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Prescribing Discrepancies Likely to Cause Adverse Drug Events after Patient Transfer

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Abstract

Background—Medication prescribing discrepancies are used as a quality measure for patients transferred between sites of care. The objective of this study was to quantify the rate of adverse drug events (ADEs) caused by prescribing discrepancies and the discrimination of an index of high-risk transition drug prescribing.

Methods—We examined medical records of patients transferred between 7 nursing homes and 3 hospitals between 1999–2005 in New York and Connecticut for transfer-associated prescribing discrepancies. ADEs caused by discrepancies were determined by 2 clinician raters. We calculated the fraction of medication discrepancies that caused ADEs in each of 22 drug classes by calculating positive predictive values (PPVs). We calculated the discrimination of a count of high-risk drug discrepancies, selected from published lists of high-risk medications and using observed PPVs.

Results—208 patients were hospitalized 304 times. Overall, 65 of 1350 prescribing discrepancies caused ADEs, for a PPV of .048 (95%CI .037–.061). PPVs by drug class ranged from 0 – .28. Drug classes with the highest PPVs were opioid analgesics, metronidazole, and non-opioid analgesics. Patients with 0, 1–2, and ≥ 3 high-risk discrepancies had a 13%, 23%, and 47% chance of experiencing a discrepancy-related ADE, respectively.

Conclusions—Discrepancies in certain drug classes more often caused ADEs than other types of discrepancies in hospitalized nursing home patients. Information about ADEs caused by medication discrepancies can be used to enhance measurement of care quality, identify high-risk patients, and inform development of decision-support tools at the time of patient transfer.

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COMPETING INTERESTS

The authors have no competing interests to report. The sponsors had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. Dr. Boockvar had full access to study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Keywords

Medication systems; nursing homes; hospitals; medication error; opioid analgesics

Medication discrepancies are common during transfer between sites of care^{1, 2}. Since they are sometimes the result of lapses in documentation, transcription, and provider-provider or patient-provider communication they have been used to measure the quality of transfer documentation and communication³. In addition, medication discrepancies may be a result of medication changes made by providers that do not have a clear clinical rationale (e.g., the omission of a patient's longstanding antidepressant when he or she is admitted to the hospital for pneumonia and does not have any contraindication to antidepressants). The potential for medication discrepancies to occur during patient transfer between sites of care as a result of errors in communication or decision-making is the rationale behind the establishment of medication reconciliation as a national patient safety standard during patient handoffs by The Joint Commission (formerly The Joint Commission on Accreditation of Healthcare Organizations)⁴.

Medication reconciliation consists of creating a complete and accurate prior medication use list, identifying discrepancies between current and prior medication use, and ensuring prescriber awareness of current and prior medication use to inform prescribing decisions. Since 2006 healthcare organizations have adopted a variety of approaches for implementing medication reconciliation and have used resolution of medication discrepancies as a measure of successful implementation and effectiveness⁵⁻¹¹. However, variation in the success of medication reconciliation remains, as a result of 1) difficulties in staffing a task that is labor-intensive, 2) risk of clerical errors during reconciliation, 3) lack of prescriber awareness of reconciliation findings, and 4) lack of influence of reconciliation findings on prescriber decision-making.

As a measure, medication discrepancies may be the product of communication, data synthesis, and decision-making processes, but it is not a health outcome. Good quality measures should have a strong link to health outcomes and target those at highest risk¹². Like measures of inappropriate prescribing¹³ and other prescribing "signals,"^{14, 15} only a subset of medication discrepancies may cause adverse drug events (ADEs) and affect health.

The objective of this study was to examine the predictive value of medication discrepancies for ADEs in nursing home patients transferred to and from the hospital. We examined nursing home patients 1) because for these patients pre- and post-transfer medication regimens can be determined exactly, avoiding the ambiguity in regimens that sometimes exists with outpatients² and 2) because nursing home patients commonly experience inter-site transfers and transfer-related problems^{16, 17}. We calculated the positive predictive value (PPV) of prescribing discrepancies in specific drug classes for ADEs, created indices of transition drug prescribing, and compared their performance in discriminating patients who might and might not experience a discrepancy-related ADE.

METHODS

Setting and Participants

Participants were patients in 7 nursing homes in New York and Connecticut who were admitted to 1 of 3 hospitals that were the primary referral hospitals for the nursing homes. Four of the nursing homes and 2 of the hospitals were Veterans Affairs (VA) facilities; the remaining facilities were non-governmental, non-profit facilities. When patients were transferred between VA nursing home and hospital, transfer information was conveyed electronically via the VA's

Computerized Patient Record System (CPRS). When patients were transferred between non-VA nursing home and hospital, handwritten or printed transfer documents were used to communicate patient information in each direction of transfer.

Eligible patients were individuals transferred from nursing home to hospital and admitted, and who remained in the hospital at least 24 hours. Individuals who were seen in the emergency department alone were excluded. Individuals were included whether or not they survived to hospital discharge and whether or not they returned to the nursing home from which they originated. Institutional review boards of each study institution approved the study. Since data were collected by retrospective medical record review, a waiver of informed consent was obtained from each institutional review board.

Measurements

Medication Discrepancies—Trained research personnel reviewed nursing home and hospital charts to identify differences in medication regimens between sites. Sources of medication data reviewed were: 1) nursing home and hospital orders, 2) nursing home-to-hospital and hospital-to-nursing home transfer documents, 3) hospital and nursing home medication administration information, 4) and hospital discharge instructions. Medication prescribing instructions from chronologically sequential sources were matched and compared in dosage, route and frequency of administration. Codes were assigned for: 1) no change, 2) increase in daily dose, 3) decrease in daily dose, 4) route change, 5) change from routine to as needed (PRN) administration, 6) change from PRN to routine administration, 7) substitution for a medication with the same indication (excluding substitutions between generic and brand-name versions of the same drug), and 8) discontinuation. Any of codes 2–8 was considered a prescribing discrepancy. Medications were divided into pharmacologic classes as shown in Table 2. A priori high-risk discrepancies were defined as those in the Institute for Healthcare Improvement's High Alert medication drug classes (anticoagulants, opioid analgesics, insulin, and sedatives)¹⁸, and those in high-risk drug classes for nursing home patients (non-steroidal anti-inflammatory drugs, digoxin, insulin, antipsychotics, sedatives/hypnotics, and anticoagulants)^{19, 20}. Topical agents, vitamins, minerals and most as-needed medications were not included since they were not considered potential causes of ADEs over the study follow-up period. As previously reported, the interrater reliability for recording number and types of medication discrepancies was high, with a weighted kappa²¹ of .89¹.

Adverse Drug Events—Patients were followed for the duration of the hospital stay up to 2 months, and for patients transferred back to the nursing home, for two months after nursing home readmission. Two physicians or one physician and one pharmacist reviewed nursing home and hospital records for medical incidents that were defined in advance and included new or worse symptomatic conditions (including new or worse bleeding, congestive heart failure, delirium, diarrhea, dyspnea, fall, decrease in alertness, incontinence, pain, rash, urinary retention, vomiting), blood pressure abnormalities (new systolic blood pressure >185 or <95, diastolic blood pressure >105), fever (temperature >100.5F), and abnormal tests of kidney function (creatinine increase >.5), liver function (doubling of AST or ALT), or over-anticoagulation (INR >4.0). Other laboratory abnormalities (e.g., hypo- or hyperglycemia, hyperkalemia) were recorded if symptomatic or if they caused a cardiac arrhythmia.

Raters then matched each recorded medical incident with a prescribing discrepancy at the time of nursing home-to-hospital and hospital-to-nursing home transfer that physiologically could have caused the incident -- if one existed -- and rated whether the discrepancy could have caused the incident using structured implicit review. Implicit review criteria included: 1) whether there was a note in the medical record that suggested that a medication discrepancy caused the incident (yes or no), 2) the time interval between incident and discrepancy (i.e.,

timing “plausible” or “improbable”), 3) whether the incident could have been caused by something other than a medication discrepancy (i.e., competing causes: “many,” “some,” or “few/none”), 4) whether the incident was a known possible reaction to this medication discrepancy (yes or no), and 5) whether the patient’s condition improved after correction of the medication discrepancy (i.e., dechallenge response: “none/weak,” “suggestive,” or “convincing”).

Each rater rated the certainty that the incident was caused by a medication discrepancy using a six-point Likert scale, with 1 indicating “little or no” certainty and 6 indicating “almost total” certainty²². The 2 raters discussed each event and provided a final consensus certainty rating. “Possible,” “probable,” and “definite” ADEs were those for which the final certainty ratings were 4, 5, and 6, respectively. Raters further categorized ADEs as 1) asymptomatic, 2) causing temporary symptoms, 3) causing temporary disability, 4) causing a prolonged or an additional hospital stay, 5) causing permanent disability, or 5) causing death. Finally, if there was no appropriate clinical rationale for the prescribing discrepancy or the discrepancy deviated from prescribing norms, the ADE was considered to be the result of a prescribing error. Prescribing errors were categorized as 1) wrong omissions, 2) wrong dosages, or 3) wrong dosing frequencies.

Characteristics of Patients and Their Hospital Stays—Information was collected on patient age, gender, race, presence or absence of dementia, and duration of nursing home stay from the nursing home medical record. A score for burden of chronic disease, adapted from Charlson et al.,²³ was calculated from chronic medical problems listed in the nursing home medical record. Information on hospital diagnoses, hospital length of stay, and time of admission (8 a.m.–6 p.m. Monday–Friday vs. off-hours) were obtained from the hospital medical record. A modified Acute Physiology and Chronic Health Evaluation (APACHE) score²⁴ was calculated from initial laboratory data and vital signs in the hospital medical record to ascertain initial illness severity.

Analysis

More than one hospital admission was allowed per participant. The unit of analysis was hospital admission. Number of prescribing discrepancies was calculated as the sum of prescribing discrepancies during nursing home-to-hospital and hospital-to-nursing home transfers. Number of ADEs was calculated as the sum of medical incidents caused by prescribing discrepancies with possible, probable, or definite certainty. Positive predictive values (PPVs) were calculated as the number of ADEs caused by discrepancies in a drug class divided by the number of prescribing discrepancies in that class. PPVs were also calculated for “enriched” subgroups of episodes in which a patient experienced a medical incident that is commonly captured by automated data systems (pain, vital sign, or laboratory data) and also was exposed to a prescribing discrepancy that physiologically could have caused the incident (e.g., pain/analgesic discrepancy). The PPV was calculated as the fraction of such episodes in which the prescribing discrepancy was rated as causing the incident, indicating an ADE.

We ascertained discrimination of 3 indices of transition drug prescribing for ADE: number of drugs prescribed prior to transfer, number of drug discrepancies after transfer, and number of high-risk drug discrepancies after transfer. Number of high-risk drug discrepancies was calculated as the sum of those with PPVs at least as high as those in the a priori high-risk category; i.e., all drug classes with a $PPV \geq .04$. The sample was stratified by quartile of each of the 3 indices and percent with ADE in each quartile was calculated. Unadjusted logistic regression models were estimated in which each prescribing index was the key independent variable and occurrence of ADE (yes or no) was the dependent variable. Adjusted logistic regression models were estimated with each index as key independent variable; relevant

demographic (gender, age), clinical (comorbidity score, APACHE score), and circumstantial (off-hours admission, duration of follow-up) variables as covariates; and occurrence of ADE (yes or no) as dependent variable. Models for drug discrepancies and for high-risk drug discrepancies included number of pre-transfer drugs as a covariate. Findings were similar whether or not we accounted for clustering of observations within patients and facilities; only findings without clustering are shown. 95% confidence intervals (95% CI), p-values, and c-statistics were calculated using standard formulae. In absence of having a validation sample for high-risk drug discrepancies, a bootstrap validation was conducted with 1000 repetitions. All analyses were performed using SAS software (Cary, NC).

RESULTS

Two hundred and eight patients were hospitalized 304 times. Characteristics of patients and their hospital stays are shown in Table 1. Forty-two percent of hospitalizations were in the VA setting. The most common reasons for hospital admission were pneumonia, urinary tract infection, dehydration, and exacerbations of congestive heart failure and chronic obstructive pulmonary disease. Median hospital length of stay was 7 days (range 1–296). Median length of follow-up for ADE ascertainment was 63 days (range 1–120).

Patients received a mean of 6.5 (s.d. 2.9) medications prior to hospital admission and had a mean of 2.8 (s.d. 2.1) prescribing discrepancies associated with nursing home-to-hospital transfer. Patients received a mean of 6.1 (s.d. 3.2) medications prior to hospital discharge and had a mean of 1.5 (s.d. 1.7) prescribing discrepancies associated with hospital-to-nursing home transfer. The total number of prescribing discrepancies observed in the study sample was 1350 and the total number of discrepancy-associated ADEs observed was 65. Of these, 51%, 39%, and 9% were possible, probable, and definite ADEs. Forty-six percent were asymptomatic ADEs, 42% were associated with temporary symptoms, 10% caused temporary disability, and 3% caused a prolonged or an additional hospital stay. No ADE caused permanent disability or death. Finally, 48% of prescribing discrepancies that caused ADEs were considered to be prescribing errors; 46% of these errors were wrong omissions, 46% were errors in dosing frequency, and 8% were errors in dosage.

Overall, 65 of 1350 prescribing discrepancies caused ADEs for a PPV of .048 (95%CI .037–.061). Positive predictive values of prescribing discrepancies by drug class are shown in Table 2; they ranged from 0 – .28. The drug classes with the highest PPVs were opioid analgesics, metronidazole, and non-opioid analgesics. Among episodes in which medical incidents commonly captured by automated data systems and suspect prescribing discrepancies both occurred, episode PPVs ranged from .07–.37, as shown in Table 3.

Examination of the discrimination of 3 indices of transition drug prescribing – number of drugs prescribed prior to transfer, number of drug discrepancies after transfer, and number of high-risk drug discrepancies after transfer – is shown in Table 4. Number of high-risk drug discrepancies demonstrated the best discrimination, as demonstrated by the highest c-statistic and best risk gradient. Patients with 0, 1–2, and ≥ 3 high-risk discrepancies (representing first quartile, second and third quartiles together, and fourth quartile) had 13%, 23%, and 47% chance of experiencing a discrepancy-related ADE, respectively. In a multivariable logistic regression model that included relevant demographic (gender, age), clinical (comorbidity score, APACHE score, number of medications at baseline), and circumstantial (off-hours admission, duration of follow-up) variables as predictors, number of high-risk discrepancies was the only statistically significant predictor of ADE with an odds ratio (OR) of 1.71 (95% CI 1.28–2.28; $p=.0003$), indicating an additional 71% risk of ADE with each additional high-risk discrepancy. Bootstrap validation resulted in an OR of 1.71 (95%CI 1.16–2.28) and c-statistic of .713 (95%CI .654–.774).

DISCUSSION

This study examined the link between medication discrepancies at the time of patient transfer and ADEs as a patient health effect in patients transferred between nursing home and hospital. We found that less than 5% of discrepancies caused ADEs, which is consistent with authoritative reviews that suggest that a small fraction of errors result in harm^{25, 26}. However, certain classes of drugs had PPVs substantially higher than 10%, including opioid analgesics, metronidazole, and non-opioid analgesics. In addition, an index that was a count of discrepancies in 15 high-risk drug classes at the time of transfer discriminated between those with lower and higher risk of ADE. Patients with 0, 1–2, and ≥ 3 high-risk discrepancies had 13%, 23%, and 47% chance of experiencing a discrepancy-related ADE, respectively.

These results suggest a link between medication discrepancies and health outcomes, and the capability of an index of high-risk transition prescribing to identify those at highest risk, which are characteristics of a sound quality measure¹². Sound measurement of drug prescribing during patient handoffs is important because The Joint Commission established medication reconciliation as a national patient safety standard during patient handoffs⁴. Our results provide partial support to patient safety organizations that have promulgated medication discrepancies as a measure of the effectiveness of medication reconciliation for inpatients and outpatients⁵. On the other hand, our results suggest that prescribing information matched with automated clinical event information would more often identify episodes that were true discrepancy-related ADEs (as shown by higher PPVs in Table 3, ranging up to .37) and identification of such episodes would be a more accurate measure of the effectiveness of medication reconciliation.

Results of this study also may be used to inform development of decision support tools for nursing homes or hospitals. Tools could be designed to identify high-risk medication discrepancies, identify patients at higher risk of ADE, and alert providers taking care of patients who are transferred between sites of care. Targeting discrepancies in medications used for chronic symptomatic conditions may be particularly effective. We and others have previously reported a suggested beneficial effect on pain of medication reconciliation, presumably as a result of improving the continuity of analgesia prescribing^{27, 28}. On the other hand, decision support systems (e.g., computerized feedback and reminders) have been shown to have a weak impact on drug prescribing²⁹. In a previous study we found that nursing home providers changed orders corresponding to only 10% of alerted discrepancies²⁸.

This study has important limitations. First, it includes only patients admitted to the hospital from a nursing home. Other groups may have different base rates of overall prescribing discrepancies, prescribing discrepancies by class, and discrepancy-related ADE, resulting in different PPV calculations. Second, we did not ascertain ADEs caused by non-discrepant medication use (i.e., medications that are continued unchanged after a transfer). Therefore, we could not calculate the negative predictive value of medication discrepancies (the chance of not experiencing an ADE in the absence of a discrepancy), nor its sensitivity (the fraction of ADEs that it captures). In this regard, medication discrepancies are just one of several measures being examined as “signals” of ADE; others include abnormal laboratory findings such as an elevated digoxin level and prescription of ADE antidotes such as flumazenil^{14, 15}. Medication discrepancies could be used in conjunction with these to approximate ADE. This study is also limited by the lack of a true validation cohort for the index of high-risk prescribing, which was derived in part using data from this study (informed by published lists), as well as by small sample size numbers in some of the drug classes that result in wide PPV confidence intervals.

In summary, discrepancies in certain drug classes, in particular opioid and non-opioid analgesics, more often caused ADEs than other types of discrepancies in hospitalized nursing

home patients. Number of high-risk discrepancies discriminated between patients that experienced a discrepancy-related ADE and those that did not. Information about ADEs caused by medication discrepancies can be used to enhance measurement of care quality, identify high-risk patients, and inform development of decision-support tools at the time of patient transfer.

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Table 1

Characteristics of patients and their hospital stays.

Patient	N	208
	Female (%)	43.8
	White (%)	60.2
	African-American (%)	27.7
	Age (mean years (s.d.))	77.2 (12.7)
	Duration of nursing home residence (median months (range))	7.2 (0–165)
	Comorbidity score ²³ (median (range))	4 (0–15)
	Dementia (%)	46.63
Hospital stay	N*	304
	VA Setting (%)	41.8
	APACHE score ²⁴ (mean (s.d.))	5.2 (3.9)
	Length of stay (median days (range))	7 (1–296)
	Urinary tract infection (%)	18.1
	Pneumonia (%)	20.7
	Congestive heart failure (%)	9.5
	Dehydration (%)	13.8
	COPD (%)	4.9
	Off- hours Admission (%)	55.6

* More than one hospital stay was allowed per patient.

Table 2
Predictive value of prescribing discrepancies for ADE.

Drug or drug class	Prescribing discrepancies (N) [*]	ADEs (N)	Positive predictive value (N/N) (95% CI)	Example: Discrepancy (ADE)
Opioid analgesics	54	15	.28 (.17–.42)	Oxycodone omitted (pain)
Metronidazole	25	4	.16 (.05–.37)	Metronidazole omitted (diarrhea)
Non-opioid analgesics	37	5	.14 (.05–.30)	Acetaminophen omitted (pain)
Levothyroxine	17	2	.12 (.02–.38)	Levothyroxine omitted (constipation)
Anti-prostate agents	12	1	.08 (.00–.35)	Terazosin omitted (urinary retention)
Anti-arrhythmic agents	13	1	.08 (.00–.38)	Digoxin dose changed (elevated level)
Nitrates	43	3	.07 (.02–.20)	Nitrate route change (hypotension)
Warfarin	45	3	.07 (.02–.19)	Warfarin dose changed (thrombosis)
Calcium blockers	45	3	.07 (.02–.19)	Felodipine omitted (hypertension)
Benzodiazepines	30	2	.07 (.01–.24)	Clonazepam omitted (agitation)
Angiotensin blockers	80	5	.06 (.02–.15)	Lisinopril increased (creatinine increase)
Anti-epileptic agents	53	3	.06 (.02–.17)	Carbamazepine omitted (seizure)
Insulin	65	3	.05 (.01–.14)	Insulin omitted (hyperglycemia)
Anti-psychotic agents	55	2	.04 (.01–.14)	Risperidone omitted (agitation)
Laxatives	80	3	.04 (.01–.11)	Tegaserod omitted (constipation)
Diuretics	86	3	.03 (.01–.11)	Furosemide dose increased (hypotension)
Beta-blockers	62	2	.03 (.01–.12)	Metroprolol omitted (hypertension)
Bronchodilators	111	2	.02 (.00–.07)	Albuterol omitted (dyspnea)
Proton-pump inhibitors	123	2	.02 (.01–.08)	Pantoprazole omitted (epigastric pain)
Antibiotics ^{**}	176	1	.01 (.00–.04)	Antibiotic switch (angioedema)
H2 blockers	74	0	0 (0–.06)	
Oral hypoglycemics	64	0	0 (0–.07)	

* Indicates prescribing omission, dose change, route change, or switch to a new medication for the same indication. Drugs or drug classes are included that had at least 10 discrepancy occurrences.

** Excluding metronidazole, which is shown separately.

Table 3

Predictive value of co-occurrence of a medical incident commonly captured by automated data systems and a suspect prescribing discrepancy.

Incident/example of suspect discrepancy	Occurrences (N)[*]	ADEs (N)	Positive predictive value (N/N) (95% CI)
Pain ^{**} /analgesic discrepancy	59	22	.37 (.25–.51)
High blood pressure ^{**} /antihypertensive discrepancy	32	8	.33 (.16–.55)
Renal insufficiency ^{**} /angiotensin blocker discrepancy	14	4	.29 (.10–.58)
Low blood pressure ^{**} /antihypertensive discrepancy	34	6	.18 (.07–.35)
Fever ^{**} /antibiotic discrepancy	28	2	.07 (.01–.25)

* Episode types are included that had at least 10 occurrences.

** Pain: new or worse pain; fever: temperature > 100.5 F (38 C); high blood pressure: new systolic blood pressure > 185, or diastolic blood pressure > 105, or an increase in systolic or diastolic blood pressure of 30mm; low blood pressure: new systolic blood pressure < 95, or a drop in systolic blood pressure of 30mm; renal insufficiency: new creatinine increase >0.5 mg/dl.

Association of ADE from a medication discrepancy with 3 prescribing indices: number of medications prescribed prior to transfer, number of medication discrepancies that occurred after transfer, and number of high-risk medication discrepancies that occurred after transfer.

Table 4

Index:	Pre-Transfer Medications	Medication Discrepancies	High-Risk Discrepancies
Quartile of index:	Range in quartile:	Percent in quartile with ADE: Range in quartile:	Percent in quartile with ADE: Range in quartile:
1	0-3	15 0	14 0
2	4-5	13 1	17 1
3	6-7	27 2-3	19 2
4	≥8	24 ≥4	32 ≥3
Unadjusted odds ratio (95% CI); C-statistic	1.08 (.98-1.19); .578	1.19 (1.05-1.36); .600	1.65 (1.26-2.16); .621
Adjusted** odds ratio (95% CI); C-statistic	1.07 (.97-1.19); .637	1.20 (1.02-1.41); .666	1.71 (1.28-2.28); .691

* Odds ratio indicates the additional risk of ADE with a 1-point increase in each prescribing index; c-statistic indicates the area under the receiver operating characteristic (ROC) curve

** Adjusted for gender, age, comorbidity score, APACHE score, off-hours admission, and duration of follow-up