

Effects of Adverse Drug Reactions and Adverse Drug Events in Hospital Admission Rates and Re-Hospitalization of Patients

Festina Balidemaj

Lunds Universitet Medicinska Fakulteten, Lund, Sweden
Northwestern Health Sciences University, Minneapolis, Minnesota, USA

Abstract

Background: ADRs and ADEs have a great potential to hospitalize and/or re-hospitalize patients. According to McDonnell and Jacobs, one ADR or ADE could lead a patient to a hospital length of stay of an average of 6.1 days. This can lead to lost days of work, a longer recovery time and even economic implications. **Methods:** A thorough evaluation of the relevant extracted literature has been analyzed thoroughly in order to find out how ADRs and ADEs impact the levels of hospitalization and re-hospitalization of patients and whether strategies, such as reporting systems, can aide in decreasing their overall occurrence. **Results:** As the level of hospital admissions/re-hospitalizations due to ADRs and ADEs depends on different factors, such as age and location, the data is separated in the following categories: pediatric population, general adult populations and geriatric population. Where data were available, location has been specified within each category as well. **Conclusion:** ADR and ADE-related hospital admission and readmission rates are age-group related, elderly being at the highest risk. However, these rates are not dependent on whether a country is developed or developing. Also, there are strategies that can be utilized by healthcare providers in order to decrease these rates in the future, such as to provide medication reviews and follow-ups.

Keywords: Adverse drug reactions, adverse drug events, hospital admission rates, hospital readmissions

Introduction

Adverse drug reactions (ADRs) and adverse drug events (ADEs) are among the leading causes of hospitalization and re-hospitalization in many patient groups and often lead to significant financial costs, as well as significant morbidity and mortality [12]. However, in order to be able to understand the implications of ADRs and ADEs, it is crucial to understand the definition of each and the difference between the two. An ADR is a reaction or a response to a medication that is not intended to occur at normal doses used as a therapy for treatment of a disease or for prophylactic

purposes. An ADR also differs from the term side effect (SE), as a side effect is generally a documented and an expected reaction to a certain medication therapy, which is not that medication's intended therapeutic outcome. The term side effect has somewhat been criticized as it tends to normalize the notion of damage from drugs. A concrete example of an ADR would be an allergic reaction to a drug expressed by the immune response through its mediation in hives or a rash [22].

An adverse drug event (ADE), on the other hand, is harm that occurs during the use of the drug, whether caused by it or not, including overdoses, dose reductions and medication therapy discontinuation [5]. In addition, about 25% of ADRs leading to hospitalization are at a level measured as serious to life threatening, which are a result of patient noncompliance, inappropriate dosing or insufficient therapy monitoring. All of these causes have been deemed as controllable, rendering ADRs as often preventable through different strategies that can be applied among physicians, pharmacists and other healthcare providers and even patients, including targeting communication and education [12].

What makes ADRs important in healthcare and likely to cause unexpected hospital admissions and re-hospitalizations is that they are not all discovered during the mandatory clinical trials (established to determine drug efficacy and get drug approval and release it into market). The most important method to detect unknown and additional ADRs of drugs is through ADR reporting in reporting systems by healthcare providers and by patients themselves. This reporting is done through reporting systems that are different depending on which country the ADR is being reported (for example, in United Kingdom they have a system called the UK Yellow Card scheme). Ultimately, updating reported ADRs would detect the possibility of ADR occurrences and enable their early detection of prevention of hospital admissions/readmissions due to them [5].

ADRs and ADEs have a great potential to hospitalize and/or re-hospitalize patients. According to McDonnell and Jacobs, one ADR or ADE could lead a patient to a hospital length of stay of an average of 6.1 days [12]. This can lead to lost days of work, a longer recovery time and even economic implications. Hence, the level of hospitalization and re-hospitalization due to ADRs and ADEs, as well as their impact on patient outcome, burden to the healthcare system, lifestyle and economy will be studied and discussed in this paper.

The purpose of this study is, therefore, to understand the level of ADR and ADE-related hospital admissions and re-hospitalizations, what causes them (whether the incidences are age-related or related to socio-economic status of the locations), and to explore possible strategies that can be utilized by healthcare providers and patients in order to decrease their overall incidence and prevalence, as decreasing ADRs and ADEs would lead to a significant decrease in healthcare costs and would lead to better quality of life of patients under ADR and ADE-prone drug therapies.

Methods

A systematic literature review via PubMed, Lund University libraries, and Rochester Institute of Technology online library database searches were conducted in an iterative manner during the year of 2018 and 2019, to retrieve articles related to adverse drug reactions and adverse drug events and their impact in hospitalization and re-hospitalization of patients. The searches included literature from 2000 to 2018, including keyword searches, such as adverse drug reactions, adverse drug events, hospitalization, re-hospitalization, reporting systems, side effects, clinical trials, etcetera, under both basic and advanced searches. A collection of relevant articles was extracted from this secondary literature review and analyzed thoroughly in order to find out how ADRs and ADEs impact the levels of hospitalization and re-hospitalization of patients and whether strategies, such as reporting systems, can aid in decreasing their overall occurrence.

Results

Patients have been categorized in pediatric and geriatric categories, as well as patients living in developing or developed countries. While different variables may predict the level of potential hospitalization within a population, it has been stated by Pirmohamed et al. that the burden of ADRs and ADEs is high and it accounts for a significant level of morbidity and mortality, as well as extra healthcare costs, in this case in England. While these drugs that cause ADRs and ADEs are used to treat conditions in order to improve patient health, it is crucial to also look at the harm versus benefit ration to determine whether certain treatments are worth the risk of potential ADRs and ADEs leading to health harm and healthcare burden [17]. However, looking at a harm versus benefit ration, ADRs cannot all be generalized at the same level of potential danger, as they have been categorized in different levels depending on their potential to be avoided: Definitely avoidable, Possibly avoidable and Unavoidable. Using this categorization system, Pirmohamed et al. found that out of 1225 hospital admissions due to an ADR, 80% of the cases were directly related to an ADR and the median bed stay was eight days. These admissions accounted for four per cent of total hospital bed capacity, leading to a 446 million British pounds annual cost and an overall fatality of 0.15%. These ADRs that led to hospitalization were deemed as either definitely or possible avoidable, shining a light on the potential for improvement. Common drugs that lead to ADRs in this study included aspirin, NSAIDs, diuretics and warfarin; the most common ADR being gastrointestinal bleeding [17]. In addition, Menendez-Conde et al. found that immunosuppressants and antineoplastic therapy caused 38% of ADRs [13].

As the level of hospital admissions/re-hospitalizations due to ADRs and ADEs depends on different factors, such as age and location, the data is separated in the following categories: pediatric population, general adult populations and geriatric population. Where the data was available, location has been specified within each category as well.

ADRs and ADEs causing hospital admissions in pediatric population (aged 19 and under)

In a study done in the Czech Republic, it was found that ADRs cause a significant number of pediatric hospital admissions. 2.2% of hospital admissions were due to an ADR, of which 35% were due to anticancer drugs, 18% due to antibiotics, 9% due to vaccines and 9% due to immunosuppressants [9]. In addition, Feinstein et al. found that 3% of hospital admissions per day were due to possible drug events [4].

ADRs and ADEs causing hospital admissions in general adult population

As a point of comparison to the other population categories, hospital admissions in the adult population represent 8.1% of total hospitalizations in Singapore [3]. 2.4% to 3.6% of ADR-related hospitalizations among the adult population occurred in Australia, and 3.1% to 6.2% in the United States. The mortality rate was found to be similar in both countries (0.21%) [18].

ADRs and ADEs causing hospital admissions in geriatric population

It has been found that the highest incidence of ADR and ADE--related hospital admissions is among the geriatric population. According to Nair et al., 6% to 12% of all hospital admissions among older patients are due to ADRs, a percentage higher than in any other patient population [14]. However, Laatikainen et al., found that up to 23.1% of hospital admissions were likely medication-related (including ADRs and ADEs) [8]. A similar study found the rate to be 8.37% in the emergency department [15]. In addition, 22% of re-hospitalized patient cases were considered avoidable [6]. Four per cent of urgent hospital admissions were due to ADRs, most of which (90%) occurred in older patients who were on multiple medications at once [16].

Population within a developed country versus underdeveloped country

A comprehensive review of prevalence of ADR and ADE-related hospitalizations in developing and developed countries led to conclusions that 6.3% and 5.5% of hospitalizations occurred in developed and developing countries, respectively. In addition, of those hospitalizations, 71.7% and 59.6% were preventable reactions and events in developed and developing countries, respectively [1]. In addition, a study of incidence of ADR-caused hospital admissions in France found that 3.6% of admissions were due to ADRs, 32% of which were preventable and 16.5% potentially preventable [2].

Studies exploring the rate of ADR-related hospital admissions in England found that within the period of 1999-2009, 0.9% of total hospital admissions pertained to ADR causes [21]. Veeren and Weiss also found that in 2014/2015 the number of emergency hospital admissions increased by 12.1% in England as well [20].

Conclusion

In order to handle healthcare problems caused by ADRs and ADEs it is also very important to create a utility of tools in order to be able to identify high-risk patients,

such as older patients in order to intervene and prevent ADR and ADE-related hospital admissions. At this time there are no validated tools that help evaluate the risk of adverse drug reactions in a primary care setting [14]. It was also found to be beneficial to provide medication reviews with follow up services on hospital admissions in older polypharmacy patients. Pharmacists were found of particular help and benefit in this case. They found that the percentage of ADR related admissions in patients receiving follow-up medication review was significantly lower [10].

In conclusion, ADR and ADE-related hospital admission and readmission rates are age-group related, elderly being at the highest risk. However, these rates are not dependent on whether a country is developed or developing. Also, there are strategies that can be utilized by healthcare providers in order to decrease these rates in the future, such as to provide medication reviews and follow ups.

Discussion

While hospitalization and/or re-hospitalization among patients due to ADRs and ADEs is a problem in public health, studies such as that of Pirmohamed et al. (2004) make it clear that there is a possible solution to the problem, regardless of how major it is. They found that the ADRs causing hospitalizations were avoidable or definitely avoidable. When an ADR is in an 'avoidable' category, it means that something can be done about it, some strategy can be applied in order to avoid the ADR. They also found that the major ADR was gastrointestinal bleeding due to aspirin, NSAIDs, warfarin or diuretics. This implies that the problem is possible at the level of patient drug education. There are several steps patients can take in order to avoid GI bleeds due to these drugs, such as the time of day the drugs are taken, foods with which they are mixed, proper dosing, appropriate tests, etcetera. These steps can be achieved by also improving patient-provider communication and follow-up appointments. There are also steps that can be taken to avoid ADEs. While ADEs can occur during the process of drug prescription, administration or purchasing, etcetera, physicians and pharmacists can play a major role in avoiding ADE-related hospital admissions and re-hospitalizations by recognizing and selecting patients that have a potential to be at a higher risk for ADE-occurrence and involving multi-disciplinary team work within the healthcare setting, providing the maximal care and greatest possible avoidance of ADEs by providing a more thorough patient education, having two or more healthcare providers review new and old prescribed medications of patients and recognizing possibilities of events beforehand [17].

Overall, it seems that older patients (ages > 65 years) have the highest incidence of hospital admissions due to drug reactions or events. However, when it comes to location, whether a developed or underdeveloped country is being studied, the incidence of ADR and ADE-related hospital admissions does not differ significantly. Hence, these cases do not seem to be a problem of poverty but more so of patient education and awareness of the effect that the drugs they take may have on their

health. This makes the challenge of ADR and ADE hospitalization hopeful in the sense that application of additional patient education in the future may have an effect in decreasing the issue of the current situation. This could also open many doors for improvement in the future. A possible future study could include examining the effect of thorough patient education about their medication lists, including administrations route, handling, storage, etcetera, on the rate of ADR and ADE-related hospital admissions and re-hospitalizations.

In addition, it was stated by Klarskov et al. that drug safety profile updates are impaired due to most ADRs and ADEs not being reported to authorities, as clinical trials are not a mirror of drug use in real life situations [7]. This being said, better methods to increase rates of ADR reporting to authorities should be established as knowing possible drug ADEs and ADRs would make it possible for them to be seen as possible side effects and foreseen as potential events, not unexpected or even surprise occurrences. A relevant future study would be to survey healthcare providers on the type of reporting system that they would prefer and would be more likely to use (paper-based system, or online) and to find out reasons why they may avoid reporting an ADR or ADE. This data would help us understand current issues of under-reporting of recognized ADRs and ADEs by healthcare providers and lead us into designing a reporting system that would be easier and friendlier to use, ultimately leading to increased ADR and ADE reporting.

A particular strength of this study is the inclusion of different age-groups in understanding the levels of hospital admission and readmission rates due to ADR and ADE (as susceptibility is age-related), and this leads to better understanding of which group population needs greater attention in order to decrease the overall rates. Also, the study focused on whether the level of country development plays a role on these rates. This is important as it finds out whether the solution to this problem is possible achievable without having to first focus on a much larger issue, such as poverty level, etc.

A limitation of this study includes lack of further literature review of current ADR and ADE reporting rates by healthcare providers and their effect on lack of recognition of possible ADRs and ADEs. Recognizing this rate can lead us to future study avenues that could potentially decrease lack of recognition of ADRs and ADEs before they occur. Another limitation includes the lack of further research of the link between level of patient education (by provider, about the drug(s) being taken) and the incidence of ADR and ADE-related hospital admission and readmission rates.

Funding

No funding was received for the implementation of this study.

Conflict of Interest

There is no conflict of interest from the author.

Key Points

- Adverse drug reactions (ADRs) and adverse drug events (ADEs) have a great potential to hospitalize and/or re-hospitalize patients, which can lead to lost days of work, a longer recovery time and even economic implications.
- ADR and ADE-related hospital admission and readmission rates are age-group related, elderly being at the highest risk.
- Hospital admission and readmission rates are not dependent on whether a country is developed or developing.
- Public health strategies that can be utilized by healthcare providers in order to decrease these rates in the future, such as to provide medication reviews and follow ups, have been utilized.

References

- [1] Angamo M, Chalmers L, Curtain C, Bereznicki L. Adverse-Drug-Reaction-Related Hospitalisations in Developed and Developing Countries: A Review of Prevalence and Contributing Factors. *Drugs and Aging*. 2006; 39(9): 1179-1942.
- [2] Benard-Laribiere A, Miremont-Salame G, Perault-Pochat M, Noize P, Haramburu, F. Incidence of hospital admissions due to adverse drug reactions in France: the EMIR study. *Fundamental and Clinical Pharmacology*. 2006; 29(1).
- [3] Chan S, Ang, X, Sani L, Ng H, Winther M, Liu J, Brunham L, Chan, A. Prevalence, and characteristics of adverse drug reactions at admission to hospital: a prospective, observational study. *British Journal of Clinical Pharmacology*. 2016; 82(6): 1636-1646.
- [4] Feinstein J, Dai D, Zhong W, Freedman J, Feudtner, C. Potential drug-drug interactions in infant, child, and adolescent patients in children's hospitals. *American Academy of Pediatrics*. 2015; 135(1): 99-108.
- [5] Ferner, R. Adverse drug reactions. *Clinical Pharmacology*. 2016; 44(7): 416-421.
- [6] Hauviller L, Eyvrard F, Gernault V, Rousseau V, Molinier L, Montastruc J, Bagheri, H. Hospital re-admission associated with adverse drug reactions in patients over the age of 65 years. *European Journal of Clinical Pharmacology*. 2016; 72(5): 631-639.
- [7] Klarskov P, Andersen J, Christensen H, Christensen M, Jimenez-Solem E. Adverse, Drug reactions as cause of Hospital admission - a study Protocol. *Clinical Therapeutics*. 2015; 37(8): 118-119.
- [8] Laatikainen O, Sneck S, Bloigu R, Lahtinen M, Lauri T, Turpeinen M. Hospitalizations due to adverse drug events in the elderly - a retrospective register study. *Frontiers in Pharmacology*; 2016: 13(7).
- [9] Langerova, P, Vrtal, J & Urbanek, K 2014, 'Adverse Drug Reactions Causing Hospital Admissions in Childhood: A Prospective, Observational, Single-Centre Study', *Basic and Clinical Pharmacology and Toxicology*, 115(6).
- [10] Malet-Larrea A, Goyenchea E, Garcia-Cardenas V, Calvo B, Arteché J, Aranegui P, Zubeldia J, Gastelurrutia M, Martinez-Martinez F, Benrimoj S. The impact of a medication review with follow-up service on hospital admissions in aged polypharmacy patients. *British Journal of Clinical Pharmacology*. 2016; 82(3): 831-838.

- [11] Mannesse C, Derkx F, Ridder M, Veld A, Cammen, T. Contribution of adverse drug reactions to hospital admission of older patients. *Age and Aging*. 2000; 29(1): 35.
- [12] McDonnell P, Jacobs M. Hospital Admissions Resulting from Preventable Adverse Drug Reactions. *Annals of Pharmacotherapy*. 2002; 36(9): 1331-1336.
- [13] Menendez-Conde C, Vicedo T, Silveira E, Accame E. Adverse Drug Reactions Which Provoke Hospital Admission. Elsevier. 2011; 35(5): 223-286.
- [14] Nair N, Chalmers L, Peterson G, Bereznicki B, Bereznicki, L. Hospitalization in older patients due to adverse drug reactions –the need for a prediction tool. *Clin Interv Aging*. 2016; Volume 11: 497-505.
- [15] Olivier, P, Bertrand, L, Tubery, M, Lauque, D, Montastruc, J & apeyre-Mestre, M 2009, 'Hospitalizations because of Adverse Drug Reactions in Elderly Patients Admitted through the Emergency Department: A Prospective Survey', *Drugs and Aging*, 26(6), pp. 475-82.
- [16] Pedros C, Quintana B, Rebolledo M, Porta N, Vallano A, Arnau J. Prevalence, risk factors and main features of adverse drug reactions leading to hospital admission. *European Journal of Clinical Pharmacology*. 2014; 70(3): 361-367.
- [17] Pirmohamed M, James S, Meakin S, Scott A, Farrar K, Park K, Breckenridge, A. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*, 2004; 329(7456): 15-19.
- [18] Pouyanne P, Haramburu F, Louis J, Begaud, B. Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. *BMJ*. 2011; 320(7241): 1036.
- [19] Schmiedl S, Rottenkolber M, Hasford J, Rottenkolber D, Farker K, Drewelow B, Hippus M, Salje K, Thurmann P. Self-medication with over-the-counter and prescribed drugs causing adverse-drug-reaction-related hospital admissions: results of a prospective, long-term multi-centre study. *Drug Safety*. 2014; 37(4): 225.
- [20] Veeren J, Weiss M. Trends in emergency hospital admissions in England due to adverse drug reactions: 2008–2015. *Journal of Pharmaceutical Health Services Research*. 2016; 8(1).
- [21] Wu T, Jen M, Bottle A, Molokhia M, Aylin P, Bell D, Majeed A. Ten-year trends in hospital admissions for adverse drug reactions in England 1999–2009. *J R Soc Med*, 2010; 103(6): 239-250.
- [22] World Health Organization (WHO). A guide to detecting and reporting adverse drug reactions: Glossary. 2005.