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Prescription-Event Monitoring of 10 895 Patients Treated with Alprazolam

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'Prescription-event monitoring' (PEM) is one of two national systems of post-marketing surveillance in operation in Britain. It identified 22 065 patients who had received NHS prescriptions for alprazolam, and data available on 10 895 of these were analysed. The main reasons for treatment with alprazolam were anxiety and depression. The patients provided 3360 patient-years of treatment and 7540 patient-years of follow-up. No serious events clearly associated with treatment were recorded. The main events reported during treatment, albeit infrequently, were drowsiness and depression, although depression is more likely to be due to the disorder being treated than to the drug. Some of the other alleged unwanted effects of alprazolam in published reports were not encountered. Since PEM is unable to determine the dependence potential of alprazolam, further evaluation of this problem is called for.

Alprazolam is a triazolobenzodiazepine which, like other benzodiazepines, has antianxiety, anticonvulsant and muscle-relaxant properties (Dawson *et al*, 1983). In contrast to other benzodiazepines, it has been shown in placebo-controlled trials to have antidepressant properties (Feighner *et al*, 1983; Rickels *et al*, 1985, 1987). No serious unwanted effects were encountered in these or in other controlled studies (Rickels *et al*, 1982; Rush *et al*, 1985; Weissman *et al*, 1985; Overall *et al*, 1987), but even in trials involving relatively large numbers of patients, such as that of Rickels *et al* (1987), in which 241 patients were included (with 58 being randomly allocated to the alprazolam group), the chances of discovering an uncommon or rare effect are small. To encounter a unique reaction occurring with a frequency of 1 in 1000 cases, 3000 patients would have to be included in the trial for the reaction occurring just once to be detected with 95% confidence. For a reaction occurring with a frequency of much less than this in a population with an appreciable background incidence of the reaction, hundreds of thousands, if not millions, of patients would have to be included for the reaction to be detected with the same confidence (Lewis, 1981). The problem is compounded by the fact that the vast majority of clinical trials are of short-term treatment, lasting only a few weeks, some even shorter, giving an exposure to the drug of only a few patient-years. To help overcome these difficulties, large-scale systems of safety monitoring have been designed and we report here the results of 'prescription-event monitoring' (PEM) of a large cohort of patients treated with alprazolam.

We studied 10 895 patients treated with alprazolam for a mean of 3.7 months, giving a treatment exposure of 3360 patient-years. The patients were subsequently monitored for an average of 8.3 months, giving 7540 patient-years of follow-up.

Method

The Drug Safety Research Unit (DSRU) carries out PEM. This, and the 'yellow-card' system of the Committee on the Safety of Medicines (CSM), are two complementary national systems of drug safety monitoring in Britain. The DSRU is a registered charity, associated with the University of Southampton, that carries out independent non-promotional post-marketing surveillance of most new compounds introduced into clinical practice in the UK, and also of older products that have been suspected of causing particular problems. About 70% of the 23 000 general practitioners in Britain provide data on patients (see below), reflecting prescribing in the 'real world' rather than under the artificial conditions of a clinical trial. The population surveyed is about ten times larger than in any other system in the world.

Patients receiving alprazolam and the family physicians who prescribed for them were identified by the Prescription Pricing Authority (PPA). The PPA was set up by the Secretary of State to remunerate pharmacists for the medicines they dispense and to provide the Department of Health and local family practitioner committees (FPCs) with information on the quantity and cost of drugs provided under the British National Health Service. Prescriptions are processed by 11 processing divisions throughout England. In 1983/84 (the period when our study was carried out) they dealt with more than 300 million prescription items, costing £1.3 billion per year (PPA, personal communication 1985).

The PPA provided the DSRU with photocopies of 127 803 prescriptions for alprazolam written by family practitioners throughout England between 1983 and 1984. These were sorted into the 90 FPC areas and legible prescriptions written by doctors for up to a maximum of four patients per practitioner were selected for the study.

The names and addresses of the doctors were checked against the DSRU's register of doctors and 8727 practitioners were sent 'green-form' questionnaires on which they were asked to provide data on 22065 patients.

The practitioners were asked to record on the questionnaire any event that occurred during or following treatment with the drug. An 'event' was defined as any new diagnosis, any reason for a referral to a consultant or admission to hospital, any unexpected deterioration or improvement in a concurrent illness, any suspected drug reaction, or any other symptom or non-medical event that was considered of sufficient importance to be entered on the patient's records. The doctor was not required to decide if there was a causal connection between the event and the drug treatment, as this might have been dependent on preconceived ideas and could possibly have influenced the reporting of events. Wherever possible all recorded events were matched with those in an 'event dictionary' (created while processing 130 000 green forms) and then categorised into 'event groups' based on the physiological system they predominantly affect (see Table 2). Details of concurrent medication were obtainable from the copies of the prescriptions. Information provided was treated in strict confidence. Further details of the PEM method have been reported by Inman *et al* (1986).

Table 1
Sex, age, duration of treatment and length of follow-up

	Men (n = 2842)	Women (n = 7985)	Total (n = 10895[1])
Age: years			
mean	48.5	48.3	48.3
s.d.	16.1	16.6	16.4
Duration of treatment: months			
mean	3.8	3.7	3.7
s.d.	4.2	4.2	4.2
range	1-20	1-19	1-20
Length of follow-up: months			
mean	8.4	8.2	8.3
s.d.	3.8	3.7	3.8
range	1-20	1-22	1-22

1. The sex of 68 of the patients was not recorded.

Results

Of the 22 065 green forms sent to family doctors, 12 573 were returned, giving a response rate of 57%. Of these, 1678 did not provide useful information; 10 895 (49% of the original sample) were thus available for analysis.

The age and sex of the patients, duration of treatment and length of follow-up are shown in Table 1. The female:male ratio is 2.8:1.

The ages and duration of the treatment and length of follow-up are similar for each sex. In the case of 7334 patients on whom information concerning the indications

Table 2
Events occurring during and after treatment

Event group	Rate of events per 1000 patients		Rate of events per 1000 patient-years	
	during treatment	after treatment	during treatment	after treatment
Neuropsychiatric	99.4	62.4	322.3	90.2
depression	11.5	12.8	37.2	18.6
drowsiness	11.5	0.4	37.2	0.5
headache	10.2	8.3	33.0	11.9
dizziness	7.5	4.2	24.4	6.1
insomnia	7.3	5.3	23.8	7.7
malaise	6.9	2.4	22.3	3.4
sedation	5.3	0.1	17.3	0.1
Gastrointestinal	66.2	50.8	214.6	73.5
Respiratory	56.7	69.2	183.9	100.0
Non-medical events	45.4	36.1	147.3	52.1
Musculoskeletal	33.8	39.2	109.5	56.6
Dermatological	26.5	24.5	86.0	35.4
Gynaecological	26.3	32.6	85.4	47.1
Cardiovascular	20.8	18.9	67.6	27.3
Accidents	15.6	16.9	50.6	24.4
Renal (including genito-urinary male)	14.8	13.9	47.9	20.0
Worsening of disease	14.3	17.5	46.4	25.3
Auditory	8.0	8.7	25.9	12.6
Ophthalmic	7.5	8.1	24.4	11.7
Deliberate overdose	6.8	2.8	22.0	4.0
Surgical	6.0	10.6	19.3	15.4
Metabolic	5.5	3.1	17.9	4.5

The following had less than 3 events per 1000 patients and less than 8 events per 1000 patient-years on treatment: hepatic, endocrine, haematological, pregnancy, congenital abnormalities, malignant neoplastic, benign neoplastic, accidental overdose, other unclassified.

for prescribing alprazolam was provided, 70.8% (71.4% of men, 70.6% of women) were given the drug for anxiety, 16.4% (15.0% of males, 16.9% of females) for depression, and the remainder for various other conditions.

The events categorised into the individual 'event groups' and expressed as the number per 1000 patients and 1000 patient-years are summarised in Table 2. More events were reported during treatment than during follow-up, but the incidence of individual events was low. Not surprisingly when dealing with a psychotropic drug, neuropsychiatric events were reported most often. The most common of these were drowsiness and depression, each accounting for 11.5% of the total number of neuropsychiatric events (2.5% of all events), but even these were reported with only a frequency of 11.5 per 1000 patients, 37.2 events per 1000 patient-years. Depression was also the most common (although infrequent) event reported in follow-up (incidence 12.8 per 1000 patients, 18.6 per 1000 patient-years), but drowsiness was reported with only a frequency of 0.4 per 1000 patients, 0.5 per 1000 patient-years during this period. Four patients had 'convulsions, unspecified', eight 'major convulsions' and one 'minor convulsions' during treatment, the corresponding figures following treatment being six, five and nil respectively.

No other individual event occurred with a high frequency or much more often during treatment than after.

Seventy-five patients took deliberate overdoses of drugs during treatment with alprazolam, giving a rate of 6.8 per 1000 patients, 22.0 per 1000 patient-years. This is to be compared with 34 overdoses – 2.8 per 1000 patients, 4.0 per 1000 patient-years – during follow-up. Fifty-four of these 75 patients took overdoses of alprazolam together with other drugs and one of them died. None of the 21 patients who took overdoses of alprazolam alone died. Two other patients killed themselves while on alprazolam and three others killed themselves during follow-up, but the way in which they took their lives was not specified in the green forms.

Twenty-one pregnancies were recorded during the treatment period and there was one case of congenital abnormality – recorded as 'multiple abnormalities'. Unfortunately, no further information concerning the case was provided on the green form.

Discussion

This PEM study was the first one carried out in the DSRU on a psychotropic drug and we therefore do not have comparative data on similar drugs. We are, however, conducting larger studies of other psychotropic drugs, and these will allow for interesting future comparisons. Other limitations of the study are uncertainty as to the degree of compliance with treatment – although most patients are presumed to have taken their drugs as they return for repeat prescriptions and have to pay prescription charges – and the low response rate. The latter suggests the possibility that physicians whose patients had drug-related problems were less likely to return the questionnaires, but we have learnt from previous experience with other (non-psychotropic) drugs that more likely reasons for not returning the green forms were patients leaving practices or being temporary residents and doctors themselves changing practices. Some practitioners may not have been able to identify their patients from the information provided on the form, since this is reliant on the legibility of the photocopied prescriptions. Less than one doctor in 200 had previously indicated that they did not wish to participate in PEM through fear of breach of confidentiality and consequent damage to the doctor–patient relationship, even though strict confidentiality has been guaranteed since the inception of the DSRU.

Prescription-event monitoring is able to identify unique events that occur with a frequency of more than one in 3000 patients. It is meant to complement, rather than substitute for, the yellow-card system of the CSM that screens larger populations for many years after a drug has been marketed, thereby allowing for the detection of rarer events. Neither should it be regarded as a substitute for isolated case reports in the literature, although in these there are particular difficulties in establishing a cause-and-effect relationship (Edwards, 1981).

Prescription-event monitoring helps to identify important events by noting higher rates of occurrence during treatment than after treatment. These act as signals that help shorten the long delay in recognition of adverse drug reactions that has occurred so often in the past. The ratios of drug related events on:off treatment are rarely less than 2–3:1 and most have a ratio of 8–10:1. Clues to a causal connection may also be obtained from comparisons between drugs. We know from previous studies that many events are reported regardless of which drug is being investigated, while drug-induced reactions stand out against this background low incidence of unrelated events.

It is theoretically possible to quantify the probability of a particular event as being drug-related by using a causality-assessment algorithm, but this requires knowledge of several factors that are often not available from the green forms (Rawson, 1987). To obtain this information extensive follow-up is required. It would be impracticable to follow-up all events, although those of particular importance or scientific interest can be investigated further as separate studies.

Despite its limitations, the present study is the largest survey of the safety of a psychotropic drug that has ever been carried out, and there are no other comparable data on such a large cohort – almost 11 000 patients. PEM is not meant to provide an

accurate measure of incidence, but aims at identifying uncommon adverse drug reactions that are unlikely to be found in clinical trials, and at generating hypotheses on the relationship between events and drug treatment, rather than answering all the questions we would like answered. Frequent side-effects that are not serious are likely to be underestimated, because patients do not always report them to their general practitioner, and a proportion of those that are reported are not recorded in their doctor's case records.

The greater number of women than men who received prescriptions for alprazolam in our study presumably reflects the higher prevalence of affective symptoms in females (Boyd & Weissman, 1982) and the fact that psychotropic drugs are prescribed more often for women than for men (Balter *et al*, 1984). The main reason why more events were recorded during treatment than during follow-up is that, after treatment, patients attended their family doctors less frequently for repeat prescriptions and there were therefore fewer opportunities for the doctors to ask about their health and to record events.

Depression was the most frequently encountered event. It has previously been regarded as an unwanted effect of diazepam (Ryan *et al*, 1968; Hall & Joffe, 1972; Danielson *et al*, 1981), but critical reviews of the evidence in support of this allegation (Johnson, 1983; Edwards, 1989) have suggested more likely causes, especially the psychiatric disorder for which the drug was prescribed. Although depression can lead to attempted or successful suicide, and such events were reported during our study, their occurrence during follow-up lends support to the view that they are more likely to be due to the underlying illness than to alprazolam.

There have been a number of published reports of mania (France & Krishnan, 1984*a*; Arana *et al*, 1985; Goodman & Charney, 1987) and hostility (Rosenbaum *et al*, 1984; Rapaport & Braff, 1985; French, 1989) during treatment with alprazolam. In our study mania was reported in three patients during treatment (none following treatment), while aggression was noted in nine (two following treatment). There is disagreement as to whether or not antidepressants cause a switch from depression to mania, but in a study of patients treated between 1920 and 1981, Angst (1987) showed that the proportion who changed from depression to mania did not significantly increase after the introduction of antidepressants into clinical practice in the 1950s. Soloman *et al* (1990) compared the drug treatment that patients with bipolar affective disorder were receiving at the time of switching from depression to mania with the drugs they received on admissions when there was no switch. They concluded that switches occurred regardless of the treatment status. Both studies suggest that mania is more likely to be due to a spontaneous swing than to be drug-induced.

Drowsiness was the second most frequently reported event, and this occurred more often during than after treatment. Confusion, however, was only encountered in one patient, although it has previously been reported as an unwanted effect of alprazolam (France & Krishan, 1984*b*). Oversedation and other disturbed mental states have long been considered as contributing factors to accidents. Although there was a higher incidence of accidents per 1000 patient-years during treatment than during follow-up in our study, the incidence per 1000 patients was similar. Alprazolam has been shown to cause impairment of memory acquisition and retrieval (Block & Berchou, 1984), but PEM identified no complaints of memory disturbance.

There was a low incidence of autonomic nervous symptoms and the incidence of cardiovascular events during treatment was similar to that found after treatment. This is in keeping with the fact that benzodiazepines in general are not considered to cause troublesome autonomic symptoms or to be cardiotoxic.

Ejaculatory inhibition (Munjack & Crocker, 1986) and sexual dysfunction (Sangal, 1985; Lydiard *et al*, 1987) have previously been reported as unwanted effects of alprazolam. PEM identified impotence in two patients during treatment with alprazolam and in three patients after treatment. This disorder is more likely to be related to the underlying illness, or to be a coincidental finding, than a consequence of treatment.

We received two separate reports of liver disease – one of hepatitis and one of hepatomegaly – but we also had a case of jaundice and another of hepatomegaly after treatment. With such a low incidence and the occurrence of these events after treatment, we cannot confidently incriminate alprazolam. This holds true also for the two cases of alprazolam-related hepatitis that have appeared in the literature (Roy-Byrne *et al*, 1983; Judd *et al*, 1986).

At the time our study was carried out, our system of follow-up was not as highly developed as it is at present, and there was inadequate information on the green form concerning the case of congenital abnormalities. However, no conclusions can be drawn from an isolated report of this kind and there have been no subsequent publications suggesting that alprazolam has dysmorphogenic properties.

During recent years concern has been expressed over dependence on, and problems of withdrawing

from, alprazolam (Breir *et al*, 1984; Levy, 1984; Browne & Hauge, 1986; Fyer *et al*, 1987). In the present study we did not encounter a high incidence of events similar to the symptoms seen on discontinuing benzodiazepines (including convulsive seizures) during follow-up, although PEM would only be able to recognise dependence if continued for a longer period and if it sought further details such as mode of discontinuation.

If it is true that alprazolam is as effective as the tricyclic antidepressants in the treatment of major depression, it will have an advantage over these drugs in not having troublesome autonomic and cardiotoxic effects (Burgess & Turner, 1981; Warrington *et al*, 1989) or causing convulsive seizures (Edwards *et al*, 1987). Against these possible advantages, however, is the risk of dependence, which calls for further evaluation.

Overall, our results show that serious events, including uncommon adverse drug reactions, do not occur during treatment with alprazolam to any great extent.

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