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ECONOMIC BURDEN OF ADVERSE DRUG REACTIONS IN A TERTIARY HOSPITAL

DIMITRIOS STAVROPOULOS[1]*, OSKAR HEDLUND[2], LINNEA NYBERG[3]

Affiliation [1]Department of Pharmacoeconomics, Macedonia Plain Institute of Pharmacy, Serres, Greece
[2]Department of Pharmacoeconomics, Norrland Institute of Clinical Pharmacology, Umea, Sweden
[3]Department of Pharmaceutical Management, Norrland Institute of Clinical Pharmacology, Umea, Sweden

*Corresponding author: Dimitrios Stavropoulos, d.stavropoulos@mpip.gr
ORCID iD: Dimitrios Stavropoulos 0000-0001-0510-2506; Oskar Hedlund 0000-0001-0493-5928; Linnea Nyberg 0000-0001-2447-4399

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Abstract

Adverse drug reactions are a leading source of avoidable harm in hospital medicine, and they carry costs that rarely appear as a single line in a hospital budget. This short communication is a narrative review that reports no new data. It summarises published evidence on how often adverse reactions cause admission or arise during stay, how their costs are classified and measured, what proportion is preventable, and how costing methods influence the figures. Studies agree that reactions prolong admissions and add substantial expenditure, while estimates differ widely because of definitions, case finding and cost components. Hospitals seeking to use such figures should recognise these limits and build local, transparent costing before relying on borrowed estimates.

1. INTRODUCTION

Every medicine that works has the potential to harm, and in hospital, where patients take several drugs at once and are often elderly or acutely ill, that potential is realised more often than most clinicians expect. A frequently cited systematic review and meta-analysis of studies in hospitalised patients estimated that adverse drug reactions (ADRs) affected a notable fraction of them [1]. A Dutch prospective study of acute admissions found that medication-related events accounted for a meaningful share of them, and that many were potentially preventable [2]. Those findings changed how hospital medicine thinks about drug safety, and they raised a follow-on question about cost.

Hospital managers and pharmacists have good reasons to ask what ADRs cost. Money spent on avoidable harm cannot be spent on care, and a figure, even an approximate one, can justify investment in pharmacovigilance, clinical pharmacy services or electronic prescribing. Yet cost estimates in the literature are hard to compare. Some count only the extra days spent in hospital, others add drug and laboratory expenses, and a few include lost productivity and litigation [3, 4]. This short communication, which reports no new data and is not a costing study of any one institution, reviews the published literature on the economic burden of ADRs in hospital settings such as a tertiary referral centre, and sets out how its findings can be used locally.

The review is organised around five questions. What is an ADR for costing purposes? How often do reactions cause or complicate admission? Which costs are attributable, and what do the available studies report? How much of the burden could be prevented? And what should a tertiary hospital consider before adopting published figures as its own? Findings are brought together in table 1, which lists representative studies by theme, and the distribution of entries is shown in fig. 1. A narrative approach was chosen because study designs differ too much for pooling, and because the aim is to explain the logic of costing rather than to produce a single number [3, 5].

2. DEFINITIONS AND SCOPE

Terminology determines what is counted. The World Health Organization describes an ADR as a response to a drug that is noxious and unintended and occurs at doses normally used in humans for prophylaxis, diagnosis or therapy. A more recent usage, set out by Aronson and Ferner and in Aronson's later discussion of medication errors, stresses the causal link with the drug and separates reactions from errors and from overdose [6, 7]. Adverse drug events (ADEs) are wider still, covering any injury resulting from medication use, including medication errors and non-adherence. A study of ADEs will find more events, and more costs, than one limited to reactions at normal doses, and the two cannot be set side by side without adjustment [8].

Table 1: Representative published studies on the occurrence and cost of adverse drug reactions in hospital

Study or source|design	Principal finding	Ref.
Miguel et al. Meta-analysis	Reactions occurred in a notable share of hospitalised patients, with marked heterogeneity	[1]
Leendertse et al. Prospective admissions	Medication-related events caused a meaningful proportion of acute admissions, many preventable	[2]
Bouvy et al. European review	Reactions were common among inpatients and a notable cause of admission	[9]
Senst et al. Network costing	Adverse drug events in a health care network added measurable cost per event	[10]
Schneider et al. University hospital	Medication-related problems carried a substantial cost	[11]
Rottenkolber et al. Internal medicine	Reactions leading to admission carried substantial direct costs	[12]
Rottenkolber et al. German microcosting	Prolonged stay was the dominant cost driver of events	[13]
Howard et al. Systematic review	A considerable share of drug-related admissions was judged preventable	[14]
Formica et al. Systematic review	Few economic studies of preventable reactions, with wide variation in method	[5]
Johnson and Bootman Cost-of-illness model	National drug-related morbidity cost estimated in tens of billions of dollars	[15]

Causality assessment adds a second layer. Most studies apply a structured instrument, of which the Naranjo algorithm is the most widely used and which comparisons show do not always agree, to classify events as definite, probable, possible or doubtful, and a decision is then needed about which categories to include [16]. Including only definite and probable events lowers the count and the cost, whereas adding possible events raises both. Preventability criteria are used to separate avoidable events from those that could not have been foreseen, and work such as that of Hallas and colleagues showed that the proportion judged preventable depends heavily on the definitions applied and the

intensity of data collection [17]. Cost estimates should state which categories they contain, and a surprising number do not.

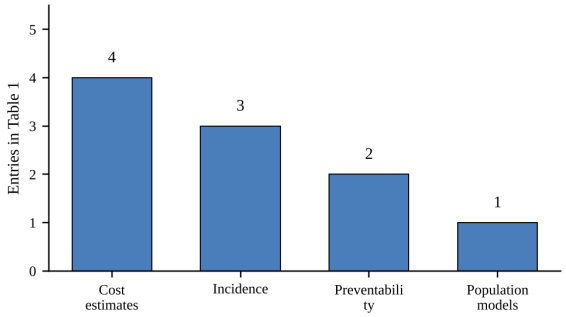


Fig. 1: Number of entries in table 1 by theme

Drug class shapes both the frequency and the price of reactions. Prospective studies repeatedly identify anticoagulants, antiplatelet agents, non-steroidal anti-inflammatory drugs, opioids, diuretics and antibiotics among the agents most often involved, which mirrors how widely they are used in acutely ill patients [2, 9, 18]. Bleeding from anticoagulants or gastrointestinal damage from anti-inflammatory drugs may demand transfusion, endoscopy or surgery, while an opioid reaction may need only a dose change and an observation period. Averages that mix these events hide a skewed distribution in which a minority of severe reactions account for most of the expenditure, which is why median and mean costs in a study can differ greatly.

The distinction between reactions and medication errors has economic meaning too. Studies of ADEs, which include errors, found that a large proportion of preventable events arose at the ordering stage and that many errors were intercepted before reaching the patient, so-called potential events [19]. Counting intercepted errors as costs would exaggerate the burden, while ignoring them would hide the benefit of existing safeguards. For a hospital that wants to estimate the burden of reactions only, restricting the analysis to events at normal doses and with a documented causality assessment is simpler to defend, even though it will understate total medication harm [7, 8].

3. INCIDENCE AND ADMISSIONS

Incidence data come from three kinds of study: prospective surveillance of inpatients, analysis of admission records, and systematic reviews. The meta-analysis by Miguel and colleagues pooled studies of hospitalised patients and reported that reactions occurred in an appreciable proportion of them, with marked heterogeneity between studies that reflected differences in definition and case finding [1]. Pooled figures of this kind describe the literature better than they describe any single hospital. The conclusion that ADRs are common, serious and often unrecognised has nevertheless been supported by later studies [9, 18].

Age and the number of drugs taken are the most consistent risk factors. In the Dutch admissions study, preventable events were commoner in older patients and in those taking several medicines, and a handful of drug classes accounted for a large share of the cases [2]. An Australian review of medication problems in acute care made the same observation and found wide differences between studies [20]. Prospective work in an Asian tertiary hospital reached similar conclusions about polypharmacy, which suggests that these risk patterns are not confined to Western health systems [21]. For cost purposes, they imply that an ageing inpatient population will carry a higher burden whatever the safety culture of the hospital.

Admission-based studies give a more direct figure for the burden on acute services. The Dutch prospective study found that medication-related events were the cause of a notable share of acute admissions to several hospitals, with the elderly and those taking several drugs most affected [2]. An Australian review of acute-care medication problems reached comparable conclusions and noted that a great deal of variation across studies reflected case-finding methods more than true differences between countries [20]. In England, hospital episode statistics over a decade showed a rising number of admissions coded for ADRs, although coding practice is itself a source of uncertainty [22].

Reactions arising in hospital have been studied through chart review, trigger tools and prospective ward-based monitoring. A European review of observational studies found that reactions were common among hospitalised patients and a notable cause of

admission, with the drug classes most often implicated being those used widely in acute care [9]. A Boston study of adult inpatients, though it used the broader category of ADEs, showed that errors at the prescribing stage accounted for many of the preventable events [19]. The trigger tool approach, built on markers such as antidote orders or abnormal results, offers a practical way to measure harm without relying on spontaneous reports [23].

4. COST COMPONENTS AND PUBLISHED ESTIMATES

Economists divide the costs of illness into direct, indirect and intangible categories [24, 25]. Direct costs include the extra drugs, laboratory and imaging tests, procedures, nursing time, and bed-days attributable to the reaction. Indirect costs cover lost earnings and productivity of the patient and carers. Intangible costs concern pain, suffering and reduced quality of life and are seldom valued in money. Most hospital studies cover direct costs only, usually from the hospital's perspective, and a few extend to the health service or society. The perspective chosen governs the answer, and the recommendations of the US Panel on Cost-effectiveness in Health and Medicine ask analysts to state it clearly [26].

Two American studies from the 1990s set the template for inpatient costing. One costed ADEs across a health care network by combining event frequency with unit costs and found that each event added measurable expense [10]. The other, set in a university hospital, estimated the cost of medication-related problems and found it substantial, which supported the case for prevention programmes [11]. Both used 1990s dollars and US hospital charges, which limits the transferability of their absolute numbers, while their relative message that ADEs add measurable expense per affected patient has been repeated in many settings.

Later work extended the evidence to other health systems. A German analysis of internal medicine hospitalisations estimated the direct costs of reactions leading to admission and showed that they consumed a substantial amount of resources [12]. A separate German microcosting study of adverse drug events in hospital gave detailed cost breakdowns, identifying prolonged stay as the dominant driver [13]. An American analysis of community hospitals reported lower per-event costs than those from academic centres, a reminder that case mix matters [27]. Reviews of this literature conclude that the cost per event varies by more than an order of magnitude according to severity, setting and method [3, 4].

Costs are not limited to the bed. A serious reaction may call for transfer to a higher level of care, an antidote, dialysis, extra monitoring or repeat imaging, and each of these adds its own charge. Cost analyses from hospitals in the United States and Germany describe how a small number of events requiring intensive care unit (ICU) admission or procedures account for an outsized fraction of event-related cost [10, 11, 13]. A community hospital study found that costs per event were more modest where reactions were managed on general wards [27]. Reporting costs by severity band, and not just as an overall average, gives managers a more realistic basis for budgeting than a single mean.

Population-level models try to scale such findings to a national cost. The cost-of-illness model proposed by Johnson and Bootman estimated the annual cost of drug-related morbidity and mortality in the United States in tens of billions of dollars, and an update by Ernst and Grizzle, using later data, produced a far larger sum [15, 28]. These models rest on assumptions about incidence and about the proportion of ambulatory events needing treatment that are difficult to verify, and their results are best read as order-of-magnitude statements. They are valuable in policy arguments but offer little guidance for the budget of a single tertiary hospital, which needs local data [4, 5].

Comparing published figures calls for adjustment. Costs reported in different years need to be inflated to a common price year using a suitable index, and those in different currencies converted with purchasing-power parities rather than market exchange rates, since hospital labour and drug prices do not track currency markets. Methodological texts recommend stating the price year and the

source of unit costs [24, 26]. Many of the reviews cited here quote original figures without adjustment, so a table of costs from several decades can be misleading if the numbers are read at face value [3, 4]. A simple rule is to compare relative effects, such as percentage prolongation of stay, before comparing money.

Length of stay deserves separate comment, since it is the largest cost driver in most studies and also the most contentious. Patients who develop reactions are generally sicker and older, so a simple comparison of stay with and without a reaction overstates the effect. Matched cohorts and regression adjustment reduce the problem, yet some bias is likely to remain, since a reaction may be both a cause and a consequence of a longer stay [11, 13]. Methodological papers have emphasised that excess stay attributed to an event should be reported with an explanation of how confounding was handled, and a few recommend sensitivity analysis showing how the cost changes under alternative assumptions [3, 24, 26].

5. PREVENTABILITY AND COSTING METHODS

Preventability changes the economic argument. If every reaction were unavoidable, the cost would be a fixed price of treatment, whereas a large preventable share means that spending on prevention could return savings. A systematic review of drug-related admissions found that a considerable proportion were judged preventable, with a small group of widely used drug classes responsible for most of them [14, 29]. A systematic review focusing on economic evaluations of preventable reactions found that studies were few, mostly from high-income countries, and varied in method, so that no pooled estimate of the cost of preventable reactions could be recommended [5]. The uncertainty is real, and it cuts both ways.

Typical preventable events involve known patterns: doses not adjusted for renal function, drug interactions that were avoidable, allergies not checked, monitoring not performed, or inappropriate drugs in older patients [2, 19]. These problems can be addressed with decision support, pharmacist review and better communication at transitions of care. The Harvard Medical Practice Study showed that drug complications were among the commonest adverse events in hospital and that many reflected substandard care, which shaped later hospital safety programmes [30]. A finance department weighing the cost of a ward pharmacist against savings from avoided events needs evidence on both sides of the equation, and the cost side is better documented than the benefit side [4, 5].

Methods for collecting cost data also vary. Top-down costing divides hospital expenditure by activity units such as bed-days and assigns an average cost per day, which is easy but ignores the fact that the extra days used by a reaction are usually cheaper than the average day, since the patient is mostly in recovery. Bottom-up or microcosting follows individual patients and records what was actually used, which is more accurate and more expensive to carry out [13, 27]. The textbook by Glick and colleagues on economic evaluation alongside clinical studies sets out these approaches and recommends that analysts select the one proportionate to the decision being supported [24]. For internal budget planning, a hybrid is often adequate.

Electronic health records (EHR) create new opportunities for detection. Rules that flag antidote orders, abrupt drug withdrawal, rising creatinine or abnormal drug levels can screen large numbers of patients at low marginal cost, and the trigger-tool approach has been adopted widely as a result [23]. Under-reporting remains a concern for any approach that relies on clinicians to volunteer information, which is why reviewers have urged combining sources [31]. The cost of building and maintaining such surveillance has to be set against the value of better data, a trade-off that few economic analyses have examined. Automated detection is promising, but it needs clinical validation before its output can support costing.

Case finding is the other big influence on results. Studies that use voluntary reports, discharge coding or pharmacist interventions each identify different subsets of events. A

hospital-wide estimate generated from voluntary reports will be low, while one generated from detailed chart review of selected wards can be extrapolated incorrectly [23, 31]. Trigger tools and prospective monitoring give better completeness but require staff time. A sensible approach is to combine sources, report the proportion of events found by each, and state the likely direction of bias, so that readers can judge how far the final estimate can be trusted [3, 8].

6. IMPLICATIONS FOR TERTIARY HOSPITALS AND LIMITATIONS

What does this mean for a tertiary hospital? First, published unit costs should not simply be imported. They come from different currencies, periods and health systems, and a tertiary hospital's case mix of complex, polymedicated patients is likely to give higher costs per event than a general hospital [21, 27]. Second, internal estimates should be built from routinely collected data where possible: pharmacy dispensing records, laboratory orders, coded diagnoses, bed-day costs from finance, and pharmacovigilance reports. Third, the estimate should be accompanied by a clear statement of which events and costs were included. A modest, transparent figure is more useful to decision makers than a large one that cannot be defended [3, 26].

Perspective is a further consideration for hospital decision makers. In a publicly funded system such as the National Health Service (NHS), savings from fewer admissions accrue to the payer and may free beds for other patients, which is an opportunity cost and not a cash saving. In an insurance-based or private setting the same event may be a revenue line. Costing guidance therefore asks analysts to say who bears each cost and over what time horizon [24, 26]. Cost-of-illness figures, as Rice originally argued, describe the scale of a problem and do not by themselves show that an intervention would be good value [25].

Several limits apply to the evidence summarised here. Most studies are from North America and Europe, and data from low- and middle-income countries are scarce, yet those are the settings where hospital resources are most constrained. Studies use differing definitions, time periods and currencies. Many are observational and subject to confounding, and few include indirect or intangible costs [4, 5]. Because this is a narrative review and a short communication, the selection of sources reflects the authors' judgement, and some relevant studies will have been missed. No new data are reported, and no institutional cost estimate is offered. The reference to a tertiary hospital in the title describes the setting to which the literature is applied [1, 18, 20].

Presentation of results matters as much as their calculation. Clinicians are more likely to respond to patient-level examples and length-of-stay (LOS) figures than to aggregate currency totals, whereas managers want costs and likely savings. A short report that states the definition used, shows the three or four largest drivers, gives a range instead of a single number and identifies preventable fractions can serve both audiences [3, 4, 5]. Overclaiming has a price. If a hospital promises savings that do not appear in the accounts, support for pharmacy and safety programmes can weaken, so cautious estimates presented with honest caveats protect the credibility of the work.

Priorities for future work follow from these limits. Multi-centre studies using common definitions and active surveillance would give more comparable cost estimates. Studies that follow patients after discharge would show how much of the burden currently falls outside hospital accounts [2, 22]. Economic evaluations of interventions such as clinical pharmacist review and electronic alerts should report costs and effects together, using the reporting standards already available [24, 26]. Finally, valuing the intangible costs of harm, including effects on quality of life, would make the case for prevention more complete than direct hospital expenditure alone can do [4, 25].

7. CONCLUSION

The published literature leaves little doubt that adverse drug reactions impose a real economic burden on hospitals, through admissions, prolonged stays and the extra

care that follows (fig. 1). Studies from several countries and decades agree on the direction of the effect, and the better-designed ones show that part of it is preventable [2, 10, 11, 14]. They disagree on the size, mainly because of differences in definition, case finding, cost components and currency, so a single figure borrowed from another setting is unlikely to describe a given tertiary hospital [3, 5, 13].

A practical response is local, transparent costing that states what was counted, combines more than one source of case finding and reports uncertainty honestly [24, 26]. Where such work shows that part of the cost arises from known, preventable patterns, investment in pharmacist review, decision support and better transitions of care can be argued on economic as well as clinical grounds [19, 30]. Reliable estimates will also need multi-centre studies and fuller attention to settings that have so far been underrepresented in the literature [4, 18, 20, 27]. Even a rough local figure, honestly derived, will serve better than a precise one borrowed from elsewhere.

8. ABBREVIATIONS

ADR-Adverse drug reaction, ADE-Adverse drug event, WHO-World Health Organization, ICU-Intensive care unit, LOS-Length of stay, NHS-National Health Service, EHR-Electronic health record

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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