LEADING ARTICLE

Drug Safety 1998 Nov; 19 (5): 343-353
0114-5916/98/0011-0343/$05.50/0

Post-Marketing Studies

The Work of the Drug Safety Research Unit

Fiona Jean Mackay

Research Fellow, Drug Safety Research Unit, Southampton, England

Abstract

The Drug Safety Research Unit (DSRU) is the centre for prescription-event monitoring (PEM) in England. PEM studies are noninterventional observational cohort studies which monitor the safety of newly marketed drugs. The need for post-marketing surveillance is well recognised in the UK and general practice is an ideal source of data.

PEM studies are general practitioner (community)-based and exposure is based on dispensed prescription data in England. To date, 65 PEM studies have been completed with a mean cohort size of 10 979 patients and the DSRU database has clinical information on over 700 000 patients prescribed new drugs. Unlike spontaneous reporting schemes, PEM produces incidence rates for events reported during treatment. Comparative studies can be conducted for drugs in the same class. The DSRU aggregates outcome data for pregnancies exposed to new drugs. Data for children and the elderly can also be specifically examined. PEM data have a number of advantages over data from computerised general practice databases in the UK. PEM is the only technique within the UK capable of monitoring newly marketed drugs in such a comprehensive and systematic way.

The Drug Safety Research Unit (DSRU) in the UK has been conducting post-marketing safety studies since 1980[1,2] and operates in association with the University of Southampton. The DSRU is a registered independent charity. It is the centre for prescription-event monitoring (PEM) in England. The unit is expanding and currently employs 5 full-time research staff and over 28 additional staff to manage data handling, information technology, administration and secretarial duties. The DSRU conducts a variety of pharmacoepidemiological projects including case control studies.[3] PEM is the principal activity of the DSRU however, and this article will focus on the value of PEM.

The need for effective post-marketing surveillance in the UK is well recognised.[4,5] The median number of patients included in pre-marketing safety studies of drugs released on the UK market between 1987 and 1989 was 1528.[6] This number will not usually allow the detection of rare (even lethal) adverse effects with a prevalence of less than 1 in 500. In addition, pre-marketing trials usually involve highly selected patients studied for relatively short periods.

General practitioners (GPs) in the UK deal with most episodes of patient illness and have records of patient illnesses treated elsewhere. General practice is therefore the most obvious source of patient data for epidemiological studies in the UK.[7]

Adverse effects constitute a wide range of complaints and many different mechanisms are involved. A single approach to the detection of all adverse events is impractical.[8] Different adverse

effects need different methods of detection. A variety of post-marketing surveillance techniques has been developed within the UK using different sources of data, and 2 techniques are suitable for the monitoring of new drugs. They are the 'yellow card' scheme and PEM.

1. The 'Yellow Card' Scheme

The 'yellow card' scheme for reporting suspected adverse drug reactions was developed by the Committee on Safety of Drugs (later Medicines) [CSM] in 1964. Newly marketed drugs are recognised by a black triangle in UK prescribing information. Doctors, dentists, pharmacists and coroners are requested to identify all suspected adverse reactions to newly marketed drugs, however minor, to the Committee on Safety of Medicines via the 'yellow card' scheme. Spontaneous reporting schemes are probably the only practical method of obtaining adverse drug reaction data for all drugs all of the time. In addition, such schemes have proven effective.[9]

All spontaneous reporting schemes have important limitations however, and the 'yellow card' scheme has been associated with substantial underreporting. In the past, fewer than 10% of all reactions have been reported.[10] Reasons for underreporting by doctors include lack of time, lack of report forms and the misconception that absolute confidence in the diagnosis of an adverse drug reaction is important.[11] Biased reporting also occurs, e.g. adverse drug reactions are reported more frequently with new drugs than old drugs, with the greatest number of adverse drug reactions being reported within 2 to 3 years after release on the market and increased reporting associated with publicity.[12] These limitations, along with the lack of denominator figures for the calculation of incidence rates dictate the need for a complementary drug surveillance system.

2. Prescription-Event Monitoring (PEM)

PEM is quite different from spontaneous reporting schemes. PEM studies are noninterventional observational cohort studies conducted in general practice. The methodology of PEM has been well described.[13-15] Briefly, patients are identified from electronic prescription data, supplied in confidence by the Prescription Pricing Authority (PPA) immediately after the launch of a monitored drug in the UK (fig. 1). Pharmacists send the PPA a record of all dispensed National Health Service prescriptions for reimbursement purposes. Prescription data supplied to the DSRU include the name of the patient and the prescribing GP. Questionnaires ('green forms') are usually sent to each

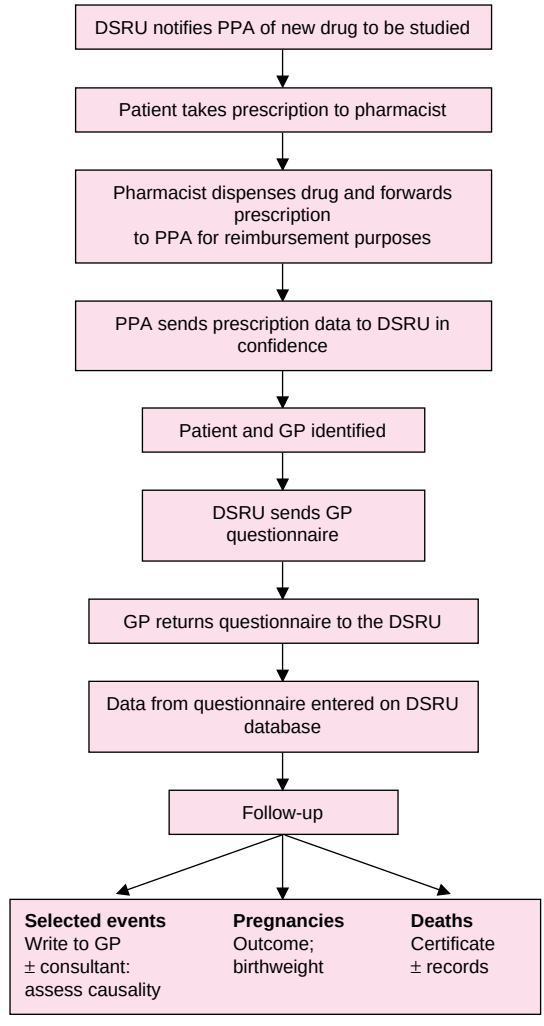

Fig. 1. Prescription event monitoring in England. **DRSU** = the Drug Safety Research Unit; **PPA** = Prescription Pricing Authority.

prescribing GP 6 months following the first prescription for each patient. Questionnaires request patient age, indication for treatment, starting and stopping dates of treatment, dosage, events during and after treatment and reasons for discontinuation. Questionnaires are customised for each drug and additional questions can be added. One questionnaire is sent per patient and no GP is sent more than 4 'green forms' in 1 month.

An 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, any alteration of clinical importance in laboratory values, or any other complaint which was considered of sufficient importance to enter in the patient's notes'. The exposure data are the dispensed prescription data. Incidence rates are calculated for all reported events. Events of particular importance (e.g. serious drug reactions, pregnancies during treatment and deliberate or accidental overdoses) are followed up by writing to the patients' GPs for additional information. Long-latency events have also been investigated by sending long term follow-up questionnaires a year or more later. The first study to use this technique achieved a response rate in excess of 80%.[16]

PEM studies are conducted in accordance with the International Ethical Guidelines for Biomedical Research.[17] Patients are allocated a unique identification number and the section of the 'green form' returned to the DSRU is identifiable only by this number. Data are stored on the DSRU database using only the identification number.

The DSRU selects drugs for PEM which widespread general practice use is anticipated. Priority is given to drugs in a novel class and to those intended for long term use. Ideally, drugs should be intended for monotherapy although successful studies have been conducted on drugs licensed for 'add-on therapy'.[16]

2.1 The Value of PEM

There have been 65 PEM studies completed to date, with a mean cohort size of 10 979 patients. PEM studies are therefore large, national in scale and add considerably to the pre-existing safety data for newly marketed drugs. The DSRU database now has clinical data on over 700 000 patients. Studies are systematic in the sense that all patients dispensed a newly marketed drug in England are identified. PEM does not influence the doctor's choice of medication to be prescribed to each individual patient and therefore the method is non-interventional.

In common with the yellow card scheme, PEM studies are essentially hypothesis-generating and aim to exclude or identify serious adverse reactions. PEM studies provide relative incidence rates for events reported in 'every day' practice and allow contextual comparisons to be made. For example, the incidence of rash during treatment with lamotrigine can be compared with the incidence of other adverse effects.[13,16] Incidence figures can be calculated for any time period on or off treatment and for specific age groups or gender. In order to investigate specific events of interest, crude background rates can be calculated from reports of the event occurring after stopping treatment or reports occurring in comparable patients not exposed to the drug.[18] Incidence rates can be examined against time after exposure.

PEM data for drugs in the same class can be compared e.g. fluvoxamine, fluoxetine, sertraline and paroxetine.[19] Differences in rates can be adjusted for patient age and gender, indications for prescribing and other confounding variables.

In addition to examining specific drugs, it is possible to use the extensive DSRU database to examine rare events or medical conditions of importance. The DSRU collected clinical data on 12 patients with Stevens-Johnson syndrome (SJS) during the lamotrigine study in 1996. Ten patients required hospitalisation, 9 of the 12 took concomitant valproic acid and 5 of the 12 were aged less than 8 years. In 1996 the DSRU database held data for 49 other completed PEM studies. There were 7 additional reports of SJS on the database and in 1 of these reports, SJS was also associated with lamotrigine.[16]

Many drugs are not licensed for use during pregnancy. Exposure to frequently prescribed drugs (often accidental) does occur during pregnancy and such cases reported to the DSRU are prospectively followed up. The outcomes of such pregnancies have been reported.[20] 831 pregnancies were exposed during the first trimester and only 74 during the second or third trimester. This implies that doctors rarely prescribe new drugs during known pregnancy. At the time of reporting first trimester pregnancies on 'green forms' the outcomes are unknown by GPs. There is no bias as a result of selectively reporting abnormal outcomes. The numbers of reported pregnancies involved are too small for detailed statistical analysis but the outcome data are qualitatively important as these may be the only aggregated data for exposure during human pregnancy.

PEM studies collect data on use of newly marketed drugs in children. Unlicensed and 'off-label' use of drugs occur in this group.[21] The main indications for prescribing risperidone in children were found to be different from those in adults[22] and the use of risperidone in this age group was unlicensed at the time of study. In the lamotrigine study, skin reactions were reported more frequently in children.[16]

The UK is not alone in recognising the value of systematic monitoring systems based on dispensed prescription data. The New Zealand Intensive Medicines Monitoring Programme (IMMP) is a similar system for monitoring new drugs in the early post-marketing period. Each drug is monitored for 4 to 5 years usually and the average size for each cohort is 10 228.[23] Selection criteria are similar to those used by the DSRU with priority given to drugs of a novel character and intended for widespread, long term use.[24]

2.2 Response Rates

The mean response rate for 65 completed PEM studies has been 57.6% (range 39.6 to 74.1%). The response rate could seem rather low although this is fair when compared with general practice surveys in general.[25] A response rate of 60% is im-

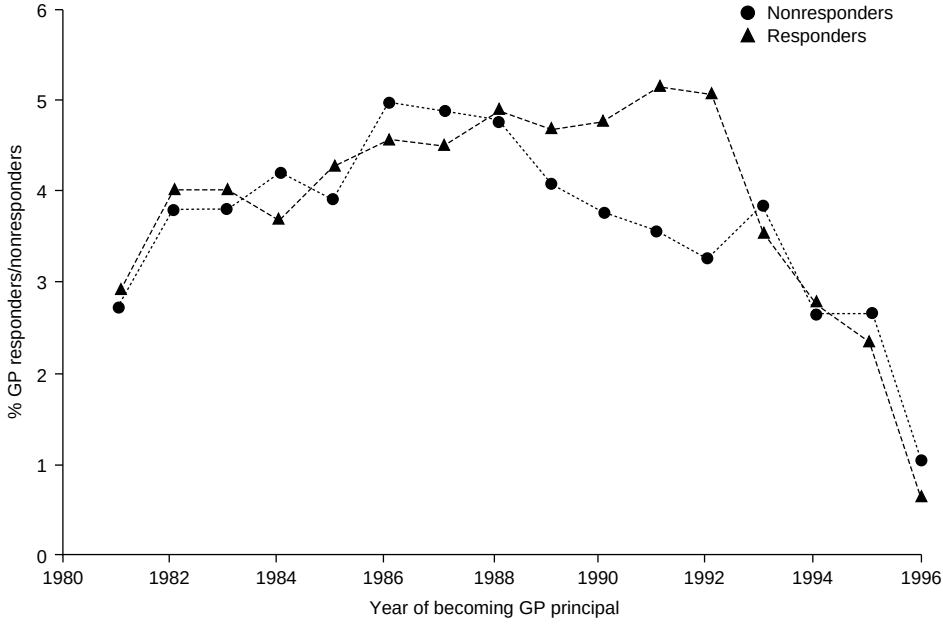

Fig. 2. Characteristics of general practitioners (GPs) who submit 'green forms' ('responders') and those who do not ('nonresponders'): year of becoming a GP principal (practice partner).

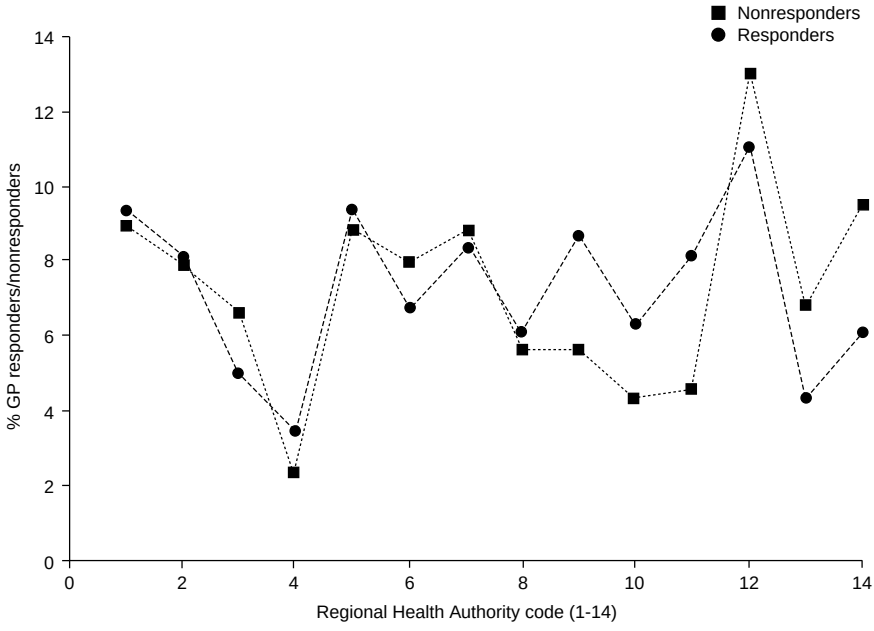

Fig. 3. Characteristics of general practitioners (GPs) who submit 'green forms' ('responders') and those who do not ('nonresponders'): variation between the 14 regional health authorities within England.

portant only if the 40% of patients for whom there are no data are different from the 60% for whom there are data. We consider this unlikely. PEM is noninterventional and GPs are simply asked to report events already recorded in patients' records. It is unlikely that GPs who do respond have different patients from those who do not respond. The characteristics of GP responders have, however, been compared with those of nonresponders (GPs can be identified from their personal identification number on prescriptions which indicates the year of becoming a GP principal from 1981).

We examined the characteristics of GPs who were involved in the PEM study of risperidone (1996). 58% of nonresponders and 62% of responders became principals from 1981. There was no difference between the year of becoming a GP principal between responders and nonresponders (fig. 2). In addition, there were only minor regional differences between responders and nonresponders (fig. 3). The DSRU is now sending second questionnaires to nonresponding GPs for 1 drug being monitored. If modifying the technique of PEM in this way is successful, it should shorten the completion time of studies in addition to improving response rates.

PEM studies have shown that drugs intended for widespread, long term community use are rarely associated with serious adverse drug reactions.[13] This is reassuring and does not mean that PEM is unnecessary. If 10 000 systematically identified, heterogeneous patients have taken a drug without ill effect, then prescribers can justifiably reassure patients about the relative safety of the drug. Similar safety claims cannot be based on data from the few highly selected patients involved in pre-marketing trials. Table I lists some findings from the most recently completed PEM studies.[26-29] The advantages and disadvantages of PEM are summarised in table II.

3. Alternative Sources of Data Within the UK

There has been a rapid growth in the routine collection of computerised data within UK general

Table I. Findings from recently completed prescription-event monitoring studies (1996 to 1998)

Drugs	Cohort size (n)	Response (%)	Findings of interest	Reference
Venlafaxine	12 642	54.6	13 overdoses, non-fatal. 37 pregnancies exposed during first trimester	26
Moclobemide	10 835	58.8	Galactorrhoea associated with drug	18
Alendronate	1523	63.3	Oesophageal reactions quantified	27
Lamotrigine	11 316	67.9	Reports of Stevens-Johnson syndrome quantified. Skin reactions more frequent in children	16
Vigabatrin	10 178	69.2	Visual field defects associated with drug	28
Bambuterol	8098	50.8	Unlabelled adverse drug reactions identified. Increased risk non-fatal cardiac failure	29
Risperidone	7684	64.7	Data for 98 children <15y (unlicensed use). Extrapyramidal symptoms rare	22
Fluvoxamine Fluoxetine Sertraline Paroxetine	10 983 12 692 12 734 13 741	59.9 58.4 60.1 61.6	Comparison. Fluvoxamine had highest incidence of adverse events. Event profiles similar for other 3 drugs for frequent events but differences for less frequent events identified	19
34 Drugs	392 334	≈60	831 pregnancies exposed to new drugs during first trimester. Outcomes being reported	20
40 Drugs	425 508	≈60	Full event data presented for each drug	13

practice. Computerised databases now provide a readily available source of patient data. Problems with aggregating general practice computerised data are well recognised. Communication links must allow the uncorrupted transmission of patient data in an anonymous, confidential manner, and a common coding structure for diseases, activities and patient characteristics has to be established to ensure accurate inter-practice comparison.[30] Another problem is that computerised practices represent a highly select group of practices. GPs in such practices are not necessarily representative.

Other problems concern the data themselves. Incomplete recording of data is the most serious concern. In 1991, only 1 in 3 practices enrolled in the Value Added Medicinal Products (VAMP) scheme [now the General Practice Research Database (GPRD)] were up to standard.[7] Jick et al.[31,32] conducted 2 validation studies involving the VAMP database. In 1991, 87% of consultant diagnoses and 90% of newly diagnosed drug-inducible illness were recorded on computer. In 1992, 96% of consultant diagnoses were recorded with 100% of drug inducible disease. Unfortunately, these were the only 2 outcomes reported. Concordance of data on concomitant medication, duration of therapy and reasons for stopping medication etc, were not reported.

Table II. Advantages and disadvantages of prescription-event monitoring (PEM)

Advantages of PEM	Disadvantages of PEM
Useful for monitoring new drugs	Response rate approximately 60%
Can detect unsuspected adverse drug reactions	Incidence rates for reported events only
National in scale: large studies	No control group
Dispensed prescription data	No data on ‘over the counter’ medication
Systematic identification of patients	No guarantee of compliance
Heterogenous population of patients and doctors	
Follow-up enquiries possible	
Quantification of reported events	
Data for children, elderly, pregnancy	
Comparisons with drugs in same class	
Long term follow-up studies	
Well supported by general practitioners	

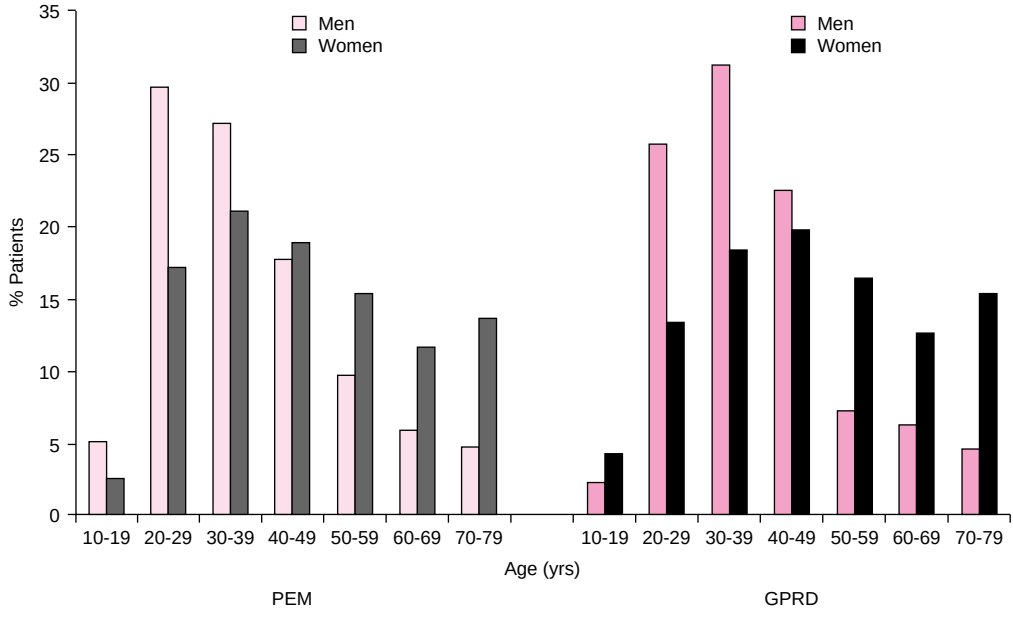

Fig. 4. Age and gender distributions of patients taking risperidone identified by means of prescription-event monitoring (PEM) and from the General Practice Research Database (GRPD).

In 1989, in 1 winter month, 89 of 548 Meditel practices recorded no respiratory infections and a further 26 could not supply data on list size.[33] One explanation for the poor quality of data at the time was that some practices consistently recorded only what their contracts with the computer suppliers specified.[7] Pringle et al.[30] examined the completeness and accuracy of data recording in 4 practices using the Egton Medical Information System (EMIS) from 1992 to 1994. Along with the VAMP studies,[31,32] practices were selected with the highest commitment to recording data on computer. Comparison with manual records showed that with regard to diagnoses, 82% of items were recorded (100% of prescriptions and 67% of referrals), but computer recording missed most of the remaining data that manual records captured. Computerised databases provide data on issued prescriptions. For the purposes of post-marketing surveillance, dispensed prescription data are preferable.[34]

The main factor which limits the use of computerised databases for the study of newly marketed drugs is the relatively small population for whom data are available. Market penetrance of new agents tends to be low in the first few years after launch. The largest of the UK databases, the GPRD has a population of 3.4 million, 6.4% of the population of England and Wales (6% of the UK).[35]

4. A Direct Comparison Between PEM and a Computerised Database

4.1 The Data

The DSRU has conducted 2 studies of the drug risperidone, 1 using standard PEM[22] and the second using the GPRD. Both studies were conducted using data recorded during the same time period (July 1993 to April 1996), immediately after release of risperidone on the UK market. PEM received data for 7684 patients dispensed risperidone compared with 617 patients identified on the GPRD. The GPRD also identified patients prescribed chlorpromazine and haloperidol over the same time period. PEM received specific data on indications for prescribing risperidone, reasons for stopping the drug and dates of starting and stopping therapy. Information on concomitant medica-

tion was poor. The GPRD did not provide linked indications for prescribing but did provide comprehensive data on concomitant medication.

4.2 Results

The age and gender profiles of the patients identified in both techniques were very similar (fig. 4). The GPRD failed to provide linked indications for prescribing and therefore events recorded on the date of first prescription had to be taken to include indications (table III).

The characteristics of the 2 cohorts were very similar and this argues against selection bias differentially affecting 1 method. GPRD data were provided in the form of Oxford Medical Information System (OXMIS) codes and 'freehand comments' as written by GPs. Raw data from PEM questionnaires and GPRD data were entered onto the DSRU database using the same coding conventions and terms. The event profiles were very different (table IV). Drowsiness/sedation was the most frequently reported event for the PEM study and this corresponds to reports in clinical trials (drowsiness and sedation has been reported in up to 25% of patients taking risperidone).[36] The incidence of drowsiness and sedation in the first month recorded on the GPRD was 1.7 per 1000 patient-months. Some of the differences in ranking of events may be due to a higher percentage of administrative terms recorded on the GPRD. Equally there may be underreporting of 'unrelated' events such as minor surgery and respiratory tract infections by GPs on PEM questionnaires. We are concerned, however, that the most frequently reported event in the PEM study of risperidone was ranked 77th for the most frequently recorded events recorded on the GPRD, less frequent than extrapyramidal symptoms, oral candidiasis and lichen planus.

5. Cost

At present, the annual running cost of the DSRU including staff salaries and overheads is about £1million. Most PEM studies involve data collection from 18 to 24 months and another 6 to 12 months for follow-up and data analysis. The estimated cost per completed green form questionnaire is £25. This estimate is based on printing, postage and percentage of staff time for data entry, analysis and follow-up. An approximate cost of £250 000 has been estimated for completed PEM studies involving a cohort of 10 000 patients. The Office for National Statistics (ONS) charged the DSRU £10 000 for providing the basic OXMIS data for the risperidone study (1996, above). Data handling, data entry and analysis were conducted at the DSRU. Additional follow-up enquiries (letters to prescribing GPs) would have cost the DSRU an extra £100 per case. Follow-up enquiries are contracted out by the ONS in order to retain anonymity of data. The DSRU is unaware of current ONS charges or how these compare for data from alternative com-

Table III. Ranked indications for prescribing risperidone

Prescription-event monitoring indication	No. of patients	%	General practice research database: events reported on date of first prescription	No. of patients	%
Schizophrenia	3376	44	Schizophrenia	84	17
Psychosis	1120	15	Psychosis	50	10
Depression	338	4	Depression	38	8
Hallucinations	238	3	Psychiatric NOS	10	2
Paranoia	194	3	Paranoia	10	2
Delusions	151	2	Hallucinations	8	2
Agitation	101	1	Anxiety	7	1
Depression, manic	66	1	Manic depression	5	1
Hyperactive	64	1	Agitation	4	1
Others	2036	26	Others	271	56
Total	7684	**100**	**Total**	**487**	**100**

NOS = not otherwise specified.

Table IV. Events recorded after the start of treatment with risperidone: most frequent events reported during prescription-event monitoring (PEM) compared with the most frequently recorded events on the General Research Practice Database (GRPD), during the same period of study

PEM event	N_1	I_1	N_A	I_A	GPRD event	N_1	I_1	N_A	I_A
Drowsiness	87	13.2	243	4.6	Schizophrenia	67	111.3	150	30.4
Admission	56	8.5	388	7.3	Hospital referral	43	71.4	136	27.6
Dose increase	54	8.2	160	3	Depression	37	61.4	109	22.1
Malaise	45	6.8	176	3.3	Psychosis	29	48.2	66	13.4
Respiratory tract infection	44	6.7	325	6.1	Condition improved	19	31.6	56	11.3
Nausea/vomiting	41	6.2	139	2.6	Respiratory tract infection	18	29.9	120	24.3
Extrapyramidal	39	5.9	170	3.2	Minor surgery	17	28.2	32	6.5
Agitation	37	5.6	131	2.5	Insomnia	11	183	45	9.1
Headache	35	5.3	90	1.7	Agitation	10	16.6	32	6.5
Depression	31	4.7	197	3.7	Dose increased	10	16.6	38	7.7
Dizziness	30	4.6	88	1.6	Hallucination	10	16.6	32	6.5
Hallucination	30	4.6	150	2.8	Dose reduced	8	13.3	29	5.9

I_1 = total number of reports per 1000 patient-months in first month of treatment; **I_A** = total number of reports per 1000 patient-months during the total treatment period; **N_1** = total number of reports during first month of treatment; **N_A** = total number of reports of each event during the total treatment period.

mercialised databases. Unlike commercialised companies, the DSRU is a nonprofit organisation.

6. Record Linkage Techniques

The Medicines Monitoring Unit (MEMO) based in Tayside, Scotland, conducts studies using record linkage techniques.[37] National Health Service patients registered in Tayside are allocated a unique identification number. MEMO has access to dispensed prescription data, Scottish Morbidity Records (which include coded information on diagnostic and operative measures and hospital certified deaths). In addition, MEMO has access to linked cancer registration data, child development records, maternity records and laboratory data.[37] Such comprehensive data are invaluable for pharmacoepidemiological studies. The disadvantage of record linkage in Scotland is that the population is approximately 400 000. The ability to monitor newly marketed drugs within the first few years is therefore limited.

7. The Pharmaceutical Industry

Company sponsored post-marketing surveillance studies have made little contribution to drug safety in the UK. One review found that most studies lacked a comparator group and included significant selection bias. Studies were also slow to recruit patients and no study expanded the database by more than 4-fold.[5]

8. Conclusions

The need for post-marketing surveillance is well recognised in the UK and general practice data is ideal for such studies. There is no 'gold standard' technique for post-marketing surveillance: the choice of technique will depend on the time available for a study, and the cost and nature of the data required. The 'yellow card' spontaneous reporting scheme relies on the reporting of suspected drug reactions. The scheme missed the practolol-induced oculomucocutaneous syndrome in the 1970s because prescribing doctors did not attribute symptoms to practolol and failed to report them to the Committee on Safety of Medicines.[1] Computerised databases in the UK provide readily accessible data for drug surveillance but are limited in size. Doctors who work in 'up to standard' fully computerised practices are a highly select group. To identify problems early, drug monitoring schemes must include a representative sample of doctors. Record linkage schemes such as that in

Scotland, provide a highly comprehensive source of data.

Along with computerised databases, record linkage techniques in the UK are limited in size and therefore, ability to monitor newly marketed drugs within the first few years. PEM uses dispensed prescription data and patients are registered with all types of GPs, irrespective of list size or computerisation status. PEM has the potential to identify unsuspected adverse events and the method identifies the national cohort exposed to a drug. PEM has proven effective. The incidence of some serious adverse reactions have been quantified but equally importantly, many drugs with widespread community use have been demonstrated to be reassuringly free of adverse effects.

PEM has recognised limitations. The proportion of adverse effects that go unreported to doctors is unknown. PEM studies produce reported event rates rather than true incidence rates. This is the same for all studies based on medical record data (including computer databases and record linkage) and there is no other practical method of obtaining data. There is no control group in standard PEM studies and the true background incidence for events is therefore not known. Comparative studies can be conducted for drugs within the same class however, and the frequency of events during treatment can be compared with the frequency of events after stopping treatment.

The DRSU is now in the process of formally validating the technique of PEM and investigating the reasons for non-response by GPs.

PEM is the principal activity of the DSRU. The annual running costs of the DSRU are modest and approximately 20 PEM studies are in progress at any 1 time. The technique of PEM will continue to improve with experience, as statistical techniques advance, and with the ongoing support of the DSRU.

Acknowledgements

I wish to thank the Prescription Pricing Authority and all the GPs for their invaluable support, without which prescription-event monitoring (PEM) would not be possible. I would also like to thank hospital consultants, members of local health authorities and the Office for National Statistics for their work with follow-up investigations. The Drug Safety Research Unit (DSRU) is grateful for noncontractual donations received from pharmaceutical companies. Finally, I would like thank my colleagues at the DSRU who have collaborated in PEM studies in the last 2 years, especially Mrs Gill Pearce, Mr Shayne Freemantle and Dr Lynda Wilton. The conduct of these studies and additional projects would not have been possible without the present director of the DSRU and I therefore, particularly wish to thank Dr R.D. Mann.

References

1. Rawson NSB, Pearce GL, Inman WHW. Prescription-event monitoring: methodology and recent progress. J Clin Epidemiol 1990; 43 (5): 509-22
2. Rawson NSB. Post-marketing surveillance. In: Hansch C, Sammes PG, Taylor JB, editors. Comprehensive medicinal chemistry. Vol. 1. General principles. Oxford: Pergamon Press, 1990: 625-55
3. Dunn NR, Thorogood M, De Caestecker L, et al. Myocardial infarction and oral contraceptives, a retrospective case control study in England and Scotland ('MICA' Study). Pharmacoepidemiol Drug Saf 1997; 6: 283-9
4. Joint Committee of ABPI, BMA, CSM and RCGP. Guidelines on post-marketing surveillance. BMJ 1988; 296: 399-400
5. Waller PC, Wood SM, Langman MJS, et al. Review of company postmarketing surveillance studies. BMJ 1992; 304: 1470-2
6. Rawlins MD, Jefferys DB. United Kingdom product licence applications involving new active substances, 1987-1989: their fate after appeals. Br J Clin Pharmacol 1991; 302: 223-5
7. Pringle M, Hobbs R. Large computer databases in general practice. Of little use unless high quality data are collected. BMJ 1991; 302: 741-2
8. Meyboom RHB, Egberts ACG, Edwards R, et al. Principles of signal detection in pharmacovigilance. Drug Saf 1997; 16 (6): 355-65
9. Waller PC, Coulson RA, Wood SM. Regulatory pharmacovigilance in the United Kingdom: current principles and practice. Pharmacoepidemiol Drug Saf 1996; 5: 363-75
10. Bem JL, Mann RD, Rawlins MD. Review of yellow cards 1986 and 1987. BMJ 1988; 296: 1319
11. Belton KJ, Lewis SC, Payne S, et al. Attitudinal survey of adverse drug reaction reporting by medical practitioners in the United Kingdom. Br J Clin Pharmacol 1995; 39: 223-6
12. Carson JL, Strom BL, Maislin G. Screening for unknown effects of newly marketed drugs. In: Strom BL, editor. Pharmacoepidemiology. 2nd ed. Chichester: John Wiley & Sons, 1994: 431-47
13. Freemantle SN, Pearce GL, Wilton LV, et al. The incidence of the most commonly reported events with 40 newly marketed drugs – a study by prescription-event monitoring. Pharmacoepidemiol Drug Saf 1997; 6 Suppl. 1: S1-S62
14. Mann RD. Prescription-event monitoring: its role in ensuring new drug safety. Prescriber 1996; 7 (5): 102-4
15. Mann RD, Wilton LV, Pearce GL, et al. Prescription-event monitoring (PEM) in 1996 – a method of non-interventional observational cohort pharmacovigilance. Pharmacoepidemiol Drug Saf 1997; 6 Suppl. 3: S5-11
16. Mackay FJ, Wilton LV, Pearce GL, et al. Safety of long-term lamotrigine in epilepsy. Epilepsia 1997; 38 (8): 881-6

17. Council for International Organisations of Medical Sciences in collaboration with the World Health Organization. International Ethical Guidelines for Biomedical Research involving human subjects: Geneva, 1993
18. Dunn N, Freemantle S, Pearce G, et al. Galactorrhoea with moclobemide [letter]. Lancet 1998; 351: 802
19. Mackay FJ, Dunn NR, Wilton LV, et al. A comparison of fluvoxamine, fluoxetine, sertraline and paroxetine examined by observational cohort studies. Pharmacoepidemiol Drug Saf 1997; 6: 235-46
20. Wilton L, Pearce G, Martin RM, et al. The outcome of pregnancy in women exposed to newly marketed drugs in general practice in England. Br J Obstet Gynaecol 1998; 105: 882-9
21. Turner S, Longworth A, Nunn AJ, et al. Unlicensed and off label drug use in paediatric wards: prospective study. BMJ 1998; 316: 343-5
22. Mackay FJ, Wilton LV, Pearce GL, et al. The safety of risperidone: results of a post-marketing surveillance study on 7684 patients. Hum Psychopharmacol Clin Exp 1998; 13 (6); 413-8
23. Coulter DM. Reasons for stopping drugs are monitored in New Zealand. BMJ 1996; 313: 756
24. Coulter DM, Edwards IR, McQueen EG. Post-marketing surveillance in the general population: New Zealand. In: Inman WHW, editor. Monitoring for drug safety. 2nd ed. Lancaster: MTP Press, 1986: 119-34
25. McAvoy BR, Kaner EFS. General practice postal surveys: a questionnaire too far? BMJ 1996; 313: 732-3
26. Sinclair J, Birtwhistle J, Baldwin D. The tolerability of venlafaxine. Rev Contemp Pharmacother 1998; 9; 333-44
27. Mackay FJ, Wilton LV, Pearce GL, et al. United Kingdom experience with alendronate and oesophageal reactions. Br J Gen Pract 1998; 48: 1161-2
28. Stephens MBD, Wilton LV, Pearce Gl, et al. Visual field defects in patients taking vigabatrin [abstract]. Pharmacoepidemiol Drug Saf 1997; 6 Suppl. 2: S18
29. Martin RM, Dunn NR, Freemantle SN, et al. Risk of non-fatal cardiac failure and ischaemic heart disease with long acting β_2 agonists. Thorax 1998; 53: 558-62
30. Pringle M, Ward P, Chilvers C. Assessment of the completeness and accuracy of computer medical records in four practices committed to recording data on computer. Br J Gen Pract 1995; 45: 537-41
31. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ 1991; 302: 766-8
32. Jick H, Terris B, Derby L, et al. Further validation of information recorded on a general practitioner based computerised data resource in the United Kingdom. Pharmacoepidemiol Drug Saf 1992; 1: 347-9
33. Johnson N, Mant D, Jones L, et al. Use of computerised general practice data for population surveillance: comparative study of influenza data. BMJ 1991; 302: 763-5
34. Beardon PHG, McGilchrist MM, McKendrick AD, et al. Primary Non-compliance with prescribed medication in primary care. BMJ 1993; 307: 846-8
35. The general practice research database: information for researchers. London: Office for National Statistics on behalf of the GPRD Advisory Management Board, 1996
36. Kane JM. Newer antipsychotic drugs: a review of their pharmacology and therapeutic potential. Drugs 1993; 46: 585-93
37. MacDonald TM, McDevitt DG. The Tayside Medicines Monitoring Unit (MEMO). In: Strom BL, editors. Pharmacoepidemiology. 2nd ed. Chichester: John Wiley & Sons, 1994: 245-355

Correspondence and reprints: Dr *Fiona Jean Mackay*, Research Fellow, Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton SO31 1AA, England.
E-mail: drmann@dsru.u-net.com