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REVIEW ARTICLE

Pharmacoepidemiologic research in Australia: challenges and opportunities for monitoring patients with rheumatic diseases

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Abstract The topic of drug safety has received great attention in recent years. Pharmacoepidemiology is the study of the use and effects of medicines in large populations using epidemiological methods. Pharmacoepidemiologic research can fill the knowledge gaps due to the limitations of existing pharmacovigilance systems that rely on randomised controlled trials and voluntary reporting. This review discusses the present state of pharmacoepidemiologic research in Australia. In Australia, linking administrative data on use of medications and medical services is possible to a certain extent. Data from patient registries with respect to rheumatology are also available. These data are valuable for better understanding of the beneficial and adverse effects of medicines. Opportunities and challenges of using these data sources to address issues from clinical pharmacology are also highlighted. Australia is well-placed internationally to make major contributions to the knowledge base of outcomes of medicines in the real-world setting. Developments in pharmacoepidemiology are critical to clinicians treating patients with rheumatic and other conditions.

Keywords Australia · Data linkage · Observational studies · Pharmacoepidemiology · Rheumatic diseases

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Introduction

Arthritis and musculoskeletal conditions have a high prevalence in Australia, with more than six million Australians having one or more of these conditions [1]. They impose considerable societal burden in terms of disability, health-related quality of life and health care costs [1]. Decision-making with respect to medicines for optimal patient management is increasingly complex. This is partly because the pharmacotherapeutic options for many conditions have increased, and more patients are exposed to a broadening array of medicines and thereby increasing the likelihood of an adverse event. Thus, pharmacoepidemiological scientific results are important to rheumatologists.

Pharmacoepidemiology is an observational science that focuses on patterns of medication use and the associations between medicines and outcomes (good and bad) in non-experimental situations [2]. The topic of drug safety has received increasing attention in the past several years. In part, this attention was renewed by the withdrawal of rofecoxib, a decision made after the safety monitoring board of the APPROVe trial found an increased risk of cardiovascular events in patients treated with rofecoxib compared to placebo [3]. Numerous articles have discussed the impact of and lessons learnt from this largest prescription-drug withdrawal in history [4–6]. Other notable examples of questioning drug safety and effects include the cardiac effects of rosiglitazone [7], the association between aprotinin and increased mortality [8], cardiac effects of non-steroidal anti-inflammatory drugs [9], gastrointestinal bleedings induced by selective serotonin reuptake inhibitors [10] and protective effects of HMG-CoA reductase inhibitors ('statins') against osteoporotic fractures and dementia [11]. Such controversies emphasise

the need for constant revision of product information and a proactive surveillance of the effects of medicines.

The aims of this review are to (1) outline the limitations of today's methods used in pharmacovigilance, (2) describe how pharmacoepidemiologic research can contribute, (3) discuss the existing data sources in Australia for monitoring utilisation patterns of medicines for rheumatic diseases and patient outcomes and (4) discuss the challenges faced by Australia for research using secondary data.

Pharmacovigilance systems

Pre-marketing evaluation by clinical trials

Pre-marketing evaluation of pharmaceuticals for safety and efficacy involves three phases: phase I tests basic safety of a drug for the first time in humans; phase II examines drug efficacy; and phase III involves confirmatory studies of both safety and efficacy in larger patient populations, and these are often double-blind randomised controlled trials (RCTs). RCTs are regarded the most rigorous approach to determine whether a cause–effect relationship exists between a treatment and an outcome and, therefore, this method has been the gold standard for evaluating the effects of new medicines. However, RCTs cannot fully explore the effects of pharmaceuticals. Major limitations include: RCTs are generally conducted over a relatively short period of time; patients must meet specific criteria to enter in RCTs and thus there is an under-representation of the patient population seen in clinical practice, in particular, the young, the elderly, ethnic minorities and those with comorbidities are often excluded in trials; rare side effects are likely to be missed in short-term trials involving only limited numbers of patients; risk is often under-estimated because RCTs assume patient compliance to allocated treatment(s); and patients taking other treatment(s) are generally excluded from RCTs to simplify testing for marketing approval, thus drug interactions are not investigated [12, 13].

Post-marketing spontaneous reporting

Many countries maintain a register of reports of adverse reactions to drugs. In general, the spontaneous reporting approach has the advantage of covering a nationwide population. There are multiple reporting routes (suspected adverse reactions data are collected on a voluntary basis with reports submitted by medical practitioners, pharmacists, dentists, patients and pharmaceutical industry) and it is useful for detecting unusual or rare events [14].

Australia relies on a voluntary surveillance reporting system that is administered by the Adverse Drug Reaction Unit within the Therapeutic Goods Administration. This unit monitors the reporting of suspected adverse reactions to medications, and these reports are reviewed by medical professionals who are members of the Adverse Drug Reactions Advisory Committee. The Australian reporting system for adverse drug reactions has been acknowledged as one of the best in the world; about half of the reports are submitted voluntarily by health professionals [15]. However, incidence of events cannot be reliably calculated based on data gathered from a spontaneous reporting system and the adverse events data may be influenced by unrecognised biases. Some influencing factors include: the clinical status of the patient, the number and types of medications that the patient was receiving, prior knowledge of the drug, extent of drug use, severity of reaction and the final outcome of adverse events are often not reported, nor linked to administrative data sets where some clinical and economic information at the individual level could be obtained. Other disadvantages of spontaneous reporting include: incomplete and missing data, recall bias, errors in prescription records and differential bias in reporting adverse drug reactions for various age–gender groups. Furthermore, in the absence of a comparison group, often times it is not possible to distinguish between the influence of the drugs and the influence of the indications for their use [16]. Therefore, definitive conclusions about the significance of the reported events or causality with respect to a particular drug cannot be drawn. Such systems remain very much alerting mechanisms for possible adverse drug reactions.

The role of pharmacoepidemiology and outcomes research

Monitoring the outcomes of medication use is a core component of the national Quality Use of Medicines (QUM) strategy, a pillar of Australia's National Medicines Policy [17]. Examining the cost effectiveness of subsidised medicines in practice is also an initiative of the federal government.

Pharmacoepidemiologic studies have become more prominent as computer-based databases have become more available during the past 20 years. Electronic health care databases are valuable sources for drug surveillance purposes [18]. Regulatory authorities also recognise their usefulness for drug safety studies; the US Food and Drug Administration is developing guidance about how to use large electronic health care databases for this purpose [19]. Carefully conducted longitudinal observational studies can provide additional, yet complementary information to that gained from RCTs and overcome the limitations found with the current pharmacovigilance systems.

There are a number of areas where pharmacoepidemiologic research can contribute [2]:

1. Defining medication needs: defining the prevalence and burden of a particular clinical problem to identify the clinical place for the new therapeutic agent,
2. Assessing patterns of drug utilisation: examining medication use to identify problems such as under-use or over-use; examining utilisation patterns by type of patient or by type of prescriber specialty can help to identify target population for educational interventions to improve medication use,
3. Addressing issues such as medication adherence by better understanding of utilisation patterns of drugs,
4. Monitoring the effectiveness of medicines: effectiveness describes how well a medication performs in real-world setting, that is, when it is used by typical doctors treating average patients over a prolonged period of time and in comparison with other available therapeutic alternatives and
5. Surveillance of adverse effects by quantifying the frequency and severity of adverse effects of a drug or drug class.

The most important challenge when evaluating treatment effects using observational studies is confounding by indication, that is, the risk of an adverse event is not associated with the medicine itself but with the indication for medication use [20]. Another major criticism of observational studies is that unrecognised confounding factors may influence the results [21]. However, most of the biases in these data can be controlled by using appropriate case inclusion criteria [22]. Comparisons of observational studies with RCTs have shown that these studies often produce similar results and that well-designed observational studies do not systematically over-estimate the magnitude of treatment effects and do provide valid additional information [23, 24]. Further, observational health care data portray the use of medicines in actual practice and their long-term consequences.

Administrative data sources

Administrative databases contain information about the delivery of services or a record of events, collected primarily for funding purposes. Some examples of such data sources in Australia include: payments to Medicare for non-drug medical services, subsidy records of prescription medicines, hospital admission and separation records and death records.

In Australia, the majority of prescription medicine use (~80%) is publicly funded via the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS), and the Medical Benefits Scheme covers a wide range of medical services provided by medical practitioners and allied health professionals. From 2002, patients for whom each subsidised prescription has been written are identified via their unique Medicare number and their demographics (e.g. age and gender) are recorded; previously, only information on concessional patients was captured. Medicare Australia is a government statutory authority that administers the R/PBS, the Medical Benefits Scheme and other health programs.

Studies have used data from Medicare Australia on R/PBS prescription claims to define trends in drug use [25, 26], evaluate educational interventions related to drug dosing [27], examine prescribing restriction changes [25, 28], as well as to provide feedback to general practitioners about their prescribing practices [29]. Estimates of medicine utilisation using prescription claims databases have advantages over those that rely on self-reports of drug consumption [30]. Because the data are collected for administrative purposes, there is a good level of compliance with reporting and the accuracy of data submitted is usually high [31]. Important limitations of Australia's prescription medicine claims data include: longitudinal data are available for only a maximum of a 5-year period, the lack of information on dosage and the clinical indication for which a medicine was prescribed, the use of medicines in public hospitals is not captured and the use of non-subsidised (i.e., private and below co-payment) prescriptions is not captured. Estimates of dispensing of non-subsidised prescription medicines from a sample of pharmacies are included in the dataset maintained by the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee [25, 32].

State and territory health authorities maintain data on episodes of care for patients admitted to public, private and psychiatric hospitals and day hospital facilities. Information available includes sex, age, Aboriginal and Torres Strait Islander status, area of usual residence, diagnoses and procedures. Diagnoses and procedures are coded using the International Statistical Classification of Diseases and Related Health Problems, Australian Modification [33]. Each state and territory also maintains information pertaining to deaths by the Registrars of Births, Deaths and Marriages. Such records contain information on sex, age at death, date of death, area of usual residence, Aboriginal and Torres Strait Islander status, country of birth and cause of death. The cause of death is certified by the medical practitioner or the coroner and coded by the International Classification of Diseases. Australia is, therefore, replete with health care data in linkable databases as a result of administrative data routinely collected for management and claim purposes.

Linking data on medication use and health outcomes in Australia

Data linkage involves the amalgamation of records relating to the same individual from different sources, based on there being individual-identifying information in each of the databases to enable linkage [34, 35]. Data linkage is particularly useful in longitudinal studies. It can provide a rich resource for evaluation of health policies and for clinical and epidemiological research and, thereby, make a major contribution to the understanding of relationships between medication use and health outcomes [35, 36]. Ideally, the key data components informing evaluation of patient outcomes (namely, medication used and clinical outcomes via proxy measures such as laboratory tests and results and records of medical care services use) recorded by separate databases would be linked by unique patient identifier.

National level data linkage

Australia's Department of Veterans' Affairs (DVA) maintains several administrative databases that capture comprehensive information on medicines and medical services provided to entitled veterans and eligible dependents. The eligible treatment population includes approximately 281,600 veterans in June 2008. The majority is elderly, of whom 77% are aged >65 years [37]. DVA beneficiaries account for 10% of Australians aged 65 years and over and 25% of Australians aged 80 years and over [38].

The DVA pharmaceutical claims database contains records of all prescription medicines dispensed to veterans that are reimbursed by the RPBS. It is a valuable resource for examining prescription medication use in a subgroup of elderly Australians. Details include patient identifier, prescriber identifier, dispensing pharmacy identifier, pharmaceutical item (coded according to the World Health Organisation Anatomical and Therapeutic Chemical classification), date of supply and quantity supplied. DVA also maintains a client file that contains demographic details such as date of birth, date of death, gender and family status. Moreover, DVA maintains private and public hospital datasets that include dates of admission and discharge, primary and secondary diagnoses and procedures performed. The medical and allied health care database includes claims data on medical, radiology, pathology and allied health services subsidised by DVA. Linking pharmaceutical data to DVA datasets on medical services claims has enabled investigation of the potential relationships between medication use and associated health outcomes on a longitudinal basis. Examples include trends of cardiovascular medicine use among diabetic patients [39], quality of diabetes processes of care [40], use of antidepressants and avoidable drug interactions [41] and inappropriate prescribing [42]. The ability to link de-identified datasets is an encouraging example of what can be achieved.

DVA datasets have also enabled a program in support of QUM, known as the Veterans' Medicines Advice and Therapeutics Education Services (Veterans' MATES; http://www.dva.gov.au/health/veteransmates/). This program aims to improve the use of medicines in the veteran community. Data on patterns of dispensing and service delivery are used to identify areas of medication misadventure. Patient-based feedback is provided, primarily for the veterans and their general practitioners and community pharmacists, to assist in improving the management of their medicines [43]. Clinical modules are also produced as a result of this program several times a year, each focusing on a particular aspect of medication management (for example, use of adjunctive medicines in diabetes and use of beta-blockers in congestive heart failure). A survey of general practitioners and veterans found on average a high degree of satisfaction (more than 75%) with such feedback and therapeutic information, and that prescribers were likely to review their patients as influenced by recommendations in the clinical modules [43].

State level data linkage

There is the potential to link some of the databases on a state level which could provide results generalisable nationally. Developments and successes with state-based linkage of data such as that established in Western Australia [44–46] have been encouraging. A world-leading data linkage system, the Western Australia Data Linkage System (WADLS), was first established in 1995. It uses computerised probabilistic matching to link seven core datasets (birth registrations, death registrations, hospital morbidity data, mental health records, midwives' notifications, cancer notifications and electoral registrations) held in Western Australia and covering 1.7 million individuals, with some of the datasets from as early as 1970s [38, 44]. A protocol has been designed to ensure both strong privacy protection and accurate linkage of these data [46]. While there are some known limitations due to weaknesses inherent in administrative data (for example, lack of details on end points needed to evaluate the effects of health services or medicines) [44], WADLS has supplied data for over 250 projects [47]. This system has enabled evaluation of health services and outcomes in areas including cancer care [48, 49], psychiatry [50, 51], health effects of air travel [52] and indigenous health [53]. More recent developments of this system involve linking existing state databases with Commonwealth records pertaining to aged care, prescription claims and medical procedure claims. Such linkage

will enable individual level studies of medicine use and associated health outcomes. If the Western Australian experience and example is extended, other legitimate research groups can start to undertake important data linkage projects. Another state level data linkage facility using similar approach has recently been established in New South Wales and the Australian Capital Territory—the Centre for Health Record Linkage ("CHeReL")—a collaborative venture funded by a number of organisations and hosted by the Cancer Institute of New South Wales. Other Australian states, including Queensland and South Australia, are currently establishing mechanisms for data linkage.

Patient registries

Patient registries are also valuable sources for tracking the outcomes of medical treatments, including medicines. With respect to rheumatology, a voluntary database (the Australian Rheumatology Association database, ARAD) has been established by the Australian Rheumatology Association [54]. This longitudinal registry collects health information of patients with inflammatory arthritis for the purpose of monitoring outcomes associated with the use of anti-rheumatic medicines (with a special focus on biological drugs).

In November 2008, there was a total of 2,642 patients enrolled in this database from 199 participating rheumatologists. This included 291 patients on infliximab, 1,253 on etanercept, 910 on adalimumab, 11 on anakinra, 738 on rituximab and nine on abatacept [55]. In March 2008, a number of patients (n=714) had discontinued biological therapy [56]. The majority of patients were taking more than one disease-modifying anti-rheumatic drug in addition to their biological therapy. The most common reasons for discontinuation reported were 'lack of efficacy' (40%) and 'side effect' (26%). A small proportion of patients did not continue with biological treatment due to 'failed PBS criteria' (5%) [56]; subsidised ongoing treatment via the PBS requires evidence of sufficient clinical improvement as assessed by a rheumatologist according to specified criteria [25, 26]. Examination of humanistic outcomes (e.g. health-related quality of life) is possible with ARAD as enrolled patients are required to complete such questionnaires regularly. Using this national patient registry, studies have examined rates of infection before and 6 months after initiation of biological therapy among patients with inflammatory arthritis [57] and described baseline comorbidities in patients with rheumatoid arthritis [58] and among patients with ankylosing spondylitis [59] who initiated biological therapy.

Another patient registry relevant to arthritis and musculoskeletal conditions is the National Joint Replacement Registry, which monitors all joint replacements (partial and total) that take place in Australian hospitals (both public and private) [60]. This registry was first established in South Australia in September 1999 and became a national database in 2002 and is monitored by the Australian Orthopaedic Association. The registry contains information predominantly on hip and knee replacements. Details recorded include age, gender, diagnosis and outcomes (mainly surgery revision) of the patient and the type of prosthesis and surgical techniques used.

Challenges in Australia for pharmacoepidemiologic research

Australia is replete with observational health care data that are valuable for evaluation of health outcomes associated with prescription medicines. The current situation in Australia is that individual level linkage of data on medicines and health services use is theoretically possible but not feasible at the national level. While there are clearly technological hurdles to linking medicines and health outcomes data nationally, the major barriers to date include concerns about patient privacy, a lack of political will and legislative restrictions on access to, and linkage of, the various data collections [12]. Nationwide data linkage requires cross-jurisdictional collaboration between the Commonwealth (custodian of R/PBS, MBS and national death data) and all State/Territory governments (the custodians of hospital separation data) and the adoption of appropriate linkage protocols to ensure adequate privacy protection.

While Western Australia has the capacity for monitoring individual patients' use of medicines and their outcomes, the sample size may be insufficient for many important questions. Further, although the linked data from DVA on veterans are valuable, findings from studies using such data may not always be generalisable to the general Australian population. Kelman et al. [12] have proposed a routine system be established for the ongoing examination of post-marketing experience of medicines nationwide using health care data routinely collected for many years. Government-subsidised access to effective prescription medicines via the R/PBS is, in effect, 'purchasing' health outcomes with the public purse. There is, therefore, an obligation to monitor the outcomes of this important investment to determine whether the expected health improvements are actually realised. Findings from regular and systematic evaluation using linked data would improve safety monitoring substantially by complementing evidence from pre- and post-marketing trials and voluntary reporting. An important milestone for pharmacovigilance in Australia is that the development of a nationwide data linkage capability is

currently underway ("Population Health and Data Linkage"); this is a recent government initiative as part of the National Collaborative Research Infrastructure Strategy (http://ncris.innovation.gov.au/).

In summary, recent events such as drug withdrawals and controversies around drug safety have led to a major push for improving the existing pharmacovigilance systems. Information on medication use and various aspects of health and well-being is available from a number of administrative and non-administrative databases in Australia. While most of these data from separate sources are currently not linked, an Australian-wide data linkage capability is now a national research priority as a result of increased attention and initiatives by multiple stakeholders. These observational health care data describe large patient populations and provide promising opportunities for proactive, longitudinal surveillance of the safety and effectiveness of medicines in clinical practice. Australia is well-placed internationally to make major contributions to the knowledge base of outcomes of medicines in the real-world setting. Timely, quality and relevant data for monitoring patient outcomes will enable informed improvements of policies, practices, services and quality of life for patients.

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Disclosures None

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