Newer antidepressants: a comparison of tolerability in general practice

F R MACKAY

N R DUNN

R M MARTIN

G L PEARCE

S N FREEMANTLE

R D MANN

SUMMARY

Background. *An increasing number of antidepressants have been released on the United Kingdom market in recent years, and these are being prescribed more frequently in general practice. Clinical trials suggest that such agents have similar efficacy and the choice of drug is probably based on tolerability, toxicity in overdose, and cost.*

Aim. *To compare the tolerability and safety profile of six, newly marketed antidepressants used in general practice.*

Method. *Studies have been conducted for six antidepressants: fluoxetine, sertraline, paroxetine, moclobemide, venlafaxine, and nefazodone, using the technique of prescription-event monitoring. Patients were identified using incident dispensed prescription data. Questionnaires were sent to patients' general practitioners six months after the date of first prescription. Questionnaires asked for date of birth, sex, indication for prescribing each drug, and all events entered in the patients' records after the date of first prescription.*

Results. *Each cohort exceeded 10 000 patients. Nausea/vomiting was the most frequently reported event for all drugs. The difference in incidence rates for drowsiness/sedation, male sexual dysfunction, and hypertension is shown. Mortality data are also reported.*

Conclusion. *Frequently reported events were similar for all six drugs but there were clinically and statistically significant differences for less frequently reported events. The adjusted mortality rate was identical between the six drugs. This study provides valuable comparative data for six, widely used antidepressants in general practice.*

Keywords: antidepressants; general practice; patient records; tolerability.

Introduction

AN increasing number of antidepressants have been licensed for use in recent years, and such drugs are being prescribed more frequently in general practice.[1] Side-effects, particularly anticholinergic effects and weight gain, influence non-compliance, and clinical studies have shown large differences between older and newer antidepressants, with higher non-compliance rates found in patients taking older drugs.[2] Higher discontinuation rates have also been reported for tricyclic antidepressants than for selective serotonin reuptake inhibitors (SSRIs) in an observational study in general practice.[3]

Selective serotonin reuptake inhibitors, the monoamine oxidase inhibitor, moclobemide, and the two newer agents, venlafaxine and nefazodone, have all been reported to have similar efficacy to tricyclic antidepressants in clinical trials.[4-6] The choice between such antidepressants is therefore based on tolerability, toxicity in overdose, and cost. An adverse drug reaction has been defined as any noxious or unintended reaction to a drug that is administered in standard doses by the proper route for the purpose of prophylaxis, diagnosis or treatment.[7] Such reactions are common and have been reported to result in discontinuation of therapy in up to 15% of patients prescribed antidepressants in general practice.[3] Although side-effect profiles for SSRIs are broadly similar for frequently reported symptoms (e.g. gastrointestinal disturbance), differences have been reported for less frequent events such as sedation, impotence, and withdrawal symptoms.[8] Hypertension has been reported with venlafaxine[6,9] and moclobemide.[10] There have been reports of hypomania with venlafaxine,[11] and akathisia with nefazodone.[12] Such reports are often anecdotal and the incidence rates of such events are not known. The incidence rates of these events among patients prescribed other antidepressant drugs are also unknown.

Our aim was to compare the incidence rates for reported events occurring in observational cohort studies of fluoxetine, sertraline, paroxetine, moclobemide, venlafaxine, and nefazodone when used in general practice in England.

Method

We analysed the Prescription-Event Monitoring database at the Drug Safety Research Unit in Southampton. Sixty-four studies have been completed by Prescription-Event Monitoring with a mean cohort size of 10 970. The methodology of Prescription-Event Monitoring has previously been described.[8,13] Patients were identified from dispensed prescription data supplied in confidence by the Prescription Pricing Authority immediately after the launch of each drug (fluoxetine 1989, sertraline 1991, paroxetine 1991, moclobemide 1993, venlafaxine 1995, and nefazodone 1996). All patients who were dispensed each drug in the immediate post-marketing period in England were identified. Questionnaires were posted to prescribing general practitioners (GPs) six months following the first prescription for each patient. Questionnaires requested age, indication for treatment, starting and stopping dates of treatment, events during and after treatment, and reasons for discontinuation. GPs were also asked to give an opinion as to whether the drug had been effective. Identical methodology was employed for each study. An event was 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 other complaint which was considered of suffi-

F R Mackay, BM, MRCGP, clinical research fellow; N R Dunn, MA, MSc, DM, MRCGP, senior research fellow; R M Martin, BMedSci,, BM BS, MRCGP, research fellow; G L Pearce, BSc, MIInfSc, manager, data processing; S N Freemantle, BSc, systems analyst; and R D Mann, MD, FRCP, FRCGP, FRCP(Glasgow), FFPM, senior professorial fellow and director, Drug Safety Research Unit, Southampton.

Submitted: 7 July 1998; final acceptance: 21 May 1999.

cient importance to enter in the patient's notes'. One questionnaire was sent per patient and the observation period for individual patients was six months. Reported deaths, for which no cause was stated, were followed up by obtaining death certificates from the Office for National Statistics.

Analysis

Incidence rates were calculated for events reported during exposure to each study drug. The rates are expressed as the number of first reports per 1000 patient-months of treatment. Rate ratios or odds ratios were calculated using fluoxetine as the index drug. We adjusted for age (in six categories), sex, and indication (in six categories), as appropriate. Calculations were performed using STATA statistical software.[14] Those patients treated for mania, hypomania, agitation, and anxiety (pre-existing conditions) were excluded from this analysis.

Results

Response rates (the proportion of questionnaires returned) were similar for all six studies (range = 54.9% to 64.1%). Response, cohort size, and indications for prescribing the six drugs are shown in Table 1. The age and sex distributions of the cohorts were significantly different ($P<0.001$ for both variables). Depression and anxiety/depression were the main indications for which all six drugs were prescribed. More than 80% of doctors recorded their opinion about whether the drug was effective for each patient, and the results are shown in Table 1.

Percentages of patients who continued to be prescribed each drug in each month after starting treatment are shown in Figure 1. A larger percentage of patients continued with venlafaxine after six months than with the other antidepressants.

Incidence rates of the most frequently reported events in the first month of therapy are shown in Table 2. The most frequent event for all six drugs was nausea/vomiting and this was reported most frequently with venlafaxine. Comparative rates for specific events are shown in Table 3. Drowsiness and sedation were reported most frequently with nefazodone and paroxetine, and male sexual dysfunction with paroxetine and venlafaxine. There were more reports of mania during 90 days with fluoxetine than the other five drugs, even after exclusion of patients with pre-existing mania (1.2 reports per 1000 patient-months of treatment), although the difference between the numbers of reports of mania with the six drugs was not significant (χ^2 test with 5 degrees of freedom, $P = 0.06$).

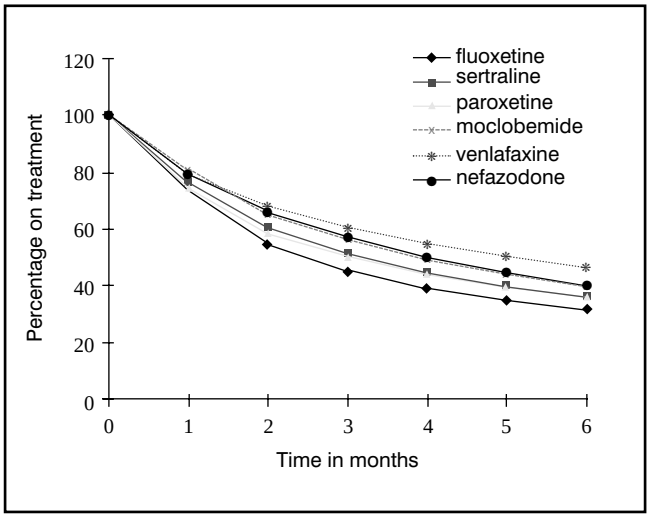

Figure 1. Duration of treatment.

Numbers of patients who died during the six-month observation periods, and odds ratios adjusted for age and sex, are shown in Table 4. There are no significant differences between the drugs after adjustment.

Discussion

Newer antidepressants have been developed 'rationally' as a result of improved understanding of central and peripheral mechanisms of action, and this has led to claims of improved tolerability and safety.[15] Guidelines for the prescribing of antidepressants balance tolerability against cost.[2] Economic modelling studies have demonstrated little overall difference in costs between antidepressants but costs are distributed between many different budgets.[2] Clinically, the choice between antidepressants probably lies in their safety and tolerability to the patient. This study compares the results of six Prescription-Event Monitoring studies, each involving cohorts in excess of 10 000 patients. The studies systematically identified patients and provided the first data for

Table 1. Cohort data.

	Fluoxetine	Sertraline	Paroxetine	Moclobemide	Venlafaxine	Nefazodone
Cohorts (Response rate)	12962	12734	13741	10835	12642	11834
	58.4%	60.2%	61.6%	64.1%	54.6%	54.9%
Males						
Number (%)	3690 (29.1)	3910 (30.7)	4373 (31.8)	3941 (36.6)	4349 (34.4)	4418 (37.3)
Mean age (SD)	50.1 (17.0)	49.2 (17.1)	48.6 (16.5)	48.9 (15.8)	47.6 (16.1)	45.5 (15.0)
Females						
Number (%)	8863 (69.8)	8729 (68.5)	9279 (67.5)	6826 (63.4)	8214 (65.0)	7347 (62.1)
Mean age (SD)	49.4 (18.1)	48.1 (18.1)	48.8 (18.0)	50.2 (17.9)	47.6 (17.9)	44.9 (16.8)
Sex not specified	139	95	89	68	79	69
Age not specified	1306	1010	1088	1328	1200	1077
Indications where specified, n	10952	10900	11886	9058	9191	8816
Depression (%)	81.9	94.5	92.7	87.1	85.5	80.2
Anxiety/depression (%)	9.3	–	–	6.4	8.9	13.7
Anxiety (%)	2.3	1.7	3.7	2.2	1.6	2.3
Others (%)	6.5	3.7	3.6	4.3	4.0	3.7
Is the treatment effective?						
Yes (%)	57.3	63.6	62.1	48.9	62.4	60.5
No (%)	42.7	36.4	37.9	51.1	37.6	39.5
Response (%)	83.4	87.3	86.4	87.9	84.1	82.2

Table 2. Most frequently reported events in the first month of treatment ranked by fluoxetine. Rate of occurrence per 1000 patient-months of treatment.

Event	Fluoxetine	Sertraline	Paroxetine	Moclobemide	Venlafaxine	Nefazodone
Nausea/vomiting	26.3	34.6	52.9	27.9	71.9	46.1
Malaise	16.3	12.0	17.8	9.9	19.0	25.0
Respiratory tract infection	12.7	9.9	11.7	9.8	8.5	13.3
Headache	12.5	13.1	13.1	23.9	20.2	25.1
Insomnia	9.4	7.9	13.0	18.7	15.0	10.2
Anxiety	8.3	2.7	4.3	8.4	11.4	9.0
Drowsiness	8.2	7.3	20.5	8.1	13.2	25.5
Diarrhoea	7.2	11.9	7.7	5.9	7.3	5.1
Dizziness	6.7	8.7	11.5	15.7	19.9	31.9
Dyspepsia	6.5	6.2	4.6	4.6	5.3	3.8
Agitation	5.9	4.9	5.0	10.0	7.5	5.3
Tremor	5.7	6.2	12.4	2.2	8.0	3.8
Abdominal pain	5.6	6.1	4.5	4.3	5.2	5.7
Suicide/parasuicide	4.7	2.7	3.1	5.5	5.6	3.9

Table 3. Reported rates per 1000 months of exposure, and rate ratios, for events of specific interest.

	Number of patients with one or more episode	Patient-months of exposure	Rate	Rate ratio (95% CI) adjusted for age, sex (where appropriate) and indication
Agitation/anxiety				
Fluoxetine	208	47 078	4.4	1.0
Sertraline	132	60 531	2.2	0.6 (0.4–0.7)
Paroxetine	163	63 498	2.6	0.6 (0.5–0.8)
Moclobemide	278	48 260	5.8	1.3 (1.1–1.6)
Venlafaxine	264	55 255	4.8	1.1 (0.9–1.3)
Nefazodone	217	53 084	4.1	0.9 (0.7–1.1)
Drowsiness/sedation				
Fluoxetine	111	47 279	2.3	1.0
Sertraline	105	60 621	1.7	0.7 (0.5–0.9)
Paroxetine	286	63 511	4.5	2.0 (1.6–2.5)
Moclobemide	111	48 516	2.3	1.0 (0.7–1.3)
Venlafaxine	183	55 440	3.3	1.4 (1.1–1.8)
Nefazodone	318	53 103	6.0	2.2 (1.7–2.8)
Impotence/ejaculation failure				
Fluoxetine	3	14 182	0.2	1.0
Sertraline	13	19 644	0.7	3.1 (0.9–10.9)
Paroxetine	54	21 212	2.5	11.1 (3.5–35.8)
Moclobemide	3	18 669	0.2	0.5 (0.1–2.9)
Venlafaxine	30	19 995	1.5	5.8 (1.8–19.3)
Nefazodone	16	20 846	0.8	2.0 (0.6–7.5)
Hypertension				
Fluoxetine	32	47 202	0.7	1.0
Sertraline	12	60 635	0.2	0.3 (0.2–0.6)
Paroxetine	18	63 612	0.3	0.5 (0.3–0.9)
Moclobemide	13	48 588	0.3	0.5 (0.2–0.9)
Venlafaxine	34	55 443	0.6	1.0 (0.6–1.7)
Nefazodone	16	53 342	0.3	0.4 (0.2–0.7)

Table 4. Number of deaths and odds ratios with fluoxetine as index drug.

Drug	Number of deaths in first six months	Unadjusted odds ratio (95% CI)	Odds ratio (95% CI) adjusted for age and sex
Fluoxetine	228	1.00	1.00
Sertraline	230	0.79 (0.66–0.94)	0.97 (0.73–1.30)
Paroxetine	249	0.79 (0.66–0.94)	0.98 (0.74–1.30)
Moclobemide	130	0.52 (0.42–0.64)	0.96 (0.72–1.30)
Venlafaxine	162	0.56 (0.46–0.68)	1.00 (0.75–1.34)
Nefazodone	109	0.40 (0.32–0.50)	0.78 (0.55–1.09)

national cohorts who were dispensed each drug immediately after launch on the United Kingdom market. The value of the data is that large cohorts in a well-defined population have known exposure data. Non-compliance with antidepressants has been reported to be as high as 50%.[2] Prescription-Event Monitoring studies are based on dispensed prescription data and, although these hold no guarantee of compliance, they are superior to information based on the number of prescriptions only.[16]

Possible sources of bias

The response rates for the studies of venlafaxine and nefazodone were slightly lower than for the four other studies. The response rates for all six studies were acceptable when compared with general practice surveys in general,[17] and GPs were not paid for completing questionnaires. It could be argued that the population of patients registered with non-responder doctors experienced different events from patients whose doctors did respond. This is unlikely in reality. The principal factor associated with response rates has been shown to be the number of questionnaires sent to each doctor.[18] Any potential response bias is likely to have affected all six studies comparably and a bias operating differentially is unlikely.

The six antidepressants were marketed sequentially and studies were conducted between 1989 and 1996/7. A new comparative exercise would not guarantee incident prescriptions of drugs. Patients who experience an adverse reaction are unlikely to receive a second course of treatment. Studies based on non-incident prescriptions could involve a greater proportion of patients who have already tolerated the drug. One advantage of our comparison is that these studies were not affected by such 'survival bias'.

Antidepressants may be withdrawn if treatment is effective, if treatment is ineffective, or the drugs are not tolerated. Prescription-Event Monitoring studies cannot provide a formal measure of clinical efficacy. Nevertheless, each GP's opinion about effectiveness is probably the single, most important factor that will determine whether treatment is continued. Disadvantages of comparing sequential studies include possible selection bias as doctors became accustomed to using the drugs for specific groups of patients and changes in prescribing behaviour.

A consensus agreement for the recognition and management of depression in general practice was published in 1992 and recommends that antidepressant therapy should continue for four to six months after the successful treatment of the acute episode in order to prevent relapse.[19] The percentages of patients who continued with treatment between four and six months were lowest for fluoxetine, sertraline, and paroxetine. These three drugs were considered by GPs to be no less effective than the subsequent three antidepressants. These three studies were conducted before 1992 and the results may therefore reflect a change in prescribing policy rather than difference in tolerability or effectiveness.

A further bias would have resulted if doctors increasingly recognized and reported adverse events already known to be associated with antidepressants. Examination of sequential Prescription-Event Monitoring studies for angiotensin-converting enzyme inhibitors suggested such a reporting bias for cough.[20] However, no obvious reporting bias occurred for sequential studies of non-steroidal anti-inflammatories and proton pump inhibitors, and the reporting of 'non-publicized' events appears to be unaffected by order of drug release on the market. Prescription-Event Monitoring studies are conducted in the immediate post-marketing period of new drugs, often when there is comparatively little publicized data on tolerance, and doctors are not asked to give an opinion about the causality of any event. These studies are capable of detecting unsuspected drug reactions and are least likely to be affected by publicity bias.

The events

Nausea/vomiting was the commonest reported event with all six drugs, and most frequent with venlafaxine. Drowsiness/sedation was reported most frequently with paroxetine and nefazodone. These drugs may be advantageous for improving sleep. The incidence rates for agitation and anxiety were significantly lower for sertraline and paroxetine than the other drugs. Previous reports have suggested an association between fluoxetine and the precipitation of manic/hypomanic episodes.[19] After exclusion of all patients with pre-existing mania, hypomania, or bipolar affective disorder (as indications), the incidence rate for mania was highest with fluoxetine; however, the difference between the numbers of reports for each drug was small and not statistically significant.

Hypertension has been reported with venlafaxine and moclobemide.[6,9,10] Prescribing information for venlafaxine recommends routine blood pressure monitoring for those patients taking more than 200 mg daily.[9,23] The dose-dependent increase in blood pressure with venlafaxine is thought to be associated with inhibition of the norepinephrin-uptake pump at higher doses and its action as an indirect adrenergic agonist.[15] Although there were statistically significant differences between the drugs in the rate of reported hypertension, the number of events was small and it would be unwise to assume that this result has clinical importance.

Fluoxetine, sertraline, paroxetine, and venlafaxine all inhibit neuronal reuptake of serotonin and might be expected to cause some degree of male sexual dysfunction.[15] Such problems are probably under-reported if patients are uncomfortable about discussing them. Adverse effects on sexual function can also appear to occur relatively late because they are not an issue until after the depression has appreciably improved.[15] Nefazodone is thought to cause less sexual dysfunction than other antidepressants.[2,15] Fluoxetine and moclobemide had the lowest reported rates of male sexual dysfunction, although, again, the number of events was small, with wide confidence intervals for the rate ratios.

The differences in crude numbers of deaths occurring as a result of illness in the first six months of treatment with each drug seemed substantial. However, adjustment for age and sex showed that these were entirely due to confounding, and the adjusted odds ratios for mortality were, in fact, identical.

Conclusion

This study compares event data for six antidepressants studied by Prescription-Event Monitoring. The design of the study has particular strengths. The cohorts were large, comparable in terms of indications for prescribing, and exposure is based on incident dispensed prescription data. Nausea/vomiting was the most frequently reported event with all six drugs. Drowsiness/sedation was more frequently reported with nefazodone and paroxetine, and male sexual dysfunction was reported more frequently with paroxetine and venlafaxine. Incidence rates for hypertension were similar for venlafaxine and fluoxetine and higher than for the other four drugs. One disadvantage of this study was that the comparison was based on sequential cohort studies. Differences in duration of therapy may be associated with changes in doctors' prescribing behaviour as a result of clinical guidelines.

References

1. Donoghue J, Tylee A, Wildgust H. Cross sectional database analysis of antidepressant prescribing in general practice in the United Kingdom, 1993-5. *BMJ* 1996; **313:** 861-862.

2. Hale AS. ABC of mental health: Depression. *BMJ* 1997; **315:** 43-46.
3. Martin RM, Hilton SR, Kerry SM, Richards N. General practitioners' perceptions of the tolerability of antidepressant drugs: a comparison of selective serotonin reuptake inhibitors and tricyclic antidepressants. *BMJ* 1997; **314:** 646-651.
4. Song F, Freemantle N, Sheldon T, *et al*. Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *BMJ*. 1993; **306:** 683-687.
5. Freeman H. Drug Profile: Moclobemide. *Lancet* 1993; **342:** 1528-1532.
6. Medicines Resource Centre. Citalopram, nefazodone and venlafaxine: three new antidpressants. *MEREC Bulletin* 1996; **7(2):** 1-3.
7. Vervloet D, Durham S. Adverse reactions to drugs. *BMJ* 1998; **316:** 1511-1514.
8. Mackay FJ, Dunn NR, Wilton LV, *et al*. A comparison of fluvoxamine, fluoxetine, sertraline and paroxetine examined by observational cohort studies. *PDS* 1997; **6:** 235-246.
9. Anonymous. *Efexor (venlafaxine hydrochloride).* [Data sheet.] Maidenhead: Wyeth Laboratories, December 1994.
10. Laux G, Philipp M, Kohnen. Hypertension with moclobemide. *Lancet* 1996; **347:** 1330.
11. Wilson R, Jenkins P. Suspected complication of treatment with venlafaxine. *J Clin Psychopharmacol*. 1997; **323:** 17.
12. Eberstein S, Adler LA, Angrist B. Nefazodone and akathisia. *Biological Psychiatry* 1996; **40:** 798-799.
13. Mann RD, Wilton LV, Pearce GL, *et al.* Prescription-Event Monitoring (PEM) in 1996 - A method of non-interventional observational cohort pharmacovigilance. *PDS* 1997; **6(suppl 3):** S5-S11.
14. StataCorp. *Stata Statistical Software: Release 5.0* College Station, TX: Stata Corporation, 1997.
15. Preskorn SH. Comparison of the tolerability of Bupropion, Fluoxetine, Imipramine, Nefazodone, Paroxetine, Sertraline and Venlafaxine. *J Clin Psychiatry* 1995; **56(suppl 6):** 12-21.
16. Beardon PHG, McGilchrist MM, McKendrick AD, *et al.* Primary non-compliance with prescribed medication in primary care. *BMJ* 1993; **307:** 846-848.
17. McAvoy BR, Kaner EFS. General practice postal surveys: a questionnaire too far? *BMJ* 1996; **33:** 732-733.
18. Inman W, Pearce G. Prescriber profile and post-marketing surveillance. *Lancet* 1993; **342:** 658-661.
19. Paykel ES, Priest RG. Recognition and management of depression in general practice: consensus statement. *BMJ* 1992; **305:** 1198-1202.
20. Wilton LV, Pearce GL, Mann RD. Cough with ACE Inhibitors: an example of reporting bias in observational cohort studies. *PDS* 1996; **5(suppl 1):** S13.
21. Peet M. Induction of mania with selective serotonin reuptake inhibitors and tricyclic anti-depressants. *Br J Psychiatry* 1994; **164:** 549-550.
22. Feder R. Fluoxetine induced mania. *J Clin Psychiatry* 1990; **51:** 524-525.
23. British Medical Association and Royal Pharmaceutical Society of Great Britain. Venlafaxine. In: *British National Formulary*. London: BMA and RPSGB, 1996; 179-180.

Acknowledgements

We would like to thank all the GPs and doctors who volunteered their help and support for these studies, without whom Prescription-Event Monitoring would not be possible. We would also like to record our appreciation of the Prescription Pricing Authority, the Health Authorities of England, and the Office for National Statistics for their participation.

Address for correspondence

Dr N R Dunn, Drug Safety Research Unit, Bursledon Hall, Southampton SO31 1AA, UK. E-mail: ndunn@dsru.u-net.com