

Cost of Adverse Drug Reactions (ADRs) Induced Hospitalization: A Systematic Review

C. Siltharm, M. Thavorncharoensap*

Social and Administrative Pharmacy Division, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok 10400 Thailand

Abstract

Adverse Drug Reactions (ADRs) are common causes of hospitalization leading to unnecessary morbidity and mortality. Evidences on cost of ADRs induced hospitalization are of benefits in drawing attention of hospital administration and health care policy makers to save the unnecessary cost. To date, several reviews were conducted to identify prevalence and factors associated with ADRs induced hospitalization. Nevertheless, no attempt has been made to review economic burden of ADRs induced hospitalization. Our study, therefore, aims to systematically review the economic costs of ADR induced hospitalization. A literature search was conducted in MEDLINE database using the following terms: (“Cost of Illness” [Mesh] OR costs OR cost OR economic) AND “drug toxicity” [Mesh]. Studies were included if they met the following criteria: 1) provided sufficient data on cost per case of ADR induced hospitalization that occurred in any hospital department including emergency, and 2) published in English. Based on the 12 studies included, incidence of ADR admissions ranged from 0.60% to 7.0% with the median length of hospital stay ranged from 3 to 8.7 days. Direct medical cost was calculated in all studies while indirect cost was calculated in only 2 studies. Cost per case of ADR induced hospitalization ranged between US\$ 180 to 7,038 in 2013. Based on our findings, ADR induced hospitalizations are significant public health problem leading to substantial economic burdens. Special attention should be made to improve quality of drug use thus to reduce the incidence and cost of ADR induced hospitalization.

Keyword: ADR, cost-of-illness, hospitalization

INTRODUCTION

According to the World Health Organization (WHO)¹ adverse drug reactions (ADRs) are defined as any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. ADRs related to hospital admission or ADRs induced hospitalization is a significant healthcare problem leading to unnecessary morbidity, mortality, and health care services worldwide. Several previous studies revealed that ADR induced hospitalization are common.²⁻⁵ Recent review found that prevalence of ADRs induced hospitalization ranged from 0.16% to 15.7% with the median of 5.3%.⁴

Evidence on economic burden of

ADR induced hospitalization is clearly needed to bring attention of hospital administrators and health care policy makers to improve patient safety as well as to save the unnecessary cost. Nevertheless, to date, systematic review on cost of ADRs induced hospitalization has not been performed. Thus, we aims to systematically review the economic cost of ADRs induced hospitalization.

METHODS

A comprehensive search of MEDLINE /PubMed database was performed during 1996 to July 2013, using the following terms: (“Cost of Illness” [Mesh] OR costs OR cost OR economic) AND “drug toxicity” [Mesh]. Bibliographies of identified articles and related review were also manually searched

*Corresponding author: Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand. Email: montarat.tha@mahidol.ac.th

for additional references. Two review authors independently performed the study selection. Studies were included if they met the following criteria: 1) provided sufficient data on cost of ADR induced hospitalization that occurred in any hospital department including through emergency department, and 2) published in English. We excluded studies that addressed cost of specific types of ADRs (i.e. cutaneous ADR) or cost of specific drug category (i.e. ADR related to neoplastic drugs) or cost of ADR occurred during hospitalization, or focus on medication related to hospital admission but not specific to ADR (i.e. medication error, or adverse drug event). Data from eligible studies were then independently extracted by 2 authors, using standardized data extraction forms. For each study, the following data were extracted: study design, setting, duration of study, patients, definition of ADRs, method of ADR detection, incidence of ADR induced

hospitalization, length of stay, % avoidable ADR, type of cost included, perspective, method of cost calculation, and cost per case. To facilitate the comparison across different settings and years, costs per case were also presented in US\$2013 by inflating the original costs to its 2013 value using country specific GDP inflators.⁶ The costs were then converted into US dollars using the exchange rate in 2013.

RESULT AND DISCUSSION

Study identification

A total of 897 identified articles were from the database, 7 studies⁷⁻¹³ were eligible for the review. After searching bibliographies of the identified studies and the related reviews, 5 additional studies¹⁴⁻¹⁸ were further identified, resulting in 12 studies included in the review, as shown in Figure 1.

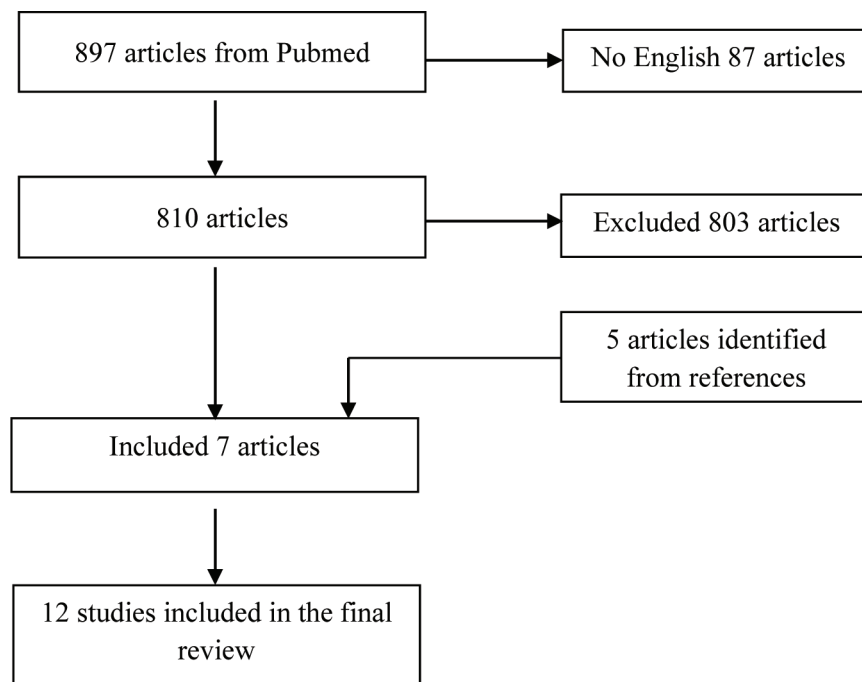


Figure 1. A systematic review process

Characteristics of the included studies

Characteristics of all 12 studies⁷⁻¹⁸ were presented in Table 1. It was found that 8 studies were conducted in Europe,^{7-8,11-12,14-15,17-18} 2 in Asia,^{10,16} 1 in North

America,¹³ and 1 in South Africa.⁹ Seven studies included patients of all ages,^{7-8,12-13,15,17-18} while 4 studies focused on adults,^{10-11,14,16} and 1 study focused on pediatric patients.⁹ Duration of the study ranged between 6 weeks¹⁶ to 6 years.⁷

Table 1. Characteristics of studies that show detail of patients included in each study.

Study	Author	Year of study	Duration	Setting	Patients
1	Carrasco-Garrido P, <i>et al.</i> ⁷	2001-2006	72 months	More than 95% of Spanish hospitals	All patients admitted to the hospitals during the study period were identified from MBDS database.
2	Goettler M, <i>et al.</i> ¹⁴	1995	N/A	Department of internal medicine in Germany	Adult patients.
3	Lagnaoui R, <i>et al.</i> ⁸	1996-1997	4 months	1 university hospital in France	All patients admitted to a 23-bed systemic diseases-oriented internal medicine unit during study period were assessed.
4	Moore N, <i>et al.</i> ¹⁵	1993	6 months	a 29-bed ward of the department of internal medicine of a general hospital in France	All patients admitted to the ward over 6 months.
5	Oshikoya I KA, <i>et al.</i> ⁹	2006-2007	18 months	pediatric wards of 1 University Teaching Hospital in Nigeria	Patients admitted for less than 24 hours or with repeated admissions, and those whose medical records were unavailable for review, either during the admission or following discharge, were excluded from the study.
6	Patel KJ, <i>et al.</i> ¹⁶	2005	6 weeks	Medical Emergency Department (ED) of a tertiary referral center in India	Only adults (age > 18 years).
7	Pattanaik S, <i>et al.</i> ¹⁰	2005	4 months	Medical emergency department of a tertiary care public hospital in northern India.	All visits to the ED of patients aged >12 years.

Table 1. Characteristics of studies that show detail of patients included in each study. (cont.)

Study	Author	Year of study	Duration	Setting	Patients
8	Pirmohamed M, et al.11	2001-2002	6 months	2 large general hospitals in England	18,820 patients aged over 16 years who were admitted over the study period were assessed. Patients aged < 16 years, women with obstetric or gynecological complaints, patients with either deliberate or unintentional overdose, or patients who relapsed because of non-compliance were excluded.
9	Rottenkolber D, et al.12	2006-2007	24 months	internal medicine wards in 4 hospitals in Germany	57,000 hospital admissions to department of internal medicine during the study period were screened. Patients receiving cancer chemotherapy or suffering from severe cutaneous ADRs were excluded.
10	Schneeweiss S, et al.17	1997-2000	30 months	All departments of internal medicine and emergency units in 2 urban regions in Germany	All patients admitted between October 1997 and March 2000. Patients with severe cutaneous reactions and patients undergoing cancer chemotherapy were excluded.
11	Wasserfallena JB, et al.18	1994	6 months	Emergency department of 1 University hospital in Switzerland	All patients admitted to the medical emergency department during the study period. Patients with adverse reactions to alcohol or illicit drug abuse or chemical intoxication without concomitant drug use were excluded.
12	Yee JL, et al.13	2003	12 weeks (the second week of each hospital, USA month)	a large, tertiary care, Veterans Affairs	All patients visiting the ED during the second week of each month between January 1 and December 31, 2003, were included in the study. Patients without adequate documentation of the ED visit (i.e., chart documentation was not found) or patients <18 years of age were excluded.

Table 2. Characteristics of studies examining the study design, definition of ADR, prevalence or incidence of ADRs induced hospitalization.

Study	Author	Study design	Definition of ADRs	Method of ADR detection	Incidence	Length of stay
1	Carrasco-Garrido P, <i>et al.</i> ⁷	Retrospective study	As defined by World Health Organization ¹	Record-based study analysis	1.69%	8 days (median)
2	Goettler M, <i>et al.</i> ¹⁴	Cross-sectional study	As defined by World Health Organization ¹	Literature review of studies published during 1975- 1996	5.8%	8.7 days (median)
3	Lagnaoui R, <i>et al.</i> ⁸	Prospective study	A clinical or biological abnormality associated with the use of a drug.	Assessed by healthcare professional	7%	6 days (mean)
4	Moore N, <i>et al.</i> ¹⁵	Prospective study	Serious reactions are defined as those causing hospitalization, fatal or life-threatening, or resulting in significant changes in the patients treatment. Only serious reactions were studied.	Medical chart review Only serious reactions were studied.	3%	8.3 days (mean)
5	Oshikoyal KA, <i>et al.</i> ⁹	Prospective study	As defined by Edwards and Aronson ¹⁹ which excludes ADRs that required no intervention	Completion of specific questionnaire during admission + medical chart review + patient interview	0.6%	-
6	Patel KJ, <i>et al.</i> ¹⁶	Prospective study	As defined by World Health Organization ¹	Assessed by healthcare professional	6.89%	5 days (mean)

Table 2. Characteristics of studies examining the study design, definition of ADR, prevalence or incidence of ADRs induced hospitalization. (cont.)

Study	Author	Study design	Definition of ADRs	Method of ADR detection	Incidence	Length of stay
7	Pattanaik S, <i>et al.</i> ¹⁰	Prospective study	As defined by World Health Organization ¹	Assessed by healthcare professional Only ADR that required >48 hours of stay were included	1.4%	3 days (median)
8	Pirmohamed M, <i>et al.</i> ¹¹	Prospective study	As defined by Edwards and Aronson ¹⁹	Assessed by healthcare professional	6.5%	8 days (median)
9	Rottenkolber D, <i>et al.</i> ¹²	Prospective study	As defined by Edwards and Aronson ¹⁹	Assessed by healthcare professional	3.25%	8 days (median)
10	Schneeweiss S, <i>et al.</i> ¹⁷	Prospective study	N/A	Medical chart review Only drugs that possibly, likely, or very likely caused the hospital admissions were used for incidence calculation	9.4 per 10,000 treated patients	13±10.6 days. (mean)
11	Wasserfallena JB, <i>et al.</i> ¹⁸	Prospective study	As defined by World Health Organization ¹	Medical chart review	7.00%	9 days (mean)
12	Yee JL, <i>et al.</i> ¹³	Retrospective study	As defined by World Health Organization ¹	Medical chart review	1.1% (24/2,169)	6.3 days (mean)

Table 3. Cost of ADRs induced hospitalization

Study	Author	% Avoidable/ preventable ADR	Type of cost	Perspective	Method of cost calculation	Cost/case as reported in the study*	Cost/case in US\$ 2013
1	Carrasco-Garrido P, <i>et al.</i> ⁷	N/A	Direct medical cost	Health insurance perspective	Using diagnosis related groups (DRG)	£ 3,857 in 2001 £ 4,382 in 2006	\$7,038 in 2001 \$6,786 in 2006
2	Goettler M, <i>et al.</i> ¹⁴	30%	Direct medical cost	Hospital perspective	Total cost = LOS (8.7 days) * total admission (4.5 million)* cost per day (465 DM)* Incidence of ADR induced hospitalization (5.8%)	DM 4,046 (1DM = 0.68 US\$)	\$1,961
3	Lagnaoui R, <i>et al.</i> ⁸	80% (definitely +probably preventable)	Direct medical cost	Hospital perspective	number of days in hospital multiply by the reference daily hospital charge (454 Euro per day)	£ 2,721 per patients	\$4,631
4	Moore N, <i>et al.</i> ¹⁵	N/A	Direct medical costs	Hospital perspective	Total number of excess days are multiplied by the daily hospital cost, given by the hospital administration (1,923 FF or 287.15 Euro)	£ 2,940	\$4,332
5	Oshikoyal KA, <i>et al.</i> ⁹	N/A	Direct cost (direct medical costs to the hospital + direct medical cost to the patient + direct non-medical costs) + indirect costs.	Patient, provider, and society perspective	Direct medical costs to hospital equal to the sum of all medication, diagnostic and visit costs. Direct medical costs to the patients refers to any bill incurred by the patient on medication, diagnostic investigation or medical procedure while on admission or during follow-up visits. Direct non-medical cost includes all transportation, food, and hotel expenses incurred during the hospital admission for ADR. Indirect cost is the sum of each parent's estimated daily wage based on the minimum monthly wage (7,500 naira) for workers multiplied by lost workdays.	Societal perspective: Cost of treating severe ADR was \$1,988 while cost of moderate ADR was \$310	\$350 to \$2,242

Table 3. Cost of ADRs induced hospitalization (cont.)

Study	Author	% Avoidable/ preventable ADR	Type of cost	Perspective	Method of cost calculation	Cost/case as reported in the study*	Cost/case in US\$ 2013
6	Patel KJ, <i>et al.</i> ¹⁶	59.62% (Definitely + possible avoidable)	Direct medical costs	Hospital perspective	Cost per patient was computed as the product of total number of admission days of with ADR and hospital expenditure per day	INR 6,197 (\$150)	\$180
7	Pattanaik S, <i>et al.</i> ¹⁰	N/A	Direct medical, direct non-medical (traveling, food), and indirect cost (loss of productivity)	Societal perspective	Total cost = cost of hospital stay + cost of food (0.83 Euro per meal) and stay+ cost of travel (autrickshaw fee for all local patient or ordinary bus fare for all patients living further away)+ cost of productivity loss (1.13 – 5.8 Euro per head per day)	£ 214	\$428
8	Pirmohamed M, <i>et al.</i> ¹¹	28%-30%	Direct medical cost	Hospital perspective	N/A	\$3,312 (\$414 per medical bed day x 8 days)	\$4,383
9	Rottenkolber D, <i>et al.</i> ¹²	N/A	Direct medical cost	Health insurance perspective	Each ADR was assigned to a corresponding DRG (G-DRG Version 2009). Hospital reimbursement rates were calculated by multiplying the relative cost weight of the respective DRG by the base rate. If the patients suffered from more than 1 ADR leading to hospitalization, the most severe one was chosen, as the major diagnosis. Cost per patient was computed by multiplying length of stay with the cost per day (287 Euro)	Euro 2250 per single ADR	\$3,291
10	Schneeweiss S, <i>et al.</i> ¹⁷	N/A	Direct medical cost	Hospital perspective	Cost per patient was computed according to the number of days spent in the different wards.	£ 3,731	\$6,150
11	Wasserfallena JB, <i>et al.</i> ¹⁸	32%	Direct medical cost	Hospital perspective	Costs of health care resources were retrieved through the VA Decision support system, an activity-based costing system implemented to determine the cost of VA department.	3,586 CHF (1CHF= 0.56 US\$)	\$2,297
12	Yee JL, <i>et al.</i> ¹³	N/A	Direct medical cost	Hospital perspective		\$ 3,704	\$4,707

* 1Euro = 1.32 US\$ (Sep 2013), 1 DM = 0.68 US\$

Methods used to identified ADR, incidence, length of stay, and % avoidable

As shown in Table 2, several methods were used to detect ADRs. These methods included 1) assessed by healthcare professional (5 studies^{8,10-12,16}), 2) medical chart review (4 studies^{13,15,17-18}), 3) record-based study analysis (1 study⁷), 4) literature review (1 study¹⁴), and 5) questionnaire combined with medical chart review and patients interviewed (1 study⁹). The definitions of ADR used in the 12 included were varied. About half of the studies^{7,10,13-14,16,18} used the definition given by World Health Organization while 3 studies^{9,11-12} used the definition given by Edwards and Aronson.¹⁹

From our review, the prevalence rate of ADR induced hospitalization ranged from 0.6%⁹ to 7.0%⁸ which was in line with the previous review.⁴ The median length of hospital stay ranged from 3.0¹⁰ to 8.7¹⁴ days. With regard to proportion of ADR induced hospitalization that was considered avoidable, similar to previous meta-analysis,²⁰ which found that 45% of ADRs occurred in inpatients were preventable, our study found that proportion of avoidable ADR induced hospitalization is sizable, ranging from 28%¹¹ to 80%.⁸

Method of cost calculation

Regarding the types of cost included in the analysis, all 12 studies calculated direct medical cost associated with ADR induced hospitalization.⁷⁻¹⁸ Only 2 studies^{9,10} included indirect cost and direct non-medical cost. Similar to the previous review on the cost of drug-related morbidity,²¹ 10 studies^{7-8,11-18} were conducted from a hospital or health insurance perspective. Only 2 studies^{9,10} were conducted from a societal perspective.

Several methods were used to calculate cost of ADRs, as shown in Table 3. It was found that most studies (8 studies^{8,12-18}) calculated cost by multiplying the length of stay due to ADR induced hospitalization with the cost of hospital day, while 2 studies,^{7,12} using diagnosis related groups (DRG) to determine such cost.

Cost of ADRs induced hospitalization

Costs per case of ADRs induced hospitalization in each country were shown in Table 3, ranged between US\$180¹⁶ to US\$7,038⁷ in 2013. Total cost per case of ADRs induced hospitalization in Europe and North America ranged from US\$1,961¹⁴ to US\$7,038⁷ (in 2013). On the other hand, the cost per case in Africa and Asia were lower than those of North America and Europe, ranging from US\$350⁹ to US\$2,242,⁹ and US\$180¹⁶ to US\$428¹⁰ (in 2013), respectively.

Similar to the previous study,⁴ we believed that different methods as well as definition of ADR are the important factors leading to the variation in incidence of ADR detection, the median length of stay as well as cost per case reported in each study. As most of the studies were conducted in hospital perspective, so it should be noted that the cost estimated was likely to be underestimated the true cost of ADRs. Therefore, more studies using standardized methodology, examining the cost of ADR in societal perspective are clearly needed.

CONCLUSION

Notwithstanding the disparities in methodologies and definition of ADRs used in each study, and the facts that most studies included only direct medical cost, this review clearly confirmed that the economic burden of ADR induced hospitalization is substantial. Given that ADR induced hospitalization are common, large percentage of the cases were avoidable, and that cost per case were quite high, more attention should be focused on the interventions aims at reduction of the incidence of ADR induced hospitalization in order to reduce such unnecessary cost and to promote patients safety.

REFERENCES

1. World Health Organization: International drug monitoring. The role of the hospital. Geneva: Switzerland: World Health Organization. 1966.

2. Beijer HJM, De Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci* 2002;24:46-54.
3. Impicciatore P, Choonara I, Clarkson A, et al. Incidence of adverse drug reactions in paediatric in out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* 2001;52:77-83.
4. Kongkaew C, Noyce PR, Ashcroft DM. Hospital Admissions Associated with Adverse Drug Reactions: A Systematic Review of Prospective Observational Studies. *Ann Pharmacother* 2008;42:1017-25.
5. Smyth RM, Gargon E, Kirkham J, et al. Adverse drug reactions in children- a systematic review. *PLoS One* 2012; 2012:3.
6. IMF. World Economic Outlook Database 2013. Available from: <http://www.imf.org/external/pubs/ft/weo/2013/01/weodata/index.aspx>; (accessed 19 August 2013).
7. Carrasco-Garrido P, Ana de Andrés L, Barrera V H, et al. Trends of adverse drug reactions related-hospitalization s in Spain (2001-6). *BMC Health Services Research* 2010;10:287.
8. Lagnaoui R, Moore N, Fach J, et al. Adverse drug reactions in a department of systemic diseases-oriented internal medicine: prevalence, incidence, direct costs and avoidability. *Eur J Clin Pharmacol* 2000;55:181-6.
9. Oshikoya KA, Chukwura H, Njokanma OF, et al. Incidence and cost estimate of treating pediatric adverse drug reactions in Lagos, Nigeria. *Sao Paulo Med J* 2011;129:3153-64.
10. Pattanaik S, Dhamija P, Malhotra S, et al. Evaluation of cost of treatment of drug-related events in a tertiary care public sector hospital in Northern India: A prospective study. *Br J Clin Pharmacol* 2009;67:363-9.
11. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. *BMJ* 2004; 329:15-9.
12. Rottenkolber D, Schmiedl S, Rottenkolber M, et al. Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations. *Pharmacoepidemiol Drug Saf* 2011;20:626-34.
13. Yee JL, Hasson NK, Schreiber DH. Drug-related emergency department visits in an elderly veteran population. *Ann Pharmacother* 2005;39:1990-5.
14. Goettler M, Schneeweiss S, Hasford J. Adverse Drug Reaction Monitoring - Cost and Benefit Considerations Part II: Cost and Preventability of Adverse Drug Reactions Leading to Hospital Admission. *Pharmacoepidemiol Drug Saf* 1997;6: S79-S90.
15. Moore N, Lecointre D, Noblet C, et al. Frequency and cost of serious adverse drug reactions in a department of general medicine. *Br J Clin Pharmacol* 1998;45: 301-8.
16. Patel KJ, Kedia MS, Bajpai D, et al. Evaluation of the prevalence and economic burden of adverse drug reactions presenting to the medical emergency department of a tertiary referral centre: a prospective study. *BMC Clinical Pharmacology* 2007;7:1-5.
17. Schneeweiss S, Hasford J, Goettler M, et al. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. *Eur J Clin Pharmacol* 2002;58:285-91.
18. Wasserfallen J-B, Livio FO, Buclin T, et al. Rate, type, and cost of adverse drug reactions in emergency department admissions. *Eur J Clin Pharmacol* 2001; 12:442-7.
19. Edwards IR, Aronson J. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356:1255-9.
20. Hakkarainen KM, Hedna K, Petzold M, et al. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions--a meta-analysis. *PLoS One* 2012;7:e33236.
21. Gyllensten H JA, Rehnber C, Clarlsten A. How are the costs of drug-related morbidity measured? A systematic literature review. *Drug Safety* 2012;35: 207-19.