ORIGINAL RESEARCH ARTICLE

Drug Saf 2012; 35 (9): 733-743
0114-5916/12/0009-0733/$49.95/0

Methods for Retrospective Detection of Drug Safety Signals and Adverse Events in Electronic General Practice Records

Andrew Tomlin,[1] *David Reith*,[2] *Susan Dovey*[3] and *Murray Tilyard*[4]

1 Best Practice Advocacy Centre, Dunedin, New Zealand
2 Women's and Children's Health, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
3 Department of General Practice and Rural Health, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
4 South Link Health Inc., and Department of General Practice and Rural Health, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

Abstract

Background: Examination of clinical data routinely recorded in general practice provides significant opportunities for identifying and quantifying medicine-related adverse events not captured by spontaneous adverse reaction reporting systems. Robust pharmacovigilance methods for detecting and monitoring adverse events due to treatment with new and existing medicines are required to estimate the true extent of adverse events experienced by primary care patients.

Objectives: The aim of the study was to examine evidence of adverse events contained in general practice electronic records and to study observed events related to selective serotonin reuptake inhibitors (SSRIs) as an example of drug-specific pharmaceutical surveillance achievable with these data.

Methods: Electronic clinical records for a cohort of 338 931 patients consulting from 2002 to 2007 were extracted from the patient management systems of 30 primary care clinics in New Zealand. Medical warnings files, prescription records and free text consultation notes were used to identify physician-recorded treatment cautions, including adverse events and medicines they were associated with. A structured chronological analysis of prescriptions, consultation notes and adverse events relating to patients prescribed the SSRI citalopram was undertaken, and included investigating reasons for switching treatment to another SSRI (fluoxetine or paroxetine) as a method for detecting evidence of drug safety signals. We compared the number of adverse events identified for patients at one practice with the number spontaneously reported to New Zealand's Centre for Adverse Reactions Monitoring (CARM).

Results: During the 6-year study period, 173 478 patients received 4 811 561 prescriptions. There were 37 397 allergies, adverse events and other warnings

recorded for 24 994 patients (7.4%); adverse events relating to 65 different types of drug were reported. Medicines most frequently implicated in adverse event reports were antibacterials, analgesics, antihypertensive medicines, lipid-modifying agents and skin preparations. Citalopram was prescribed for 5612 patients, and 701 adverse events relating to citalopram were identified in the electronic health records of 473 (8.4%) patients. A total of 713 (12.7%) patients changed treatment from citalopram to another SSRI, and 164 reasons for the switch were identified: suspected adverse drug effects for 129 (78.7%), lack of effect for 29 (17.7%) and patient preference for 6 (3.7%). The most common adverse events preceding the switch were anxiety, nausea and headaches. Of the 725 adverse events and medical warnings recorded at one practice, 21 (2.9%) were spontaneously reported to the CARM.

Conclusions: Routinely recorded general practice data provide a wealth of opportunities for monitoring drug safety signals and for other patient safety issues. Medical warning records and consultation notes contain a wealth of information on adverse events but structured search methodologies are often required to identify these.

Background

At the time new medicines are first given market approval their risks have not been fully quantified and ongoing monitoring (pharmacovigilance) is needed. During the pre-registration development of a new chemical entity it is unlikely that sufficient people have used the medicine to discover uncommon or rare adverse drug reactions (ADRs). These are usually identified after a drug has been approved for marketing, and the process of comprehensively understanding each medicine's ADRs may take many years. With the increased use of routine electronic data recording in healthcare, new approaches to pharmacovigilance are becoming available that have the potential to speed up the identification and quantification of risk.

Spontaneous adverse event reporting systems have traditionally been the principal method of pharmacovigilance research internationally. Primarily used for the early detection of signals of new, rare and serious ADRs,[1] innovations in the analysis of their reports have been driven by their high resource costs and the need for more precision in identifying medication risks.[2,3] Data mining techniques, focusing on the automated identification of signals from large electronic databases, have been successfully applied to several major databases containing reported ADRs,[3-5] and the methods involved may be useful for detecting both drug-specific and class-specific adverse reactions.[6] Despite the proven value of spontaneous reporting systems in detecting significant drug safety issues, voluntary reporting by health practitioners remains selective and underreporting is acknowledged.[7,8]

In the last few years, major new initiatives for integrating and analysing data from multiple healthcare databases have been established internationally to improve drug safety monitoring in the postmarketing phase.[9-13] Combining data from established databases of primary care medical records, administrative claims, hospital discharges and other health registry information, these projects are investigating data models and methods of analysis for detecting drug safety signals, quantifying event incidence rates and using epidemiological approaches to assess patient risk of adverse outcomes. They will complement the reporting and analysis from spontaneous reporting systems and may be used to verify drug safety signals detected from the analysis of voluntary reports.

In New Zealand, the Ministry of Health's medicines strategy seeks enhancement of pharmacovigilance practices in this country through

the use of existing electronic healthcare data to identify possible drug safety signals for medicines and other therapeutic products.[14] Spontaneous reports of suspected adverse reactions to medicines, vaccines and herbal products are currently collected and evaluated by the Centre for Adverse Reactions Monitoring (CARM), administered by the New Zealand Pharmacovigilance Centre at the University of Otago. The Pharmacovigilance Centre also conducts prospective cohort studies of selected new medicines using Prescription Event Monitoring as part of its Intensive Medicines Monitoring Programme (IMMP).[15] The reporting rate by health professionals is much greater through the IMMP than by spontaneous reporting alone and the recording of all new adverse clinical events means the reporter is not required to make a judgement about a possible adverse reaction.

Primary care medical records provide the opportunity to examine data collected in routine clinical practice to detect signals of possible adverse effects, assess incidence rates and test hypotheses across the entire range of prescribed medicines. Methods of applying information technology, natural language processing and automated computer adverse event monitors to a variety of data have been used in the hospital setting for many years[16-19] and these approaches have also been demonstrated in the hospital outpatient setting with encouraging results.[20,21] Primary care electronic health records in New Zealand may have substantial untapped potential for data mining as they include prescriptions, diagnoses, clinical comments and drug allergy/reaction alerts. The General Practice Research Database in the UK, for example, has been used to explore signals derived from other pharmacovigilance schemes and to proactively monitor therapeutic products to detect drug safety signals as they occur in the primary care population.[22,23]

In this study we aimed to examine evidence of drug safety signals contained in routinely recorded primary care electronic data in New Zealand to determine the potential of such data for contributing to post-clinical trial pharmacovigilance of new and existing medicines. We investigated safety signals associated with the antidepressant drug group selective serotonin reuptake inhibitors (SSRIs) to provide an example of approaches to detecting adverse events and for estimating the frequency with which these events occur in primary care patients. We also assessed the reasons why, and frequency with which, patients switch medicines within this therapeutic group as a method for detecting drug safety signals.

Methods

Study Data

Data for the study were provided by 30 New Zealand general practices contributing routine data for research as members of the South Link Health General Practice Research Network. All practices were located in the South Island of New Zealand, with 12 practices situated in urban areas, 9 in rural areas and the remaining 9 providing healthcare services for patients living in both urban and rural environments. Many of these practices have contributed data for research since the early 1990s.[24-27] All practices now use the same practice management system software (MedTech 32, Medtech Global Ltd, Auckland, New Zealand), which enabled a standard set of clinical record files to be collected from each clinic. The primary care clinical records analysed for this study included those of all patients attending these practices over the 6-year period from 2002 to 2007.

The records extracted from the patient management system of each clinic were recorded on a day-to-day basis by physicians and their practice staff in the course of attending to their patients. A single electronic record comprises the seven different files shown in figure 1. The data used in this research included all records of patient consultations with patient demographic data, text notes recorded at the time of consultation, prescriptions and laboratory investigations ordered, immunizations, and drug allergies and other adverse events recorded in dedicated medical warnings files. Each patient is allocated a unique code within the system that is non-identifiable but enables linking between the different data tables. Dates were recorded for all consultations, prescriptions,

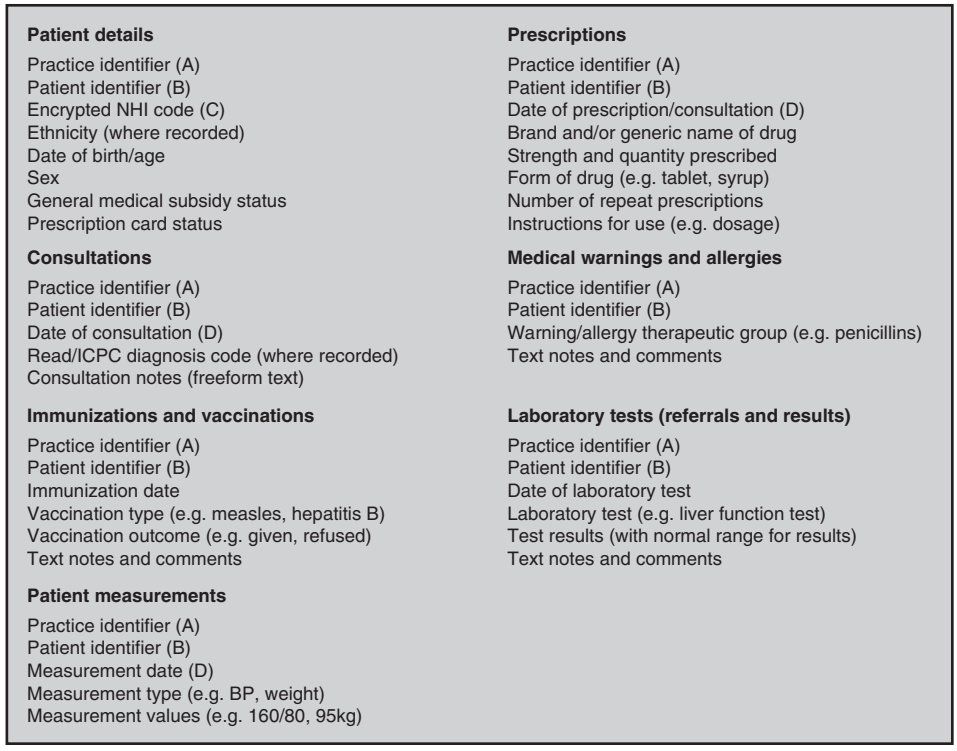

Fig. 1. General practice data collected from practice management systems for pharmacovigilance. (A–D) are key fields for linking data; (C) is the link field to hospital and mortality data. **BP** = blood pressure; **ICPC** = International Classification of Primary Care; **NHI** = National Health Index.

laboratory tests and immunizations but medical allergies and warnings data are kept in registers that are updated by physicians as required for their future reference. The data extraction program collected no patient identifiable information with the exception of the National Health Index (NHI) code of the patient, which was encrypted as part of the data collection process. A unique NHI code is allocated to every New Zealander on first accessing any part of the New Zealand health system. The NHI code allowed us to identify patients attending more than one of the 30 study practices during the study period. These patients were counted only once although their computer records were derived from multiple practices.

The investigation to detect drug safety signals utilized records from the medical warnings, consultations and prescriptions data files. Details of adverse events and their possible causes were recorded in the medical warning files within abbreviated free-form text but in most cases both the event and the drug or substance thought to be responsible was clearly named, e.g. 'penicillins – bad rash'. These files contain only information on patient safety issues such as allergies and other adverse outcomes resulting from medical care. Recording of relevant information in medical warnings files is at the discretion of practice staff.

Prescription data included the brand and/or generic name of each medicine and the date of prescription. It included all scripts written by primary care physicians at clinics providing data and did not represent claims data for reimbursement of pharmaceutical subsidies. Consultation records included the date of consultation and free-form text notes recorded by the family practitioner at the time of the consultation. These notes can pertain to any aspect of patient care and may include patient diagnoses, but these are more frequently recorded in separate Read code diagnosis files.

Definitions

We defined 'drug safety signals' as circumstances recorded in the medical records that were considered likely to indicate patients had experienced some sort of harm that they or their physician considered was probably associated with their use of a drug. For example, we interpreted switching from one long-term drug to another as a drug safety signal. 'Adverse events' we defined as harms experienced by patients, over and above the normal consequences of their disease or health condition, that patients or their physicians attributed to the consumption of a drug. Examples include minor symptoms such as a rash or headache through to severe symptoms such as anaphylaxis.

Detecting Drug Safety Signals

Two methods were used to detect possible drug safety signals relating to the use of SSRIs. SSRIs were chosen as the test drug group since they are commonly used in New Zealand and were the antidepressant drug group most often prescribed at clinics providing data for this study. They also have a well-defined adverse event profile presented by New Zealand's medicines and medical devices safety authority (Medsafe) in its medicine datasheets; this allowed us to compare our findings with the known adverse events listed.

Using Recorded Medical Warnings as Text Search Criteria in Consultation Notes

The contents of the medical warnings files were analysed first by record review and recorded allergies and adverse events aggregated for all medicines and other causes.

Using the most widely used SSRI, citalopram hydrobromide, as the test drug for assessment, we identified all patients prescribed this drug and collated their consultation records. Next, the list of adverse events associated with citalopram recorded in the medical warnings files was combined with citalopram's generic and brand names as search criteria for selecting consultation records with text notes containing evidence of a possible adverse event due to treatment with citalopram. As an example, one dataset resulted from a search for records that contained both of the terms 'citalopram' and 'headache'. Case notes were then scrutinized record-by-record by two of the authors (AT and SD) to identify events positively identified by the physician.

We also measured the number of times patients with an adverse event recorded in the medical warning files were nevertheless prescribed the drug after the event had been recorded. This was achieved by identifying prescription dates for the patient and drug concerned occurring after the date of entry of the event into the medical warnings register.

Identification of Patients Switching Drugs Within a Therapeutic Group

We identified patients who had changed medication from one SSRI to another drug in this therapeutic group and the subset of these patients who later switched back to the original medication after trialling a second drug. This included all patients with a prescription date for a new SSRI within 90 days of the prescription date for the previously used SSRI. This time period was selected since 99.2% of prescriptions for SSRIs were issued with an intended treatment duration of 90 days or less.

The analysis of why patients switched medicines included the three SSRIs citalopram, fluoxetine hydrochloride and paroxetine hydrochloride, which together accounted for 99.7% of all SSRI prescriptions. For each patient, consultation text notes created within 30 days of the prescription dates for the SSRIs used prior to and after switching medication were collated. Search algorithms were then employed to reduce the number of records in this dataset by identifying records with consultation notes containing the brand or generic name of both antidepressants involved in the change of medication. Final datasets were then examined by record review to identify, where possible, the reason for the change in therapy.

Results

There were 338 931 patients consulting at one or more of the practices from 2002 to 2007, and for whom consultations, medical warnings and prescriptions were recorded. Over the 6-year period, 4 811 561 prescriptions were issued.

All Medical Warnings

From the combined medical warnings files of all practices, there were 37 397 allergies, adverse events and other warnings recorded relating to 24 994 patients (7.4% of all consulting patients) [table I]. Adverse events for a total of 65 different types of drug were reported. Of these, the drug types most frequently implicated in reports were antibacterial medications (48.5% of all product events), analgesics (18.1%), antihypertensive medicines (6.7%), lipid-modifying agents (3.7%) and skin preparations (3.7%). The drugs featuring most prominently were penicillin (9.6% of all drug reports), amoxicillin/clavulanic acid (9.3%), amoxicillin (5.0%) and cotrimoxazole (4.9%). The adverse event most often reported was a rash (17.8% of reports), but severe events such as anaphylaxis were also reported (1.4% of reports). Indications that the patient had no known allergies or adverse events were written in 5318 (14.2%) of all medical warning records. Only 1.4% of drug reports were for SSRIs.

Adverse events listed in the medical warnings files were mainly for female patients (69.5%), who constituted 51.4% of all consulting patients (figure 2). In total, 744 patients at 24 different practices were prescribed 797 medicines despite having a medical warning recorded indicating an associated adverse event. Most of these medicines were antibacterials (47.9%), NSAIDs (10.5%) and analgesics (7.8%). On only three occasions was a patient prescribed the medication at a different general practice to the practice recording the medical warning.

Table I. Adverse events, allergies and medical warnings recorded by general practitioners

Medical warning for patient	N (%)
Adverse event due to at least one drug treatment (up to five events per patient)	19 745 (52.8)
Adverse event with treatment unspecified	10 396 (27.8)
No known allergies or adverse events	5 318 (14.2)
Personal characteristics increasing risk for adverse health outcomes	618 (1.7)
Food allergies	575 (1.5)
Allergic reactions to animals, insects or other environmental hazards	397 (1.0)
Interactions and contraindicated treatments	200 (0.5)
Special procedures to follow for the patient	82 (0.2)
Family risks for negative healthcare outcomes, including drug-related reactions	66 (0.2)
All medical warnings	37 397 (100.0)

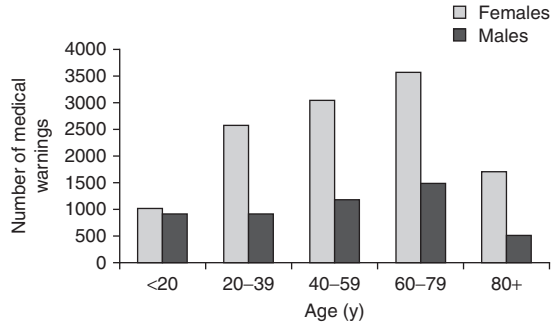

Fig. 2. Number of drug-related adverse events recorded in medical warning files by patient age and sex.

Evidence of Adverse Events Related to Selective Serotonin Reuptake Inhibitors

Over the 6-year study period, 5612 patients had been prescribed citalopram and there were 283 970 consultation records for these patients available for analysis. There were 106 adverse events related to citalopram recorded for 76 separate patients in the medical warnings files (table II). In querying the dataset of consultation records, the computer text-searching programs identified 4138 consultation records of 2006 patients with case notes containing one of these listed events and 'citalopram' or its brand names. After reviewing these case notes, 518 adverse events were positively identified in 340 patients. Only 14 of these events were recorded in both the medical warnings data and the consultation notes for the same patient. The descriptions of the events listed in table II are the terms recorded by general practitioners in the case notes. The most common adverse events were nausea, headaches, sweating, sedation, tremors, diarrhoea and insomnia. All of the listed events were also specified as 'adverse effects' of citalopram in Medsafe's datasheets, although implicitly in some cases. For example, loss of appetite was not listed in the citalopram datasheet but weight decrease and anorexia were.

The investigation of the drug safety signal of patients switching SSRIs identified a total of 713 patients who had been using citalopram (12.7%) and who had changed treatment from citalopram to another SSRI. Of these, 119 (16.7%) switched treatment back to citalopram at some point from 2002 to 2007. There were 1555 patients (16.5%) changing treatment from fluoxetine (10.9% switching back) and 1148 patients (21.9%) changing from paroxetine (14.3% switching back). In many cases, more than one consultation provided evidence regarding the reason for the patient's change in treatment. In total, 91 of the 129 adverse events identified as reasons why patients switched from citalopram to another SSRI were not listed for the patients concerned in the medical warnings

Table II. Adverse events related to citalopram by clinical record type and patient reasons for changing to new selective serotonin reuptake inhibitor therapy[a]

AE	Source of evidence for AE		Reasons for changing to another SSRI		
	Medical warnings	Consultation notes	Citalopram to fluoxetine/paroxetine	Fluoxetine to citalopram	Paroxetine to citalopram
Nausea	16 (15.1)	140 (27.0)	12 (7.3)	31 (8.3)	12 (4.5)
Headaches	3 (2.8)	71 (13.7)	12 (7.3)	18 (4.8)	9 (3.3)
Sweating	5 (4.7)	47 (9.1)	5 (3.0)	14 (3.7)	14 (5.2)
Sedation/drowsiness	5 (4.7)	27 (5.2)	9 (5.5)	6 (1.6)	8 (3.0)
Tremors/shaking	8 (7.5)	25 (4.8)	4 (2.4)	14 (3.7)	9 (3.3)
Diarrhoea	5 (4.7)	20 (3.9)	3 (1.8)	8 (2.1)	5 (1.9)
Insomnia	3 (2.8)	20 (3.9)	5 (3.0)	13 (3.5)	3 (1.1)
Anxiety/increased anxiety	2 (1.9)	18 (3.5)	13 (7.9)	48 (12.8)	25 (9.3)
Dizziness	0 (0.0)	17 (3.3)	2 (1.2)	0 (0.0)	9 (3.3)
Lightheadedness/'spaced out'	3 (2.8)	13 (2.5)	2 (1.2)	6 (1.6)	4 (1.5)
Skin rash	6 (5.7)	12 (2.3)	1 (0.6)	4 (1.1)	1 (0.4)
Vomiting	6 (5.7)	11 (2.1)	2 (1.2)	4 (1.1)	0 (0.0)
Gastrointestinal upset	2 (1.9)	8 (1.5)	5 (3.0)	6 (1.6)	4 (1.5)
Tiredness	0 (0.0)	7 (1.4)	6 (3.7)	10 (2.7)	14 (5.2)
Vision blurred or disturbed	2 (1.9)	7 (1.4)	1 (0.6)	0 (0.0)	0 (0.0)
Dry mouth	0 (0.0)	5 (1.0)	2 (1.2)	4 (1.1)	5 (1.9)
Agitation/restlessness	2 (1.9)	4 (0.8)	3 (1.8)	8 (2.1)	3 (1.1)
Palpitations	1 (0.9)	4 (0.8)	4 (2.4)	3 (0.8)	2 (0.7)
Reduced libido/loss of libido	0 (0.0)	4 (0.8)	5 (3.0)	17 (4.5)	10 (3.7)
Panic attacks	0 (0.0)	3 (0.6)	3 (1.8)	5 (1.3)	5 (1.9)
Indigestion/heartburn	0 (0.0)	3 (0.6)	2 (1.2)	0 (0.0)	1 (0.4)
Sexual dysfunction	0 (0.0)	3 (0.6)	1 (0.6)	4 (1.1)	12 (4.5)
Lethargy	1 (0.9)	3 (0.6)	2 (1.2)	4 (1.1)	3 (1.1)
Loss of appetite	0 (0.0)	3 (0.6)	1 (0.6)	3 (0.8)	4 (1.5)
Unwell/flu-like symptoms	10 (9.4)	2 (0.4)	1 (0.6)	3 (0.8)	3 (1.1)
Sleep disturbance	0 (0.0)	0 (0.0)	5 (3.0)	27 (7.2)	12 (4.5)
Other adverse events	26 (24.5)	41 (7.9)	18 (11.0)	41 (10.9)	33 (12.3)
All adverse events	106 (100.0)	518 (100.0)	129 (78.7)	301 (80.3)	210 (78.1)
Other reasons for changing to another SSRI					
SSRI not treating depression			29 (17.7)	72 (19.2)	56 (20.8)
Patient prefers another SSRI			6 (3.7)	2 (0.5)	3 (1.1)
All reasons for changing SSRI			164 (100.0)	375 (100.0)	269 (100.0)

a Data are presented as n (%) of AEs identified in the electronic medical records.

AE(s) = adverse event(s); **SSRI** = selective serotonin reuptake inhibitor.

files. They were also not identified from the examination of case notes containing the drug name citalopram and an adverse event listed in the medical warnings files. These 91 events were recorded for 76 patients. Not all reasons for switching SSRIs were due to an identified adverse effect. In many cases, the physician was trialling a different SSRI to see if an adverse symptom or effect would disappear or be ameliorated. Often the SSRI was just 'not working' in treating the patient's depression. The identified reasons for changing therapy listed in table II often include more than one reason for individual patients.

Combining results from the investigations of medical warnings data and consultation notes, including reasons for switching SSRIs, 701 adverse events considered to be due to citalopram were identified relating to 473 patients (8.4% of the 5612 patients prescribed citalopram). Overall, 23 of these patients had a recorded event in both the medical warnings file and the consultation text notes, although there were only 16 patients with evidence of the same event in both data sources.

Discussion

The findings from this investigation indicate that data recorded in New Zealand primary care by physicians and their practice staff in the day-to-day treatment of their patients provides important information for monitoring adverse events related to medicines, vaccines and other causes of adverse health outcomes. Without doubt, the richest source of information regarding the description of adverse events was in the free-form text of physicians' consultation notes, as evidence of these events was not always recorded in the medical warnings files. Defined procedures and database search algorithms were required for identifying within these notes adverse events and their suspected causes, as well as a knowledge of primary care physician consultation note 'language' and abbreviations. With the exception of the final scrutiny of the consultation text notes, these analyses may be automated in computer programs and the potential exists to refine the search process by using other linked data, including known prescriptions and concurrent treatment along with information on adverse effects already published.

Record review of consultation notes to confirm adverse events is time-consuming. Two researchers in this study (AT and SD) reviewed 4138 records containing the drug name citalopram (or its brand names) and an adverse event listed in the medical warnings files for citalopram, and 1733 records in the switching medicines analysis in which the names of both SSRIs were recorded in the notes. On average, the review of one record took approximately 2 minutes, which represented a total of 5 weeks of review for each researcher. Automated detection of adverse events recorded in primary care consultation records is the goal but this requires language processing algorithms with a high sensitivity and is a subject for further research. To date, there have been very few studies published that use text-mining techniques of clinical notes in primary care records to investigate ADRs.[28]

Data in the medical warnings files were clearly intended for guiding the clinical care physicians provided for patients. They are patient-centred, designed to capture data of importance to individual patients, and contain a great deal of valuable information that can contribute to a realistic appraisal of how products are used. They included records of adverse events related to healthcare products and devices delivered in settings outside general practice, including events due to hospital-based care, radiological dyes, over-the-counter drugs, and complementary and alternative medicines. Although a substantial number of medicines were still prescribed despite a warning being present, in many cases, the benefit of the treatment will have been considered more important that the adverse event experienced by the patient.

Although our findings indicate that the adverse events considered by physicians to be caused by drugs and documented in the consultation notes and medical warnings may outnumber those identified by New Zealand's current spontaneous reporting system by as much as 30 to 1, many of the events identified were not of a serious nature and no unknown adverse effects were described for SSRIs. Data from the medical warnings file collected from one study practice showed there

were records relating to 725 adverse events, medical warnings and allergies occurring in 549 patients, but only 21 suspected adverse drug events (2.9%) were reported to the New Zealand CARM. Voluntary reports submitted to CARM include the physician's opinion of reaction severity, the temporal relationship between the suspected drug and the reaction, and other related information to help in clinical evaluation and causality assessment. Such information is not necessarily recorded by physicians in their day-to-day practice. The suspected adverse events reported to CARM are likely to have been those considered more serious although we were not able to verify this.

We found differences between the reasons for switching between therapeutic entities, and the adverse events listed in the medical warnings files. The adverse event profile for citalopram derived from the medical warnings file was similar to that presented in Medsafe's datasheets. The most commonly recorded adverse events in the medical warnings were nausea, tremor, sweating, somnolence, skin rash, vomiting and diarrhoea. Anxiety, however, was a prominent reason for changing treatment but was not a prominently listed adverse event. Relative to the adverse events listed by Medsafe, there may have been underreporting of sexual dysfunction. This raises the possibility that medical warnings and alerts in primary care electronic records are biased towards reporting the known adverse event profile of the drug, whereas previously unknown adverse events may be better detected through examining the reasons for switching between therapeutic entities that are recorded in consultation notes.

Detecting signals of unknown adverse events may require a more complex approach that specifically targets selected drug-event associations. Such an approach is being investigated as part of the EU-ADR project in which a ranked list of high priority events has been created to provide the initial list for signal detection. Unconstrained data mining for drug safety signals may generate an unacceptably high number of spurious signals.[29] In New Zealand primary care medical records, high priority events such as acute renal failure will usually be recorded as diagnostic codes although recording of these codes is not comprehensive for all clinics. Evidence of these events will also be documented within consultation notes as free text. For conditions likely to require hospitalization, hospital discharge diagnoses may be linked to primary care prescription data using each patient's NHI code to quantify drug-event associations. The synthesis of evidence of each event from these linked primary and secondary healthcare data sources for known cohorts of patients using a medicine can provide estimates of risk for specific health outcomes.

The limitations of the methods used in the present study include the possibility of alternative, unknown, reasons for switching medicines, incompleteness of some medical records and inability to establish causality. In addition to patient-related factors such as lack of effect or adverse events, therapeutic entities may be switched because of cost or supply issues. In this proof-of-concept study we also examined only reasons for patients switching SSRIs. Patients may also have switched treatment between different antidepressant drug groups because of suspected adverse events or a lack of effect in treating depression.

Many adverse events documented within the consultation notes will not have been identified. The search algorithms used to detect evidence of adverse events experienced by patients using citalopram included only adverse events listed in the medical warnings files and recognized by physicians, but other events may be documented elsewhere in the electronic record. In the second analysis to determine why patients switched SSRIs to or from citalopram, all recorded reasons for changing drugs were examined, yet no unknown adverse effects were documented. In total, 5612 patients used citalopram during the 6-year study period and it is likely this number is insufficient to provide evidence of possible adverse events that were previously unknown and/or rare adverse events. Expansion of the primary care pharmacovigilance database to include data from more primary care clinics should increase its potential for identifying patient risk of adverse outcomes and for providing better estimates of the frequency with which adverse events occur in primary care.

Consultation notes, drug safety signals and other medical warnings are more comprehensively

recorded at some clinics than others. The proportion of consulting patients for whom medical warnings were recorded ranged from 1.5% to 14.5% across these 30 New Zealand practices, and consultation notes were recorded for 67–96% of all consultations given. Although prescription recording is comprehensive (because the only way a prescription may be generated is electronically) and includes drug strength, dosage and quantity from which treatment duration may be determined, prescribed medicines may not have been dispensed, resulting in overestimation of the number of patients exposed.

The aim of the system used in this study was to detect evidence of possible adverse drug events recorded by primary care physicians during the treatment of their patients. The methods employed do not attempt to assess the causal relationship between the adverse events and the medicines considered by the physicians to be responsible but they do examine the extent of adverse events experienced in real-life conditions by primary care patients. Existing knowledge on the frequency of adverse events often comes from clinical trials conducted under ideal conditions. The investigation of why patients switch or discontinue medical treatment also provides information on the comparative effectiveness of medicines and has the potential to generate signals of new drug safety issues since all reasons for switching SSRIs were examined. The results from this study indicated that when SSRIs were not changed because of lack of effect or patient preference, they were changed because the physician suspected there had been an adverse drug event. Adverse events unknown to the physician were not identified however.

It is now recognized that safeguarding the public's health requires a complementary set of techniques for the detection, verification and quantification of safety issues.[30] We found that routine data collected in primary care in New Zealand has the potential for other pharmacovigilance analyses and patient safety research, including identifying prescriptions of contraindicated medicines, prescriptions exceeding maximum recommended dosages, and the monitoring of laboratory test results indicating that certain medicines should not be prescribed. Most notably, in New Zealand a unique patient identifier code is recorded in most national healthcare databases and enables primary care records to be linked with hospital discharge and mortality data and the National Pharmaceutical Collection of subsidized dispensed medicines. This provides the opportunity to examine the risk of adverse health outcomes due to the use of medicines in primary care. In addition, all prescribed medicines may be investigated to augment the Prescription Event Monitoring methods undertaken by New Zealand's IMMP in monitoring of a limited range of medicines. Currently, the extraordinarily comprehensive data in these datasets are seldom used for leveraging useful information through research.[31]

Conclusions

The strength of this primary care electronic health record data mining method is its ability to detect drug safety signals from patients switching medicines that can be explored in prospective studies and to estimate the true extent of adverse events occurring in primary care patients. Routinely recorded primary care data in New Zealand provides substantial opportunities for monitoring drug safety signals and for other patient safety issues. Medical warnings data and consultation notes contain a wealth of information on adverse events that should be more fully examined. Investigation of the reasons why patients change medicines within a therapeutic group also provides a promising method for signal detection in pharmacovigilance and research on the comparative effectiveness of medicines.

Acknowledgements

Funding for this research was initially provided by a Medsafe/Health Research Council (HRC) of New Zealand product vigilance feasibility study grant (Medsafe/HRC Feasibility Study PV-18). The authors' research and report were conducted independently of these study sponsors.

We would like to thank the doctors and practice nurses of the general practices that contributed data for this research.

Ethical approval for this research was granted by the New Zealand Multi-Region Ethics Committee, Ministry of Health, Level 2, 1–3 The Terrace, P.O. Box 5013, Wellington, New Zealand (MEC/08/04/EXP).

The authors declare no competing interests with regard to this study.

All authors were involved in the conception and design of the study. Andrew Tomlin and Murray Tilyard were responsible for the acquisition of study data. Andrew Tomlin, David Reith and Susan Dovey conducted the analysis and drafted the article. Murray Tilyard provided critical revision of the content of the article. All authors approved the final version to be published. No other person may be considered an author of this research paper.

References

1. Harmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perpectives. Eur J Clin Pharmacol 2008; 64: 743-52
2. Almenoff JS. Innovations for the future of pharmacovigilance. Drug Saf 2007; 30 (7): 631-3
3. Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. Br J Clin Pharmacol 2003; 57 (2): 127-34
4. Hauben M. Signal detection in the pharmaceutical industry: integrating clinical and computer approaches. Drug Saf 2007; 30 (7): 627-30
5. Bate A, Lindquist M, Edwards IR. The application of knowledge discovery in databases to post-marketing drug safety: example of the WHO database. Fundam Clin Pharmacol 2008; 22 (2): 127-40
6. Bate A, Lindquist M, Orre R, et al. Data-mining analyses of pharmacovigilance signals in relation to relevant comparison drugs. Eur J Clin Pharmacol 2002; 58 (7): 483-90
7. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006; 29 (5): 385-96
8. 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: i49-59
9. Platt R, Wilson M, Chan KA, et al. The new sentinel network: improving the evidence of medical-product safety. N Engl J Med 2009; 361 (7): 645-7
10. Behrman RE, Benner JS, Brown JS, et al. Developing the sentinel system: a national resource for evidence development. N Engl J Med 201; 364 (6): 498-9
11. Stang PE, Ryan PB, Racoosin JA, et al. Advancing the science for active surveillance: rationale and design for the Observational Medical Outcomes Partnership. Ann Intern Med 2010; 153: 600-6
12. Reisinger SJ, Ryan PB, O'Hara DJ, et al. Development and evaluation of a common data model enabling active drug surveillance using disparate healthcare databases. J Am Med Inform Assoc 2010; 17: 652-62
13. Coloma PM, Schuemie MJ, Trifiro G, et al. Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR project. Pharmacoepidemiol Drug Saf 2010; 20: 1-11
14. Associate Minister of Health, Minister of Health. Actioning medicines New Zealand. Wellington: Ministry of Health, 2010 [online]. Available from URL: http://www.health.govt.nz/publication/actioning-medicines-new-zealand [Accessed 2012 Jul 25]
15. Kunac DL, Harrison-Woolrych M, Tatley MV. Pharmacovigilance in New Zealand: the role of the New Zealand Pharmacovigilance Centre in facilitating safer medicines use. N Z Med J 2008; 121 (1283): 76-89
16. Classen DC, Pestotnik SL, Evans RS, et al. Computerized surveillance of adverse drug events in hospital patients. JAMA 1991; 266: 2847-51
17. Zha AK, Kuperman GJ, Teich JM, et al. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. J Am Med Inform Assoc 1998; 5 (3): 305-13
18. Bates DW, Evans RS, Murff H, et al. Detecting adverse events using information technology. J Am Med Inform Assoc 2003; 10 (2): 115-28
19. Melton GB, Hripcsak G. Automated detection of adverse events using natural language processing of discharge summaries. J Am Med Inform Assoc 2005; 12 (4): 448-57
20. Honigman B, Lee J, Rothschild J, et al. Using computerized data to identify adverse drug events in outpatients. J Am Med Inform Assoc 2001; 8 (3): 254-66
21. Seger AC, Gandhi TK, Hope C, et al. Development of a computerized adverse drug event (ADE) monitor in the outpatient setting. In: Henriksen K, Battles JB, Marks ES, et al., editors. Advances in patient safety: from research to implementation. Rockville (MD): Agency for Healthcare Research and Quality, 2005; 2: 173-83
22. Wood L, Martinez C. The general practice research database: role in pharmacovigilance. Drug Saf 2004; 27 (12): 871-81
23. Johansson S, Wallander M, de Abajo FJ, et al. Prospective drug safety monitoring using the UK primary-care general practice research database: theoretical framework, feasibility analysis and extrapolation of future scenarios. Drug Saf 2010; 33 (3): 223-32
24. Selak V, Rafter N, Parag V, et al. Cardiovascular treatment gaps: closing, but slowly. N Z Med J 2009; 122 (1293): 3564
25. Didham R, Dovey S, Reith D. Characteristics of general practitioner consultations prior to suicide: a nested case-control study in New Zealand. N Z Med J 2006; 119 (1247): U2358
26. Johansson M, Hall J, Reith D, et al. Trends in the use of inhaled corticosteroids for childhood asthma in New Zealand. Eur J Clin Pharmacol 2003; 59 (5-6): 483-7
27. Pethica BD, Penrose A, MacKenzie D, et al. Comparison of potency of inhaled beclomethasone and budesonide in New Zealand: retrospective study of computerised general practice records. BMJ 1998; 317 (7164): 986-90
28. Warrer P, Hansen EH, Juhl-Jensen L, et al. Using text-mining techniques in electronic patient records to identify ADRs from medicine use. Br J Clin Pharmacol 2012; 73 (5): 674-84
29. Trifiro G, Pariente A, Coloma PM, et al. Data mining on electronic health record databases for signal detection in pharmacovigilance: which events to monitor? Pharmacoepidemiol Drug Saf 2009; 18: 1176-84
30. Stricker BH, Psaty BM. Detection, verification and quantification of adverse drug reactions? BMJ 2004; 329: 44-7
31. Dovey S, Loh LW, Cunningham WK. Leveraging information from New Zealand statistical data: a first step to wisdom in transforming unmet need for general practice services. N Z Med J 2011; 124 (1334): 15-7

Correspondence: *Andrew Tomlin*, Best Practice Advocacy Centre, Level 8, 10 George Street, Dunedin 9016, New Zealand.
E-mail: andy.tomlin@bpac.org.nz