

Relationship between Medication Errors and Adverse Drug Events

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OBJECTIVE: To evaluate the frequency of medication errors using a multidisciplinary approach, to classify these errors by type, and to determine how often medication errors are associated with adverse drug events (ADEs) and potential ADEs.

DESIGN: Medication errors were detected using self-report by pharmacists, nurse review of all patient charts, and review of all medication sheets. Incidents that were thought to represent ADEs or potential ADEs were identified through spontaneous reporting from nursing or pharmacy personnel, solicited reporting from nurses, and daily chart review by the study nurse. Incidents were subsequently classified by two independent reviewers as ADEs or potential ADEs.

SETTING: Three medical units at an urban tertiary care hospital.

PATIENTS: A cohort of 379 consecutive admissions during a 51-day period (1,704 patient-days).

INTERVENTION: None.

MEASUREMENTS AND MAIN RESULTS: Over the study period, 10,070 medication orders were written, and 530 medication errors were identified (5.3 errors/100 orders), for a mean of 0.3 medication errors per patient-day, or 1.4 per admission. Of the medication errors, 53% involved at least one missing dose of a medication; 15% involved other dose errors, 8% frequency errors, and 5% route errors. During the same period, 25 ADEs and 35 potential ADEs were found. Of the 25 ADEs, five (20%) were associated with medication errors; all were judged preventable. Thus, five of 530 medication errors (0.9%) resulted in ADEs. Physician computer order entry could have prevented 84% of non-missing dose medication errors, 86% of potential ADEs, and 60% of preventable ADEs.

CONCLUSIONS: Medication errors are common, although relatively few result in ADEs. However, those that do are preventable, many through physician computer order entry.

KEY WORDS: medication error; adverse drug event; computer order entry.

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Injuries due to drugs were the most frequent cause of adverse events in the Harvard Medical Practice Study, in which about 1% of all hospitalized patients suffered a disabling injury related to medications.¹ Other studies have also suggested that drugs are a major mediator of iatrogenic illness.^{2, 3}

Adverse drug events (ADEs), defined as injuries resulting from medical interventions related to a drug, are common. However, spontaneous reporting, the usual means of ADE identification, overlooks as many as 95–99% of ADEs that are detectable by other methods.^{4–6} In addition, most ADEs are dose-dependent and potentially predictable; a smaller number are unpredictable, idiosyncratic, or allergic reactions to drugs.^{7–9} Almost all errors resulting in ADEs are associated with the first type of ADEs, which are particularly important because they may be preventable.

Medication errors are errors in the process of ordering or delivering a medication, regardless of whether an injury occurred or the potential for injury was present. Some medication errors result in ADEs. Medication errors can occur at any stage in the drug ordering, dispensing, and administration process.

A number of studies have evaluated the frequency of medication errors, most of which do not result in ADEs.^{10–13} Two recent studies of error frequency identified the errant orders intercepted by pharmacists in pediatric hospitals,^{10, 11} and found a rate of 3–5 medication errors per 1,000 orders. However, these studies did not determine the frequency of medication errors that were unknown to pharmacists, the number of ADEs resulting from medication errors, or the amount of rework that medication errors cause for providers. Others have developed comprehensive recommendations for error prevention, including improved education in drug properties and standardized drug labeling,^{14–17} although these recommendations have not been prioritized.

Because physician errors in writing orders account for many medication errors, one major technologic intervention that appears to have substantial potential for reducing the number of medication errors is physician computer order entry,^{18, 19} in which physicians write orders directly on the computer. Orders can be structured, reducing dose errors and legibility problems, and the computer can conduct checks for the presence of such things as drug allergies and drug–drug interactions. However, the percentage of medication errors that may be preventable using such a system is unknown.

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To develop effective strategies for improving the current drug ordering and delivery system, the frequency and types of medication errors and their relationships with ADEs must be better defined. Thus, we undertook a study to: 1) evaluate the frequency of medication errors using a comprehensive multidisciplinary approach; 2) classify medication errors according to type; 3) determine how often medication errors are associated with ADEs and potential ADEs; 4) evaluate the consequences of medication errors in terms of rework for providers; and 5) evaluate the proportion of medication errors that may be preventable using physician computer order entry.

METHODS

Patient Population

The patient population consisted of a cohort of all adults admitted to three medical units at Brigham and Women's Hospital during October and November 1992. Two general medical units and one medical intensive care unit (ICU) were studied over a 51-day period. These units were selected because we previously found in another study and separate data collection period that medical units had higher rates of ADEs than did surgical units, and ICUs had higher rates of ADEs than did non-ICUs.⁷ Interns order most of the medications on these units. The unit of evaluation was the patient-day.

Definitions

Medication errors were defined as errors occurring at any stage in the process of ordering or delivering a medication. They included the entire range of severity, from trivial errors, such as orders that necessitated clarification or missing doses (defined as instances in which a drug was not available in the medication drawer when the nurse went to give it), to life-threatening errors, such as a patient's receiving ten times the accepted dose of a drug with a narrow toxic-therapeutic ratio. *Rule violations* were orders that were faulty in some way but had little potential for harm or extra work because they were interpreted by nursing and pharmacy without clarification, presumably correctly. An example is an order such as "MgSO₄ 1 amp IV now," because ampules come in several strengths but one strength is standard.

Adverse drug events (ADEs) were defined as injuries resulting from medical interventions related to a drug. Adverse drug events may result from medication errors or from adverse drug reactions in which there was no error. For example, sedation from an overdose of a benzodiazepine and a rash caused by an allergic response to penicillin are both ADEs. Medication errors with potential for injury but in which no injury occurred were classified as *potential ADEs*. An example is an order for penicillin for a patient with a known allergy to the drug in which the order was intercepted or the patient re-

ceived the drug and experienced no allergic reaction (Fig. 1). *Incidents* were defined as occurrences that the study nurse thought might represent an ADE or a potential ADE, whether or not there was an error.

Case Finding

All new orders were evaluated to determine whether they represented potential medication errors. Renewal orders were counted but were excluded from the analyses, because we felt they would less often be associated with medication errors. Potential medication errors were detected in three ways: first, pharmacists reported any prescribing errors identified during the dispensing process; second, the study nurse reviewed all charts for evidence of medication errors; and third, a trained reviewer evaluated all medication sheets received by the pharmacy. The chart review included a careful daily reading of the progress notes in each chart, followed by a more detailed investigation if the nurse identified indications of a possible medication error (e.g., major bleeding, new confusion, unanticipated ICU transfer, use of an antidote such as naloxone, or prescription of certain medications such as diphenhydramine). The trained reviewer looked for orders that necessitated clarification or change, which was also often noted by the pharmacists on medication sheets.

Incidents that were thought to represent ADEs or potential ADEs were identified in a similar fashion, but in addition reports of incidents were solicited from nurses through daily visits to the units by the study nurse, and by daily electronic-mail notes to nurses on the units. Providers reporting incidents were assured anonymity.

Clinical data collected from the medical record for all patients involved in an ADE or a potential ADE included the date and time of the incident, the name and dose of the drug involved, complications, and the source of identification of the incident. For medication errors we determined whether contact between the provider and the staff had been necessary for the problem's resolution; for example, whether the pharmacist had called the physician to clarify an order. From this, we estimated the amount of rework (defined as additional work caused by system malfunctions) required.

Review Process

All potential medication errors were evaluated by a physician reviewer, who classified them as medication error, rule violation, or no error. A 10% sample was re-reviewed by a second physician to determine reliability. Medication errors were classified by type: dose error (overdose, underdose, missing dose, wrong dose form, dose omitted), route error (incorrect route, wrong route, route omitted), frequency error (incorrect frequency, frequency omitted), substitution error (wrong drug given, wrong patient received drug), drug-drug interaction,

inappropriate drug, illegible order, known allergy to drug, nonformulary drug, avoidable delay in treatment, and preparation error.

Incidents (suspected ADEs or potential ADEs) were evaluated independently by two reviewers, and classified into one of four categories: ADEs; potential ADEs; medication errors, when an error was present but there was no injury or potential for injury; and exclusions, when no error was made and the injury was minor. When the reviewers disagreed about the classification, they met and came to a consensus. Preconsensus reliability for judgments for presence of an ADE or a potential ADE made using this methodology was previously found to be good,⁷ with kappa scores of approximately 0.8.

The ADEs and potential ADEs were then classified according to severity and preventability, as previously reported.⁷ Severity was classified as life-threatening, serious, or significant.¹⁰ Preventability was classified using a four-point scale adapted from Dubois and Brook.²⁰ For purposes of analysis, this four-point scale was collapsed into two categories: preventable and not preventable. We previously found⁷ that kappas for judgments of ADEs regarding preventability and severity using these scales were 0.63–0.89. Medication errors were also evaluated as to the likelihood that they would be preventable, using a computerized physician order entry system. Service responsible for the incident was also identified; categories were physicians, nursing, pharmacy, secretary, other, multifactorial, and none.

Statistical Methods

Univariate analyses were carried out using the chi-square test for categorical variables. Interrater reliabilities for whether an ADE was present and for judgments of preventability and severity were calculated using the kappa statistic.²¹ Determination of interrater reliability for whether a medication error, rule violation, or neither was present was made using a three-way kappa statistic.²² The SAS statistical package was used to conduct the analyses.²³

RESULTS

The 51-day study period included 379 admissions and 1,704 patient-days, during which 10,070 medication orders were written on the three medical units. In addition, 1,532 renewal orders were written. The 10,070 orders included 3,913 ordering sets (a set is a group of

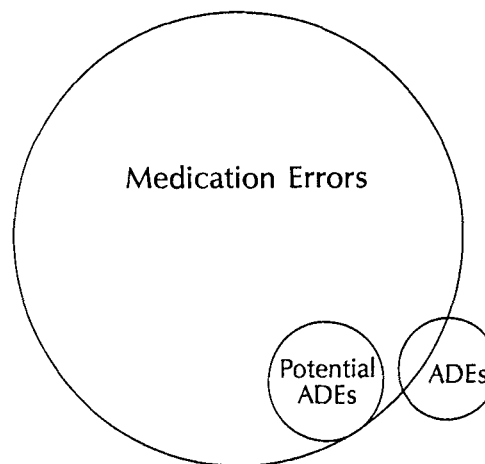


FIGURE 1. The relationships between medication errors, adverse drug events (ADEs), and potential ADEs. Only a small proportion of medication errors represent an ADE or a potential ADE, and while all potential ADEs are medication errors, only the minority of ADEs are associated with a medication error.

medication orders written at one time). Among these 10,070 orders, there were a total of 530 medication errors (5.3%), or 1.4 medication errors per admission (Table 1). In addition, 128 of the 10,070 orders were judged to be rule violations (0.08 rule violations per patient-day). The kappa between reviewers was 0.68 for the judgment of whether an order represented a medication error, a rule violation, or neither of the above.

Medication order error rates were compared by unit (Table 2). Many more orders were written in the ICU (12.6 orders/patient day) than on the two medical units (3.8 and 3.9 orders/patient-day), but the error rates were similar (4.5, 6.0, and 6.0 errors/100 orders) across the units. However, serious errors were 4.5 times more frequent in the first medical unit (0.9 serious errors/100 orders) than in the other medical unit and the ICU (0.2 serious errors/100 orders each) ($p < 0.001$). The reason for this difference is unclear, as the two medical units share staffing.

Classification of medication errors showed that 53% (280) represented missing doses, and 47% (250) were non-missing dose errors. While missing dose errors are relatively minor from the clinical perspective, they can result in significant delays in giving medications to patients. Contact between pharmacy and nursing personnel was required for all 280 of these errors.

Table 1
Medication Order and Error Rates

	<i>n</i>	<i>n</i> /100 Orders	<i>n</i> /1,000 Patient-days	<i>n</i> /Admission
Medication orders	10,070		5,910	26.6
Medication errors	530	5.3	311	1.4
Adverse drug events	25	0.25	14.7	0.07

Table 2
Medication Order and Error Rates by Unit

	Orders	Patient-days	Orders/ Patient-day	Errors/100 Orders	Serious Errors*/ 100 Orders
General unit 1	2,498	648	3.9	6	0.9
General unit 2	2,496	653	3.8	6	0.2
Intensive care unit	5,076	403	12.6	4.5	0.2

*Serious errors are defined as those associated with adverse drug events (ADEs) and potential ADEs.

Among the non-missing dose errors (Table 3), dose errors, frequency errors, and route errors were the most common. However, less frequent types of errors were sometimes serious, for example, the 11 instances in which a medication was ordered for a patient with a known allergy. Physicians were judged responsible for 81% of these errors; computerized order entry could have a significant effect on reduction of these errors, and indeed, 84% of all non-missing dose errors were judged preventable by computerized order entry. Provider contact was required for resolution of the error in 83%.

For both missing dose errors and the remainder of medication errors, antibiotics were the drug class most often involved. Antibiotics were associated with 19% of non-missing dose medication errors, followed by electrolyte concentrates (10%), cardiovascular drugs (8%), and analgesics (7%).

In all, 82% of medication errors were identified through review of medication sheets; pharmacy self-report yielded 9%, and nurse self-report and chart review yielded the remaining 9%. Missing dose errors were identified almost exclusively through review of medication sheets. Even when these errors were excluded from the analysis, review of medication sheets remained the most productive source, an unexpected finding.

ADEs and Medication Errors

During the same time period, 25 ADEs were identified, five of which were associated with medication errors and were judged preventable (Table 4). Therefore, five of 530 medication errors (0.9%) resulted in an ADE; an additional 35 medication errors (6.7%) were judged to be potential ADEs. No missing dose error was associated with an ADE or a potential ADE.

Severity of the potential ADEs and ADEs was also assessed (Table 4); no patient died of an ADE. The five preventable ADEs included a hypotensive episode, hemoptysis, gastrointestinal bleeding, a local toxic reaction, and an aspiration pneumonia. Errors associated with the five preventable ADEs included a dose error, a frequency error, an instance in which follow-up of therapy was inadequate, a drug-drug interaction, and a transcription error. Physicians were judged responsible for three and nurses for two.

Most of the potential ADEs (27 of 35, 77%) were errors that were intercepted before the medication was

administered (Table 3). In the remaining eight an adverse outcome was avoided only by chance. These eight potential ADEs included three dose errors, a frequency error, an instance in which a patient received a drug ordered for another patient, an inadvertent discontinuation of a drug, an avoidable delay in treatment, and a case in which a drug was not given when needed. Of the 27 potential ADEs that were intercepted before the medication reached the patient, 11 (41%) were the result of an order for a drug to which the patient had a known allergy. Physicians were judged responsible for 93% of the intercepted potential ADEs, and verbal orders accounted for 19%.

Computer order entry was judged to have the potential to prevent three preventable ADEs (60%), five (62%) of the nonintercepted potential ADEs, and 25 (93%) of the intercepted potential ADEs.

DISCUSSION

We found that medication errors were more common than has been suggested by other reports, that relatively few resulted in adverse events, and that they created a substantial burden of provider rework. Most medication errors appeared potentially preventable by the use of physician computer order entry.

The rate of medication errors that we found, 53 per 1,000 orders, is substantially higher than has been previously reported.^{10-13, 24-31} Clearly, the rate of detection depends on the intensity of surveillance. To maximize our ability to find errors, we used a comprehensive approach to case detection: a combination of pharmacists' review of prescriptions, patient hospital record review, solicitation of reports by nurses, and detailed review of all medication sheets. Using more limited methods, lower rates will be found. For example, two of the largest studies of medication errors identified only three to five errors per 1,000 orders, but these were restricted to ordering errors identified and prevented by pharmacists,^{10, 11} while we identified errors whether or not they were prevented, and also during the administration and dispensing processes. Others have found that when pharmacy error detection was combined with a review of all prescriptions, 32 medication errors per 1,000 orders were found.²⁴

While the exhaustive approach we used would be

prohibitively expensive for a large-scale study or for ongoing quality measurement, this limited study provides an estimate of the upper bound of error in the medication ordering, dispensing, and administration processes. The rate of seven ADEs per 100 admissions that we detected during this study period was similar to that in a previous study we conducted,⁷ and to findings in a much larger study we have recently completed on the incidence and causes of ADEs (unpublished data, 1994) so it is likely that the relationship of medication errors to injuries here described (100:1) is representative.

In classifying medication errors, many studies have found that dose errors (underdose, overdose, and wrong dose) are the most frequent type.^{10, 11, 13, 26, 31, 32} However, none of these studies made a concerted search for missing doses, which we found to be by far the most common type of medication error. We also found that

after missing doses, dose errors were the most frequent type of error. Interestingly, a small group of medication errors caused a large proportion of ADEs and potential ADEs. For example, orders for a drug to which the patient had a known allergy accounted for only 2% of the medication errors in this study, but 31% of the potential ADEs. This suggests that improvements in ordering systems should target both high-frequency errors (such as dose errors) and infrequent serious errors. For example, automated allergy checking at the time an order is placed could substantially reduce the frequency of ADEs due to a known allergy.

Several studies have assessed the potential of medication errors to cause ADEs,^{10, 11, 13, 31} but the range of estimates is very wide; proportions from 0 to 58% have been reported. Moreover, these numbers are only estimates, not actual measurements. One four-year survey

Table 3
Classification of Medication Errors Other Than Missing Doses

	Total Medication Errors* (n = 250)	Preventable ADEs† (n = 5)	Potential ADEs: Not Intercepted (n = 8)	Potential ADEs: Intercepted (n = 27)
Error type				
Dose errors	77 (31%)	1 (20%)	3 (38%)	10 (37%)
Frequency errors	43 (17%)	1 (20%)	1 (12%)	2 (7%)
Route errors	26 (10%)	0	0	3 (11%)
Illegible order	16 (6%)	0	0	0
Known allergy to drug	11 (4%)	0	0	11 (41%)
Wrong drug or patient	11 (4%)	0	1 (12%)	2 (7%)
Other	66 (26%)	3‡ (60%)	3§ (38%)	0
Service responsible				
Physicians	203 (81%)	3 (60%)	2 (25%)	25 (93%)
Nursing	34 (14%)	2 (40%)	6 (75%)	1 (4%)
Pharmacy	7 (3%)	0	0	0
Other	6 (2%)	0	0	0
Preventable by order entry				
Yes	209 (84%)	3 (60%)	5 (62%)	25 (93%)
No	41 (16%)	2 (40%)	3 (38%)	2 (7%)
Order type				
Verbal	41 (16%)	0	0	5 (19%)
Written	200 (80%)	5 (100%)	7 (88%)	21 (78%)
Unclear	9 (4%)	0	1 (12%)	1 (4%)

*Includes medication errors that were ADEs or potential ADEs, so the categories are not mutually exclusive.

†ADEs = adverse drug events.

‡Errors were: inadequate followup, drug-drug interaction, and a transcription error leading to a failure to administer the drug.

§Errors were: avoidable delay in treatment, inadvertent discontinuation of a drug, and a drug not given when needed.

Table 4
Preventability of Adverse Drug Events (ADEs) and Potential ADEs

	ADEs: Not Preventable (n = 20)	ADEs: Preventable (n = 5)	Potential ADEs: Not Intercepted (n = 8)	Potential ADEs: Intercepted (n = 27)
Life-threatening	0	1 (20%)	1 (12%)	3 (11%)
Serious	3 (15%)	4 (80%)	5 (63%)	12 (44%)
Significant	17 (85%)	0	2 (25%)	12 (44%)

of dispensing and administration medication errors found that 0.21% of these errors caused an ADE,²⁵ although medication errors due to physician orders were excluded, and the medication had to reach the patient to be considered an error. We found that approximately 1% of medication errors actually caused an ADE (2% if missing doses were excluded), and an additional 7% represented potential ADEs.

While the design of the study did not permit us to measure the hours of rework caused by medication errors, they are clearly substantial. Ninety-two percent of the errors (all of the missing doses and 83% of the remainder) necessitated at least a telephone call between nurse and pharmacist, nurse and physician, or pharmacist and physician. In previous studies in this hospital we found that the resolution of a missing dose requires an average of 8 minutes of combined nursing and pharmacy times. Published reports of missing doses also provide anecdotal evidence that missing doses are a major source of rework.³³⁻³⁶ Tracking down physicians to correct an order is even more time-consuming. If the overall average rework time is 8 minutes per error, the total amount of time wasted as a result of the 530 medication errors we found would be 71 hours, an average of about a half-hour per unit each day. Tierney et al. found that the number of times a pharmacist called a physician to clarify an order was reduced by about one third with physician order entry (Tierney W, communication, 1994). Medication errors and ADEs have substantial costs beyond those associated with rework, including increased length of stay, injury to patients, and malpractice costs. A recent estimate of the cost to the hospital of an ADE was \$2,000.³⁷

Implications for Prevention

The American Society of Hospital Pharmacists has recently created a set of comprehensive guidelines for medication error prevention, including advice for prescribers, pharmacists, nurses, patients, administrators, and drug manufacturers,¹⁴ and others have made recommendations for medication error prevention as well.^{13, 15-17, 30, 31} However, these recommendations are so encyclopedic that it would be impossible to implement all of them. This study has identified those areas most in need of attention by identifying the most common types of medication errors and those associated with ADEs.

Fortunately, relatively few medication errors have the potential to result in ADEs, and the current safety net for preventing ADEs catches most serious errors. Most potential ADEs are prevented before the patient receives the drug. However, this is an arena in which health care should, in our view, strive for a zero defect rate. One percent of medication errors' resulting in ADEs is too many.

Physician computer order entry represents a major

system change with great potential for reducing serious medication errors. In physician order entry, physicians write orders using the computer, which permits intervention at the time orders are written. Several studies have described the implementation of order entry.^{18, 19, 38-44} Targeting the physician through computer order entry should be highly effective in reducing errors, since in the present study physicians were responsible for 81% of the medication errors other than missing doses. It is expected that order entry will decrease medication errors in several ways. Drug orders will require a drug name, dose, route, and frequency, which will eliminate errors of omission. All orders will be legible, and transcription errors will be eliminated. Computerized dose checking and guided-dose algorithms should decrease the occurrence of orders with incorrect dosages. Computers can also store relevant information regarding drug-drug interactions, known allergies, and appropriate dosage schedules according to the patients's characteristics.^{40, 42-44}

This study has several limitations. We studied three medical units in one teaching hospital, so our results may not be generalizable to other settings. Also, despite a "broad net," some medication errors almost certainly escaped our detection. For example, our method did not detect cases in which the choice of the drug was inappropriate given the patient's characteristics, and we undoubtedly missed some errors in administration, because these errors occur at the last step in the medication delivery process and are the hardest to detect. Another potential bias that might decrease the ADE and medication error rates is a Hawthorne effect related to the fact that nurses and pharmacists on the study units were involved in the study. Finally, our classification of ADEs by severity and preventability is an implicit measure. However, the interrater agreement was good, and the reliability of this method has been confirmed by other studies.⁷

We conclude that medication errors are common, and that most serious errors result from errors in prescribing by physicians. However, relatively few medication errors result in ADEs, either because they have little potential for injury or because they are intercepted by pharmacists and nurses. Nonetheless, 1.4% of the patients admitted during the study suffered a potentially preventable ADE. Of these preventable ADEs, more than half could have been prevented by computer order entry. Medication errors have other costs that may be substantial, including malpractice costs, rework for providers, and waste for hospitals.

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