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Original Research Article

Profile of serious adverse drug events in a tertiary care hospital of South India - a five years experience

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ABSTRACT

Background: Adverse drug event (ADE) is said to be serious, when it is life-threatening, leads to hospitalization, disability, congenital anomaly, death or requires intervention to prevent permanent impairment or damage. The present study aimed to determine the pattern, causality, preventability of serious ADEs.
Methods: This retrospective study was carried out to profile serious ADEs reported from Bangalore Medical College and Research Institute to Adverse Drug Reaction (ADR) Monitoring Centre, under Pharmacovigilance Programme of India from 2012 to 2016. Patient demographics, clinical and drug data, details of the ADE, onset time, causal drug details, outcome and severity were collected as per CDSCO form. Causality was assessed by WHO-ADR probability scale, preventability by modified Schumock and Thornton scale.
Results: A total of 809 ADEs were reported, of which 50 (6.18%) were serious in nature. Male preponderance (74%) was observed, with 42% among patients aged 20-40 years. 56% of serious ADEs were reported from department of Dermatology. Steven Johnson Syndrome (SJS) (20%) contributed for most of the ADEs. Antiepileptics caused maximum number of serious ADEs (32%). 76% of the ADEs were found to be 'probable' and 4% were definitely preventable. 56% of them was life threatening and 86% required intensive interventions. 16% patients experienced serious ADEs during hospital stay.
Conclusions: Serious ADEs constituted 6.18% of all ADEs reported. SJS was commonly seen with antimicrobials and hepatotoxicity with ATT. Antiepileptics and ATT contributed for majority of them. This study highlights the importance of monitoring and timely management of serious ADEs to commonly prescribed medications.

Keywords: Hospitalization, Life threatening, Preventability, Serious ADE

INTRODUCTION

Pharmacotherapy plays an important role in the management of any disease. Medications are required to manage the symptoms, slow disease progression or to prevent future development of illness. While medications are helpful in treating the disease condition, they come with a risk of adverse drug events (ADEs). World Health Organization defines Adverse drug reaction (ADR) as any "noxious and unintended responses to drugs occurring at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function".[1] These ADRs can be anything from mild to serious. According to United States Food and Drug Administration (USFDA), a serious ADE is one which is life-threatening, leads to hospitalization, disability or permanent damage, congenital anomaly/birth defect, death or requires intervention to prevent permanent impairment or damage.

ADEs have a significant impact on health, being responsible for 5% to 7% of all hospitalizations and with a further 10% to 20% of all hospitalized patients experiencing an ADE during their hospital stay.[2-4] Patients hospitalized for an ADE may have longer hospital length of stay and higher risks of death than other patients.[5] About 3% to 6% of ADEs are fatal or have serious consequences, with an estimated 140,000 fatalities secondary to ADEs occurring annually in the USA. Hence it is estimated to be the 4th - 6th leading cause of mortality in USA.[6-9] The estimated impact on hospital costs exceeds $30 billion, or 5% of total hospital

running costs per annum in USA.[9-10] Ramesh et al reported that the average cost of treating ADEs in India was Rs 690 per ADE.[11]

A just and effective treatment of ADEs is an issue that all have to consider. Identifying specific patterns in the population of patients admitted to the hospital for serious ADEs also constitutes an attractive issue. To gain more insight into all of these issues, we performed the present study to determine the pattern, causality and preventability of serious ADEs at a tertiary care hospital.

METHODS

This retrospective study was carried out from 2012 to 2016 to analyze the serious ADEs reported spontaneously from various departments, attached to Bangalore Medical College and Research Institute, to Adverse Drug Reaction Monitoring Centre, under Pharmacovigilance Programme of India. Patient's demographics, clinical and drug data, details of ADE, onset time, causal drug details, outcome and severity were collected as per CDSCO form. Causality was assessed using WHO-ADR probability scale, and preventability using modified Schumock and Thornton scale. Results were analyzed using descriptive statistics.

RESULTS

Table: 1 Different therapeutic class of drugs causing serious ADEs.

S.no	Therapeutic class of drugs		Ade (n)	Total no. of ades (%)
1	Antiepileptic drugs	Phenytoin-11	Stevens-Johnson Syndrome - 2	16 (32)
			Toxic Epidermal necrolysis - 3	
			Exfoliative dermatitis - 1	
			Drug hypersensitivity syndrome - 1	
			Cerebellar ataxia - 2	
			Drug reaction with Eosinophilia and Systemic symptoms (DRESS) -1	
			Erythema multiforme - 1	
		Carbamazepine-3	Exfoliative dermatitis - 1	
			Drug reaction with eosinophilia and Systemic Symptoms (DRESS) -1	
			Stevens-Johnson Syndrome - 1	
		Phenobarbitone-1	Pemphigus vulgaris - 1	
		Sodium Valproate-1	Pancreatitis - 1	
2	Anti HIV	Nevirapine - 3	Stevens-Johnson Syndrome - 2	9 (18)
			Toxic Epidermal necrolysis - 1	
		Stavudine - 2	Breathlessness - 1	
			Pancreatitis - 1	
		Efavirenz - 2	Stevens-Johnson Syndrome - 1	
			Exfoliative dermatitis - 1	
		Zidovudine - 1	Severe anemia - 1	
		Atazanavir - 1	Hepatotoxicity - 1	
3	Antitubercular drugs	Rifampicin - 5	Hepatotoxicity - 4	9 (18)
			Severe vomiting - 1	
		Isoniazid - 4	Hepatotoxicity - 4	
4	NSAIDs	Diclofenac - 4	Erythema multiforme - 2	8 (16)
			Stevens-Johnson Syndrome - 2	
		Aceclofenac - 3	Toxic Epidermal necrolysis - 1	
			Bullous fixed drug eruption - 1	
			Exfoliative dermatitis - 1	
		Propiphenazone - 1	Angioedema - 1	
5	Antibiotics	Ceftriaxone - 2	Stevens-Johnson Syndrome - 1	5 (10)
			Anaphylactic shock - 1	
		Cefuroxime - 1	Stevens-Johnson Syndrome - 1	
		Ciprofloxacin - 1	Exfoliative dermatitis - 1	
		Azithromycin - 1	Exfoliative dermatitis - 1	
6	General anesthetics	Propofol - 1	Convulsions - 1	1 (2)
7	Antileprotic drugs	Dapsone - 1	Dapsone hypersensitivity syndrome - 1	1 (2)
8	Cough expectorant	Ambroxol - 1	Exfoliative dermatitis - 1	1 (2)

A total of 809 ADEs were reported, of which 50 (6.18%) were serious. Male preponderance (74%) was observed. Most (42%) of the serious ADEs were noted among the patients of age group of 20-40 years (Figure 1).

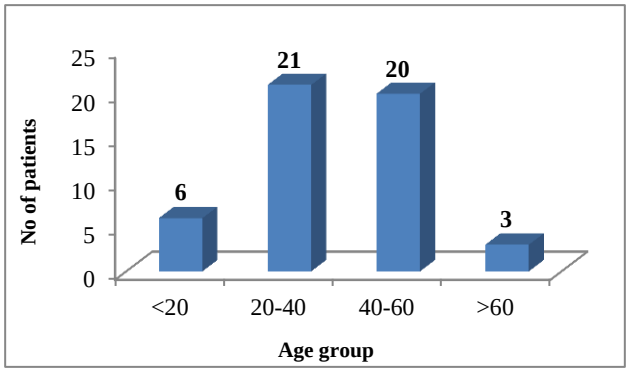

Figure 1: Age distribution among the patients with serious ADEs.

Antiepileptic drugs accounted for highest number of ADEs (32%), followed by Anti HIV drugs and Antitubercular drugs (18%) each. Among the antiepileptic drugs, phenytoin was the most common offending drug accounting for 22% of the ADEs followed by carbamazepine (6%) (Table 1).

All the cases had to be hospitalized/ had prolonged hospitalization due to the ADEs. 43 patients (86%) required intervention to prevent permanent damage and 28 patients (53%) had life threatening ADEs (Table 2).

Table: 2 Seriousness of Reaction (According to US-FDA).

	Number of ADEs (n=50)	% Of ADEs
Hospitalization initial/prolonged	50	100%
Required intervention to prevent permanent damage	43	86%
Life threatening	28	53%

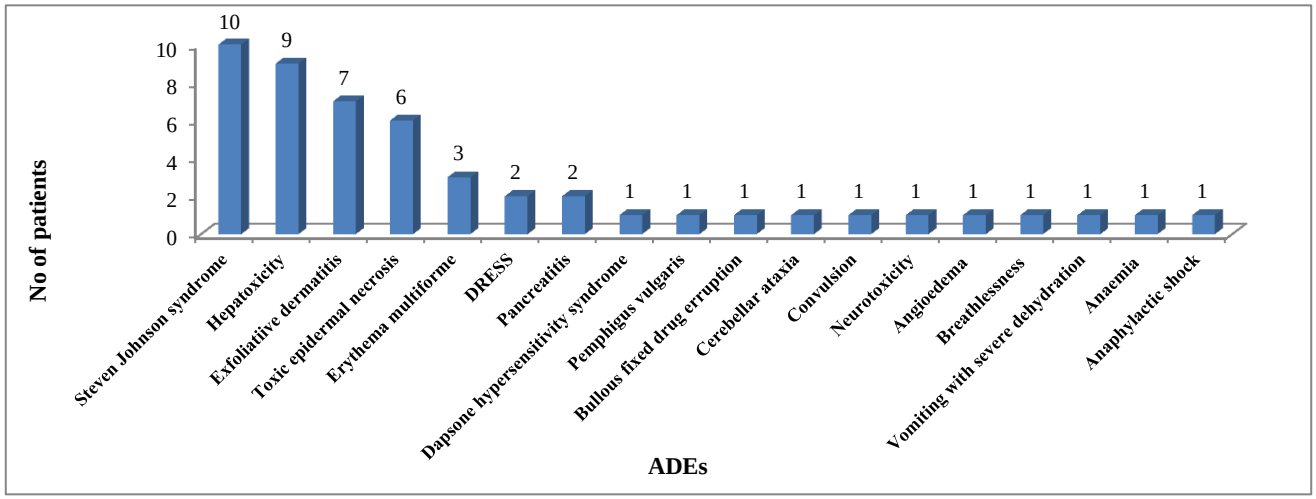

Figure 2: Spectrum of serious ADEs.

Stevens Johnson Syndrome (SJS) was the most frequently observed serious ADE which accounted for 20% of all the serious ADEs, followed by hepatotoxicity (18%). Toxic epidermal necrolysis and Erythema Multiforme were seen in 12% and 6% of the patients respectively (Figure 2).

Majority (56%) of the serious ADEs were reported from the department of Dermatology followed by Neurology (12%). Only 2% of the serious ADEs were from Orthopedics and Anesthesia (Figure 3).

WHO-ADR probability scale indicates 76% of ADEs were of 'probable' causality and 24% were possible.

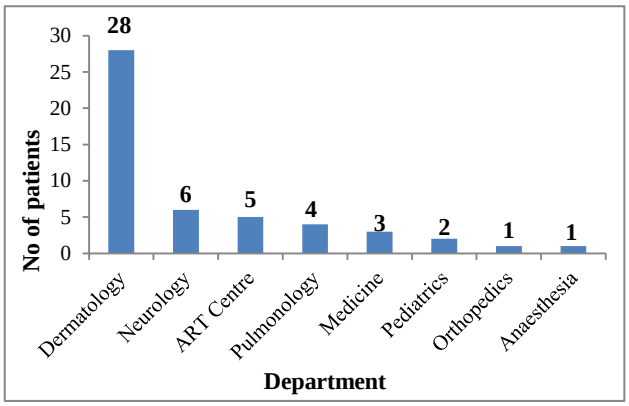

Figure 3: Various departments from which ADEs were obtained.

Among the 50 patients that required hospitalization, 42 (84%) were newly admitted to hospital due to ADE and in the other 8 (16%) hospital stay was prolonged due to ADEs (Figure 4).

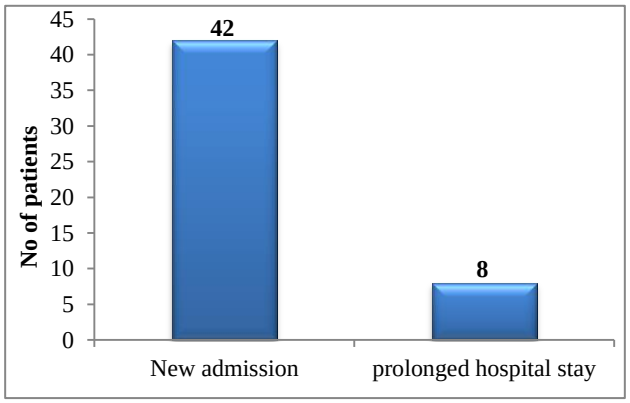

Figure 4: ADE related hospitalization.

Predictability assessment showed that 37 (74%) ADEs were unpredictable while remaining 13 (26%) were found predictable.

When analyzed for the preventability criteria, 2 (4%) ADEs were "Definitely preventable", 7 (14%) were "Probably preventable" while remaining 41 (82%) were "Not preventable". Two ADEs that were definitely preventable were Diclofenac induced Erythema Multiforme and Aceclofenac induced Exfoliative Dermatitis. They were termed definitely preventable as both of these patients administered self-medication that was inappropriate for their disease conditions (Figure 5).

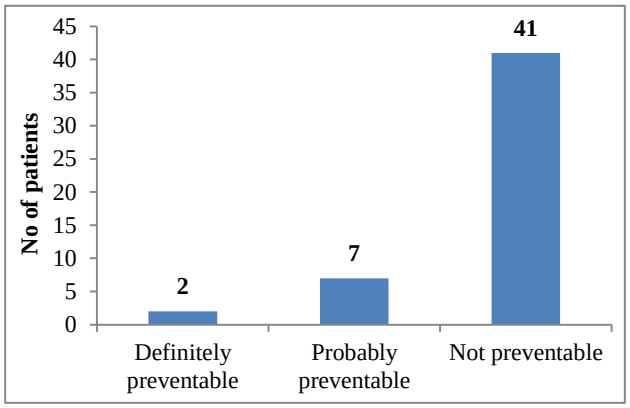

Figure 5: Preventability of ADE by using modified Schumock and Thornton Scale.

DISCUSSION

In the present study, we analyzed 809 ADEs out of which 50 (6.18%) were serious ADEs. These findings were similar to a study by Patel et al from Mumbai, India who reported 6.89% patients experienced serious ADEs which lead to hospitalization.[12] Pirmohamed et al from Merseyside, England reported that among 18,820 patients, 6.5% experienced serious ADEs which required hospitalization.[3]

We also noted that majority of the serious ADEs were experienced by the patients in the age group of 20-40 years. Serious ADEs increases the mortality and morbidity. Experiencing serious ADEs in the productive age group of 20-40 years imposes great burden on the patient physically, mentally and economically. Higher prevalence of serious ADEs in 20-40 years age group was also seen in a study by Naveen, et al.[13]

Male preponderance was observed in the present study, (74%) which was much higher as compared to other studies from Miran Brvar et al from Slovenia in which males constituted 57% of the patients with serious ADEs.[14]

In the present study, serious ADEs were caused mainly by Anti epileptic drugs (AED) (32%) followed by Anti HIV drugs and Anti tubercular drugs (18% each). This is in contrast with another study by Pirmohamed et al who reported that NSAIDS (29.6%) followed by diuretics (27.3%) were the major causative drugs for serious ADEs.[3]

Among the anti epileptic drugs, Phenytoin was the most common offending agent and most of the serious cutaneous ADEs were caused by Phenytoin. These findings were similar to another study by Sharma et al who reported that AEDs were most common group of drugs causing serious cutaneous ADEs and Phenytoin was the most common AED.[15]

An estimated 6-10 million people in India suffer from epilepsy which accounts for nearly 1/5th of global epilepsy burden.[16] Higher number of ADEs is seen with Phenytoin, as it is one of the most frequently prescribed AED for seizure disorder because of its established efficacy since many years.

Antiretroviral medications have also been associated with cutaneous ADE, ranging from mild exanthemas to life-threatening reactions, such as SJS or TEN.[17] In the present study more than half of ADEs caused by ART were cutaneous ADEs. Serious drug hypersensitivity reactions such as erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis is said to be 100 times more common in HIV patients as compared to normal population.[18]

Mechanism of SJS is uncertain but has been linked to immune dysfunction. It is presumed that owing to some genetic defect, there is altered metabolism of drug and its interaction with the immune components which provokes the reaction.CD8+ cytotoxic T Lymphocytes are believed to initiate this type IV hypersensitivity reaction. Cytotoxic molecules-FasL and granulysin are thought to be responsible for the disseminated keratinocyte apoptosis in SJS/TEN.[19] In fact the HLAB*1502 allele

has been linked with phenytoin and carbamazepine induced SJS.[20] Additionally. Phenytoin being a strong inducer of CYP450, is linked to induction of oxidative stress and generation of reactive oxygen species.[21] This may be an additive pathogenetic mechanism.

Stevens Johnson Syndrome (SJS) was the most frequently observed serious ADE which accounted 20% of all the serious ADEs. Cutaneous drug reactions are said to be one of the most common type of adverse drug reactions.[15] It occurs in 2-3% of the hospitalized patients and is potentially serious in 2% cases.[22] The reported mortality varies from 3 to 10% for SJS.[23] However no mortality was observed in the present study. A study by Sasidharanpillai et al from kerala, India, reported that SJS-TEN was the commonest type of serious cutaneous reaction.[24] In the present study SJS was seen more commonly with anti-microbial drugs, which is supported by a systematic review by Patel et al from Gujarat, India, who also reported that antimicrobials were the major causative drugs for SJS.[25]

Drug induced hepatotoxicity (18%) was the 2nd most common encountered serious ADE in the present study. The most common drug causing hepatotoxicity was rifampicin followed by isoniazid. Incidence of ATT related hepatotoxicity is ranges from 2% to 28%.[26] India is the country with the highest burden of TB. The estimated TB prevalence figure for 2015 is given as 2.5 million. Rifampicin being the first line drug for treatment of Tuberculosis and India having the highest burden of TB, ADEs with ATT is relatively common. Hepatotoxicity may reduce drug compliance and lead to development of multi drug resistance.

Pemphigus vulgaris (PV) is a chronic, autoimmune, mucocutaneous, vesiculobullous disease.[27] Drug-induced pemphigus (DIP) is a rare, but well-established type of pemphigus. It is estimated that approximately 10 % of cases of pemphigus are drug related. Drugs inducing Pemphigus can be broadly divided in two categories: thiol and non-thiol drugs. Non-thiol drugs associated with pemphigus include penicillins, phenobarbitone, cephalosporins etc. and the non-thiol drugs are more likely to induce pemphigus via immunological mechanisms.[28] Drug-induced pemphigus should be considered as a possibility in a patient with bullous disease who are on long-term use of antiepileptic medication. The withdrawal of these culprit drugs and steroid administration is proved to be the effective treatment of drug-induced pemphigus.

Dapsone is widely used for a variety of infectious, immune and hypersensitivity disorders. A rare, potentially fatal idiosyncratic systemic hypersensitivity syndrome namely dapsone hypersensitivity syndrome (DHS), characterized by fever, skin rash, eosinophilia, lymphadenopathy, hepatic, pulmonary and other systemic manifestations can complicate dapsone therapy. It develops several weeks to months after treatment initiation and the reported incidence ranges from 0.5% to 3%. Pathogenesis of DHS is unclear but proposed mechanisms implicate metabolites of dapsone, which form haptens with the production of anti-dapsone antibodies.[29] Differences in dapsone metabolism, which affect the production and detoxification of its reactive metabolites might be responsible for differential susceptibility of people to the adverse effects of dapsone.[30]

Acute pancreatitis is commonly caused by choledocholithiasis, ethanol abuse, trauma and drugs, including statins, diuretics, antiretroviral agents and anticonvulsants.[31] The incidence of sodium valproate-induced pancreatitis has been estimated to be 1:40,000.[32] The mechanism of valproate induced acute pancreatitis is "idiosyncratic," a direct toxic effect of free radicals on the pancreatic cell membrane by depletion of superoxide dismutase, catalase, and glutathione peroxidase has been assumed.[33,34]

Long-term antiretroviral drug-based treatments cause serious toxic effects. The incidence of acute pancreatitis may reach up to 40% of HIV seropositive individuals a year, which is considerably higher than for the general population, that has an incidence of 2%.[35] Pancreatitis has been predominantly associated with the usage of nucleoside reverse transcriptase inhibitors (NRTIs) such as didanosine and stavudine.[36]

Being used widely and frequently, NSAIDs are often associated with ADEs.[37] The main safety concerns while using NSAIDs are gastrointestinal, renal, cardiovascular, hematologic effects, hepatic and allergic reactions.[38] However, we noted majority of cutaneous ADEs in the present study, with 7 out of 8 serious ADEs being cutaneous in nature. NSAIDs being widely used as over the counter (OTC) medications for pain relief, there is a continuum risk of ADEs. Health care providers can be instrumental in educating patients about using OTC NSAIDs at the lowest effective dose for the shortest required duration to balance its efficacy and safety and thus preventing ADEs.[39]

ADEs may prolong hospital stay, it is important to appreciate that those patients who stay longer in hospital are at an increased risk of ADEs.[40] In the present study, 84% of the patients were admitted as a result of ADE which was similar to another study by Pirmohamed et al from England who reported that in 80% of the cases ADEs directly lead to hospitalization.[3]

Our findings on preventability showed about 18% of ADEs were preventable while 82% were non-preventable. Among the preventable ADEs 4% were definitely preventable because of inappropriate self-medication by the patient. Remaining 14% were found probably preventable, as necessary laboratory tests were not performed or preventative measures not taken while administering drug to patient. Our study results were

comparable with the studies carried out by Dartnell et al who reported that 5.5% of the ADEs were definitely preventable.[41] Another study by Kanagaratnam et al reported that 27% of the serious ADEs were preventable, while 73% were non-preventable.[42]

CONCLUSION

Serious ADEs constitute a significant health issue. The present study gives us an insight about the occurrence of serious ADEs in a tertiary care hospital of south India. High occurrence of serious ADEs among males and high incidence of serious cutaneous ADEs especially SJS is highlighted in this study. There is a clear need to design intervention strategies to prevent ADE-related hospitalization. Future research focused on identifying and minimizing the risks of serious ADEs is needed, to aid in the optimal use of pharmacotherapy. Serious ADEs to most commonly prescribed drugs like NSAIDs and Antimicrobial agents, highlights the importance of raising awareness among clinicians and patients for early recognition and management of serious ADEs.

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REFERENCES

1. International drug monitoring. The role of the hospital. World Health Organ Tech Rep Ser. 1969;425:5-24.
2. Davies EC, Green CF, Mottram DR, Pirmohamed M. Adverse drug reactions in hospitals: a narrative review. Curr Drug Saf. 2007;2(1):79-87.
3. Pirmohamed M. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15-9.
4. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse Drug Reactions in Hospital In-Patients: A Prospective Analysis of 3695 Patient-Episodes. PLoS ONE. 2009;4(2):e4439.
5. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1997;277(4):301-6.
6. Moore N, Lecointre D, Noblet C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine: Hospital cost of adverse drug reactions. Br J Clin Pharmacol. 2002;45(3):301-8.
7. Wester K, Jönsson AK, Spigset O, Druid H, Hägg S. Incidence of fatal adverse drug reactions: a population based study. Br J Clin Pharmacol. 2008;65(4):573-9.
8. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279(15):1200-5.
9. White TJ, Arakelian A, Rho JP. Counting the costs of drug-related adverse events. PharmacoEconomics. 1999;15(5):445-58.
10. Patel K, Kedia M, Bajpai D, Mehta S, Kshirsagar N, Gogtay N. 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 Clin Pharmacol. 2007;7(1):8.
11. Ramesh M, Pandit J, Parthasarathi G. Adverse drug reactions in a south Indian hospital-their severity and cost involved. Pharmacoepidemiol Drug Saf. 2003;12(8):687-92.
12. Patel KJ, Kedia MS, Bajpai D, Mehta SS, Kshirsagar NA, Gogtay NJ. 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 Clin Pharmacol. 2007;5:59.
13. Naveen K, Pai V, Rai V, Athanikar S. Retrospective analysis of Steven Johnson syndrome and toxic epidermal necrolysis over a period of 5 years from northern Karnataka, India. Indian J Pharmacol. 2013;45(1):80.
14. Brvar M, Fokter N, Bunc M, Mozina M. The frequency of adverse drug reaction related admissions department specialty. BMC Clin Pharmacol. 2009;8:1-8.
15. Sharma V, Sethuraman G, Minz A. Stevens Johnson syndrome, toxic epidermal necrolysis and SJS-TEN overlap: A retrospective study of causative drugs and clinical outcome. Indian J Dermatol Venereol Leprol. 2008;74(3):238.
16. Suresh SH, Chakraborty A, Virupakshaiah A, Kumar N. Efficacy and Safety of Levetiracetam and Carbamazepine as Monotherapy in Partial Seizures. Epilepsy Res Treat. 2015;2015:1-6.
17. Khan DA, Solensky R. Drug allergy. J Allergy Clin Immunol. 2010;125(2):S126-37.e1.
18. Yunihastuti E, Widhani A, Karjadi TH. Drug hypersensitivity in human immunodeficiency virus-infected patient: challenging diagnosis and management. Asia Pac Allergy. 2013;4(1):54.
19. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis. 2010;5(1):39.
20. Locharernkul C, Loplumlert J, Limotai C, Korkij W, Desudchit T, Tongkobpetch S, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. Epilepsia. 2008;49(12):2087-91.
21. Kandil AO, Dvorak T, Mignano J, Wu JK, Zhu JJ. Multifocal Stevens-Johnson syndrome after concurrent phenytoin and cranial and thoracic radiation treatment, a case report. Radiat Oncol. 2010;5(1):49.

22. Sharma VK, Sethuraman G. Adverse cutaneous reactions to drugs: an overview. J Postgrad Med. 1996;42(1):15-22.
23. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol. 2000;136(3):323-7.
24. Sasidharanpillai S, Riyaz N, Khader A, Rajan U, Binitha M, Sureshan D. Severe cutaneous adverse drug reactions: A clinicoepidemiological study. Indian J Dermatol. 2015;60(1):102.
25. Patel T, Barvaliya M, Sharma D, Tripathi C. A systematic review of the drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Indian population. Indian J Dermatol Venereol Leprol. 2013;79(3):389.
26. Pandit A, Sachdeva T, Bafna P. Drug-Induced Hepatotoxicity: A Review. J Appl Pharm Sci. 2011;2:233-43.
27. Chaidemenos G, Apalla Z, Koussidou T, Papagarifallou I, Ioannides D. High dose oral prednisone vs. prednisone plus azathioprine for the treatment of oral pemphigus: a retrospective, bi-centre, comparative study: Daily prednisone vs. LMT in oral pemphigus. J Eur Acad Dermatol Venereol. 2011;25(2):206-10.
28. Golberg O, Harman KE. Drug-Induced Pemphigus. In: Katsambas AD, Lotti TM, Dessinioti C, D'Erme AM, editors. European Handbook of Dermatological Treatments. Berlin, Heidelberg: Springer Berlin Heidelberg. 2015;p725-30.
29. Rieder MJ, Uetrecht J, Shear NH, Cannon M, Miller M, Spielberg SP. Diagnosis of sulfonamide hypersensitivity reactions by in-vitro "rechallenge" with hydroxylamine metabolites. Ann Intern Med. 1989;110(4):286-9.
30. Vinod K, Arun K, Dutta T. Dapsone hypersensitivity syndrome: A rare life threatening complication of dapsone therapy. J Pharmacol Pharmacother. 2013;4(2):158.
31. Yazdani K, Lippmann M, Gala I. Fatal pancreatitis associated with valproic acid: review of the literature. Medicine (Baltimore). 2002;81(4):305-10.
32. Gerstner T, Büsing D, Bell N, Longin E, Kasper JM, Klostermann W, et al. Valproic acid-induced pancreatitis: 16 new cases and a review of the literature. J Gastroenterol. 2007;42(1):39-48.
33. Asconapé JJ, Kiffin P, Dreifuss FE, Riela A, Mirza W. Valproate-associated pancreatitis. Epilepsia 1993;34:177-83.
34. Pippenger CE, Xianzhong M, Rothner AD. Free radical scavenging enzyme activity profiles in risk assessment of idiosyncratic drug reactions: probable mechanism of valproate induced pancreatitis and hepatotoxicity. In Levy RH, Penry JK, editors. Idiosyncratic reactions to valproate: clinical risk patterns and mechanism of toxicity. New York: Raven Press; 1991:75-88.
35. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol. 2005;39(8):709-16.
36. Van Oosterhout JJ, Mallewa J, Kaunda S, Chagoma N, Njalale Y, Kampira E, et al. Stavudine toxicity in adult longer-term ART patients in Blantyre, Malawi. PloS One. 2012;7:e42029.
37. Scheiman JM, Hindley CE. Strategies to optimize treatment with NSAIDs in patients at risk for gastrointestinal and cardiovascular adverse events. Clin Ther. 2010;32(4):667-77.
38. Gaskell H, Derry S, Moore RA. Treating chronic non-cancer pain in older people- More questions than answers? Maturitas. 2014;79(1):34-40.
39. Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs. Ther Clin Risk Manag. 2015;11:1061-75.
40. Beijer HJM, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADE): a meta-analysis of observational studies. Pharm World Sci. 2002;24(2):46-54.
41. Dartnell JG, Anderson RP, Chohan V, Galbraith KJ, Lyon ME, Nestor PJ, et al. Hospitalisation for adverse events related to drug therapy: incidence, avoidability and costs. Med J Aust. 1996;164(11):659-62.
42. Kanagaratnam L, Abou Taam M, Heng M, De Boissieu P, Roux MP, Trenque T. Serious Adverse Drug Reaction and Their Preventability in the Elderly Over 65 Years. Thérapie. 2015;70(5):477-84.

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