

Chapter 22

Evaluation of Provincial Pharmacy Network

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22.1 Introduction

Adverse drug events (ADEs) are a concern in both inpatient (Evans, Lloyd, Stoddard, Nebeker, & Samore, 2005; Bates et al., 1995; Baker et al., 2004) and outpatient (Budnitz et al., 2005; Zed et al., 2008) settings. An ADE is defined as an iatrogenic hazard or incident that is created either through omission or commission of the administration of a drug or drugs (prescription or non-prescription), harming a patient whose outcome is always unexpected and unacceptable to the patient and healthcare provider (Tafreshi, Melby, Kaback, & Nord, 1999; Nebeker, Hoffman, Weir, Bennett, & Hurdle, 2005). Such events are a significant cause of morbidity and mortality (Juntti-Patinen & Neuvonen, 2002; Alexopoulou et al., 2008), and result in significant resource utilization, including increased emergency room (ER) and physician visits, diagnostic tests, medication use, and hospital admissions. Studies conducted in the United States estimate that such events account for 17 million ER visits and 8.7 million hospital admissions each year (Bates et al., 1997; Johnson & Bootman, 1995). Between 1995 and 2000, costs associated with ADEs rose from US\$76.6 billion to over US\$177.4 billion (Johnson & Bootman, 1995; Ernst & Grizzle, 2001). It would be expected that if a Pharmacy Network were deployed and that it included complete medication profiles and automatic drug utilization reviews, then adverse drug events resulting in an ER visit would be reduced in the population.

22.2 Current State of Evidence

ADES have been mostly studied among patients admitted to hospital, and it has been estimated that 5% to 25% of hospital admissions are drug-related (Samoy et al., 2006; Pirmohamed et al., 2004). However, ADES occurring in outpatient settings and treated in ERS receive less attention, even though more than 80% of community-dwelling adults use medications on a weekly basis, and approximately threefold more patients are treated in ERS for ADES compared to those admitted to hospital (Budnitz et al., 2005; McCaig & Burt, 2003; Kaufman, Kelly, Rosenberg, Anderson, & Mitchell, 2002). The Institute of Medicine (1999) report, *To Err Is Human: Building a Safer Health System*, concluded that the solution to preventing medical errors is “building a safer health system” that identifies patient safety as a prerequisite to high-quality care. Despite widespread recognition of the need for a safer health system, ADES occurring in community settings remain a substantial cause of ER visits. A Pharmacy Network is a regional drug information system that offers population-based online, real-time medication profiles and an interactive database to assist pharmacists and physicians in producing optimal medication treatment. Such networks would also provide the tools to monitor, track, and mitigate ADES and medication errors that occur in the community.

22.2.1 Synthesis of Current Evidence

ADES are a major public health problem given that such events are the most common type of injuries experienced by hospitalized patients (Institute of Medicine, 1999). ADES may lead to hospitalization, or occur during hospitalization and contribute to an increased length of stay. The recent focus on patient safety and the concern about the number of negative outcomes resulting from drug use, rather than the underlying diseases, has prompted health care professionals to take a critical look at these drug responses.

A series of studies examined ADES among hospitalized patients in the United States and Australia (Bates et al., 1995; Lazarou, Pomeranz, & Corey, 1998; Roughead, Gilbert, Primrose, & Sansom, 1998; McDonnell & Jacobs, 2002; Zhang et al., 2009); however, less research is available about these events in hospitalized patients in Canada. A u.s.-based meta-analysis by Lazarou et al. (1998) revealed that the incidence of serious ADES in hospitalized patients was 2.1%, while for those newly admitted to a hospital it was 4.7%. A subsequent study reported ADES were between the fourth and sixth leading cause of death (Tafreshi et al., 1999). Other studies have found ADES occurred in between 2% and 20% of hospitalized patients (Roughead et al., 1998; McDonnell & Jacobs, 2002; Zhang et al., 2009). Baker and colleagues (2004) provided a national estimate of the incidence of adverse events among adult patients in Canada (7.5 per 100 hospital admissions). After extrapolating to the entire population of Canada, the number of hospital admissions attributed to adverse events was estimated between 141,250 and 232,250 in 2000 (Baker et al., 2004). Further-

more, Canadian incident reporting data indicated a 35% increase of adverse reactions from 2008 to 2009 (Health Canada, 2010).

ADES are common and can have serious consequences in an older population. According to recent population estimates, Canadians 65+ population grew by 12% between 2001 and 2006 and this demographic now represents about 16% of the total population (Statistics Canada, 2007; Canadian Institute for Health Information, 2010; CBC News, 2015). Elderly individuals are vulnerable to ADES because of their multiple drug consumption patterns and biologic changes, which may restrict their drug consumption and inhibit physiological processes they take to manage multiple comorbid conditions and because of pharmacokinetics and pharmacodynamics changes (Zhang et al., 2009; Bates, 1998). Furthermore, ADES can be recurrent events, in that an individual may experience one or more such events over a period of time. It is important to identify the magnitude of ADES in this high-risk group to aid physicians in their decisions about prescribing, delivering, administering, and monitoring drug therapies. If predictive factors can be identified, this would allow providers to identify early symptoms of ADES and to offer rapid response to the patient (Field et al., 2001).

Although prior research (Zhang et al., 2009; Field et al., 2001; French, 1996; Fialová et al., 2005; Onder et al., 2002; Onder et al., 2003; Chrischilles, VanGilder, Wright, Kelly, & Wallace, 2009) has identified several risk factors for the occurrence of ADES among older adults (e.g., age, sex, and drug regimen), little is known about the risk factors associated with recurrent ADES. For public health planning and the evaluation of quality management programs, it is important to study recurrent ADES, rather than only the first event (Donaldson, Sobolev, Cook, Janssen, & Khan, 2009). Given the risk of both health service utilization and the patient's burden of illness increasing with each subsequent ADE, the number of ADES is a more robust indicator of risk than a single event (Glynn & Buring, 1996).

22.2.2 Summary of Key Findings

ADES have been mostly studied among patients admitted to hospital, and it has been estimated that between 5% and 25% of hospital admissions are drug-related. However, ADES occurring in outpatient settings and treated in ERS receive less attention, even though more than 80% of community-dwelling adults use medications on a weekly basis, and approximately threefold more patients are treated in ERS for ADES compared to those admitted to hospital.

22.3 Selected Case Study – Adverse Drug Events in Adult Patients Leading to ER Visits

22.3.1 Setting and Study Population

The study setting was two adult acute care hospitals, the Health Science Centre (HSC) and St. Clare's Mercy Hospital (SCMH), both of which deliver tertiary care

in the capital city of St. John's in Newfoundland and Labrador (N.L.), Canada. These two hospitals serve a catchment area of approximately 280,000 residents, and together have an average of 28,000 acute separations and 80,000 ER visits per year. Both hospitals capture electronic summary data on all ER visits in an emergency room triage database. Eligible subjects for this study included all patients aged 18 years or over that were residents of N.L. and presented to one of the two ERs between January 1, 2005 and December 31, 2005.

ER visits with a high probability of not being due to an ADE (e.g., motor vehicle accident, substance abuse, drug abuse, attempted suicide, cut- or burn-related injuries, etc.) were excluded. It should be noted that conditions such as attempted suicide and drug abuse would not likely be the presenting complaint. Therefore, these ER visits may not have been excluded from the sampling frame; rather they were excluded later (if selected) from the study sample during the chart review phase of the study. Patients who presented to ERs through a referral process, but were subsequently identified as a valid ER visit, were included in this study.

22.3.2 Study Sample

Charts were selected from the sampling frame using a stratified random sampling design. There were six strata based on patients' sex and age at ER visit (Male 18 to 44, Male 45 to 64, Male 65+, Female 18 to 44, Female 45 to 64, and Female 65+). Evidence in the literature regarding the prevalence of ADEs in admissions was found to be inconsistent, ranging from 5% to 25%, which can be mostly attributed to differences in study designs and patient demographics (Kaufman et al., 2002; Institute of Medicine, 1999; Lazarou et al., 1998). We estimated 10% of ER visits would be attributed to ADEs in patients aged 18 years and older. To achieve a 95% confidence interval ($\pm 4\%$), we determined that we would need a sample size of 217 ER visits for each stratum, resulting in a total of sample 1,302 ER visits. To reduce the sampling error, and to compensate for the exclusion of ER visits that would be attributed to suicide attempts and drug abuse, we added a 10% over-sample to the sample. After the chart review was completed, the final sample size for the study was 1,458, resulting in a 12% over-sample. This difference of 2% was attributed to inclusion of ER visits through referrals. For patients with multiple ER visits during the study period, only one visit was selected at random as the index visit for review.

22.3.3 Outcomes and Definitions

An ADE is defined as any undesirable effect caused by the interaction of a drug (prescription or non-prescription) with a patient (Morimoto, Gandhi, Seger, Hsieh, & Bates, 2004). Events may be the result of normal or inappropriate use of a medication, and could range from minor reactions such as a skin rash to serious and life-threatening events, even death. Medication errors (MEs) are mishaps that occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug. Medication errors are more common than

adverse drug events, but result in harm less than 1% of the time, with about 25% of adverse drug events attributed to medication errors (Nebeker, Barach, & Samore, 2004). We studied ADES, defined as “injury resulting from the use of a drug” (Nebeker et al., 2005) that encompasses all traditional adverse effects plus harm from any MES. We also used “possible adverse drug event” (PADE), defined as an event that may have been related to a current medication (e.g., viral infection), but it could not be confirmed. ADES and PADES involving either prescription or over-the-counter drugs were included.

22.3.4 Data Collection

Data collection involved a two-step review of ER charts using the Meditech system. Meditech is a hospital information system where all electronic patient information, including ER summaries, are scanned and uploaded to the patient’s profile. In the first step, the ER summaries of each selected chart were reviewed by a team consisting of a physician and a registered nurse using a Trigger Assessment Tool. This tool listed 39 screening criteria (triggers) known to be sensitive to the occurrence of ADES among the adult population. The reviewers combined any triggers found in the ER chart with the patient’s history of medication use, as well as a subjective assessment, to determine if an ADE was the reason for the ER visit. If it was classified as being a probable ADE, the reviewers through a consensus process coded the reason for the ER visits as having either a high, moderate, low, or very low probability of being an ADE.

The second step included a full review of all ER charts identified as having “high” and “moderate” probability ADES, and a random sample of the “low/very low” probability ADES. As part of the validation exercise, a full review was also carried out on a sample of those ER visits classified as having “no” probability of being ADE. In Step 2, two ER physicians and two clinical pharmacists independently reviewed each of the patient’s charts using a data collection tool, which was a modified version of the tool by Gandhi et al. (2003). The reviewers were blinded to the first step review that identified probable ADES. The reviewers first obtained demographic and clinical information, including presenting complaints, past medical history, drug history, history of allergy, medication dose, frequency, and reaction for the event, as well as the patient’s most recent laboratory records.

The reviewers used this information to assess whether the ER visit was a result of an ADE, PADE or ME. Each reviewer also classified the event according to its severity and preventability. Preventability was based on additional information that would have been available had a Pharmacy Network been available. Using an adapted version of previously published criteria (Bates et al., 1995; Gandhi et al., 2003; Gurwitz et al., 2003), severity was classified as being “fatal”, “life threatening”, “serious” or “significant”; and preventability was classified as “error intercepted”, “definitely preventable”, “probably preventable”, “probably not preventable”, or “definitely not preventable”. Disagreements about classification of ADES, and their severity and preventability were resolved during con-

sensus meetings. In this analysis we used two data sets: (a) a limited amount of data collected on all patients from the first review, and (b) detailed information on the subsample of patients that were collected through the chart review.

22.3.5 Statistical Analysis

We generated descriptive statistics including means, standard deviations, and ranges. The primary outcome variables – ADES and PADES – were combined into a single variable of ADES/PADES in order to reduce the random error associated with the small number of events identified. The unit of analysis was the ER visit. Prevalence of ADES/PADES was calculated per 100 ER visits and presented with *p*-values using the binomial proportion test. Each study subject was assigned a sample weight based on the inverse probability of selection. The overall prevalence of ADE/PADES was estimated using sampling weights to adjust for stratification in the sampling design.

The estimates by age group and sex were kept non-weighted since each patient in the sample frame had an equal chance of being selected within the corresponding age/sex stratum. Events that were assessed as error intercepted, definitely, or probably preventable were merged into one category “preventable”, and those assessed to be definitely or probably not preventable were merged into one category “not preventable”. The rate of severity and preventability of ADE were derived by dividing the number of events in the respective categories by the total number of ADES. Mantel-Haenszel chi-square analysis was performed to determine whether there was an association between severity and preventability of ADES. The number of ADES was extrapolated to the study population by multiplying the overall prevalence rate by the number of ER visits in the sample frame. Number of preventable ADES and hospitalization due to ADES were extrapolated to the study population in a similar manner. All data were entered and stored electronically using Microsoft Access and were analyzed using SPSS 15.0 software package (Statistical Package for Social Sciences, Chicago, IL).

22.3.6 Results

During the study period 82,516 adult ER visits to the HSC and SCMh were identified. Of these, 2,749 visits were excluded because they were by non-residents of N.L. and 12,076 visits were excluded since they did not meet the inclusion criteria, leaving 67,691 ER visits (41,135 unique patients). The mean age (\pm SD) of this cohort was 46.9 (\pm 19.6) years, with 54.4% (36,814 out of 67,691) of the visits by females. Of the 1,458 ER visits sampled from the 67,691 visits, 44.8% (653) were identified as having a high (29), moderate (135), low (218), or very low (271) probability of being the result of an ADE.

Gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea) and skin rashes were found to be the most common manifestations of patients identified as high or moderate probability of being an ADE. Patients identified as having a “high” ($n = 29$) or “moderate” ($n = 135$) probability of having ADES, along with a random sample of 170 ER visits classified as having a “low” or “very low” prob-

ability of having ADES, were independently reviewed by two ER physicians and two clinical pharmacists. The mean (\pm SD) number of co-morbidities and current medications for this group were 3.5 (\pm 1.9) and 5.6 (\pm 3.6), respectively. Fifty-five of the 334 patients were identified by the team to either have an ADE (n = 29) or a PADE (n = 26). After weighting for stratification in the sampling design, the overall prevalence of ADES/PADES was 2.8% (95% CI, 2.0-3.7). The mean (\pm SD) age for patients with ADE/PADE was 69.9 (\pm 14.2); (71.6 \pm 9.9 for males versus 68.7 \pm 16.5 for females). No statistically significant difference was found between genders (P = 0.13). For both males and females, the prevalence of ADES/PADES increased with age, peaking at 9.1% for females aged 65 years and older. For all age groups, the prevalence of ADES/PADES was slightly higher among females than males. In this study, 23 of the 55 patients with ADES/PADES (41.8%) required hospitalization.

The mean age for patients with ADES/PADES was higher than those having no drug-related visits (69.9 versus 63.8 years, p < 0.01). A higher number of co-morbidities and medications were significantly associated with drug-related visits (p < 0.05 and p < 0.01, respectively). Of the 55 confirmed ADE/PADE patients, one (2%) case was fatal, two (4%) were life-threatening, 25 (46%) serious, and 27 (49%) identified as significant. Approximately 29% of the 55 ADES/PADES identified were considered to be preventable had additional information been available through a Pharmacy Network. Of the serious, life-threatening, and fatal events, 35.7% were identified as potentially preventable, compared with 22.2% of the significant events; however, the difference was not statistically significant. Of the 23 hospitalizations due to ADE/PADES, eight (35%) were considered preventable.

Based on these 55 ADE/PADE patients, we estimate that approximately 1,900 adult patients (95% CI: 1,354-2,505) were treated in the St. John's region for ADES/PADES in the two ERs during the study period (January to December 2005), of which an estimated 550 were preventable. Further, of the 1,900 it is estimated that 800 were subsequently hospitalized. This estimate is based on all ER visits (n = 67,691), excluding those not attributed to ADES (e.g., alcohol-related, suicide attempt, car accidents, cut, burn, wound dressing, etc.). Hematologic complications (e.g., bleeding) were the most common complications associated with ADES/PADES (43.6%), followed by gastrointestinal (32.7%), neurological (14.5%), skin (12.7%), cardiovascular (12.7%), metabolic (9.1%), respiratory (7.3%), and renal (5.5%) complications. The medications most frequently associated with ADES/PADES, either on their own or in combination with other agents, were such anti-platelets as aspirin (24%), warfarin (18%), antibiotics (15%), anti-hypertensive agents (13%), and chemotherapy agents (11%). Warfarin, divalproex, and chemotherapy agents, medications with a narrow therapeutic index (NTI) and a high risk for toxicity, were found to be the cause of nearly one-third (31.7%) of ER-treated ADES/PADES in patients aged 65 years or older. Note that, as part of the validation process, a sample of 192 charts from 805 ER visits classified as "no" probability for ADE visits were reviewed for the validation of the trigger tool exercise. None of these 192 visits were found to be ADE-related.

22.4 Issues, Guidance and Implications

There is considerable research available on ADEs that occur in hospitals, but considerably less so on those that occur in the community. This study is one of the few studies in Canada to investigate ADEs among adult patients presenting to ERs. Our study found that adverse drug events accounted for 2.8% of ER visits, of which about a third were considered preventable if a Pharmacy Network were available. Patients with ADEs/PADEs were found to be older, prescribed more medications, and had a higher number of co-morbidities. Although there is debate in the literature as to whether age itself is a risk factor for an ADE-related visit or hospitalization, the mechanism relating age to risk for ADEs may include the administration of multiple drugs in treating multiple co-morbidities which is more common among the elderly population. In addition, while an aging population tends to take a higher average number of medications, they are also less likely to tolerate certain medications for various reasons, as outlined in the Beers Criteria (Donaldson et al., 2009). In this current study, medications such as warfarin, divalproex, and chemotherapy agents with NTI and high risk for toxicity caused about one-third of ER-treated ADEs in patients aged 65 years or older.

Comparisons with other studies are challenging since there are many variations in case definitions (e.g., ADE, PADE, ME, etc.), study designs, and patient populations. It is argued that the benefit of a Pharmacy Network is its ability to provide a complete patient drug profile on which the pharmacies' drug utilization review software can run, and that that this complete drug profile provides accurate and complete medication information across the continuum of patient care (i.e., Medication Reconciliation). This argument carries significant weight in cases when the patient uses multiple pharmacies when obtaining prescription medications. Conversely, others would argue that where patients only use one pharmacy for all their prescription medications, either out of preference (e.g., knowing the pharmacy staff) or necessity (i.e., the only pharmacy in the community), the benefits of a Pharmacy Network to the patient are minimal.

Another expected benefit of a Pharmacy Network is the reduction in double doctoring, as prescription-dispensing records would be available to all pharmacies on the network in real time. The other issue sometimes raised is that there is usually a cost to the pharmacy for being part of the network (e.g., hardware and software upgrades, Internet access, lost productivity, etc.) and that the pharmacy is a private company that for the most part generates revenue through dispensing medications, not providing additional patient care. While there can be several valid arguments, both for and against a Pharmacy Network, ultimately if it provides increased patient safety and improves quality of care, both government and the private sector need to work towards the deployment of such a network across their population.

This study faced several limitations. Firstly, using a retrospective chart review design may underestimate the true frequency of emergency visits as being caused by an ADE. Ideally, a prospective design with a large sample including patient interviews and obtaining key information would have increased the ac-

curacy of estimates of drug-related visits and their preventability. Secondly, compared to patients aged 65 years or more, we found fewer ADES in younger age groups, which makes our estimates of ADE prevalence more prone to sampling error in these age groups. Nevertheless, the prevalence of ADE among elderly patients was 8.4%, which is very close to our pre-study assumption of 10% considered in the study design.

Thirdly, in preparing the sampling frame, we excluded 12,076 visits from the study population using pre-defined exclusion criteria. However, based on a cursory review of these excluded visits, we concluded that the criteria used in excluding non-drug related visits might not have been as precise as we had hoped. The main reason for this lack of precision was that the exclusion criteria were applied to the patients' self-reported complaint, and not the diagnosis provided by the attending health professional after the encounter. As such, exclusion of any drug-related visits may have resulted in leaving out a low-risk subset of ER visits instead of a no-risk subset, and thereby resulted in overestimating the prevalence of ADES in the study sample. Fourthly, we did not extrapolate our data to the entire province, since the HSC and SCMH are located in the capital city of St. John's and cannot be considered representative of all hospitals in the province.

22.4.1 Summary of Evaluation Issues

The evaluation of a Pharmacy Network presented issues that exist with most evaluations, in that there is a lack of standards in undertaking evaluations overall, which limits the amount of comparability one study has. The methodological approach to evaluations is not new, with most employing age-old research methods (e.g., surveys, interviews, chart reviews, administrative data, etc.) to determine whether whatever is being evaluated has met its objectives. The challenge is getting a consistent approach so that peer-to-peer comparisons can be made and best practices identified. In the absence of such comparisons, we are limited to comparing results in the same environment pre- and post-implementation, with no idea if the pre-intervention indicators are any better (or worse) than our peers. In the case of this current study, the team is waiting until the Pharmacy Network has been fully deployed for 12 months before doing the post-Pharmacy Network intervention. This is expected to occur in early 2018.

22.4.2 Guidance for Future Directions

Evaluating the benefits of a Pharmacy Network is not only resource intensive and costly, but is delivered within a government's policy framework and as such is not under the control of the evaluation team. When evaluating a government intervention, whether it is a policy, a program, or a new technology, always consider that many issues that will arise will be out of your control and you must mitigate them as best you can in the design of your evaluation.

22.4.3 Policy and Practice Implications

In implementing a Pharmacy Network it is in the interest of government to provide its population with a sustainable, high quality, and safe service in relation to the usage of prescription medications. Through that lens it seems logical that a Pharmacy Network would deliver on these three fronts, ignoring the costs to actually implement the network. However, in the practice environment it is not so linear, as some pharmacies may not perceive any benefits if they believe their client population is non-nomadic. If a Pharmacy Network does not include all pharmacies within the population, health professionals may not be provided with their patient's complete drug profile, reducing double doctoring is compromised, and the data will be incomplete in the development of new policies and programs.

22.5 Summary

Emergency room visits as a result of ADEs are not uncommon. A focus on further education along with the tools need to be in place so that physicians and pharmacists can collaborate more closely to improve prescribing practices and monitoring, particularly among high-risk patients, and thereby contribute to reducing the subset of ADEs that is potentially preventable. The authors believe that if a Pharmacy Network were deployed it would allow authorized healthcare providers to access and share information, which would contribute to reducing the frequency of adverse events related to drugs in the community.

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