Association of ICU or Hospital Admission With Unintentional Discontinuation of Medications for Chronic Diseases

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Context  Patients discharged from acute care hospitals may be at risk for unintentional discontinuation of medications prescribed for chronic diseases. The intensive care unit (ICU) may pose an even greater risk because of the focus on acute events and the presence of multiple transitions in care.

Objective  To evaluate rates of potentially unintentional discontinuation of medications following hospital or ICU admission.

Design, Setting, and Patients  A population-based cohort study using administrative records from 1997 to 2009 of all hospitalizations and outpatient prescriptions in Ontario, Canada; it included 396,380 patients aged 66 years or older with continuous use of at least 1 of 5 evidence-based medication groups prescribed for long-term use: (1) statins, (2) antiplatelet/anticoagulant agents, (3) levothyroxine, (4) respiratory inhalers, and (5) gastric acid-suppressing drugs. Rates of medication discontinuation were compared across 3 groups: patients admitted to the ICU, patients hospitalized without ICU admission, and nonhospitalized patients (controls). Odds ratios (ORs) were calculated and adjusted for patient demographics, clinical factors, and health services use.

Main Outcome Measures  The primary outcome was failure to renew the prescription within 90 days after hospital discharge.

Results  Patients admitted to the hospital (n=187,912) were more likely to experience potentially unintentional discontinuation of medications than controls (n=208,468) across all medication groups examined. The adjusted ORs (AORs) ranged from 1.18 (95% CI, 1.14-1.23) for discontinuing levothyroxine in 12.3% of hospitalized patients (n=6831) vs 11.0% of controls (n=7114) to an AOR of 1.86 (95% CI, 1.77-1.97) for discontinuing antiplatelet/anticoagulant agents in 19.4% of hospitalized patients (n=5564) vs 11.8% of controls (n=2535). With ICU exposure, the AORs ranged from 1.48 (95% CI, 1.39-1.57) for discontinuing statins in 14.6% of ICU patients (n=1484) to an AOR of 2.31 (95% CI, 2.07-2.57) for discontinuing antiplatelet/anticoagulant agents in 22.8% of ICU patients (n=522) vs the control group. Admission to an ICU was associated with an additional risk of medication discontinuation in 4 of 5 medication groups vs hospitalizations without an ICU admission. One-year follow-up of patients who discontinued medications showed an elevated AOR for the secondary composite outcome of death, emergency department visit, or emergent hospitalization of 1.07 (95% CI, 1.03-1.11) in the statins group and of 1.10 (95% CI, 1.03-1.16) in the antiplatelet/anticoagulant agents group.

Conclusions  Patients prescribed medications for chronic diseases were at risk for potentially unintentional discontinuation after hospital admission. Admission to the ICU was generally associated with an even higher risk of medication discontinuation.

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For editorial comment see p 878.
during the remainder of their hospitalization and after discharge.

Measuring and monitoring errors of omission is a difficult and complex task. We sought to determine whether the potentially unintended discontinuation of common, evidence-based medications for chronic diseases occurs after acute care hospitalization and whether an ICU admission is associated with greater risk. By focusing on evidence-based medications prescribed over the long-term (>1 year) and excluding patients when there were deliberate reasons for discontinuations, we aim to minimize the potential for misclassification of the outcome.

METHODS

We conducted a population-based cohort study that used linked administrative records between 1997 and 2009 of all hospitalizations in Ontario, Canada, for residents aged 66 years or older who had at least 1 year of continuous medication use in at least 1 of 5 medication groups: (1) statins; (2) antiplatelet or anticoagulant agents; (3) levothyroxine; (4) respiratory inhalers; and (5) gastric acid–suppressing drugs. Patients were required to demonstrate a minimum of 1 year of continuous use of the medication for study entry. This time frame was selected because previous research suggests that patients who are nonadherent to their prescribed medication regimen for chronic diseases typically stop using their medications within the first few months.14-18

We identified 3 distinct cohorts: (1) patients who were discharged after a hospitalization that included an ICU admission; (2) patients who were discharged after a hospitalization that did not include an ICU admission; and (3) patients who were not hospitalized (controls). Patients who died during hospitalization were excluded. These 3 patient cohorts were assessed for the outcome of failure to renew the prescription within 90 days after hospital discharge.

Setting and Databases

The linked administrative data between April 1, 1997, and March 31, 2009, were encrypted with unique identifiers and were from 4 separate databases: (1) the Ontario Drug Benefits database (all medications prescribed to persons aged ≥65 years)19; (2) the Canadian Institute for Health Information Discharge Abstract Database (hospitalizations, surgeries, and procedures); (3) the Ontario Health Insurance Plan database (physician services billings); and (4) the Registered Persons Database (demographic and vital status, deaths). Excellent agreement has been found between administrative hospitalization data and chart audit.20,21 The analyses are considered population-based because of the comprehensive nature of universal health insurance in Ontario and the negligible volume of patients who seek care outside of the country.22,23

Patients and Medication Groups

All patients aged 66 years or older who were prescribed medication continuously for 1 year or more from at least 1 of the 5 medication groups were included. These groups included: (1) statins; (2) antiplatelet or anticoagulant agents (ie, clopidogrel, warfarin); (3) levothyroxine; (4) respiratory inhalers (anticholinergic, β-agonist, or steroid); and (5) gastric acid–suppressing drugs (histamine 2 blockers and proton pump inhibitors). All of these medications are commonly used in older patients (≥66 years), have documented adherence estimates for large populations,19,13,24-26 and are evidence-based therapies with established long-term efficacy.1,7,14-18,24,26

Our medication choices represent different theorized approaches to medication prescribing, medication taking, and medication delivery systems (eg, tablet vs inhaler). They include medications for the treatment of symptomatic and asymptomatic diseases. A few are medications (respiratory inhalers and gastric acid–suppressing drugs) that are also used in the ICU for prophylaxis but may be routinely stopped upon transfer.15-11 Earlier work using a structured chart review process showed that at least one-fifth of patients in the ICU who were taking medications in these medication groups experienced an error of omission upon hospital discharge and were unintentionally discontinued from their medication for chronic diseases.10

This study was approved by the ethics committees of the Sunnybrook Health Sciences Centre and St Michael’s Hospital. We used the protocols of the Institute for Clinical Evaluative Sciences in Ontario, including the waiver of patient consent, to maintain data confidentiality and patient anonymity.

Assessment of Drug Continuity Prior to Hospitalization

The Ontario Drug Benefits database was used to estimate the intended duration of each prescription. Patients who were dispensed a prescription renewal prior to the end of their previous prescription period had the excess drug carry over to the next period. A grace period of 20% to refill the next prescription was given for all medication groups with the exception of warfarin, which was allotted 50% because this allows for possible alterations in dose due to regular laboratory monitoring. For example, a patient with a 30-day statin prescription would have 36 days to refill that prescription and still be considered to have continuous use. If the patient did not refill the prescription within these parameters for the entire year prior to their index date, they were excluded from the cohort.

Exposure and Index Dates

Three cohorts of patients were identified under each of the 5 medication groups: (1) patients who were discharged after a hospitalization that included an ICU admission; (2) patients who were discharged after a hospitalization that did not include an ICU admission; and (3) patients who were not hospitalized (controls). These cohorts were identified using...
hospital records and specific physician billing codes. The index dates for patients with any hospitalization were assigned by the discharge date. For the individuals in the control group of nonhospitalized patients, the index dates were randomly assigned from within the study period.

Exclusions
We excluded patients hospitalized within the 6 months prior to the index date. Patients also were excluded if they died or were readmitted to the hospital within the 90 days following their index date or if they were hospitalized for longer than 15 days. Patients transferred from or discharged to a long-term facility, chronic care facility, or between acute care hospitals also were excluded. Patients displaying complications or contraindications to medications (eg, bleeding ulcer and warfarin prescription) also were excluded. These contraindications were specific to each medication group to minimize the possibility that there was an indication for intentional medication discontinuation (eTable 1 at http://www.jama.com). The hospitalization was the point of interest; individual patients could be included more than once within and across each medication group, but only once as part of the nonhospitalized patient control category per medication group.

Outcomes
The medications included were selected because they are evidence-based therapies with established long-term efficacy. Therefore, the discontinuation of the selected medications was considered to indicate an increased future risk for an adverse event. The primary outcome was defined as an absence of prescription renewal in the drug benefit database 90 days after the index date, expressed as an odds ratio (OR) with patients in the control group being the reference. A within-class change of medication (eg, between different types of statins) or changes in medication dose were not considered outcomes.

Sensitivity Analysis and Secondary Outcomes
Individuals who died within 90 days after the index date were included in a sensitivity analysis to estimate the level of potential underestimation of medication discontinuation introduced by our cohort selection method that excluded these deaths. Following assessment of the primary outcome at 90 days after the index date, patients were followed up from day 91 through day 365. They were evaluated for the composite patient outcomes of death, emergency department visit, and hospitalization to estimate some of the downstream effects of potentially unintentional discontinuation of medications prescribed for chronic diseases.

Covariates
We controlled for confounding factors that might influence medication discontinuation. These patient-level factors included age, sex, low-income status, length of stay, and comorbid disease burden as determined by the number of distinct medications dispensed in the year prior to cohort entry. The number of medications dispensed in the year prior to cohort entry included acute treatments and medications taken intermittently or for brief periods (eg, antibiotics and lorazepam).

The models also included the number of primary care and internal medicine specialist physician contacts prior and subsequent to the index date to account for differences in the intensity of ambulatory care and necessary medication changes. In the adjusted model, we added variables known to be associated with predicting nonadherence among patients taking medications for symptomatic and asymptomatic chronic diseases. The variables included were age, sex, low-income status, number of different prescriptions, and number of primary care or specialist visits.

Statistical Analysis
Separate analyses were performed for each of the 5 medication groups. Multivariate logistic regression was used to examine the effect of hospitalization on medication discontinuation in each of the 5 medication groups and to adjust for the effects of confounding variables. Based on sample size calculations from earlier work with statins and warfarin, we anticipated that we would have more than 99% power to detect a relative difference of less than 2% in the proportion of patients continuing medications with a 2-tailed α level of .05. Relative differences smaller than these are not likely to be clinically important. All statistical analyses were conducted in SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS
The study included 187 912 hospitalized patients and 208 468 controls (Table 1). A total of 4120 hospitalizations were excluded due to contraindications and another 23 224 were excluded due to death within 90 days of the index date (eTable 2 at http://www.jama.com). Among the hospitalized patients, 16 474 individuals were admitted to the ICU (Table 1). The majority were women and about one-quarter had low-income economic status. Almost all patients were in contact with a primary care physician during the year prior to their index date (Table 1). In addition, the majority (n = 348 814; 88%) fell into 3 medication groups: statins, levothyroxine, and gastric acid suppressors (Table 2).

Medication Discontinuation
There was a range in the proportion of patients in the separate medication categories experiencing the primary outcome of medication discontinuation at 90 days. The highest rate of medication discontinuation occurred in the antiplatelet or anticoagulant agent group (n = 5564; 19.4%) (Table 3). In this group, there were 552 patients (22.8%) with an ICU admission who discontinued these medications after hospital discharge (Table 4). In contrast, of the 21 490 patients in the control group who were receiving antiplatelet or anticoagulant medications, only 2535 (11.8%) experienced the primary out-
come of medication discontinuation at 90 days (Table 3).

The respiratory inhaler group had the lowest rate of medication discontinuation (n=231; 4.5%) (Table 3). Of the patients who experienced the primary outcome of medication discontinuation, 5.4% were in the ICU admission group (n=20) compared with 3% in the control group (n=79) (Table 3 and Table 4).

Adjusted Analyses

All medication groups had statistically significant adjusted ORs (AORs) for hospitalized patients experiencing the primary outcome of discontinuation compared with nonhospitalized patients. The lowest AOR was 1.18 (95% confidence interval [CI], 1.14-1.23) for discontinuing levothyroxine and the highest AOR was 1.86 (95% CI, 1.77-1.97) for discontinuing antiplatelet or anticoagulant agents (Table 3). Overall, the increased risk of medication discontinuation in patients with an ICU admission was statistically significant in 4 of the 5 medication groups compared with hospitalized patients without an ICU admission. The effect was observed for antiplatelet or anticoagulants agents, gastric acid suppressors, statins, and levothyroxine. The lowest AOR was 1.11 (95% CI, 1.05-1.18) for discontinuing statins and the highest AOR was 1.29 (95% CI, 1.17-1.41) for discontinuing levothyroxine (Table 4).

ICU Exposure

There is an increased risk of medication discontinuation in patients with an ICU admission compared with nonhospitalized patients. The lowest AOR was 1.48 (95% CI, 1.39-1.57) for discontinuing statins and the highest AOR was 2.31 (95% CI, 2.07-2.57) for discontinuing antiplatelet or anticoagulant agents (Table 3). Overall, the increased risk of medication discontinuation in patients with an ICU admission was statistically significant in 4 of the 5 medication groups compared with hospitalized patients without an ICU admission. The effect was observed for antiplatelet or anticoagulants agents, gastric acid suppressors, statins, and levothyroxine. The lowest AOR was 1.11 (95% CI, 1.05-1.18) for discontinuing statins and the highest AOR was 1.29 (95% CI, 1.17-1.41) for discontinuing levothyroxine (Table 4).

**Sensitivity Analysis and Secondary Outcomes**

When our primary analyses were repeated to include patients who died within the 90 days following their index date, the resulting AORs for medication discontinuation were higher than the reported estimates for all medication groups and remained statistically significant. Patients experienced the composite outcome of death, emergency department visit, or emergent hospitalization from day 91 through day 365 after the index date at varying rates across the medication groups (Table 5). The comparison of patients who had continuous prescriptions (n=30 791; 36.5%) with patients who experienced discontinuation of their statins yielded an AOR of 1.07 (95% CI, 1.03-1.11). Similarly, patients who experienced discontinuation of antiplatelet or anticoagulant medications had a higher risk of these adverse events (AOR, 1.10; 95% CI, 1.03-1.16). Nonsignificant results were found for all other medication groups (Table 5).

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Table 2. Sample Size by Study Group

<table>
<thead>
<tr>
<th>Medication group</th>
<th>All (n = 187,912)</th>
<th>Without ICU Stay (n = 171,438)</th>
<th>With ICU Stay (n = 16,474)</th>
<th>Controls (n = 208,468)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>97,533</td>
<td>87,395</td>
<td>10,138</td>
<td>108,944</td>
</tr>
<tr>
<td>Antiplatelets or anticoagulants</td>
<td>28,721</td>
<td>26,298</td>
<td>2,423</td>
<td>21,490</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>55,570</td>
<td>51,476</td>
<td>4,094</td>
<td>64,927</td>
</tr>
<tr>
<td>Respiratory inhalers</td>
<td>51,490</td>
<td>47,777</td>
<td>3,727</td>
<td>26,581</td>
</tr>
<tr>
<td>Gastric acid suppressors</td>
<td>57,099</td>
<td>52,738</td>
<td>4,361</td>
<td>46,192</td>
</tr>
</tbody>
</table>

Abbreviation: ICU, intensive care unit.

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COMMENT

Our study of just under 400,000 individuals who were continuous users of medications for chronic diseases assessed the risk of hospitalization and ICU admission based on the rate of potentially unintentional discontinuation of common evidence-based therapies. We evaluated this effect across 5 medication groups used to treat common chronic diseases and diagnoses. The medications were selected because their discontinuation has been associated with adverse events.1-7,27

After controlling for covariates and confounding factors, all medication groups demonstrated an elevated risk of potentially unintentional discontinuation at 90 days following hospital discharge. We found an additional risk of discontinuation associated with ICU admission in 4 of the 5 medication groups. Furthermore, 2 of the 5 medication groups showed an increased adjusted risk of death, hospitalization, and emergency department visit up to 1 year after hospital discharge. This underscores the widespread prevalence of potential errors of omission and the risk for long-term harm following hospitalization.

Medication reconciliation studies have documented prescription errors after hospital discharge, demonstrating that unintentional medication discontinuation is a common occurrence.31-33 These earlier studies mostly had single site, cross-sectional designs that were limited in their patient population and medication types. Our study examined potential errors of omission on a systemwide basis for an extended period in a diverse patient population with a focus on important long-term medications for chronic diseases.

The results of our study are consistent with findings from a structured implicit review of clinical data from 3 ICUs that identified the drug classes at risk of discontinuation and confirmed the potentially unintentional nature of the medication discontinuation.30 This study provided the basis for the selected medication groups examined herein. Earlier work applying a similar method in elective surgery patients also found that hospital exposure may lead to potentially unintentional medication discontinuation.30 The effect was detected in patients treated with warfarin but not statins. This difference may reflect some differences in the outcome definition as well as clinical surgical practices that focus more on anticoagulation management than other medications for chronic diseases. In contrast, our present findings have broad implications in that they identify an elevated risk for medication discontinuation across all tested medication groups and all areas of the hospital.

Our study also found that treatment in an ICU places patients at even greater risk for potentially unintentional discontinuation of their medications. This may relate to the additional transitions inherent in ICU care. The deliberate suspension of certain medications for resuscitation is often required, which later may be forgotten or overlooked upon discharge. Moreover, the clinical focus of the ICU is on acute care and medications for chronic diseases are often not prescribed because they can complicate the management of patients.

Future quality improvement intervention strategies should focus on formal medication reconciliation efforts at ICU discharge.34-37 Some facilities have used their critical care rapid response teams to provide post-ICU discharge follow-up.38,39 Incorporating formal
medication reconciliation into this process may be a natural extension of this practice so that potential errors of omission in the ICU are detected and do not persist after hospital discharge.

Some of the selected medications in our study had higher risks than others for medication discontinuation after hospital discharge. This may relate to inherent differences between the medications as a consequence of different theorized approaches to medication prescribing, medication taking, and medication dispensing.40 For example, many patients on a ventilator in the ICU are prescribed bronchodilators to improve lung function even in the absence of chronic lung disease. When they are discharged, these medications may be unintentionally discontinued because they were (mistakenly) perceived to have been initially prescribed in the ICU. Still, the observed effect appears to be consistent across all medication groups examined.

The downstream effects of unintentional discontinuation of the various medications vary in severity according to the individual medication group. In our findings for the secondary outcome analysis, some medication groups showed an increased adjusted risk of death, emergency department visit, and hospitalization while others did not. Some outcomes may be more severe than others and may differ depending on the individual medication and its original indication. Discontinuing a proton pump inhibitor may result in gastrointestinal tract symptoms or peptic ulcer, whereas an unintended discontinuation of warfarin medication in a patient with atrial fibrillation increases the risk of an embolic stroke.41-43 In general, the unintentional discontinuation of common evidence-based medications can further exacerbate chronic disease management following an acute care hospitalization when there is an elevated risk of hospital readmission or death.44

Better communication and a system-based method have been advocated as possible solutions to improve medication continuity and safety. These strategies can range from customized integrated hospital computer systems to simple preprinted forms.45 However, their success is contingent on including all relevant clinicians and the patients themselves.46 Formal programs such as medication reconciliation and standard discharge summaries can provide a means to improve interdisciplinary communication, including with primary care clinicians.34,36,37,47 Identification of high-risk patients and transfers in care may help improve program efficiency and focus valuable resources.48-51

Our study has several important limitations. First, we used administrative data that can measure associations but cannot prove causality. Still, the data sources have demonstrated good reliability and the techniques applied have been validated in previous work studying medications in elderly patients.1,2,23,26

Second, the data lacked sufficient clinical detail to guarantee our classification of medication discontinuation as unintentional. Some medications may have been intentionally discontinued and there may be positive patient-related effects, such as those associated with polypharmacy.52,53 However, we designed our study to minimize the likelihood that the observed medication discontinuation was intentional. Specifically, we included long-term medications and required 1 year of continuous medication use to exclude the possibility that the medication was discontinued due to a completed course of treatment. This provision also minimized possible confounding from patient nonadherence because the greatest reduction in adherence typically occurs within the first 6 months of treatment.14-18 Patients were excluded if they had any diagnoses related to a possible indication for intentional medication discontinuation (eg, myositis and statin prescription). Furthermore, our use of a control group helped estimate the baseline risk of medication discontinuation. Hospital admission and ICU admission may provide additional opportunities to review medications compared with control groups. Therefore, we cannot exclude the possibility that some of these medication discontinuations were intentional, but consider this to be an unlikely scenario for medications such as levothyroxine or statins because hospitalization is unlikely to introduce any contraindications to receiving these medications. We excluded individuals hospitalized for any reason 90 days after the index date to prevent including those with active medical issues. Moreover, an earlier chart review study with extensive clinical information yielded similar findings.50

Third, as with any observational study, our findings may be influenced by bias or confounding. However, we

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discontinued comparable patient groups through our inclusion criteria, matching strategy, use of a control group, and covariate adjustment, including internal medicine and primary care consultations that address the issue of clinical attention to account for baseline differences.

Fourth, the reasons for hospitalization, especially for those patients admitted to the ICU, were different and we cannot exclude the possibility that some of the medication discontinuations were related to the individual indications for hospitalization. Fifth, even though our study cohort only included elderly patients (≥66 years), the findings are likely generalizable to the general population even though older individuals may be more susceptible to these types of errors because they are prescribed more medications and are hospitalized more often than younger people.54-58

Sixth, due to limitations in the available data, we were unable to adjust for hospital characteristics, including staffing models such as hospitalist care, directly. However, we adjusted for primary and specialist care visits before and after the index date as a means of addressing this potential bias.

Finally, we excluded individuals who died after hospital discharge. Because unintentional medication discontinuation could be associated with adverse health outcomes and death, exclusion of these patients from our analysis could lead us to underestimate the true risk of medication discontinuation. Taken as a whole, it is unlikely that any of the various limitations would invalidate our principal findings of an increased risk of potentially unintentional discontinuation of selected medications for chronic diseases after hospitalization and the elevated risk attributable to an ICU admission.

Gaps in the continuity of care are an area of vulnerability for patient safety. We found that patients discharged from the hospital have an elevated risk of not continuing their long-term medications for chronic diseases and that treatment in the ICU appears to further increase this risk. These findings emphasize the importance of a systematic approach to transitions in health care to ensure medication continuity. In this way, success in the management of hospitalized patients can translate into success in the management of community patients.

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Author Contributions: Dr Bell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bell, Brener, Bierman, Scales, Bajar, Zwarenstein, Urbach. Acquisition of data: Bell, Brener, Gunraj, Scales, Urbach. Analysis and interpretation of data: Bell, Brener, Gunraj, Huo, Bierman, Scales, Zwarenstein, Urbach. Drafting of the manuscript: Bell, Brener, Huo, Scales, Zwarenstein.

Critical revision of the manuscript for important intellectual content: Bell, Brener, Gunraj, Bierman, Scales, Bajar, Zwarenstein, Urbach. Statistical analysis: Bell, Brener, Gunraj, Huo, Scales, Zwarenstein.

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Online-Only Material: eTable 1, eTable 2, and eTable 3 are available at http://www.jama.com.

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REFERENCES


DISCONTINUATION OF PRESCRIPTION MEDICATIONS POSTHOSPITALIZATION


