

Clinical and economic burden of adverse drug reactions

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ABSTRACT

Adverse drug reactions (ADRs) are unwanted drug effects that have considerable economic as well as clinical costs as they often lead to hospital admission, prolongation of hospital stay and emergency department visits. Randomized controlled trials (RCTs) are the main premarketing methods used to detect and quantify ADRs but these have several limitations, such as limited study sample size and limited heterogeneity due to the exclusion of the frailest patients. In addition, ADRs due to inappropriate medication use occur often in the real world of clinical practice but not in RCTs. Postmarketing drug safety monitoring through pharmacovigilance activities, including mining of spontaneous reporting and carrying out observational prospective cohort or retrospective database studies, allow longer follow-up periods of patients with a much wider range of characteristics, providing valuable means for ADR detection, quantification and where possible reduction, reducing healthcare costs in the process.

Overall, pharmacovigilance is aimed at identifying drug safety signals as early as possible, thus minimizing potential clinical and economic consequences of ADRs. The goal of this review is to explore the epidemiology and the costs of ADRs in routine care.

Key words: Adverse drug reactions, costs, pharmacovigilance, randomized controlled trials

INTRODUCTION

The World Health Organization has defined pharmacovigilance as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems”.^[1] Such ‘drug-related problems’ include adverse drug reactions (ADRs), unintended injuries or complications that arise from iatrogenic drug related causes and which cause or prolong hospital admission and result in disability or death.^[2-4] The risk of ADRs is necessarily

an inherent risk of all drug therapy and is modulated by several factors, including dose and frequency of administration, genotype, and pharmacokinetic characteristics of special populations, such as pediatric and geriatric patients and those with hepatic or renal impairment. Due to the high frequency and potentially serious consequences, ADRs may have a dramatic impact in clinical practice both from a clinical and economic perspective. The aim of this review is to explore the impact of ADRs in clinical practice from both the clinical and economic perspective.

Limitation of premarketing drug safety evaluations

Along with evaluations of drug efficacy, the detection and quantification of risks associated with drug treatment is a critical component of preclinical studies as well as the clinical phases (phases 1-3) of the drug development process before a drug is released in the market. Randomized controlled trials (RCTs), the main component of the premarketing clinical phases of drug development are the gold standard

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for evaluating drug efficacy but are much less effective at detecting ADRs.^[15]

RCTs have several limitations with regard to ADR detection. There are several issues that limit the generalizability of RCT results to clinical practice, such as limited study population size and duration of study, the selective recruitment of patients with resulting limited heterogeneity and the consideration of few predefined ADRs. The generalizability of clinical findings from RCTs to clinical practice, including that concern ADRs, has often been criticized as being inadequate and a major limitation.^[6-13] The selection of patients for RCTs may also not be representative of patients who will receive the treatment and who may be more vulnerable to ADRs. It has been observed that often, less than 10% of patients in RCTs in most areas of medicine and surgery have the relevant disorder under investigation.^[14-19] In addition, the inclusion criteria for RCT patients are frequently not reported, leading to significant limitations in conclusions regarding which populations are most at risk of the ADRs detected in RCTs.^[20] Even in patients with the relevant disease, the severity and staging of the disease as well as comorbidities in RCTs may not reflect those found in routine clinical care and affect the extrapolation of RCT results to populations in clinical practice.^[21] In particular, the frailest populations such as pediatric and geriatric patients are often underrepresented in RCTs, leading to limited premarketing drug-safety information about these patients.^[22-24]

Another main limitation of ADR detection and quantification using RCTs is their limited sample size.^[25-27] With a small sample size, RCTs can detect ADRs that are common and that develop over short periods,^[22] but their relatively short follow up time compared with the length of drug use in clinical practice, particularly in the cases of interventions that require chronic treatment such as epilepsy and schizophrenia, limits the ability of RCTs to detect ADRs.^[28-31] This presents an obstacle to detecting ADRs that appear at a time lag from the drug exposure, such as cancer, or those that develop after chronic use such as the long-term ADRs of oral contraceptives and hormone replacement therapy that can take years to develop.^[26] In addition, rare ADRs cannot be detected by RCTs because RCTs do not contain sufficiently large populations.^[32]

The low quality of ADR reporting in RCTs and the known publication bias associated with the pharmaceutical industry are other obstacles to ADR detection, quantification, and dissemination.^[33] On one hand, RCTs often have few or no predefined ADR screening protocols and cannot detect ADRs that are genuinely unexpected and for which no screening tests may therefore be carried out. This is a limitation inherent to the RCT design and such new ADRs can only be detected serendipitously. On the other hand, the quality of published RCT reports have been heavily criticized for a lack of transparency in their published ADRs reports.^[34] A

review of 113 RCTs published in high impact factor journals found that 15% of studies did not provide numerical data on the frequency of ADRs, 27% provided no information on the severity of ADRs, and 48% did not report the number of patients drop-outs due to ADRs.^[35] There are several cases of such suspected low-quality ADR reporting in the literature. A review of 25 non-steroidal anti-inflammatory drug (NSAID) RCTs with a total of 2566 patients, found that not one of the trials explicitly reported any renal ADRs, potentially suggesting underreporting.^[24] Although renal damage is not common, it is unlikely that not a single patient experienced renal ADRs. In RCTs, warfarin had much lower reported ADR rates than in clinical practice, contributing to concerns about the validity of RCT ADR data that consequently led to under-prescribing of warfarin in patients who could most benefit from warfarin therapy.^[36-38] The low-quality ADR reporting in RCTs has prompted concerted efforts to improve ADR reporting, as through the Consolidated Standards of Reporting Trials (CONSORT) guidelines.^[39] Nevertheless, the quality of published ADR reporting from RCTs has remained low.^[35]

Inappropriate use of medicine as cause for ADRs

The relevance of pharmacovigilance to ADR detection is highlighted by considering that a major cause of ADRs is the inappropriate use of medicines.^[40] However, the use of drugs in RCTs is according to strict protocols, often in patients who are not frail and in a very controlled environment, which is very unlike the use of drugs observed in the more dynamic clinical settings where the mode and consequences of drug use can be more complex. RCTs therefore cannot detect ADRs due to inappropriate drug use. ADRs arising from inappropriate drug use can be due to inappropriate dosage or duration of treatment, drug interactions, off-label use or use in contraindicated circumstance^[40,41] all of which can occur in the general population or in a hospital setting. ADRs arising from inappropriate medications use are a particular risk in the elderly, due to increased susceptibility as a result of age-related pharmacokinetic and pharmacodynamic changes as well as comorbidities and multiple drug use.^[42] The proportion of patients using potentially inappropriate medication increases from the community to the hospital setting.^[43] This risk of inappropriate drug use is compounded by patients self-medicating with over-the-counter medications. The role of pharmacovigilance in detecting and quantifying ADRs due to inappropriate medication use in a clinical setting is particularly important because such ADRs are potentially preventable.^[44]

Epidemiology of adverse drug reactions in clinical practice

Several epidemiological studies have been conducted that give an indication of the frequency of ADRs and the related healthcare costs in clinical practice. Such consequences include drug-related hospital admission, prolongation of hospital stay, and emergency department visits. Estimates from France

suggest that up to 123,000 patients a year present to their general practitioner with an ADR.^[45] Drug related causes are also often the cause of hospital admission.

ADRs account for 4.2-30% of hospital admissions in the USA and Canada, 5.7-18.8% of admissions in Australia, and 2.5-10.6% of admissions in Europe.^[46] Some studies focused on more vulnerable populations such as the pediatric and geriatric patients. Between 2.1% and 5.2% of ADRs in children lead to hospitalization, and up to 39% of ADRs in pediatric patients can be life-threatening or fatal.^[47] A national study from the USA estimated that 11.4-35.5% of emergency department visits in older adults are due to drug-related causes.^[48] Studies from Europe similarly found that up to 20% of ambulatory patients experience ADRs and approximately 10-20% of geriatric hospital admissions are drug-related.^[49,50] Another consequence of ADRs is the prolongation of hospital stay.^[51] A prospective study showed that ADRs increased the mean hospital stay from a mean of 8 days in patients without ADRs to 20 days in patients with ADRs.^[52] Davies *et al.* also found an increased risk of mortality in patients who experienced an ADR compared with those who did not.^[52] A high frequency of ADRs is also seen in nursing homes, with 32-65% of ADRs occurring in these populations.^[53-54] In general the role of drug surveillance measures is highlighted considering that between 32% and 69% of drug-related admissions were reported as definitely or possibly preventable.^[7] Through these pharmacovigilance and active drug monitoring studies, potential general *a priori* predictors of drug related adverse reactions such as female sex, increasing age and polytherapy have been identified.^[55] In addition, the type of drugs most likely to result in ADRs and the most common type of ADRs observed have also been characterized (e.g., mostly drugs that have been on the market for a long time such as NSAIDs, coumarins, antibiotics, beta-blockers etc.), facilitating their recognition and prevention.^[41,44-46,48,52,55,56]

Costs of adverse drug reactions

The impact and the management of ADRs is complex and in the USA may cost up to 30.1 billion dollars annually. ADRs may increase costs due to increased hospitalization, prolongation of hospital stay and additional clinical investigations in more serious cases. In addition ADRs may trigger prescription cascades when new medications are prescribed for conditions that are a consequence of another medication, which is often an unrecognized ADR. Examples include the use of antipsychotics in Parkinson's disease patients treated with dopaminergic drugs or the use of anticholinergic drugs for urinary retention in Alzheimer's disease patients treated with cholinesterase inhibitors.^[57] This increases the costs of pharmacotherapy as well as compounding the risk of further ADRs.

Out of incident ADRs that resulted in hospitalization, the cost per preventable ADR was estimated to be higher than

for non-preventable ADRs.^[58] Another study conducted in inpatient setting found the cost to be \$US 2262 per ADR.^[59] The costs of ADRs in inpatient setting varies within different hospital wards, costing \$US 13,994 in a non-intensive care unit (ICU), but \$US 19,685 in ICU.^[60] In addition, drug surveillance studies have been able to identify the following ADRs as those having the greatest economic burden in hospital setting: fever, bleeding, diarrhea and cardiac arrhythmia, in decreasing order.^[59] NSAIDs, antibacterial agents, anticoagulant agents and antineoplastic agents are a major cause of ADR-related costs.^[61] Both the extended duration of hospital stay as well as the out patient care as a result of ADRs constitute the source of financial burden.^[62] The main costs of ADRs in a hospital are wages, disposable goods and medications.^[63] Aside from the direct financial costs, there are also several indirect costs for patients and their care givers that are incurred by ADRs, such as missed days from work and/or morbidity such as anxiety due to the ADR episode.^[64]

Strategies for improving quality of care and reducing healthcare costs

It is clear that ADRs are a source of additional economic burden on patients, their care-givers, and the healthcare systems that treat them. It is also clear that RCTs on their own are not sufficient to detect and assess the frequency of ADRs. Postmarketing pharmacovigilance activities such as spontaneous reporting, cohort event monitoring and retrospective database studies that complement RCT data provide more clinically relevant data with longer follow up periods and larger population sizes that are necessary for a more accurate and on-going evaluation of the risk-benefit ratio for healthcare interventions.^[25,26,32] Irrespective of the type of postmarketing study, drug safety is more likely to improve when there is the joint involvement of regulatory agencies the pharmaceutical industry, and prescribers.^[65] This has recently taken place in the form of EU guidance EMA/813938/2011 Revision 1,^[66] where the EU medicines safety regulatory agency (EMA) has made postauthorization safety studies (PASS) legally binding when requested at the medicines regulating bodies' discretion and where they deem necessary. This new guidance strengthens the legal power of regulatory agencies as they regulate and process applications for the drug marketing authorization (MA). A requested PASS is legally binding both at first MA granting as well as postauthorization.

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