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ORIGINAL RESEARCH

Development of indicators for identifying adverse drug events in an Indian tertiary care teaching hospital

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Objective: Adverse drug events (ADEs) are drug-related events which continue to pose serious challenges to the safety of patients. There are a number of ways to monitor ADEs, and the use of indictors to screen them provides an alternative method for detecting them. This method helps to assess the safety of drugs by the manual record review technique. The aim of this work was to develop a list of indicators to use in medical units of the study hospital to identify ADEs.

Setting: Tertiary care teaching hospital in India.

Method: An initial list of ADE indicators based on published literature was developed by a panel of three experts. The list of indicators was subjected to review by a Delphi panel of five members. The Delphi panel reviewed the list of valid indicators and also suggested an addition of new indicators. The final list of indicators was used to review 100 previously documented ADE case reports. The case reports were screened for the presence of any of the indicators from the list. Parameters studied included number of indicators per case report and the most used indicators.

Results: From the literature, a 72 item indicator list was initially prepared which was further narrowed down to a list of 63 items. The Delphi panel conducted a review with these 63 items. At the end of review, and after addition and deletion of indicators, a 49 item indicator list was finalized. When this list of indicators was used for the review of ADE case reports, 42 indicators were identified. On average, three indicators were present in the reviewed case reports.

Conclusion: An indicator list was developed for identification of ADEs in the study setup. The relevance of this indicator list was demonstrated by the presence of these indicators in the previously documented ADE reports. This is the first study from India to report on the development of ADE indicators, which might provide an alternative method to detecting ADEs in the setup of future studies.

Keywords: adverse drug events, drug safety indicators, Delphi panel

Introduction

An adverse drug event (ADE) is defined as "an injury resulting from medical intervention related to drugs".[1] ADEs continues to be a serious challenge for the safety of patients. A significant number of ADEs are preventable in nature, and therefore this represents an avoidable burden on health care.[2] ADEs are monitored in a clinical setup using a number of methods like case reports, spontaneous reporting systems, intensive event recording, case-control studies, case-cohort studies, prospective cohort studies, incident reports, retrospective or concurrent chart reviews and observational studies.[3–5] Each methodology has its own advantages and disadvantages.[6]

An indicator is a clue that helps a health care organization to identify adverse events and assess the overall harm that occurs from medical care within that organization.[7] This methodology is based on identifying and addressing errors that are

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highly associated with negative outcomes.[8,9] Indicators offer an approach to standardizing error identification that may provide more consistent and accurate information than traditional error reporting systems.[10] This system was also used for identification of adverse events along with traditional chart audits, incident reporting, or voluntary reporting. There are a number of reports on implementing electronic triggers to screen hospital records for the occurrence of ADEs.[11,12]

India is a developing country which is a member of the World Health Organization-run pharmacovigilance program. The pharmacovigilance in this country is still in its infancy.[13] ADE monitoring is carried out sporadically, and studies have reported that under-reporting is common in many of the study sites.[14–16] This study was carried out in a tertiary care teaching hospital in South India. The ADE monitoring program was initiated in the current setup around a decade ago, but the level of participation of clinicians in this program is low.[17] It was planned to use indicators to identify ADEs in the current setup. For this purpose there was a need to develop a list of indicators specific for this setup. The present work was aimed to develop an indicator list based on available literature and modify it suitably with the help of a Delphi panel review and review of adverse event case reports.

Methodology

Development of indicators list

An initial list of ADE indicators was prepared based on published literature.[7,18–23] These indicators were reviewed by a panel of three experts (two clinical pharmacists and a clinician). The indicators which were relevant to the study setup were selected. The indicators relevant to general medical practice were kept in the list, whereas the indicators related to other specialties like psychiatry, intensive care unit (ICU), and surgery, were deleted. The review team collectively decided on whether to keep or delete a particular indicator from the list. This exercise was carried out to condense the list, so that the Delphi panel could work on it for the development of a final set of indicators.

Delphi panel review

A Delphi panel was formed with three clinicians and two clinical pharmacists. The members evaluated the indicator list anonymously and scored it. The panel members rated each item on the list on a Likert scale which represented a score from 1 to 5. During this review panel members were asked to suggest any additional indicators which could be added to the list. At the end of the first review, the scores were summarized and this was presented to the panel members along with their own scores. In the second review, panel members were encouraged to reassess their opinion in light of scores given by other members. Additional indicators were added to the list for review. After the second review, the mean score for each item was calculated. The mean score of 3 and above, out of 5, was considered as criteria for inclusion into the list. For the newly added indicators, one more review was conducted and mean scores were calculated. The final comprehensive list was divided into four categories, namely: (1) abnormal changes in clinical condition, (2) changes in patient care process, (3) drug-related alterations, (4) changes in lab investigations. (Tables 1–4)

After the preparation of a comprehensive list of indicators, they were used to screen previously identified and documented ADE case reports. A set of 100 previously documented ADE reports were randomly picked from the documented database. These adverse events were identified by clinical pharmacists from medicine wards during their rounds with clinicians. These reports contain complete details of the case which included medical history, diagnosis, lab investigations, therapy and ADE. Reports were reviewed for the presence of any indicators from the prepared list. The following four factors were then assessed: mean number of indicators per case report, commonly identified indicators, total number of identified indicators, and indicators that were not identified in any of the case reports.

Results

Screening by expert panel

From the literature, 72 indicators were selected for the list. The expert panel conducted a review of indicators. Items were added to the list based on the relevance of indicators for the internal medicine department and the utility of specific indicators. Indicators like 'hospital visit due to depression or other psychiatric illness due to drug treatment or lack of monitoring' was removed since such cases are usually presented to the psychiatry department and do not come under the general medicine department. Specific indicators like theophylline toxicity were removed because the use of theophylline is less common and its monitoring is not carried out. Indicators like toxicity of individual antiepileptic drugs such as phenytoin, carbamazepine, and sodium valproate were combined as 'drug toxicity'. An indicator on long term use of codeine and acetaminophen for pain relief resulting in broken bones was removed since such a practice of using codeine for pain relief is not common in this setup. Indicators on gastritis and upper intestinal bleeding due to many different drugs and factors were reduced to two indicators. Many indicators were recommended to be deleted since their prevalence was thought to be low for this setup. Some indicators were combined with others since they were similar. At the end of the review, the list was modified to include 63 indicators.

Table 1 Indicators of abnormal change in clinical condition of patients

Indicators	Cause
Headache	Drug induced
Over-sedation/lethargy/hypotension	Medication-related ADE
Immobility (emboli)	Low molecular heparin
Bleeding	Use of warfarin without monitoring INR during initiation and follow-up of therapy. Concurrent use of warfarin and an oral/topical NSAID/antibiotic/ACE inhibitors/ amiodarone without monitoring the INR within 10 days.
Diarrhea/use of antidiarrheal	Antibiotics
Dyspepsia or upper GI bleed or perforation or GI ulcer or anemia/use of PPIs	Use of a beta-blocker/oral or topical NSAIDs/oral corticosteroids in a patient with a PMH or current diagnosis of peptic ulcers and/or GI bleeding. Additional reliability indicator. Use of more than one NSAID for more than two weeks without protective agents like H_2 receptor antagonists or PPIs.
GI disturbance or GI bleed	Long-term use of ferrous sulphate without monitoring hemoglobin
Melena	Drug induced GI Ulcer
Vomiting, nausea/use of antiemetics	Drug induced
Loss of seizure control or seizure activity	Use of lamotrigine/carbamazepine/phenytoin/valproic acid without drug level monitoring at least every 6 months. Use of antibiotics.
Tremor	Drug induced
Acute renal failure and/or renal insufficiency	Use of an ACE inhibitor (eg, captopril, enalapril, etc). BUN/serum creatinine not done at initiation of therapy and at least every 3 months thereafter. Use of NSAID for 3 months. Use of Lithium.
Acute urinary retention	Diagnosis/history of bladder atony due to diabetes. Use of imipramine. Diagnosis of BPH and use of an anticholinergic agent.
Acute respiratory failure	History/diagnosis of severe COPD. Use of a medium- to long- acting benzodiazepine.
Asthma exacerbation and/or status asthmaticus and/or ER visit/hospitalization due to asthma	Diagnosis of asthma. Use of a bronchodilator. No use of a maintenance corticosteroid (eg, beclomethasone, etc).
Hospital visit due to asthma symptoms	Use of an inhaled short-acting bronchodilator more than once daily or at night in an asthmatic patient with no regular inhaled 'preventer' therapy (corticosteroid, cromoglicate, or nedocromil)
ER visit/hospitalization due to hyperthyroidism	Use of a thyroid or antithyroid agent (eg, levothyroxine, propylthiouracil, etc). T_4/TSH not done within 6 weeks after initiation of therapy and at least every 12 months thereafter.
ER visit/hospitalization due to hypothyroidism	Lithium use for at least 6 months. TSH not done at least every 6 months.
Oral thrush/dysphonia/oral candidiasis	Use of an inhaled steroid by metered dose inhaler without usage of a spacer device
Edema	Chronic use of amlodipine
Skin rashes/angioedema/Steven Johnson syndrome/TEN	Drug induced
Pyrexia	Drug induced

Abbreviations: GI, gastrointestinal; PPIs, proton pump inhibitors; ER visit, emergency room visit; TEN, toxic epidermal necrolysis; ADE, adverse drug event; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; ACE inhibitors, angiotensin-converting enzyme inhibitors; PMH, postmenopausal hormone; BUN, blood urea nitrogen; BPH, benign prostate hyperplasia; COPD, chronic obstructive pulmonary disease; TSH, thyroid-stimulating hormone.

Delphi panel review

The Delphi panel reviewed the indicator list for its utility. Five reviewers independently reviewed the list and rated them on a scale of 1 to 5. At the end of the first review, 22 out of 63 items in the list were rated less than 3 points and were subsequently eliminated. Eight new indicators were suggested by the members of Delphi panel. In the second review a total of 71 items were included in the list. The panel members were asked to rate all of the items. At the end of the second review, a total of 49 indicators received scores above 3. The results were again presented to the panel members with their scores against the scores of other team members for the third review. The third review did not alter the scores, 49 were rated above 3 points, and were included in the list.

Assessment of documented adverse event reports

A total of 42 indicators were identified in previous ADE case reports. Each reviewed case report had an average of three indicators from the list. Seven indicators could not be identified in any of the reported case records. Indicators which were most frequently identified from the reports were studied (Table 5). Abrupt drug withdrawal was the most common indicator identified in the reports, followed by repeat requests for laboratory tests, and use of antihistamine/steroids for the management of drug allergies. Drug induced pyrexia, edema, raised serum creatinine, and tremors were among the least identified indicators in reviewed reports.

Table 2 Indicators of change in patient care process

Indicators	Cause
Abrupt withdrawal of medication	Any ADE
Intubation/re-intubation	Related ADE/drug induced respiratory depress
ER visit/hospitalization due to congestive heart failure	Use of a calcium channel blocker (eg, diltiazem, etc). Use of beta blockers. Oral/topical NSAID use for at least 3 months.
Use of blood products	Drug induced hematological disorder
ER visit/hospitalization due to extreme hypoglycemia	History/diagnosis of diabetes. Use of insulin/oral hypoglycemics. Use of a β-adrenergic blocking agent (eg, propranolol, nadolol). Use of fluroquinolones.
ER visit/hospitalization due to worsening renal impairment and/or acute renal failure and/or renal insufficiency	Diagnosis and/or history of kidney disease. Use of tetracycline. Use of a select urinary anti-infective agent (nalidixic acid, nitrofurantoin, or methenamine complexes).
Dose reduction	Related ADE
Admission to dialysis unit	Drug-induced ARF
Emergency visit/admission	Drug-induced complications
Readmission to ICU	Drug-related/ADE

Abbreviations: ER, emergency room; ICU, intensive care unit; ADE, adverse drug event; NSAID, nonsteroidal anti-inflammatory drug; ARF, acute renal failure.

Discussion

This report describes the development of ADE indicators in the current setup. This study used a team of clinicians and pharmacists to review the developed ADE indicators. The Delphi technique, which has been used in a number of previous studies, was used as a method of assessing the developed indicator list.

An initial list of 71 indicators selected from the literature was considered unmanageable, and after the Delphi panel review, the number of indicators was reduced to 49. In a study by Matlow et al on the development of trigger tools for pediatrics, they reported that 94 indicators were initially selected by a review committee. This list was considered as not practical for routine use, and was subsequently reduced to a manageable list of 40 indicators.[19] An indicator list containing a reasonably limited number of items is preferable since it reduces the burden on case record reviewers.

Abrupt withdrawal of drugs was identified most frequently as an indicator in the records. Since this is the first step in management of any drug-related adverse event, it could be found in many of the previously documented adverse event reports. Another commonly identified indicator was frequent requests for a specific lab investigation. Repeat requests for a particular investigation signifies a certain level of complication in the management of the patient's condition, and might be associated with drug-related adverse events.

The indicator list was classified under four major categories: abnormal clinical changes, change in patient care, laboratory investigation-related, and drug/antidote-related. Among these four classes of indicators abnormal clinical changes included 22 indicators. This showed the preference of reviewers for the indicators which can identify adverse events based on the data available from patient progress charts and follow-up. Changes in patient care and lab investigations were the other important group of indicators considered for identifying ADEs (10 each). In contrast to a study published by Handler et al in which the medication concentration signals were considered as important, abnormal clinical changes were considered as important indicators in this study.[24] In this study, even when toxicity was suspected for a drug, estimation of drug levels was not carried

Table 3 Indicators of drug-related alterations

Indicators	Cause
Use of antihistamines	Drug allergy
Digoxin toxicity	Concurrent use of digoxin and a potassium-sparing diuretic or potassium supplements without monitoring digoxin levels. Addition of amiodarone/verapamil to a patient on digoxin without reducing the digoxin dosage
Vitamin K	Bleeding/over usage of anticoagulant
Use of laxative	Drug induced (antibiotics, opioids, amlodipine, amiodarone)
Use of K-bind	Potassium toxicity
Aminoglycoside toxicity (acute renal failure and/or renal insufficiency and/or vestibular damage and/or auditory damage)	Use of an aminoglycoside. Serum creatinine not done before and after therapy (and if therapy longer than 7 days, not done at least every 7 days). At least one drug level not done.
Electrolyte/nutrient supplementation	Drug induced imbalances

Table 4 Indicators of lab investigation

Indicators	Cause
Frequent ECG request	Drug induced arrhythmias
Blood dyscrasias	Concurrent use of trimethoprim/sulfamethoxazole and methotrexate. Use of carbamazepine, ticlopidine. WBC/platelets/CBC not done at least every 4 weeks.
Major and/or minor hemorrhagic event, INR > 6, elevated APTT	Use of IV heparin, warfarin. PTT not done at least every day. Use of aspirin/clopidogrel/warfarin.
Abnormal liver function tests or clinical jaundice	Use of a statin without baseline monitoring of liver function and subsequent monitoring at 6 monthly intervals. Use of pioglitazone. No baseline and follow up LFTs for every month for first 8 months.
Abnormal LFT	Drug induced (statins, pioglitazone, isoniazid, rifampicin, pyrazinamide). LFTs not done at baseline and follow up.
Hyponatremia and/or excessive water retention and/or syndrome of inappropriate antidiuretic hormone (SIADH)	Use of carbamazepine. Electrolytes/CBC not done before therapy initiated, at least weekly during the first month of therapy, at least monthly during the next 5 months of therapy, and at least every 6 months thereafter. Thyroxine use.
Electrolyte imbalance K, Na, Cl, Ca, K	Drug induced (diuretics, ACE inhibitors, potassium supplements). No electrolyte monitoring at the frequency of 10 days to a few months.
Elevated BUN, SCr	Drug induced ARF
Raised serum creatinine	Use of an oral/topical NSAID for more than 3 months without monitoring serum creatinine at least every 3 months.
Repeated request for lab assessment of any parameter	Drug induced

Abbreviations: ECG, electrocardiography; INR, international normalized ratio; APTT, activated partial thromboplastin time; LFTs, liver function tests; SIADH, syndrome of inappropriate antidiuretic hormone hypersecretion; BUN, blood urea nitrogen; SCr, serum creatinine; WBC, white blood cell count; CBC, complete blood count; IV, intravenous; PTT, partial thromboplastin time; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARF, acute renal failure; NSAID, nonsteroidal anti-inflammatory drug.

out routinely because of economic considerations, and clinicians mostly rely on clinical signs and symptoms to assess toxicity.

Morris and Cantril validated drug-related morbidity indicators developed in the United States and United Kingdom, and studied differences between the two setups. They reported that indicators used in the USA lacked relevance to the UK. They attributed this to the difference in clinical practice and philosophical view points of professional practice. But they concluded that if suitable validation processes can be developed, indicators from one setup can act as a starting point for another setup.[22] The current work used indicators reported from various studies and attempted to validate such indicators for the study setup. This exercise gave insight into the viewpoints of health care professionals in the study center. The methodology of using specific triggers or indicators offers flexibility in using this system for a variety of health care systems. The indicators can be modified suitably according to individual setup.[7] Several institutions have used this approach in their setup and have reduced harm up to 50%. Even though this method itself may not result in improvement in prevention of adverse events concerned, it provides a good platform for any organization which attempts to reduce adverse events. Record review using indicators might provide a better chance of detecting ADEs compared with many other commonly

Table 5 Most used indicators

Indicators	Cause	No. of times indicator identified in the case review (100 cases)
Abrupt withdrawal of medication	Any ADE	82
Repeated request for lab assessment of any parameter	Drug induced	36
Use of antihistamines	Drug allergy	20
Skin rashes/angioedema/Steven Johnson syndrome/TEN	Drug induced	18
Emergency visit/admission	Drug induced complications	18
Electrolyte imbalance K, Na, Cl, Ca, K	Drug induced (diuretics, ACE inhibitors, potassium supplements). No electrolyte monitoring at the frequency of 10 days to a few months.	16
Electrolyte/nutrient supplementation	Drug induced imbalances	12
Dose reduction	Related to ADE	10
Frequent ECG request	Drug induced arrhythmias	8
Vomiting, nausea/use of antiemetics	Drug induced	8

Abbreviations: TEN, toxic epidermal necrolysis; ECG, electrocardiography; ADE, adverse drug event; ACE, angiotensin converting enzyme.

used methods like voluntary reporting, intensive monitoring, and reporting of summary data. Use of this technique is also more economical when compared to other approaches. There are few limitations in this study which need to be considered. Even though indicators developed for one setup could be adopted for another setup, indicators adopted from a predominantly Western setup may not have relevance in the Indian setting. Unless the indicators are assessed by using them in the record review, the list might not reflect the useful indicators relevant for the current setup. Further validation is needed for this indicator list by actually using it for adverse event screening from the medical records.

Conclusion

The current work resulted in the development of an indicator list for identification of adverse events in the current setup. The list was prepared using the expert review and Delphi panel review. The final list contained a total of 49 indicators. The relevance of this indicator list was demonstrated by the presence of these indicators in the previously documented ADE case reports. This is the first study from India to report on the development of indicators, and this might provide an alternative method to detect ADEs in the studied health care setting.

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Disclosure

The authors report no conflicts of interest in this work.

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