Adverse drug events in general practice patients in Australia

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ABSTRACT

Objective: To investigate the frequency, cause, and severity of adverse drug events (ADEs) among general practice patients.

Design: Between May 2003 and February 2004, a subsample of 282 general practitioners in the BEACH (Bettering the Evaluation And Care of Health) data collection program recorded patient responses to questions about ADEs.

Main outcome measures: Frequency, cause, and severity of ADEs; and frequency of hospitalisation and proportion of events that were preventable.

Results: From 8215 encounters, GPs reported that 852 patients (10.4%) had experienced an ADE in the previous 6 months. Patients aged over 45 years (versus under 45 years), children aged 1–4 years (versus older children), and female patients (versus male patients) were significantly more likely to have experienced an ADE.

Most patients (83.5%) had experienced only one ADE, with 10.7% and 5.8% experiencing two and three or more events, respectively. For 71.9% of patients, one reason for the most recent event was a recognised side effect, followed by drug sensitivity (12.4%) and allergy (11.0%). Over half of patients were rated as having a "mild" event, with 35.8% rated as "moderate", and 10.0% as "severe". GPs classified 23.2% of events as preventable, and 7.6% of events resulted in hospitalisation.

Conclusion: Our study reveals the high frequency of ADEs in patients attending general practice. This level of morbidity makes ADEs one of the most significant causes of morbidity in the Australian community.

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A recent editorial in the *MJA* on the status of patient safety in Australia, a decade after the Quality in Australian Health Care Study[1] (and, coincidentally, nearly 10 years after the first, and to date the only, government-sponsored study of patient-safety incidents in general practice[2]), lamented that "... the absence of recent system-wide data on patient safety ... makes a mockery of the tenets of continuous quality improvement", and advanced that we "manage what we measure". Bagian et al, in reporting the development of the US Veterans Administration patient-safety program, subtitled their article "You can't fix what you don't know about".[3] Both these truisms are even more relevant in the apparent black hole of patient-safety incident reporting in Australian general practice.

This lack of information is particularly conspicuous in the area of medication-safety incidents, which constituted half of all incidents in the general practice incident monitoring study.[2,4] Adverse drug events (ADEs) are regarded as an important subset of patient-safety incidents that cause, or have the potential to cause, harm to patients undergoing medical care.

ADEs reported by the Australian Incident Monitoring System[5] (mostly from the acute care sector), and community-based research by Roughead et al,[6] have shed some light on the problem. However, it is in the realm of postmarketing surveillance of ADEs by regulators that the deficiency in data becomes most obvious. In Australia, reporting rates by general practitioners to the Adverse Drug Reactions Advisory Committee of the Therapeutic Goods Administration (TGA) fell from 3314 in 2002 to 2075 in 2004 (Dr P Purcell, Medical Officer, Adverse Drug Reactions Unit, TGA, personal communication).

Reduction in the occurrence of ADEs, particularly those due to prescribing, dispensing and communication errors, has been an often-stated aim of the government's Better Medication Management System and its successors, MediConnect and HealthConnect.[7]

In early 2001, the Australian Government Department of Health and Ageing, MediConnect section, commissioned the study reported here of patients attending general practice in Australia to establish a baseline measure of the current quantity and severity of ADEs to allow comparison after the introduction of MediConnect.

METHODS

The subsample used in our study is drawn from the larger sample of general practice encounters in the BEACH (Bettering the Evaluation And Care of Health) program. BEACH is a continuous national cross-sectional study of general practice activity in Australia. About 1000 randomly selected GPs per year each record information about encounters with 100 consecutive consenting patients, providing morbidity and treatment data on about 100 000 encounters annually.[8]

Throughout the year, a series of substudies are conducted in conjunction with the ongoing data collection from the GP–patient encounters. In each 5-week survey period, about 100 GPs each record information for about 30 patients for each topic. These substudies, known as SAND (Supplementary Analysis of Nominated Data), investigate aspects of patient health not necessarily managed at the encounter (the full methodology is reported elsewhere).[9] Responses are recorded by the GP in discussion with the patient. Using a qualified medical practitioner to record morbidity, in conjunction with patient self-report, may provide a more accurate classification of patients' health problems than self-report alone.[10,11]

Three SAND subsamples in May–June 2003 (Survey 1), July–August 2003 (Survey 2) and January–February 2004 (Survey 3) were used to investigate the frequency, cause and severity of ADEs reported by patients to have occurred within the previous 6 months.

For the purpose of our study, an ADE is defined as an "unintended event due to the use of a medication that could have harmed or did harm the patient". "Harm" includes physical, psychological or emotional suffering. This definition is consistent with the definition of the broader concept of "clinical incidents" used in our study on patient-safety incidents in general practice in Australia.[2]

The number of questions that could be asked about the patient was limited by the space available on the recording form. Each GP was asked to record whether or not each

1 Definitions provided to participating general practitioners

Severity of the event

Mild: a reaction of limited duration which may or may not require further treatment; minimum impact on daily activities

Moderate: a reaction of longer duration or which requires further treatment; limits daily activities

Severe: a reaction of any duration which results in hospitalisation and/or long-term limitations of daily activities

Preventable event

An adverse event would be considered preventable if it is avoidable by any means currently available (unless that means is not considered standard care).[12]

For example:

- better communication between health professions;
- better communication between patient and health professions; and
- better knowledge of a patient's medical history. ◆

2 Sample size and occurrence of reported adverse drug events (ADEs) in the three surveys

	May–June 2003	July–August 2003	January–February 2004	Consolidated data
Number of general practitioners	95	87	100	282
Number of patients	2715	2537	2963	8215
Number of patients with an ADE	272	231	349	852
Percentage (95% CI)	10.0% (8.4%–11.7%)	9.1% (7.3%–10.9%)	11.8% (9.9%–13.7%)	10.4% (9.4%–11.4%)

of 30 patients had experienced an ADE in the preceding 6 months. If the response was "no", the questions ended. If a "yes" response was recorded, the GP was then asked to report how many different events had occurred. Nine options with tick-boxes were offered to record the cause of the event ("recognised side effect", "drug interaction", "contraindication", "allergy", "drug sensitivity", "overdose", "dispensing error", "don't know", and "other"). A single cause option was allowed in Survey 1 and multiple responses were allowed in Survey 2 and 3. Severity was recorded as one of four options ("mild", "moderate", "severe" and "don't know").

In Survey 1, severity was not recorded if the reason for the ADE was a recognised side effect of the drug; and hospitalisation was recorded only when the reason for the ADE was not a recognised side effect. In Survey 2, hospitalisation was recorded for all patients. In Survey 3, preventability was recorded instead of hospitalisation. GPs were asked to use their clinical judgement in assessing the type of event, its severity and preventability, but guiding definitions were provided for "severity" and "preventability" (Box 1).

Statistical methods

A cluster sample design was used. The GP was the primary sampling unit, and the unit of analysis was patients at the GP–patient encounter. All reported confidence intervals were adjusted for the design effect of the cluster sample using procedures in SAS (version 8.2, SAS Institute, Cary, NC, USA). Rates were judged significantly different by the presence of non-overlapping 95% confidence intervals.

Ethical approval

Ethics committees of the University of Sydney and the Australian Institute of Health and Welfare approved the BEACH study and this substudy.

RESULTS

Responses were received on 8285 encounter forms from 282 GPs. Of these, 70 were excluded (duplicate patients on the basis of matching demographic data), leaving a final sample of 8215 patients. The GPs reported that 852 patients (10.4%) had experienced an adverse event after using a medication in the past 6 months. This result was consistent over the three surveys (Box 2). All other results from questions repeated in the three surveys did not differ significantly and are reported here in consolidated form.

The age and sex distributions of the respondents did not differ from those of patients in the total sample of BEACH encounters for 2002–2003.[8]

Among children, those aged 1–4 years were three times more likely to have experienced an ADE than other age groups. In adults, the likelihood of an ADE increased with age to peak in those aged 65 years and over. Female patients were significantly more likely than male patients to have experienced a medication-related ADE (Box 3).

Most of the 852 patients had experienced only one such event, but one in six had experienced multiple events. For 71.9% of patients, one reason selected for the most recent adverse event(s) was "a recognised side effect" followed by "drug sensitivity" and "allergy". Dispensing errors and contraindications were rare.

A GP severity rating for the most recent ADE was provided for 551 patients. Over half (53.9%) were rated as having a "mild" event(s), with a third rated as "moderate". A "severe" rating was given for 55 patients (10.0% of those with an ADE or 6.7 per 1000 patients sampled) (Box 4).

Responses to the question on hospitalisation were received for 223 patients in Survey 2. Of these, 7.6% (95% CI, 3.6–11.6) had been hospitalised as a result of the most recent ADE (9.7 per 1000 patients in the total sample). Preventability was judged for 327 patients in Survey 3. GPs classified the ADE as preventable for 23.2% (95% CI, 17.4–29.1), made up of 19.9% of "mild" events, 25% of "moderate" and 32% of "severe" events. The severity-specific preventability rates were not significantly different due to the small numbers and the wide confidence intervals (data not shown).

DISCUSSION

One in 10 patients presenting to a GP has had an ADE in the preceding 6 months, almost 50% being in the moderate to severe range, as assessed by the GP. About 8% of patients were hospitalised as a result of the ADE.

Our study is limited, firstly, by the methodology of the SAND substudies of the BEACH program, being constrained both by the number of questions that could be asked and the time that GPs could devote, within the context of the consultation, to clarifying answers to the questions about ADEs.

Secondly, patients attend general practice at variable rates related to age and morbidity. Therefore, some groups of patients are more likely to be included in these samples. As a result, the frequency of ADEs in patients attending GPs cannot be extrapolated to a period prevalence of ADEs in the community.

Thirdly, the relationship between the adverse event and the medication was left to the judgement of the GP and the patient, and no attempt was made to grade the probability of causation. Furthermore, the individual drugs possibly causing the ADEs were not identified, nor was the duration of exposure or dosage.

Fourthly, the denominator was all patients presenting to the GP, regardless of whether or not they were receiving drug therapy. The frequency of ADEs in patients receiving drug therapy would undoubtedly be higher than that reported.

Finally, answers to the questions relied on the patient's and the GP's recall of events over a period of 6 months, a process that may result in some variable reliability.

Our study must therefore be regarded as a quantification of ADEs from the perspective of the GP and the patient. However, the overall consistency of the results over the three surveys by separate groups of about 100 GPs suggests a common interpretation of causality, severity and preventability.

A major strength of our study is that it contains data from a large sample of patients collected by hundreds of GPs representing 1.5% of all practising GPs in Australia. GPs in the BEACH program are nationally representative of all GPs practising in Australia.[8] The GPs use their medical records, knowledge of the patient, and their clinical skills and experience to interpret the reported ADEs. In the SAND substudies they act as expert clinical interviewers.

Research on under-reporting of serious ADEs in the United States[13-15] and Canada,[16-18] suggests that formal reporting rates may be as low as 1.5% of total ADEs. US estimates place the mortality from ADEs as the fifth most common cause of death after heart disease, cancer, stroke and pulmonary disease.[13]

Under-reporting of serious ADEs is only part of the problem. To prevent "overload", statutory reporting authorities actively discourage reporting of less severe ADEs and those due to known side effects of drugs. The Director of the US Food and Drug Administration (FDA) has publicly stated "If we were to get reports of all adverse reactions, we'd be overwhelmed, making it difficult for us to focus on the issues with the most public health impact".[19] Further, the FDA has stated that it "does not want reports of all adverse reactions, especially ones listed in a product's labeling".[19]

The Australian reporting system uses similar criteria. Many ADEs are therefore classified as unimportant by the health system and remain a largely hidden source of patient morbidity.

The level of morbidity due to known drug side effects is usually only explored in premarketing clinical trials conducted under very constrained circumstances, and is generally absent from postmarketing surveillance. Thus, a significant level of morbidity may escape notice. The number of reports by GPs to the Adverse Drug Reactions Advisory Committee of the TGA in 2004 (2075 reports) does not match the extrapolated results of our study. If 10.4% of the 96.3 million GP consultations in 2003–04[20] were with patients with an adverse drug reaction in the preceding 6 months, then GPs had over 10 million consultations in that year with such patients.

The level of morbidity revealed in our study places ADEs as one of the most important causes of morbidity in the Australian community. Moreover, as this was a study of patients attending general practice, the most severe result of ADEs, namely death, was not included.

The increasing frequency of ADEs with increasing age mirrors the increased prescription rate at encounters with patients in these age-groups and may therefore be due to the increased medication load. The higher frequency in the age group 1–4 years is not related to prescription rates and therefore requires further exploration.

Various interventions have been suggested and/or implemented in an attempt to reduce the occurrence of incidents, including ADEs.[21] The introduction of computer-generated prescriptions and decision-support systems are frequently advocated as possible solutions to patient-safety incidents caused by medicines.[22,23] However, doubts have been raised about computer prescription-generation systems without decision support.[23,24]

Roughead, in a recent editorial in the *MJA*, pointed out that adverse drug reactions are often considered part of the price to be paid for the therapeutic benefit of medicines. However, we, or more correctly our patients, may be currently paying too high a price.[25] While very severe ADEs may occur and be managed in the acute care sector, the large number of mild and moderate ADEs and many of the severe reactions can only be managed or prevented in the community. Many of these ADEs are (in the GP's opinion) preventable, and the patient-centred GP is ideally placed to lower the burden of this morbidity.

3 Age- and sex-specific rates of at least one adverse drug event (ADE) in general practice patients

	No. of patients with ADE	Age- or sex-specific rate (95% CI)
Age group (years) ($n = 8171$)*		
< 1	3	1.8 (0.0–3.9)
1–4	27	6.8 (4.3–9.2)
5–14	11	2.2 (1.0–3.5)
15–24	48	6.2 (4.5–7.8)
25–44	166	8.1 (6.7–9.6)
45–64	282	12.4 (10.7–14.1)
65–74	147	15.4 (12.9–18.0)
75 and over	163	15.3 (12.7–17.9)
Sex ($n = 8144$)*		
Female	544	11.4 (10.1–12.6)
Male	297	8.9 (7.7–10.0)

* Missing data removed. ◆

4 Details of adverse drug events (ADEs) — patients reporting at least one ADE in past 6 months

	Percentage of respondents (95% CI)
Number of ADEs ($n = 765$)*	
One	83.5% (80.7%–86.3%)
Two	10.7% (8.4%–13.1%)
Three or more	5.8% (3.8%–7.7%)
Type of ADEs ($n = 826$)*†	
Recognised side effect	71.9% (68.3%–75.5%)
Drug sensitivity	12.4% (9.9%–14.9%)
Allergy	11.0% (8.3%–13.7%)
Drug interaction	2.1% (0.9%–3.2%)
Overdose	1.6% (0.7%–2.5%)
Contraindication	0.4% (0.0–0.8%)
Dispensing error	0.1% (0.0–0.4%)
Other	3.0% (1.6%–4.4%)
Don't know	5.2% (3.6%–6.8%)
Severity of ADEs ($n = 551$)*	
Mild	53.9% (48.3%–59.5%)
Moderate	35.8% (31.1%–40.4%)
Severe	10.0% (6.9%–13.1%)
Don't know	0.4% (0.0–0.9%)

* Missing data removed. † Percentage may total more than 100 as more than one reason for ADE could be indicated. ◆

To encourage all participants — patients, doctors, pharmacists, educators and regulators — to collaborate in reducing ADEs, we need to monitor the real burden of ADEs in the community, not by requiring the impossible task of reporting all ADEs to the regulators, but by regular statistical sampling of the frequency and severity of ADEs, and more detailed research to further identify problem drugs and drug combinations and associated contributing factors. This could include further SAND studies of the association of ADEs with different drug groups, patient groups and morbidity patterns. It could also involve other community-based monitoring such as that suggested by Colebatch et al.[26]

As Roughead suggested "it is time to get serious".[25]

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COMPETING INTERESTS

None identified.

AUTHOR DETAILS

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REFERENCES

1 Wilson RM, Van Der Weyden MB. The safety of Australian healthcare: 10 years after QAHCS [editorial]. *Med J Aust* 2005; 182: 260-261.
2 Britt H, Miller GC, Steven ID, et al. Collecting data on potentially harmful events: a method for monitoring incidents in general practice. *Fam Pract* 1997; 14: 101-106.
3 Bagian JP, Lee C, Gosbee J, et al. Developing and deploying a patient safety program in a large health care delivery system: you can't fix what you don't know about. *Jt Comm J Qual Improv* 2001; 27: 522-532.
4 Steven ID, Malpass A, Moller J, et al. Towards safer drug use in general practice. *J Qual Clin Pract* 1999; 19: 47-50.
5 Runciman WB, Roughead EE, Semple SJ, et al. Adverse drug events and medication errors in Australia. *Int J Qual Health Care* 2003; 15 Suppl 1: i49-i59.
6 Roughead EE, Barratt JD, Gilbert AL. Medication-related problems commonly occurring in an Australian community setting. *Pharmacoepidemiol Drug Saf* 2004; 13: 83-87.
7 Wrobel JP. Are we ready for the Better Medication Management System? *Med J Aust* 2003; 178: 448-450.
8 Britt H, Miller GC, Knox S, et al. General practice activity in Australia 2002–03. Canberra: Australian Institute of Health and Welfare, 2003. Available at: http://www.aihw.gov.au/publications/gep/gpaa02-03/index.html (accessed Jan 2006).
9 Family Medicine Research Centre. SAND Method: 2002–03. Sydney: FMRC, 2003. Available at: http://www.fmrc.org.au/Beach/Abstracts/SANDmethod-2003.pdf (accessed Jan 2006).
10 Driver B, Britt H, O'Toole B, et al. How representative are patients in general practice morbidity surveys? *Fam Pract* 1991; 8: 261-268.
11 Britt H, Harris M, Driver B, et al. Reasons for encounter and diagnosed health problems: convergence between doctors and patients. *Fam Pract* 1992; 9: 191-194.
12 Thomas EJ, Brennan TA. Incidence and types of preventable adverse events in elderly patients: population based review of medical records. *BMJ* 2000; 320: 741-744.
13 Motl S, Timpe E, Eichner S. Proposal to improve MedWatch: decentralized, regional surveillance of adverse drug reactions. *Am J Health Syst Pharm* 2004; 61: 1840-1842.
14 Fischer G, Fetters MD, Munro AP, et al. Adverse events in primary care identified from a risk-management database. *J Fam Pract* 1997; 45: 40-46.
15 Moore TJ, Psaty BM, Furberg CD. Time to act on drug safety. *JAMA* 1998; 279: 1571-1573.
16 Bains N, Hunter D. Adverse reporting on adverse reactions. *CMAJ* 1999; 160: 350-351.
17 Lexchin J. Rethinking the numbers on adverse drug reactions. *CMAJ* 1999; 160: 1432.
18 Lexchin J. Adverse drug reactions: review of the Canadian literature. *Can Fam Physician* 1991; 37: 109-117.
19 Food and Drug Administration. MedWatch: FDA's "Heads Up" on medical product safety. Washington: FDA; 1999, 25 Oct. Available at: http://www.fda.gov/cder/about/whatwedo/testtube-8.pdf (accessed Jan 2006).
20 Medicare Australia. Annual Report 2003-04. Statistical tables. Canberra: Medicare Australia, [updated Dec 2005]. Available from: http://www.medicareaustralia.gov.au/about/our_organisation/annual_report/03_04/statistics.htm#1 (accessed Feb 2006).
21 Bhasale AL, Britt H, Miller G. Developing interventions which could reduce the occurrence of adverse patient incidents in general practice. Report to the Taskforce on Quality in Australian Health Care, Department of Human Services and Health. Canberra. University of Sydney: Family Medicine Research Unit, 1995.
22 Bates DW, Teich JM, Lee J, et al. The impact of computerized physician order entry on medication error prevention. *J Am Med Inform Assoc* 1999; 6: 313-321.
23 Agency for Healthcare Research and Quality. Making health care safer. A critical analysis of patient safety practices. Part III. Rockville, Md: AHRQ, 2001. Available at: http://www.ahrq.gov/clinic/ptsafety/pdf/chap6.pdf (accessed Jan 2006).
24 Coombes ID, Stowasser DA, Mitchell CA, et al. Effect of computerised prescribing on use of antibiotics [letter]. *Med J Aust* 2004; 180: 140-141.
25 Roughead EE. Managing adverse drug reactions: time to get serious [editorial]. *Med J Aust* 2005; 182: 264-265.
26 Colebatch KA, Marley J, Doecke CJ, et al. Evaluation of a patient event report monitoring system. *Pharmacoepidemiol Drug Saf* 2000; 9: 491-499.

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