Development of a Computerized Adverse Drug Event (ADE) Monitor in the Outpatient Setting

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Abstract

This paper describes the collaboration of Brigham and Women's Hospital and Regenstrief Institute to develop a computerized adverse drug event (ADE) monitor using electronic medical records from outpatient practices. We describe the steps involved in ADE monitor development and rule validation at large outpatient practices at Boston and Indianapolis. The final standard rule set adopted by both practice sites are currently being used to test the impact of basic and advanced decision support on ADE rates.

The rules used by the ADE monitor derive from coded medication names and laboratory results, as well as text from clinician notes contained within the electronic medical record systems. The nontext rules are subdivided into five categories: medication, laboratory, medication-laboratory, ICD-9 codes, or miscellaneous. Rules target various diagnostic and laboratory abnormalities caused by a broad range of outpatient medications commonly used in primary care. Text-based rules were developed for certain medications by linking the medications with symptoms (ADE) that are often associated with short- or long-term. The rules were run on 4 months of data at both sites, possible ADEs were identified and validated by chart review, and the positive predictive values of each rule were calculated. We found that clinically based rule sets can be developed and implemented at different outpatient settings using distinct information systems to identify ADEs related to commonly prescribed outpatient medications.

Introduction

Adverse drug events (ADEs) contribute to overall morbidity and mortality. Phillips et al.[1] have estimated that as many as 7,000 people die each year due to medication errors both outside and inside the hospital. It has also been reported in an academic teaching hospital that the rates are 6.5 ADEs per 100 admissions.[2] In another study, a total ADE event rate was found to be 27.4 per 100 patients in the outpatient setting.[3] These studies show that ADEs are common and many are preventable in inpatient and outpatient settings.

Previous studies have demonstrated the use of ADE detection monitors to identify ADEs[2, 4, 5] and possibly prevent further harm to the patient. Jha et al. demonstrated that the ADE monitor that they used required substantially fewer

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person-hours than did chart review and thus would require fewer resources to monitor ADEs. They also felt that it was the most practical method for ongoing quality assessment.[4] Another study has shown the ability to use an ADE monitor in inpatient pharmacy practice to provide recommendations to prescribing clinicians on a daily basis.[6] In a study by Honigman et al. an outpatient ADE monitor was developed. The utility of multiple search methods was demonstrated within their ADE monitor and the use of an electronic medical record led to the ability to include symptom terms as part of their methodology.[7] Yet another study using an ADE monitor was undertaken in the ambulatory setting using a similar set of rules.[8] These studies all demonstrate the potential feasibility of implementing ADE monitors in inpatient and outpatient settings.

While computerized monitors are not yet widely used, they offer an efficient approach for monitoring the frequency of ADEs on an ongoing basis and the Health Care Financing Administration is considering mandating them.[9] These monitors need to be evaluated and refined further; in particular, it is important to quantify the yield of collecting these data on an ongoing basis. In addition, refinement of the rules used in these monitors is necessary in the outpatient setting because, unlike hospitalized patients, outpatient clinical information is often not computerized. If computerized data are available, key pieces of information may reside in disparate systems. Therefore, development of automated systems to identify ADEs in these settings is more difficult. As computerized outpatient records become more common, further work needs to be done to adequately obtain information from nontraditional sources, such as clinic notes.

Our goal was to update outpatient rule sets previously described in Honigman et al.[7] and demonstrate use in two different practice settings with two different electronic medical records. Regenstrief Institute and Brigham and Women's Hospital collaborated to create and test an outpatient ADE monitor, using data from electronic sources. The ultimate goal was to have a well-tested monitor that can eventually be used for measurement purposes such as medication-safety related interventions.

Settings

Brigham and Women's Hospital, Boston

Brigham and Women's Hospital is a 700-bed institution that provides primary, secondary, and tertiary care in Boston, and is affiliated with Harvard Medical School and Partners HealthCare Systems. The hospital has approximately 170 clinicians who serve as primary care physicians in various practice sites, including hospital-based clinics, community-based clinics, and neighborhood health centers. Since 2000, all primary care physicians (PCPs) have used an electronic ambulatory record called the Longitudinal Medical Record (LMR) to store information on the outpatients such as demographics, problem lists, medication lists, allergy lists, test results, and visit notes. LMR currently is online

in all primary care sites, giving clinicians access to a patients' electronic medical record with Web-based browser functionality and user-friendly design. Visit notes can be entered into a patient's medical record by the clinician, although the majority of providers still dictate encounter notes to be transcribed. In addition, prescriptions can be printed electronically.

Regenstrief Institute, Indianapolis

Indiana University Medical Group Primary Care (IUMG-PC) is a physician-led, primary care practice that includes internists, pediatricians, family practitioners and obstetrician/gynecologists who deliver care to patients in 12 office locations located in central Indiana. The practice is affiliated with the Indiana University School of Medicine and Wishard Memorial Hospital. Physicians in 6 of the 12 IUMG-PC primary care practices use the Medical Gopher clinical workstation software. A version of the Gopher system has been in use for outpatient order entry since 1984.[10] The Gopher provides order entry, workflow, clinical documentation, results review, access to clinical knowledge bases and linkages to billing functions. The provider records the patient's identity, allergies, billing diagnoses, medications prescribed, tests ordered, referrals, nursing interventions ordered, and notes.

Methods

Development of ADE monitors have been described in various studies,[4, 7, 11] and rules from these prior studies were used to develop our outpatient monitor. Our goal was to enhance the effectiveness of the ADE detection monitor and implement it in two different electronic medication record (EMR) systems, using two major strategies to detect ADEs in the outpatient arena.

One detection method used non-text triggers (or rules) that search a patient's recorded laboratory values and medication list, and applies a set of logical rules to determine a possible ADE or medication error. In addition, other data sources are used in some triggers such as ICD-9 codes for toxicity due to lithium; CPT codes for an esophagogastroduodenoscopy; or demographic information such as age. The second detection method also uses the patient's medication list, but uses an algorithm to identify the presence of symptoms by using symptom concepts in the text of electronic notes and to determine when they were negated. Identifying negations is important to distinguish "no nausea" from "nausea" and minimize the number of false positive "hits."

Examples of symptom terms that might be used are "sexual dysfunction" associated with clonidine or "dizziness" associated with gabapentin. Running these two detection programs on the EMR produces a number of "hits" (i.e., possible events). Trained reviewers, using a manual chart, examined each hit to determine whether (1) it was an actual or potential event; and (2) whether these events can be classified as an adverse drug event (ADE), medication error (ME), medication error that leads to an adverse drug event (ADE/ME), or no event.

In this study, ADEs were defined as events related to medication use that resulted in patient harm. A medication error was defined as any error that occurred in the medication use process (including ordering/prescribing, dispensing, adherence, and monitoring). Medication errors that caused an injury were called preventable ADEs. Medication errors that had potential to cause injury were called potential ADEs.[12] We also noted some medication errors that we felt had little chance of causing harm, but still represented an error in the medication use process. An example of this would be a patient who has two active orders for two different proton pump inhibitors. The medication has a low adverse reaction profile, but the therapy is redundant and thus an error. Those MEs that resulted in harm to the patient were classified as an ADE/ME (also known as preventable ADEs).

At Regenstrief, data mangers were initially used to screen the results, which were then passed to a clinical pharmacist or nurse for full review. The data managers received specialized training using a manual developed at Brigham and Women's Hospital. The results were reviewed directly by a clinical pharmacist; by clinical year pharmacy students under the direction of the clinical pharmacist; or research assistants who also received specialized training. The clinical pharmacist further reviewed any ambiguous cases that were discovered by the research assistants or pharmacy students.

Nontext rules logic

To program the nontext rules we used an initial list of rules known to have been implemented in hospital based systems.[4, 11] Both sites contributed to the development of additional rules, and they were added to the list to be programmed. The new rules were created, based on the experience of the clinicians working on the project, as well as evidence-based literature reviews. An example of this is adaptation of Beer's criteria for determining potentially inappropriate medication use in the elderly population:[13] while some agents listed in this guideline were included, some were excluded because the use of the agent was related to a specific indication (digoxin) or was no longer available (phenylbutazone). We also drew from Micromedex® to develop a focused list of drug-drug interactions to be incorporated in a single rule.

The nontext rules were divided into five groups, based upon the type of data used in the trigger: (1) drug; (2) drug-laboratory; (3) laboratory; (4) ICD-9; and (5) miscellaneous.

The first category (drug) involved the use of medication data. A new order of an angiotensin receptor blocker, for example, may signify that the patient had an adverse reaction to an angiotensin converting enzyme inhibitor. Another example is the use of two medications together, such as two currently active orders for agents that contain acetaminophen, that may result in the patient receiving an excessive dose of acetaminophen. The second category (drug-laboratory) involved linking a medication with laboratory results, such as the use of a potassium sparing diuretic and the presence an elevated potassium level. The third category (laboratory) was the use of laboratory data only; for example, a positive

Clostridium difficile toxin result, an ALT result greater than 150U/L, and a serum phenytoin greater than 20 mcg/ml. The fourth category (ICD-9) was the use of ICD-9 codes, such as "poisoning by agents that affect the CV system" or "poisoning by analgesics, antipyretics and anti-rheumatics." (Brigham and Women's hospital did not return any results when using the ICD-9 codes in the outpatient setting, due to difficulties obtaining this data.) The fifth category (miscellaneous) was all the rules that did not meet the criteria for the other categories; examples inclue the use of NSAIDs and a CPT code for an EGD, any female receiving finesteride, any patient receiving ketorolac for greater than 5 consecutive days or "allergic contact dermatitis from super bill."

The rules were programmed and run on 4 months of EMR data (January 15–May 15, 2001). An initial analysis was performed at both sites to determine if some of the rules, as programmed, worked as well in the ambulatory setting as they did in the acute care setting. A positive predictive value (PPV) was calculated by using the total number of identified events divided by the total reviewed results for each rule (with the duplicate results produced within each trigger subtracted out). A PPV was calculated for each rule and for the entire set of trigger within the non-text set. A partial list of the rules can be seen in Table 1.

Table 1. Examples of nontext based rules

Rule	Type
Receiving sodium polystyrene sulfonate	Drug
Combination of 2 drugs together (DDIs)	Drug
Duplicate therapy (2 active ACE inhibitors)	Drug
Duplicate therapy (2 active Angiotensin receptor blockers)	Drug
Serum theophylline > 20 mcg/ml	Lab
Any positive "C-Diff" toxin	Lab
Any fasting blood glucose or random blood sugar < 54 mg/dL	Lab
Any QTc interval > 450 ms and medications that prolong QTc	Drug-lab
Receiving digoxin AND serum potassium < 3.5 mmol/L	Drug-lab
Receiving a HMG CoA reductase inhibitor and a CK > 500	Drug-lab
Receiving phenytoin and no phenytoin test within the past 12 months	Drug-lab
ICD-9 Delerium, Drug induced ICD-9 = 292.81	ICD-9
ICD-9 codes "Poisoning by agents that affect the CV system"	ICD-9
NSAID with EGD, CPT code = 43235, 43255, 43239	Misc. CPT
Age greater than 65 and receiving a drug in a modified Beers list	Misc. age
Any female receiving finesteride	Misc. gender
Any patient receiving > 4100 mg of acetaminophen daily (OTC)	Misc. dose
Any patient receiving greater than 5 consecutive days of ketorolac	Misc. duration

Text rule ADE monitor logic

We created a set of rules based upon a combination of medication use and symptoms that may indicate that an ADE had occurred. These rules were taken from monitors used in other studies[4, 7] and modified by review of evidence-based literature related to adverse reactions. An example of this would be the association of myopathy with an HMG-CoA reductase inhibitor. Although the rate of occurrence is low,[14] this reaction carries a high mortality, and cervistatin associated myopathy was quite well publicized.[15] A computer program was designed to identify these possible ADEs and the program used natural language processing to identify possible events. The program used two aspects of Regenstrief and Brigham and Women's Hospital systems: online physician notes for patient encounters and the patients' medication list. The program first identified visit notes in the EMR, then examined the patients' medication list, looking back 60 days from the "note date." If the patient's medication list contained a medication that was involved in the rule-set within this 60-day time frame, the program would then see if any medication-symptom matches could be made for that note-date. The Regenstrief Institute had a slightly different drug match algorithm than Brigham and Women's Hospital systems. This was because Regenstrief has more comprehensive medication utilization data from the pharmacy, and can tell whether patients have refilled medications recently. Therefore, Regenstrief used the actually fill data at the pharmacy level in the prior 60 days, while Brigham and Women's Hospital systems the presence of the targeted agent in the active medication list was used.

The note was analyzed using a text parser for symptom terms previously defined that are linked to certain medications. Examples of the text rules are angioedema associated with angiotensin converting enzyme inhibitors and synonyms of bronchospasm (such as wheezing, asthma or asthma attack) related to beta-blockers. The monitor was programmed to ignore symptom terms appearing within six words after a negation term ("not," "no," "denies," "lack of," etc.). If both a negated symptom term and non-negated symptom term (a symptom term that did not have a negation located within six words of it) were present in the note, the note was included to be reviewed. The medications that were to be studied were divided into classes, such as angiotensin converting enzyme inhibitors, beta-blockers, and hypoglycemic medications (both oral and injected insulin). It was determined that the same symptoms terms might relate to multiple classes, and it was decided that symptoms terms should be linked to clinical concepts. The symptom term "contusion," for example, would be linked with both of the clinical concepts "agranulocytosis" and "bleeding." In long-term use of an ADE monitor, this process would be easier to maintain links within the program and decrease the time needed to maintain the program. Other examples of some of the rules in the text portion of the ADE monitor are shown in Table 2.

Table 2. Examples of text-based rules

Rule
ACE Inhibitors AND hyperkalemia
Anti-seizure meds AND dizziness
Anti-depressants group 1 AND constipation
Anti-depressants group 2 (SSRI, SNRI, and bupropion) AND anorexia
Benzodiazepines AND confusion
Beta Blockers AND bradycardia
Calcium channel blockers AND peripheral edema
Diuretics AND hypokalemia
Hypoglycemics AND dizziness
Narcotics AND constipation
NSAIDs AND hyperkalemia
Potassium AND hyperkalemia
Central acting anti-adrenergic agents AND sexual dysfunction
Nitrates AND hypotension
HMG-CoA reductase inhibitors AND myopathy
Amiodarone AND thyroid abnormality
Antipsychotic agents AND sedation
Lithium AND polyuria
Steroids, Oral AND ulceration/perforation
K Sparing medications AND hyperkalemia

A PPV was calculated for each rule by adding the number of ADEs, medication errors and ADE/MEs discovered by the monitor, then dividing that by the total reviewed results for each rule (with the duplicate results produced within each trigger subtracted out). A PPV was calculated for each individual rule and for the entire set of rules within the text set. If an event was captured through multiple triggers, the event was counted only once in the overall PPV calculation. In addition, a calculation was done to remove the effect of the duplicate events from the denominator as well as the numerator to more accurately calculate the overall PPV. Ultimately some of the rules were evaluated as not providing enough clinical specificity and were removed from the monitor. In addition, if a trigger had greater than 20 results and after review, no events were identified, the trigger was designated as inactive. Based upon the PPVs, some rules were eliminated from the rules set.

Results

On some of the initial data runs there was some divergence in the predictive value for some rules, such as the rules that look for inadequate monitoring (receiving phenytoin and no phenytoin test in 12 months). To resolve these issues, we had programmers and a clinician from both sites meet and reconcile the programming methods. We also created a process for comparing the PPVs of individual triggers between the two sites. If there were significant differences between them, we created a targeted way of resolving them. We would review the programming process at both sites to ensure we were obtaining similar output from the rules. We would also look at the quality of the data; an example was our data related to some psychiatric medications indicated that although the medication was on the active medication list, the medication may not have been renewed for 3–4 years since psychiatry did not use LMR.

Rules with low predictive value were evaluated to see if improvements could be made. An example of this is the rule related to the use of topical steroids, which may indicate that a patient has had a topical allergic reaction to a medication. Each site selected 50 random rule hits from the total results returned for chart review and at both sites, no events were found to occur within the sample. It was then decided that we should create parameters to perhaps limit the hits returned, excluding patients who had either eczema or psoriasis on their electronic problem list. When these hits were again reviewed, the outcome was the same at both sites, that no events were identified in the 50 randomly selected results. Since our attempt to refine the rules in order to identify events using this particular rule resulted in no improvement, we felt that this rule should be excluded from the ADE monitor.

Similar processes were used for other rule sets that had low predictive value. For example the use of diphenhydramine and naloxone, prednisone and diphenhydramine at the same visit, and hydroxyzine and prednisone; AST level greater than 150 U/L; platelet level less than 50,000; and receiving inhaled triamcinolone and a beta-blocker were all eliminated, because of low predictive value. There were a total of 150 triggers that were initially developed and 128 that were used after excluding triggers with a low yield. There were a total of 213 rules initially developed, 137 that were programmed and 106 that ultimately were included in the final text-rule monitor.

While we attempted to work toward getting our ADE rates as similar as possible, there were some rules that stayed divergent. It is possible that this effect was due to the difference in patient populations, different systems of care (e.g., the presence of an anticoagulation service), different local treatment guidelines required by insurers, or how data is captured within the two different EMRs.

Discussion

The use of a computer-based monitoring system to measure the frequency of ADEs in the hospital setting has been documented in the literature.[4, 5, 6, 11] In this

report, we describe our methodology in developing an ADE monitor in the outpatient setting at two different sites with two different electronic medical records. The ADE monitor that we developed at both Regenstrief and Brigham and Women's Hospital was based on triggers that have been validated by other studies and enhancements that we added to improve predictive value. We implemented this monitor across a broad spectrum of patients in primary care practices to better understand the rates of ADEs in the primary care setting. The two sites worked collaboratively to ensure that consistent programming of the rules was undertaken so that the output of the program would be as close as possible.

There are differences in the monitors that are used in different care settings. In the monitor that we developed in the ambulatory setting there were some triggers that did not produce results, although they had been useful in the inpatient setting. The trigger that looked at the use of topical steroids is one example. This trigger is still currently being used in the inpatient ADE monitor at the Brigham and Women's Hospital. Conversely we developed triggers that did not have analogous counterparts in the inpatient setting, such as a trigger that looks at the use of phenytoin and the patient having no phenytoin level during the past 12 months. Since most hospitalizations are of a shorter duration, this trigger would not be effective in discovering events in the inpatient setting, but is important in outpatient settings.

In the future it might be possible to extend this type of ADE monitor to the sub-acute setting (rehabilitation and nursing home populations); however, validation and expansion of the triggers will be necessary in order to optimize the monitor in that setting. While this goal is important, the collection of the data in this setting may be problematic as most of these institutions would be unlikely to have the information technology infrastructure available to create an ADE monitor similar to the one described here.

With the total number of ambulatory prescriptions being filled in the United States approaching 3.5 billion per year and increasing at about 3 percent per year,[16] the importance of monitoring this segment of the health care system can be easily understood. As medication use escalates and the complexity of medication regimens increase, the importance of monitoring patients for medication induced effects or medication errors is easily apparent. The Medicare prescription benefit recently passed by Congress may also increase medication use in the outpatient setting, especially among the elderly by making medication more affordable to this vulnerable population, a noble goal. While these many factors are contributing to increased use of medications, we must find ways to decrease the risk of potential events related to use of these effective agents. Computerized monitoring provides a reproducible method of detecting ADEs. In addition, fewer resources are needed to capture events compared to chart review. While there is an initial outlay of money needed to allow proper programming of the various rules, in the long term this process is less expensive and it will allow medication systems to be safer.

While this methodology was able to discover many events, there are some limitations to its utility. Though the large majority of clinical notes from the text trigger portion of the monitor were able to be accessed, the availability of some specific classes of notes, such as psychiatric related notes, was very limited. As such, the monitor may not have been able to capture events identified in clinics that do not routinely dictate or enter notes into the EMR. The ability of the ADE monitor also relies on the thoroughness and accuracy of documentation within the electronic medical record. In addition there is a need to improve the ability of natural language processing to eliminate false positive results.

A limitation of this study is that significant effort was required to calibrate the rules between the two health care systems. However, this was only because this work was done for research purposes. From an operational standpoint, these rules can be implemented at individual academic or non-academic settings with computerized lab and medication data[5, 6] and can be used for real time medication safety activities. However, as IT systems become more widespread, efforts to standardize the rule sets and definitions so data could be compared across institutions would be helpful. Finally, the two sites used in this study have fairly advanced electronic medical records and information technology support capabilities. If an EMR is not available, it is extremely difficult for implementation of ADE monitors to occur.

In this report, we describe the collaboration of two institutions to implement an ADE monitor in the outpatient setting. We found that clinically based rule sets can be implemented at different sites using both text and non-text searching methods and provide a basis for improving quality by identifying adverse drug events and medication errors. This monitor will be used in the future to understand the effectiveness of ADE quality improvement interventions via measurement of impact on ADEs. By using this ADE monitor we can compare the effect of our interventions without prohibitive costs of full chart reviews. As medication use increases—due to the increased availability and effectiveness of medications in treating a greater number of conditions—we hope to be able to decrease the risk/benefit ratio related to the use of medications in the ambulatory care setting by improved identification and monitoring of ADEs.

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