_2$ was constructed in which $T_1$ is the event rate per 1000 patients during the first month of therapy and $T_2$ is the mean event rate per 1000 patients in months 2–6. PEM studies of 42 drugs carried out in the DSRU have suggested that a rate ratio ($T_1/T_2$) of 3 or more provides evidence of an association with the drug being examined. Statistical support for the validity of this assertion has been provided by Andrew *et al*., 1996. The second test uses a Poisson model to calculate the 99 per cent confidence intervals for the difference between the event rate in month 1 ($T_1$) and the mean event rate in months 2–6 ($T_2$; Kubota *et al*., 1995).

Apparent associations between drug exposure and specific events reported during the six-month period following the start of treatment were assessed with the help of information provided on the green forms. The outcome of each pregnancy was determined by sending a second questionnaire to the patient's practitioner. In the case of patients who died, the doctor was requested to give permission for the medical records to be retrieved from the Family Health Service Authority. These records were used to establish the cause of death and, when considered appropriate, copies of death certificates were obtained from the Office of Population Censuses and Surveys.

## RESULTS

A total of 24 738 patients who were treated with fluoxetine by 8546 family practitioners working throughout England were identified from prescriptions. 14 444 (58·4 per cent) of the green forms were returned but 1752 of these were void for the following reasons: patient no longer registered with the doctor — 764; no information provided on the form — 646; fluoxetine prescribed but not taken — 158; no record of treatment in patient's case records — 139; and doctor moved or retired — 45. The percentage of forms returned by individual doctors ranged from 19·0–70·4 per cent,

 

Table 1. Age distribution and sex of patients

| Age range (years) | Male Number | % | Female Number | % | Not provided Number | % | Total Number | % |
|---|---|---|---|---|---|---|---|---|
| 10–19 | 41 | 1·1 | 156 | 1·8 | 1 | 0·7 | 198 | 1·6 |
| 20–29 | 340 | 9·2 | 1079 | 12·2 | 9 | 6·5 | 1428 | 11·3 |
| 30–39 | 571 | 15·5 | 1436 | 16·2 | 17 | 12·2 | 2024 | 15·9 |
| 40–49 | 725 | 19·6 | 1645 | 18·6 | 25 | 18·0 | 2395 | 18·9 |
| 50–59 | 624 | 16·9 | 1250 | 14·1 | 17 | 12·2 | 1891 | 14·9 |
| 60–69 | 515 | 14·0 | 1079 | 12·2 | 15 | 10·8 | 1609 | 12·7 |
| 70–79 | 343 | 9·3 | 908 | 10·2 | 4 | 2·9 | 1255 | 9·9 |
| 80–89 | 120 | 3·3 | 423 | 4·8 | 1 | 0·7 | 544 | 4·3 |
| 90 or more | 8 | 0·2 | 33 | 0·4 | 1 | 0·7 | 42 | 0·3 |
| Not known | 403 | 10·9 | 854 | 9·6 | 49 | 35·3 | 1306 | 10·3 |
| Total | 3690 | 100 | 8863 | 100 | 139 | 100 | 12 692 | 100 |
| Average (range) | 50·1 ± 16·7 (14–94) | | 49·4 ± 18·1 (14–97) | | | | 49·6 ± 17·7 (14–97) | |

this percentage bearing an inverse relationship to the number of prescriptions for fluoxetine written by the practitioner and thus the number of forms sent to him or her. The final cohort on which clinically useful information was available numbers 12 692.

The *age* distribution and *sex* of the patients are given in Table 1. Of the total population 29·1 per cent were men and 69·8 per cent were women, giving a female:male ratio of 2·4 : 1. The sex of 139 (1·1 per cent) of the patients was not specified.

The *indications* for prescribing fluoxetine were reported in 10 728 cases (84·5 per cent of the total). The drug had been prescribed for a wide range of conditions, the vast majority being psychiatric. A total of 10 023 (79·0 per cent) were given the drug for depressive disorders and 250 (2·0 per cent) for anxiety.

All prescriptions written for a random sample of 1000 patients were examined to obtain information on *dosage*. Where a patient had several prescriptions for fluoxetine at different doses the highest dose was recorded. The most frequently used daily dose, prescribed in 89·4 per cent of the cases, was 20 mg (the currently recommended British National Formulary dose); 7·2 per cent of patients received 40 mg and 1·9 per cent 60 mg per day. Less than 0·3 per cent were prescribed 80 mg and 120 mg per day while the dose was not specified in 1·2 per cent of cases.

Of the patients in this sample of 1000 subjects, 595 (59·5 per cent) were given no other *concomitant medication*, while 22·8 per cent were given one other drug, 11·7 per cent two drugs and 6·0 per cent three or more drugs. The types of drugs prescribed and the percentages of patients in the sample who received them are shown in Table 2. It will be noted that 16·8 per cent of the patients were receiving an anxiolytic or hypnotic, 6·1 per cent an analgesic, 4·5 per cent an anti-psychotic and 2·8 per cent another antidepressant drug — in spite of the fact that there are rarely, if ever, indications for prescribing two antidepressants at the same

Table 2. Concomitant medication in a sub-sample of 1000 patients*

| Type of drug | Number of of patients | % of patients |
|---|---|---|
| Anxiolytic sedative and hypnotic | 168 | 16·8 |
| Analgesic | 61 | 6·1 |
| Antipsychotic | 45 | 4·5 |
| Anti-infective | 39 | 3·9 |
| Diuretic | 29 | 2·9 |
| Antidepressant | 28 | 2·8 |
| Gastrointestinal | 25 | 2·5 |
| Laxative | 24 | 2·4 |
| Hormone and contraceptive | 21 | 2·1 |
| Topical skin preparations | 19 | 1·9 |
| Beta-blocker | 18 | 1·8 |
| Vitamins/minerals | 18 | 1·8 |
| Anti-anginal | 17 | 1·7 |
| Anti-parkinson | 16 | 1·6 |
| Ulcer healing | 15 | 1·5 |
| Thyroid and anti-thyroid | 14 | 1·4 |
| Bronchodilator | 12 | 1·2 |
| Other respiratory | 12 | 1·2 |
| Antiepileptic | 11 | 1·1 |
| Other | 78 | 7·8 |

*Individual patients may be prescribed drugs from more than one category.

Table 3. Events with an incidence of one or more per 1000 patients during the first month of treatment with fluoxetine ($T_1$) and ratio of 3 or more for months 1/2–6 ($T_1/T_2$). Comparative data for fluvoxamine and paroxetine

| Events | Fluoxetine $N = 12\,692$ | | | | | Fluvoxamine $N = 10\,401$ | | | Paroxetine $N = 13\,734$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $T_1$ | $T_2$ | $T_1/T_2$ | $T_1-T_2$ | 99%CI | $T_1$ | $T_2$ | $T_1/T_2$ | $T_1$ | $T_2$ | $T_1/T_2$ |
| Neuropsychiatric | | | | | | | | | | | |
| Malaise | 10·5 | 0·8 | 12·8 | 9·7 | 7·3–12·0 | 20·9 | 0·8 | 26·5 | 10·1 | 0·6 | 15·8 |
| Headache | 9·4 | 2·3 | 4·1 | 7·1 | 4·8–9·3 | 16·6 | 2·5 | 6·6 | 10.·8 | 2·1 | 5·3 |
| Insomnia | 7·9 | 1·5 | 5·2 | 6·4 | 4·3–8·4 | 10·5 | 1·2 | 8·9 | 10·7 | 1·8 | 5·9 |
| Anxiety | 7·4 | 1·8 | 4·0 | 5·6 | 3·6–7·6 | 7·7 | 1·6 | 4·8 | 3·8 | 1·2 | 3·3 |
| Drowsiness/sedation | 6·7 | 0·7 | 10·1 | 6·0 | 4·1–7·9 | 15·0 | 1·0 | 14·9 | 16·7 | 1·1 | 15·1 |
| Dizziness | 5·4 | 1·3 | 4·1 | 4·1 | 2·4–5·8 | 17·5 | 1·3 | 13·3 | 9·5 | 1·6 | 5·8 |
| Agitation | 5·0 | 0·6 | 7·9 | 4·3 | 2·7–6·0 | 6·3 | 0·4 | 15·6 | 4·3 | 0·6 | 6·7 |
| Tremor | 4·7 | 0·9 | 5·3 | 3·8 | 2·2–5·4 | 9·0 | 0·5 | 17·0 | 10·2 | 0·6 | 15·9 |
| Panic attacks | 2·1 | 0·3 | 7·5 | 1·8 | 0·8–2·9 | 2·9 | 0·3 | 8·8 | 2·4 | 0·5 | 4·6 |
| Peripheral sensory symptoms | 1·7 | 0·5 | 3·6 | 1·2 | 0·2–2·2 | 3·3 | 0·6 | 5·3 | 1·0 | 0·5 | 2·1 |
| Confusion | 1·8 | 0·4 | 4·6 | 1·4 | 0·4–2·4 | 2·4 | 0·2 | 10·0 | 0·9 | 0·3 | 2·7 |
| Unsteadiness | 1·2 | 0·2 | 7·5 | 1·0 | 0·2–1·8 | 1·5 | 0·3 | 4·7 | 0·9 | 0·2 | 4·3 |
| Gastrointesinal | | | | | | | | | | | |
| Nausea | 16·2 | 1·6 | 9·8 | 14·5 | 11·6–17·5 | 64·0 | 2·0 | 31·8 | 35·3 | 2·1 | 17·1 |
| Diarrhoea | 5·8 | 1·5 | 3·8 | 4·2 | 2·4–6·0 | 15·7 | 1·6 | 9·7 | 6·6 | 2·0 | 3·3 |
| Vomiting | 5·4 | 1·1 | 5·0 | 4·3 | 2·6–6·0 | 20·7 | 1·4 | 14·7 | 7·9 | 1·0 | 7·8 |
| Anorexia | 2·0 | 0·5 | 4·3 | 1·5 | 0·5–2·6 | 4·2 | 0·4 | 10·9 | 1·5 | 0·2 | 8·7 |
| Other | | | | | | | | | | | |
| Sweating | 1·8 | 0·3 | 6·4 | 1·5 | 0·5–2·5 | 2·4 | 0·3 | 8·1 | 5·5 | 0·8 | 6·6 |
| Palpitations | 1·7 | 0·3 | 6·9 | 1·5 | 0·5–2·4 | 3·3 | 0·3 | 9·4 | 1·7 | 0·4 | 4·1 |
| Dry mouth | 1·4 | 0·1 | 12·8 | 1·3 | 0·4–2·2 | 2·6 | 0·2 | 15·5 | 3·5 | 0·3 | 12·0 |
| Dysuria | 1·1 | 0·3 | 3·2 | 0·8 | 0·0–1·5 | 1·1 | 0·3 | 3·7 | 0·9 | 0·2 | 4·0 |
| Dyspnoea | 1·0 | 0·3 | 3·2 | 0·7 | 0·0–1·5 | 1·0 | 0·3 | 3·0 | 0·9 | 0·3 | 3·3 |

$T_1$, event rate during first month after start of treatment; $T_2$, event rate during second to sixth month after start of treatment; 99%CI, 99% confidence interval.

time. As a co-prescribed drug need not necessarily appear on the prescription for fluoxetine these figures are likely to be underestimates.

The *duration of treatment* was known in 11 298 (89·0 per cent) of patients and the numbers and percentages of those using fluoxetine at the end of months 1–6 were: 8311 (73·6 per cent), 6164 (54·6 per cent), 5076 (44·9 per cent), 4387 (38·8 per cent), 3900 (34·5 per cent) and 3517 (31·1 per cent), respectively.

In response to the question on *effectiveness*, fluoxetine was considered by the family practitioners to have been effective in 6063 (57·3 per cent) and ineffective in 4516 (42·7 per cent) of 10 579 cases on whom an opinion was given.

After treatment with fluoxetine was stopped other *drugs* were *substituted*. Of 1878 cases in which the substituted drugs were reported on the green forms, most (1431, 76·2 per cent) had antidepressants substituted, while 141 (7·5 per cent) were prescribed anxiolytics or hypnotics, 206 (11·0 per cent) antipsychotic drugs and 100 (5·3 per cent) various other agents. In 1293 (68·8 per cent) patients a tricyclic or tricyclic-related compound was substituted. The individual antidepressant most frequently substituted was dothiepin (in 20·9 per cent of cases), followed by amitripyline and lofepramine (in 11·7 per cent and 10·8 per cent of cases, respectively).

A total of 9772 *events* were reported during the 6-month period after the start of treatment (whether or not treatment was continued), giving an average of approximately one event per patient. Of these events 2988 occurred during the first month, compared with an average of 1357 during the subsequent five months.

Events with a rate of one or more per 1000 patients during the first month following the start of treatment ($T_1$) and a $T_1/T_2$ ratio of 3 or more are shown in Table 3. This table also shows the rates of

Table 4. Events with an incidence of one or more per 1000 patients during the first month of treatment with fluoxetine ($T_1$) and a ratio of 3 or more for months 1/2–6 ($T_1T_2$) in relation to age

| | Age (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ⩽39 | | 40–59 | | ⩾60 | | All ages | |
| | Month 1 $T_1$ | Months 2–6 $T_2$ | Month 1 $T_1$ | Months 2–6 $T_2$ | Month 1 $T_1$ | Months 2–6 $T_2$ | Month 1 $T_1$ | Months 2–6 $T_2$ |
| Neuropsychiatric | | | | | | | | |
| Malaise | 5·5 | 0·7 | 11·0 | 1·0 | 18·0 | 0·9 | 10·5 | 0·8 |
| Headache | 9·3 | 3·3 | 11·0 | 2·1 | 8·1 | 1·9 | 9·4 | 2·3 |
| Insomnia | 8·2 | 1·4 | 8·4 | 1·7 | 9·0 | 1·6 | 7·9 | 1·5 |
| Anxiety | 7·1 | 1·7 | 6·3 | 2·0 | 9·6 | 2·2 | 7·4 | 1·8 |
| Dizziness | 6·3 | 0·7 | 7·7 | 0·7 | 7·0 | 0·7 | 6·7 | 0·7 |
| Drowsiness/sedation | 4·9 | 1·1 | 6·6 | 1·0 | 4·4 | 2·1 | 5·4 | 1·3 |
| Agitation | 1·6 | 0·2 | 5·2 | 0·6 | 8·4 | 1·3 | 5·0 | 0·6 |
| Tremor | 2·2 | 0·3 | 3·5 | 0·8 | 7·9 | 1·9 | 4·7 | 0·9 |
| Panic attacks | 2·2 | 0·3 | 1·9 | 0·3 | 2·3 | 0·3 | 2·1 | 0·3 |
| Peripheral sensory symptoms | 2·2 | 0·6 | 1·4 | 0·7 | 1·7 | 0·2 | 1·7 | 0·5 |
| Confusion | 0·5 | 0·0 | 1·2 | 0·1 | 3·8 | 1·1 | 1·8 | 0·4 |
| Unsteadiness | 0·3 | 0·1 | 0·2 | 0·1 | 3·2 | 0·4 | 1·2 | 0·2 |
| Gastrointestinal | | | | | | | | |
| Nausea | 13·7 | 1·3 | 17·6 | 1·6 | 19·5 | 2·2 | 16·2 | 1·6 |
| Diarrhoea | 3·6 | 1·6 | 5·4 | 1·3 | 9·3 | 2·2 | 5·8 | 1·5 |
| Vomiting | 3·3 | 1·1 | 4·9 | 0·9 | 8·4 | 1·3 | 5·4 | 1·1 |
| Anorexia | 1·9 | 0·3 | 0·5 | 0·3 | 4·4 | 1·0 | 2·0 | 0·5 |
| Other | | | | | | | | |
| Sweating | 1·6 | 0·2 | 1·9 | 0·3 | 2·6 | 0·4 | 1·8 | 0·3 |
| Palpitations | 1·4 | 0·1 | 0·7 | 0·2 | 3·5 | 0·5 | 1·7 | 0·3 |
| Dry mouth | 0·5 | 0·0 | 1·4 | 0·0 | 2·3 | 0·2 | 1·4 | 0·1 |

events reported in PEM studies of fluvoxamine carried out between 1987 and 1988 and paroxetine between 1991 and 1992.

It will be noted from the table that the 10 most frequently reported events during the first month following the start of treatment were nausea, malaise, headache, insomnia, anxiety, drowsiness/sedation, diarrhoea, vomiting, dizziness and agitation. All 10 of these and the other events listed had $T_1 - T_2$ differences that were statistically significant. The number of reports in the first month of therapy and the high rate ratios ($T_1/T_2$) suggest that, of these events, nausea, malaise, headache and insomnia are especially drug-related. However, all of the events were reported infrequently, the most common of them, nausea, being reported only once in every 62 patients during the first month after the start of treatment.

Table 4 shows the events given in Table 3 in relation to three age groups, 39 years and younger, 40 to 59 years and 60 years and older. It will be noted that of the 10 events most frequently reported during the first month following the start of treatment, malaise, agitation, tremor, confusion, unsteadiness and gastrointestinal disturbances were age-related and reported more frequently in the elderly.

In view of the concern that had been expressed by Teicher *et al.* (1990) and others over the possibility of *aggressive reactions* and *suicidal behaviour* being caused by fluoxetine, we have listed in Table 5, the rates of these and related events during treatment with fluoxetine, fluvoxamine and paroxetine. Because the phenomena were said to have occurred within two months of starting treatment with fluoxetine (Teicher *et al.*, 1990) the data presented are limited to this period.

In addition to the events listed in Table 4 a wide variety of other events occurring in all physiological systems were encountered. We report below those previously reported in the literature as being allegedly caused by fluoxetine and/or those

Table 5. Aggression, suicide and related events during treatment

| Events | Event rates per 1000 patients per month | | | | | |
|---|---|---|---|---|---|---|
| | Fluoxetine | | Fluvoxamine | | Paroxetine | |
| | Month 1 $D_1 = 10\,102$ | Month 2 $D_2 = 6889$ | Month 1 $D_1 = 7179$ | Month 2 $D_2 = 3590$ | Month 1 $D_1 = 11\,046$ | Month 2 $D_2 = 7970$ |
| Aggression | 0·8 | 0·3 | 0·8 | 0·3 | 0·1 | 0·0 |
| Agitation | 5·9 | 1·6 | 9·3 | 2·0 | 5·0 | 1·9 |
| Anxiety | 8·3 | 3·6 | 9·1 | 2·9 | 4·3 | 1·5 |
| Hyperactivity | 1·1 | 0·0 | 0·1 | 0·0 | 0·5 | 0·1 |
| Irritability | 0·6 | 0·4 | 0·1 | 0·8 | 0·5 | 0·1 |
| Mania/hypomania | 0·2 | 0·9 | 0·1 | 0·6 | 0·5 | 0·4 |
| Paranoid ideation | 0·2 | 0·1 | 0·3 | 0·3 | 0·3 | 0·0 |
| Suicide threat | 1·0 | 0·7 | 1·0 | 0·6 | 0·0 | 0·0 |
| Drug overdose | 2·7 | 1·9 | 2·8 | 2·2 | 2·3 | 0·6 |
| Drug overdose (F) | 0·1 | 0·1 | 0·0 | 0·3 | 0·0 | 0·0 |
| Self-injury | 0·0 | 0·0 | * | * | 0·3 | 0·1 |
| Suicide attempt** | 0·7 | 0·3 | 0·6 | 0·3 | 0·5 | 0·0 |
| Suicide** | 0·2 | 0·0 | 0·0 | 0·0 | 0·3 | 0·1 |
| Drug overdose accidental | 0·1 | 0·0 | 0·0 | 0·0 | 0·0 | 0·0 |

F, fatal.
*, Term not used in fluvoxamine study.
**, Other than by overdose.
$D_1$, average number of patients on treatment in month 1 for whom date of stopping drug is known or who continued treatment throughout period of observation; $D_2$, average number of patients on treatment in month 2 for whom date of stopping the drug is known or who continued treatment throughout period of observation.

of relevance to antidepressant drug treatment in general.

We received 21 reports of *mania* or *hypomania* occurring during treatment. Some of the patients may not have been manic in the psychiatric sense of the word, while some had a past history of mania. Assuming a causal connection in each case (although this cannot be proven), the rate during treatment was 1·7 per 1000 patients. Ten cases of *convulsions* were reported during treatment in non-epileptic patients who did not have a more obvious cause of their fits. This gives a rate of 0·8 per 1000 — again assuming a cause and effect relationship. The figure is similar to that for tricyclic antidepressants (Jick *et al*. 1983; Peck *et al*., 1983; Edwards *et al*., 1987) There were two reports of *dystonia*, eight of *other abnormal movements*, two of *extrapyramidal signs* and 12 of '*parkinsonian features*' (including a worsening of ideopathic or neuroleptic-induced parkinsonism), each occurring in elderly patients during treatment. These are consistent with previous publications (Meltzer *et al*., 1979; Bouchard *et al*., 1989; Lipinski *et al*., 1989; Tate, 1989; Baldwin *et al*., 1991; Boyer and Feighner, 1991).

Isolated reports of *changes in heart rate* (nine reports) and *heart rhythm* (11 reports) and a single case of *heart block* were reported , but these were in elderly patients with pre-existing heart disease and were therefore unlikely to be due to fluoxetine. Similarly, there were more likely causes of each of six hepatic events (*abnormal LFTs, hepatic failure* and *hepatomegaly*), while there was insufficient information to establish a causal connection on the one case of *jaundice* reported. We received five reports of *impotence* or *erectile difficulty*, which are consistent with previously published reports (Herman *et al*., 1990; Zajecka *et al*., 1991) but not definitely related to treatment in the subjects of our study.

*Weight loss* was reported twice as often (in 50 patients) as *weight gain* (22 patients). Fourteen patients lost 6 kg or more. In 11 patients the weight loss had started before treatment with fluoxetine or was associated with a concurrent disease. *Hyponatremia* occurred in five patients aged 78–90, each having a more likely cause. *Urticaria* was encountered (mostly during the first two months of treatment) in 21 cases and in one of these it was associated with other features of a hypersensitivity reaction. There were three reports of *hair loss* (also consistent with previous reports in the literature; Gupta and Major, 1991; Jenicke, 1991; Wheatley, 1993). We did not receive reports of

Table 6. Pregnancies

| Timing of exposure to fluoxetine | Total Number of pregnancies | Outcome | | | | |
|---|---|---|---|---|---|---|
| | | Live births | Ectopic pregnancies | Spontaneous abortion | Termination of pregnancy | Not known |
| Fluoxetine discontinued before the LMP | 43 | 22* | 0 | 8 | 3 | 10 |
| Exposed during first trimester | 57† | 31* | 2 | 6 | 7 | 11 |
| Exposed during second or third trimester | 1 | 1 | 0 | 0 | 0 | 0 |
| Dates of exposure uncertain | 2 | 0 | 0 | 0 | 0 | 2 |
| Total | 103 | 54 | 2 | 14 | 10 | 23 |

*One pair of normal twins.
†Includes one patient who had two pregnancies.

any haematological reactions for which we considered fluoxetine to be responsible.

*Pregnancy, spontaneous abortion* and *termination of pregnancy* were reported as events in 103 cases. A questionnaire was sent to the family practitioner of each of the 102 patients (one patient had two pregnancies) and 96 (94·1 per cent) were returned. Wherever possible, treatment with fluoxetine was related to the first day of the last monthly period (LMP). If this was not recorded on the green form or questionnaire it was estimated either from the date of delivery, assuming a 40-week pregnancy, or from other recorded information. The timing of exposure to fluoxetine in relation to the LMP is therefore only an approximation.

Fifty-eight women were known to have taken fluoxetine during their pregnancies or became pregnant while on treatment, 57 of them during the first trimester. There were 30 single births and one set of twins. One baby had a single palmar crease but no chromosomal abnormality, while another (whose mother had taken fluoxetine for 10 days) had congenital hypothyroidism. A third baby was born with hydrocephalus and spina bifida. The mother of this baby, a known epileptic who was being treated with sodium valproate and carbamazepine, had taken fluoxetine for five days during the ninth to tenth week of pregnancy. The outcome of 80 of the 103 pregnancies is known and is summarized in Table 6.

Three hundred and fifty-nine deaths were reported during treatment or the follow-up period. The main causes were: cancer (87 patients), ischaemic heart disease (67), cerebro-vascular catastrophes (35), chronic obstructive airways disease and bronchopneumonia (38). Thirty-four patients committed suicide, while 98 died from other miscellaneous causes.

## DISCUSSION

Like all research PEM has its strengths and its weaknesses. The former include the very large cohorts it is able to provide within a very short time of a new drug's launch on to the market. PEM provides quantitative data on common adverse events as seen from the perspective of family practice, and allows for the identification of less common untoward effects with an incidence of one or more per 3000 patients. It provides for research subsamples of patients with specific disorders, such as convulsive seizures, and cohorts of women who have become pregnant while taking drugs or have taken drugs during pregnancy, as well as important pharmacoepidemiological data on prescribing. It allows for comparisons between drugs to be made.

An apparent limitation of the method is the failure of some practitioners to return the green forms. This, however, is unlikely to influence the results to the extent that it might in other areas of research, as PEM is a naturalistic non-interventional study of family practice in England in which every medical practitioner has the opportunity to participate. Naturally, some do so to a greater extent than others, but is has been shown that a poor response is mainly related to variables in the doctor (rather than in the drugs or events), with a minority of identifiable very heavy prescribers of new drugs not returning the green forms (Inman and Pearce, 1993). There is a high response rate among the majority of practitioners who prescribe new drugs more conservatively. If

the less cooperative doctors were omitted from PEM the response rate would increase dramatically, but such an artificial (as opposed to natural) selection of respondents would deprive practitioners of the opportunity of participating in the research, prolong the data collection period and result in the loss of valuable epidemiological data on prescribing practices.

It might be considered that some doctors do not cooperate because of fear of litigation or breach of confidentiality. However, strict legally-binding confidentiality has been guaranteed since the inception of the DSRU, and less than one practitioner in 200 had previously indicated that they did not wish to participate in PEM. There is also some loss to the study resulting from patients leaving practices or being temporary residents and from doctors themselves changing practices.

The greater number of women than men who receive prescriptions for fluoxetine presumably reflects the higher prevalence of affective symptoms in females (Smith and Weissman, 1992) and the fact that psychotropic drugs are prescribed more often for women than for men (Balter *et al*., 1984).

The respondents thought that treatment with fluoxetine was effective in 57 per cent of cases. This figure is lower than the response rates reported in trials of both fluoxetine and other antidepressants. It is also lower than the response rates reported in most of the PEM studies of non-psychotropic drugs carried out in the DSRU but consistent with the low rates for other psychotropic drugs (Edwards *et al*., 1994). There are a number of possible reasons for this. Having only just been introduced to the market at the time our study was carried out, it is likely that fluoxetine was prescribed for many patients who were unresponsive to the antidepressants already available and possibly for treatment-resistant conditions in general. Furthermore, psychotropic drugs are often used in family practice to treat affective symptoms associated with various physical, as well as psychiatric disorders, many of which are serious and militate against a therapeutic response. In some cases it is also likely (as with other drugs) that adverse reactions contributed to non-adherence to treatment or masked therapeutic response.

In interpreting the relative incidence of events reported at different treatment intervals, the total number of events is important. If the number is small, large ratios will be found by chance and this could suggest an erroneous causal connection with fluoxetine. A high rate for particular events occurring during the first month may signal side-effects but may also be related to the disorder for which the drug was prescribed. A relative deficit of events during subsequent months may correspondingly be due to the beneficial effect of the drug. Thus, the decreasing incidence of *panic attacks* in the present study, for example, could be due to the anxiolytic effect of fluoxetine. Similar considerations could apply to *insomnia* and *agitation*, although previous studies have suggested that these are 'excitatory' unwanted effects (Benfield *et al*., 1986; Cooper, 1988; Edwards, 1992). This is less likely to be the case with *drowsiness/sedation* and *confusion*. It is even more difficult to decide if other events, such as *headache*, *peripheral sensory symptoms* and *unsteadiness*, are manifestations of the disorders being treated or unwanted effects of fluoxetine.

*Dry mouth, dyspnoea, palpitations* and *sweating* could have been physical manifestations of the anxiety that goes hand-in-hand with depression or side effects of fluoxetine. The higher incidence of palpitations and faintness in the first month of treatment compared with that in subsequent months (if not due to a therapeutic effect of fluoxetine on panic attacks) could be partly due to the fact that fluoxetine was prescribed for patients with cardiovascular disease, as it is less cardiotoxic than tricyclic antidepressants (Upward *et al*., 1988). Although the drug produces less anticholinergic effects than tricyclics, dry mouth was one of the more commonly reported events in our study and in previous trials of fluoxetine (Cooper, 1988).

*Malaise* [French: mal (bad)+aise (ease)] is a word used differently by different people to describe a general feeling of discomfort, which many practitioners may not distinguish from other non-specific phenomena, such as lethargy and fatigue. The discomfort may be a manifestation of the affective disorder being treated, an unwanted effect of fluoxetine, a reaction to some other side effect such as nausea or headache, or any combination of these. As it is a feature of depression, the high rate-ratio found in our study could, at least in part, be due to improvement during treatment.

The reports of *drug overdose* and *suicidal attempt/gesture* that we received are of interest because suicidal and aggressive behaviour have previously been reported during treatment with fluoxetine (Teicher *et al*., 1990; Dasgupta, 1990; Crearey *et al*., 1991; King *et al*., 1991; Koimumi, 1991; Mann and Kapur, 1991; Masand *et al*.,

 

1991). However, the rate of these events was low and their occurrence is not surprising in a population that consists mainly of depressed patients. Furthermore, our comparison of the rates of suicidal, aggressive and related events (Table 5) occurring during treatment with fluoxetine, fluvoxamine and paroxetine shows that there are no major differences. What differences there are appear disproportionately large because of the low rates of the events.

Eighty-two patients made a *suicidal gesture or attempt* by taking an overdose or by other methods — 67 within six months of starting treatment, 15 later — giving an overall rate of 6·5 per 1000. Of the 73 who took *overdoses*, 16 took fluoxetine alone, 10 fluoxetine with other substances, and 47 other drugs but no fluoxetine. Benzodiazepines were the type of drugs most often taken (by 21 patients), while temazepam was the individual benzodiazepine mostly taken (by 13 patients). Tricyclic antidepressants were taken by nine patients, paracetamol by 10 and various other substances by the remainder. The most common method of *self-injury* other than overdose was by wrist cutting.

Thirty-four patients committed *suicide* — 12 by self-poisoning and 22 by other methods, of which hanging was the most frequent. No patient died as a result or taking an overdose of fluoxetine and only one died from a tricyclic (clomipramine) overdose; that was four months after stopping treatment with fluoxetine. Although death has been reported following a large overdose of fluoxetine (Kincaid *et al*., 1990), the drug is not usually lethal in overdose with patients having survived after taking as much as 1·5 g (Borys *et al*., 1992); that is 75 times the conventional antidepressant dose and 25 times the higher dose recommended in bulimia nervosa.

It can be seen from Table 3 that *peripheral sensory symptoms* (paraesthesiae, hypoaesthesia and hyperaesthesia) were signalled as possible drug-related events. Alternatively, they could have been somatic accompaniments of affective disorders that improved with treatment. Two months after starting treatment one patient, a man aged 47, developed *polyneuritis* similar to that seen in the Guillain-Barré syndrome, with bilateral lower motor neurone weakness and diminished sensation in his face, an impaired corneal reflex, absent tendon reflexes in the legs, delayed sensory and motor conduction in all four limbs and raised cerebrospinal fluid protein. The patient was followed up for four years; during this time there was a considerable improvement but he was left with a residual facial weakness. Similar symptoms and signs were seen rarely during treatment with zimeldine but have not been reported with the newer selective serotonin reuptake inhibitors (SSRIs) and patients who had such a reaction to zimeldine did not react adversely when subsequently treated with fluoxetine (Chouinard and Jones, 1984; Montgomery *et al*., 1989).

*Nausea, vomiting* and other gastrointestinal events listed in Table 3 have previously been encountered in many trials of fluoxetine (Wernicke, 1985; Benfield *et al*., 1986; Cooper, 1988; Anonymous, 1990; Beasley *et al*., 1993; Pande and Sayler, 1992) and other SSRIs (Edwards, 1992; 1994; Edwards *et al*., 1994) and are among the most widely recognized unwanted effects of this group of drugs.

It is of concern that at least 58 women took fluoxetine during their *pregnancies* or became pregnant while on treatment. Isolated reports of abnormalities cannot prove that a drug has teratogenic properties but the findings, like those of our previous reports (Edwards *et al*., 1991, 1994), show that the important precaution of avoiding new drugs during pregnancy is being overlooked.

Fluoxetine was prescribed for patients with a wide range of concomitant physical illnesses. Many of the illnesses were serious or even terminal, as noted from the causes of death. We have no reason to suspect that fluoxetine contributed to these *deaths*.

With regard to comparisons of event rates between drugs of a similar class (in this study SSRIs), the possibility of an 'experienced prescriber bias' has to be considered. For example, nausea and vomiting observed during treatment with fluvoxamine (the first of the SSRIs referred to in this paper that was launched on to the British market) could have led to doctors withholding SSRIs subsequently introduced into practice from patients prone to gastrointestinal symptoms. This in turn could have contributed to differences in discontinuation rates; the percentages of patients still on treatment with fluvoxamine, fluoxetine and paroxetine at month 3 were: 27·6 per cent, 49·0 per cent and 53·3 per cent, respectively. The corresponding figures for month 6 were: 17·0 per cent, 32·6 per cent and 37·8 per cent.

In contrast to other areas of research, a 'negative' result revealed by PEM should be regarded as a positive finding, as it is as important to demonstrate safety as to identify untoward reactions. Our

inability to demonstrate hitherto unrecognized unwanted effects with an incidence of one or more per 3000 supports the view that fluoxetine is a safe drug, but PEM does not have sufficient power to exclude the possibility of rarer events.

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