ORIGINAL ARTICLE

# Medication Errors in the Outpatient Setting

## *Classification and Root Cause Analysis*

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**Objectives:** To understand and classify causal factors linked to medication errors and to define opportunities for systematic changes to improve the safety of prescription medication use.

**Design, Setting, and Participants:** All recipients of liver, kidney, and/or pancreas allografts followed up by an academic medical center and encountered in the acute care facility, outpatient clinic, or by telephone during 12 months (April 1, 2004, through March 31, 2005). Errors were sought by specific review of the expected and actual medication lists.

**Main Outcome Measure:** Proportion of medication errors in each of 5 classifications developed through iterative revision. Definitions included failure to provide a correct prescription (prescription error); deliver a prescribed medication to the patient (delivery error); possess enough medication for a 24-hour or greater supply (availability error); accurately use an available, prescribed medication (patient error); and identify the type, dosage, or frequency of a medication (reporting error).

**Results:** We identified 149 errors in 93 patients who were prescribed a mean of 10.9 medications each. Adverse events were associated with 48 errors (32%), including hospitalization (17 patients) or outpatient invasive procedure (3 patients) in 13%. Nine episodes of rejection and 6 failed allografts were identified. The most common error type was patient error in 83 errors (56%) with prescription errors in 20 errors (13%), delivery errors in 20 errors (13%), availability errors in 15 errors (10%), and reporting errors in 12 errors (8%). Root cause analysis identified the patient as the cause in 101 errors (68%) while pharmacies and other sectors of the health care team caused 41 errors (27%). Finances were linked to 7 errors (5%). Error frequency was estimated during 4 weeks of outpatient visits at 15 of 219 visits.

**Conclusions:** Outpatient medication errors are abundant, often occult, and associated with significant adverse events in a complex transplant population. The health care system is associated with nearly one third of errors.

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MEDICATIONS MAY BE INadequate or overly effective in treating a targeted disease or symptom. They may also cause serious adverse effects or interact with each other and are often prohibitively expensive. To adequately monitor the safety and efficacy of a drug, the prescribing provider requires accurate knowledge about how it is taken. In acute care facilities where medications are handled by trained, credentialed health care workers, acquisition of this information and control of the drug's administration has proven highly challenging. Adverse drug events reported among 6.5% of hospitalized patients were fatal in 1% of the cases and life-threatening in 12%.[1] In the outpatient environment, neither the magnitude of this problem nor the severity of the consequences has been well defined. Here, there is no structured mechanism to monitor drug use. Once a prescription is written or conveyed by telephone, a variety of factors may intervene between the intended prescription and administration of the medication, resulting in alterations in the dose, timing, and even the identity of the drug. Such interceding circumstances that remain unrecognized or underestimated are likely to preclude protection of the patient.

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Adverse drug events are only a subset of errors in which a bad outcome has occurred. The National Coordinating Council on Patient Safety has defined medication errors as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.[2] In

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acute care facilities, where one might expect the tightest control of the sequence of events leading from the decision to prescribe a drug to its administration, estimates of the frequency of medication-related incidents associated with a likelihood of causing harm are as high[3] as 4.49 per 1000 inpatient days[4] to 24.1 per 1000 days.[5] The frequency of improper or unsafe medication use outside of these controlled environments is relatively unknown. Adverse drug event estimates range from 5% to 35% of outpatients,[6,7] but the proportion of asymptomatic errors with the potential for causing harm is not reported. A cross-sectional medical record review and survey of primary care patients indicated that 18% of those taking prescription drugs reported problems related to their medications.[6] No study has yet looked at the impact of these errors on patient outcomes. It seems logical that the additional degrees of freedom introduced in the outpatient setting by the patient, caretaker, outside pharmacy, or third-party payer will result in greater confusion and error. Examples of the types of serious errors anecdotally reported to date in this setting include mix-ups between sound-alike and look-alike drugs,[8] similar looking packaging,[9] and inappropriate dosing.[10]

Prescription drug use is rising. More than 60% of US adults aged 45 to 64 years in 1999 through 2000 reported the use of at least 1 prescribed medication during the past month.[11] Coincident with this rising rate are decreasing time and funding for providers to focus on patient education.[12,13] The potential contributions of these trends to the inherent danger of medication use is supported by a 2004 report from the Institute of Medicine demonstrating that nearly half of all American adults have difficulty understanding and acting on health information.[14]

Concerned by experiences in our own practice in which transplant patients rely on the use of many drugs, we sought to understand common causal factors linked to medication errors and to define opportunities for systematic changes that might improve the safety of prescription medication use in the outpatient setting. A qualitative research approach was used to analyze all known incidents of medication errors occurring in outpatient renal, pancreas, and liver transplant recipients at the Yale New Haven Organ Transplant Center over a 12-month period.

## METHODS

### POPULATION

All recipients of liver, kidney, and/or pancreas allografts followed up by the transplant service at the Yale New Haven Organ Transplantation Center (New Haven, Conn) encountered during a 12-month period from April 1, 2004, through March 31, 2005, were candidates for medication error identification and collection. Clinical care was not altered for the purposes of this study and patients remained unaware of the data collection. Approval was obtained from the human investigations committee.

### EDUCATION

The critical importance of accurately using and reporting the individualized medication list is expressed to the patient at the initial encounter for evaluation of transplant candidacy. Education about the new medication regimen is provided prior to discharge from the hospitalization during which transplantation occurs. An individualized list of medications to which the patient refers is used for the in-hospital education and sent home. Discharge is delayed until a fundamental test assessing competency at self-administration of these medications is passed. When this does not seem feasible, a visiting nurse agency provides outpatient medication supervision. The patient is taught to prepare for each subsequent clinic visit by bringing the medication list and "brown bagging" all medications to accurately report all actively used drugs.

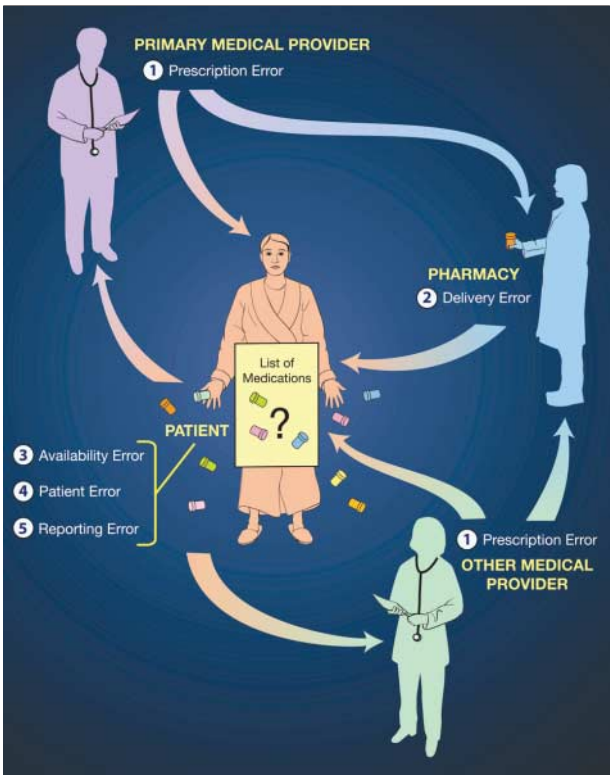


**Figure.** Types of medication errors in the outpatient setting.

### DATA COLLECTION

At every encounter, the home medication regimen is reviewed with the patient by a nurse-coordinator, physician associate, or physician and compared with the regimen prescribed at the last interaction with the patient. Encounters may include outpatient visits to the transplant team, emergency department visits, admission to the Yale New Haven Hospital, or phone conversations between transplant team members and the patient. Identification of a difference between these 2 lists prompted queries to identify a specific explanation for the discrepancy. Prescription refill requests from patients, payers, or pharmacies were verified with the most recent version of the medication regimen prescribed by the transplant team. Discrepancies were investigated as described earlier.

### ERROR CLASSIFICATION

Error categories were defined as follows (**Figure**). Prescription error was a failure to provide a prescription for a medication or the erroneous prescription for a medication. For example, a new transplant recipient was discharged from the hospital without a prescription for one of the immunosuppressant medications. Delivery error was a failure to deliver a pre-



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**Table 1. Classifications of 149 Medication Errors in an Outpatient Setting**

| Error Type | No. (%) | Mean ± SD Patient Age, y |
|---|---|---|
| Prescription | 20 (13) | 52.5 ± 15.9 |
| Delivery | 19 (13) | 50.8 ± 14.5 |
| Availability | 15 (10) | 47.8 ± 12.4 |
| Patient | 83 (56) | 51.4 ± 12.9 |
| Report | 12 (8) | 60.6 ± 11 |

**Table 2. Root Causes of 149 Medication Errors in an Outpatient Setting**

| Root Cause | No. (%) |
|---|---|
| Finance | 7 (5) |
| Pharmacy | 15 (10) |
| Other physician | 6 (4) |
| Outpatient transplant team | 5 (3) |
| Inpatient transplant team | 11 (7) |
| Nursing home | 4 (3) |
| Patient | 101 (68) |

scribed medication to the patient. An example is the patient whose medication arrived 3 days late from a mail order pharmacy despite the pharmacist's prospective assurance to the transplant coordinator that supply of a medication would be shipped overnight. Availability error was a failure to possess at least a 24-hour supply of the prescribed medication. This error type included many patients who delayed refilling prescriptions. Patient error was a failure to accurately use an available, prescribed medication. This is illustrated by the patient who was prescribed 1 tablet per day of 2.5 mg of Coumadin (Bristol-Myers Squibb, Princeton, NJ) but mistakenly took 4 tablets daily. Reporting error was a failure to report sufficient information to identify the type, dosage, or frequency of a medication. This type occurred when patients were unable to tell the study team specifically which medication (name, strength, dose, frequency) was being taken at home.

Initial medication errors were derived from the 5 central themes that emerged during compilation of medication errors. The final definitions were chosen through an iterative process. This involved the repeated categorization of medication errors by members of the research team with the given definitions. With each subsequent round of categorization, the definitions were refined such that the final definitions reflect a 97% concordance between individual raters. To compare interrater reliability and agreement, we calculated κ coefficients using the method of Fleiss.[15]

Identification of the specific cyclosporine product was required. This included identifying the name of the company that produced the brand name or generic product.

## ROOT CAUSE ANALYSIS

Root cause analysis was a process undertaken to identify the basic and contributing causes of what happened, why it happened, and what to do to prevent it from happening again.[16] The root cause was defined as a specific underlying cause that can reasonably be identified, that is in the control of the transplant team to fix, and for which effective recommendations for preventing recurrences could be generated.[17] Causal factors were defined as those contributors (human errors and component failures) that, if eliminated, would have either prevented the occurrence or reduced its severity.[10]

Analysis of each event served to identify the root cause, which was defined as the event that precipitated the error. Each medication error was reviewed by the 2 principal investigators (A.L.F., R.N.F.) and a decision was reached about the primary cause of the error.

To specifically address the frequency of medication errors in our outpatient transplant practice, every patient presenting for outpatient follow-up of a kidney transplant during a 4-week period from February 15, 2005, through March 11, 2005, was included. Every patient encountered was questioned by 2 of us (S.R.G., N.M.S.) in a standardized fashion. The number of patients with recognized errors, number of errors, and types of errors were identified.

## RESULTS

One hundred forty-nine medication errors were identified in 93 recipients of solid organ transplants: kidney (n=84), pancreas (n=3), and liver (n=6). The numbers of errors per patient were 1 (n=66), 2 (n=11), 3 (n=9), 4 (n=3), 5 (n=3), and 7 (n=1). Errors were recognized at a mean posttransplant time of 3.8 years (range, 4 days to 23.5 years). The mean±SD age of the group was 51.8±13.6 years. One patient was younger than 18 years. The mean±SD number of medications taken by the patients was 10.9±3.5 (range, 2-21).

Interrater agreement about error types was assessed by calculating κ coefficients using the method of Fleiss.[15] Pairwise comparisons of the 3 raters (A.L.F., S.K., R.N.F.) showed consistently excellent agreement with κ coefficients of 0.87, 0.93, and 0.88. The overall κ of 0.89 (95% confidence interval, 0.84-0.94) confirmed excellent overall interrater reliability.

The open-ended nature of the outpatient population in this study meant that neither the absolute number of medications taken nor the frequency of their use in these patients was known or controlled for study purposes. Thus, no denominator for the overall medication rate could be defined. Error types and frequencies are listed in **Table 1**. The most frequent type was patient error in 56% of the cases. Twenty-six percent of errors (prescription error, 13%; delivery error, 13%) occurred prior to patient involvement in the process. The age of those patients with report errors (type 5) was older than that of patients with error types 1 through 4.

Root causes were identified for all errors and are listed in **Table 2**. The most frequent root cause was the patient in 101 (68%) of 149 occurrences. Financial issues were the cause of 7 (5%) of 149 errors. Health care providers were the root cause of 41 (27%) of 149 errors, including the transplant team itself in 10%. Pharmacies were specifically identified as the root cause of 15 errors (10%). Two of these 15 were caused by pharmacists independently declining to fill prescriptions because of potential drug-drug interactions, including 1 case of tamsulosin hydrochloride and vardenafil hydrochloride (tamsulosin was not provided) and 1 case of cyclosporine and atorvastatin (atorvastatin was not provided). In neither case was the prescribing physician notified by the pharmacist. In 10 of 15 pharmacy root causes, generic cyclosporine was provided in lieu of the brand-name prod-



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**Table 3. Adverse Events in 149 Medication Errors in an Outpatient Setting***

| Error Type (No.) | None | Laboratory Abnormality | Physical Abnormality | Hospital Admission | Outpatient Invasive Procedure |
|---|---|---|---|---|---|
| Prescription (20) | 15 | 2 | 0 | 2 (Diarrhea, BP crisis) | 1 (Phlebotomy) |
| Delivery (19) | 14 | 1 | 2 (Mouth ulcer, elevated BP) | 1 (Coagulopathy) | 1 (Prolonged urinary catheter) |
| Availability (15) | 6 | 3 | 0 | 6 (1 BP crisis, 1 reversible rejection, 3 rejection/graft loss, 1 medication provision) | 0 |
| Patient (83) | 58 | 11 | 6 | 8 (1 Coagulopathy, 1 BP crisis, 1 coma, 2 reversible rejection, 3 rejection/graft loss) | 0 |
| Report (12) | 8 | 3 | 0 | 0 | 1 (Phlebotomy) |

Abbreviation: BP, blood pressure.
*In all cases, the most severe adverse event or the most invasive procedure is included without associated lesser events. For example, hospital admission for rejection also included a laboratory abnormality and an invasive procedure (biopsy) that are not separately listed.

uct Neoral (Novartis Pharmaceuticals Corp, East Hanover, NJ). In all 10 circumstances, patient failure to recognize or report the switch to the transplant center was a causal factor. Drug levels were therefore not measured to confirm appropriate dosing. Of particular concern was the pharmacy-initiated substitution of unequivalent generic forms. In 1 case, a new transplant recipient received nonmodified cyclosporine (Apotex, generic nonmodified cyclosporine; Apotex Corp, Weston, Fla) in lieu of modified cyclosporine (Neoral). In the second case, a prescription for 125 mg of brand name–modified cyclosporine was filled with 100-mg capsules of Apotex and 25 mg capsules of modified cyclosporine (Neoral).

Adverse events were detectable in 48 (32%) of 149 errors, occurred in 46 patients, and resulted in 17 hospitalizations (**Table 3**). As noted in the table, each event is counted only once. Type 3 errors, availability errors, were associated with the highest frequency of adverse events. Serious adverse events requiring an outpatient invasive procedure or hospital admission resulted from 20 (13%) of 149 errors, including 40% of type 3 errors. Nine episodes of rejection with 6 graft losses were identified. One half of these resulted from type 3 errors.

During a 4-week data-collection period, 219 posttransplant clinic visits occurred on 20 clinic days. During this same period, 45 patients failed to either cancel or show up for scheduled appointments. Medication errors were identified in 15 (6.8%) of 219 patients for a rate of 1 visit with error per 14.6 outpatient visits. Five patients with multiple errors were identified; the number of errors per patient ranged from 2 to 7. Overall, 28 errors were identified, a rate of 1 error per 7.8 visits. The error types were patient error (27, 97%) and prescription error (1, 4%). One error (4%) resulted in the need for hospitalization for inadequately controlled hypertension. All other errors were managed without use of an acute care facility.

## COMMENT

The management of chronic disease among outpatients is complicated by (1) increasing severity of illness[18] and aging of the population,[19] (2) formidable costs[20] but limited reimbursement[21] for medications, (3) decreasing prevalence of insurance coverage,[22,23] (4) increasing documentation burden during brief patient visits,[13] (5) shortened lengths of stay in acute care facilities,[24] and (6) fragmentation of care.[25] In this environment, and in the absence of centralized medical records (whether electronic or not), providers prescribe in a black box. Once prescriptions are given to a patient or pharmacy by hand, mail, or telephone, there are no reliable means of knowing whether or not a prescription was filled, whether the appropriate medication was received or administered, and what the time frame for each of these factors was. Consequently, monitoring the safety and efficacy of a medication depends on assumptions that an appropriate prescription was properly transcribed, that numerous individuals including the patient and pharmacist followed instructions, that no restricted payer formulary intervened, and that the patient or a surrogate is able to report accurately about all of these factors.

We examined these assumptions in an outpatient environment in which medications are integral to care and confirmed that our average patient was prescribed 10.9 medications. It seemed logical to expect that the sheer complexity[26] of these regimens would be associated with a high frequency of medication errors and would therefore yield sufficient end points for comprehensive analysis. Moreover, we believed the nature of a transplant practice to be an ideal model for investigation of outpatient medication errors. Since the broad spectrum of transplant team members includes physicians, nurses, physician assistants, social workers, pharmacists, and financial counselors, the entire chain of events in the prescription medication process is represented. Additionally, the active nature with which these patients are managed, often approaching the intensity of acute care, allows for error capture in an environment with similarity to one in which existing data on this topic have already been gathered while allowing the additional degrees of freedom found in the outpatient setting. Nonadherence with immunosuppressive drugs has been estimated to contribute to 20% of late acute rejection episodes and 16% of graft losses in kidney transplantation, indicating the importance of addressing this issue to improve outcomes.[27]



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Our primary aim was to develop a method of classification with which to analyze outpatient medication errors for the ultimate purpose of designing strategies and tools to prevent them. For this reason, all errors identified during the study period were included, regardless of how they were identified or the severity. We found that patients were not forthcoming about their misuse of medications. Often, although the intent had been to follow instructions, the individual failed to do so accurately and had been unaware of the mistake until we detected it. We also identified 2 patients who deliberately made medication errors to harm themselves, choosing to reveal their actions only in response to the investigator's persistence. Many errors were identified because of our team's specific focus on developing accurate records of drug use. Thus, we believe our approach of prospective error capture by researchers who were also directly involved in the care of these patients was likely more inclusive than a medical record review[28] in which unrecorded errors are not captured and may not be actively sought. Additionally, survey methodologies[29] may exclude subject groups that might be expected to have relatively high error frequencies, including those with relatively low health literacy levels,[30] non–English speakers,[31] and those who opt out of participation. All patients, except in those cases completely devoid of any interaction with our team, were included in our study.

In practice, an effective means of eliciting errors was posing the question, "During the past month, how many times do you think you missed taking a dose of your medications?" Without unilateral control of all medications prescribed to these patients, it was not possible to determine an absolute frequency rate. Nevertheless, 149 errors were uncovered in 93 patients during the 12-month study period. We believe that this represents, at best, 50% of errors that occurred because during a more controlled, prospective, month-long observation period of outpatient visits, we found a substantially higher error rate. The extent of underestimation is difficult to assess since during this month the most serious errors may have led directly to hospitalization or death, bypassing event capture through an outpatient visit. We view the limited recognition of errors even in the context of a research environment as a warning sign for the practicing physician. Nevertheless, it is probable that the 149 errors we did detect are generally representative and therefore have led us to reaching accurate etiologic conclusions.

Through an iterative process, we derived a lexicon of 5 terms (prescription error, delivery error, availability error, patient error, reporting error) to help identify and classify medication errors. These definitions identify the steps involved in the most straightforward version of the process leading from provider to patient. Two observations are of particular note. Although 64% of errors were related to a patient's inability to properly take or report medication usage, 36% of errors were related to the health care delivery system. Root cause analysis yielded a similar finding. We conclude that the health care delivery system is the cause of nearly one third of all outpatient medication errors.

Although all errors were collected, even though some appeared to be of minor significance, many related adverse outcomes were still identified. Specifically, of the 149 errors we captured, 18 resulted in a patient's hospitalization and an additional 2 resulted in an invasive outpatient procedure. The 6 allograft failures are especially relevant for our practice. Most concerning is the loss of these transplanted organs in patients who had previously experienced long-term stable allograft function. Beyond the incalculable human price, the cost to the health care system resulting from the return of these patients to dialysis is estimated to be $66 000 per year per patient.[32]

An open-ended observational study has the principle shortcoming of being unable to determine the frequency of events, but this was not our primary purpose. In addition, although we believe the mechanistic definitions we developed will apply to all types of outpatient populations, it is likely that the absolute rate of errors will be lower in less complex patient groups and less urgent settings than those encountered in organ transplantation.

The implications of our findings are substantial. First, it is clear that outpatient medication errors are abundant and, in many cases, occult. Second, there is a large economic incentive to focus resources on the development of systems to reduce outpatient medication errors because they lead to costly consequences in a significant percentage of occurrences. Third, targeted educational programs to help patients better understand their medications and to better participate in the monitoring of proper drug usage may lead to a significant reduction in errors at little cost and major benefit. Fourth, nearly 10 years after the event that brought institutional-based medication errors to the forefront of public consciousness,[33] systems are not yet in place to prevent even those outpatient errors caused directly by the health care delivery system. They are common and frequently lead to serious adverse outcomes. Future avenues of research should focus on empowering the patient, as the constant factor, to be an active participant in the chain of responsible care.

Medication nonadherence is often viewed judgmentally.[34,35] The ramifications are enormous in the field of transplantation—withholding life-saving transplants based on an unfavorable assessment of a patient's ability to serve as an appropriate guardian for the precious organ. Yet we have shown that, in fact, a substantial portion of errors are attributable solely to the health care system and not the patient. And many of those errors ascribed to the patient seem to be unintentionally caused by a failure to understand the proper method of administration, which must be viewed as a communication error. This breakdown cannot be solely considered the patient's responsibility. Although intentional nonadherence does occur, it appears to be infrequent. Cautious analysis prior to assigning responsibility to the patient will often identify a cause entirely out of the patient's control. Certainly, it seems logical that most patients strive to comply with instructions because it is they who have sought assistance to improve or maintain health. It is likely the exceptional patient who does not. Moving forward, the challenge will be to recognize and address communication gaps between providers and other providers and between providers and patients. We should strive to continue to eliminate health care system–based errors through centralized records and other streamlining methods to



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improve processes. In doing so, it seems likely that our patients will gain confidence in us and our ability to help them navigate a complex and confusing system. This seems to be the road to both improving the safety of outpatients and moving from a culture of blame to a culture of prevention, consistent with the timely call of the Institute of Medicine.

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