Effect of Computerized Provider Order Entry with Clinical Decision Support on Adverse Drug Events in the Long-Term Care Setting

Jerry H. Gurwitz, MD, Terry S. Field, DSc,*Paula Rochon, MD, MPH,† James Judge, MD,‡ Leslie R. Harrold, MD, MPH,* Chaim M. Bell, MD, PhD,§ Monica Lee, RPh,† Kathleen White, RPh,‡ Jane LaPrino, BA,‡ Janet Erramuspe-Mainard,† Martin DeFlorio, RPh,‡ Linda Gavendo, BScPhm,† Joann L. Baril, BS,* George Reed, PhD,* and David W. Bates, MD, MSc‖*

OBJECTIVES: To evaluate the efficacy of computerized provider order entry with clinical decision support for preventing adverse drug events in long-term care.

DESIGN: Cluster-randomized controlled trial.

SETTING: Two large long-term care facilities.

PATIENTS: One thousand one hundred eighteen long-term care residents of 29 resident care units.

INTERVENTION: The 29 resident care units, each with computerized provider order entry, were randomized to having a clinical decision support system (intervention units) or not (control units).

MEASUREMENTS: The number of adverse drug events, severity of events, and whether the events were preventable.

RESULTS: Within intervention units, 411 adverse drug events occurred over 3,803 resident-months of observation time; 152 (37.0%) were deemed preventable. Within control units, there were 340 adverse drug events over 3,257 resident-months of observation time; 126 (37.1%) were characterized as preventable. There were 10.8 adverse drug events per 100 resident-months and 4.0 preventable events per 100 resident-months on intervention units. There were 10.4 adverse drug events per 100 resident-months and 3.9 preventable events per 100 resident-months on control units. Comparing intervention and control units, the adjusted rate ratios were 1.06 (95% confidence interval (CI) = 0.92–1.23) for all adverse drug events and 1.02 (95% CI = 0.81–1.30) for preventable adverse drug events.

CONCLUSION: Computerized provider order entry with decision support did not reduce the adverse drug event rate or preventable adverse drug event rate in the long-term care setting. Alert burden, limited scope of the alerts, and a need to more fully integrate clinical and laboratory information may have affected efficacy. **J Am Geriatr Soc 56:2225–2233, 2008.**

Key words: patient safety; clinical decision support; computerized provider order entry; long-term care

There are nearly 1.5 million residents of long-term care facilities in the United States.[1] The intensity of medication use is high in these settings, adverse drug events occur commonly, and many of these are preventable. One study conducted in a sample of community-based Massachusetts nursing homes found that adverse drug events occurred at a rate of 1.9 per 100 resident-months, with at least half being preventable.[2] A more recent study, employing enhanced ascertainment methods, reported substantially higher rates: 9.8 per 100 resident-months, with a rate of 4.1 preventable events per 100 resident-months.[3] If findings from the more recent study are extrapolated to all U.S. nursing homes, then nearly 1.8 million adverse drug events may occur each year in U.S. nursing homes, approximately 40% of which may be preventable.

Computerized provider order entry with clinical decision support has been promoted as a promising tool for reducing medication error and adverse drug event rates in the long-term care setting,[4,5] but few long-term care facilities have implemented such systems because of cost, complexity, and logistical challenges, as well as uncertainty about how effective these systems are for reducing

From the *Meyers Primary Care Institute, University of Massachusetts Medical School, Fallon Clinic, and Fallon Community Health Plan, Worcester, Massachusetts; †Kunin-Lunenfeld Applied Research Unit, Baycrest Centre, Toronto, Ontario, Canada; ‡Masonicare, Wallingford, Connecticut; §Department of Medicine, St. Michael's Hospital and the University of Toronto, Toronto, Ontario, Canada; and ‖Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Address correspondence to Jerry H. Gurwitz, MD, Meyers Primary Care Institute, University of Massachusetts Medical School, Fallon Clinic, and Fallon Community Health Plan, 630 Plantation Street, Worcester, MA 01605. E-mail: jgurwitz@meyersprimary.org, jerry.gurwitz@umassmed.edu

DOI: 10.1111/j.1532-5415.2008.02004.x

0002-8614/08/$15.00

drug-related injuries.[6] Although the benefits of reducing medication error rates in other clinical settings have been established,[7,8] few studies in any clinical setting have assessed the effect of this technology on rates of adverse drug events.[9] The purpose of the present study was to evaluate the efficacy of computerized provider order entry with clinical decision support for preventing adverse drug events in long-term care.

METHODS

Study Settings

This study was conducted in two large, academic long-term care facilities located in Connecticut and Ontario, Canada. The two facilities have a combined total of 1,229 beds. Patients residing in areas of the facilities related to short-term care (e.g., subacute care, hospital-level care, and rehabilitation) were not included in the study population.

Each of the facilities had an existing computerized provider order entry system without a computer-based clinical decision support system. Contracted staff prescribed all medications; in one of the study facilities, this included 27 physicians, nurse practitioners, and physicians' assistants. In the other facility, 10 physicians prescribed medications. At the time of the study, providers entered approximately 90% of new medication orders using the system. The institutional review board of the University of Massachusetts Medical School, and the institutional review boards of the participating facilities approved this study. This study has been registered with ClinicalTrials.gov.

Study Design

The study was conducted over 1 year in one of the study facilities and 6 months in the other. Across the two long-term care facilities, 29 resident care units, each with existing computer provider order entry, were randomized to having a clinical decision support system (intervention units) or not (control units). Bed size of the resident care units ranged from 20 to 60. An effort was made to match the units according to bed size and general characteristics of the residents on the units. Block randomization was undertaken within categories, including dementia units, units where care was provided to residents with mental health and behavioral problems, units where the residents had complex medical needs, and units where the residents had profound deficits in physical function.

On intervention units, prescribers ordering drugs were presented with alerts in the form of warning messages; these alerts were not displayed to prescribers when ordering medications for residents of control units. Although efforts were initially made to limit crossover of prescribers between intervention and control units, over the duration of the study, some providers worked simultaneously on both types of units on a temporary (coverage) basis and permanently.

Design of the Clinical Decision Support System

A team of geriatricians, pharmacists, health services researchers, and information system specialists designed the clinical decision support system; the process of developing the clinical decision support system and its components has been described previously.[4,5] The design principles were that messages should be evidence-based, practitioners should perceive the messages to be useful and informative, and the system should have only a modest effect on the time required for the practitioner to complete an order. The team reviewed the types of preventable adverse drug events based on previous research[2,3] and widely accepted published criteria for suboptimal prescribing in elderly people available at the time of this study. All serious drug–drug interactions from a standard pharmaceutical drug interaction database were also reviewed, and alerts were included for a limited number of more than 600 potentially serious interactions that were reviewed. A summary of the alerts is provided in Appendix A.

The computerized provider order entry system in place at the time of clinical decision support system implementation was a commercially available application capable of linking some laboratory test results with current drug orders in real time, but the system had several important limitations, as described previously.[10] At the time of the study, it could not combine dose and strength information to determine the total daily dose associated with a drug order; therefore, some alerts were displayed when they may not have been necessary (e.g., the medication order was already within the recommended dose range). The underlying software was not capable of distinguishing multiple orders for the same drug in different forms or strengths or orders that had been cancelled and reordered within the same prescribing session. These orders were interpreted as multiple orders for drugs in the same category and triggered a number of inappropriate alerts about drug interactions. Despite the fact that some triggers were likely to produce a substantial number of these unnecessary alerts, it was decided to include them in the system if the potential effect of the type of drug interaction in question was considered clinically important.

For residents on the intervention units, the alerts were displayed in a pop-up box to prescribers in real time when a drug order was entered. The pop-up boxes were informational; they did not require specific actions from the prescriber and did not produce or revise orders automatically. On the control units, the alerts were not displayed to the prescribers.

Case-Finding Definitions and Classification of Events

Drug-related incidents were identified through review of medical records in monthly segments performed by trained pharmacist investigators for each eligible long-term care facility resident. These investigators, who were not aware of whether the resident was located on an intervention or a control unit, examined the records for possible drug-related incidents, such as new symptoms or events that might represent an adverse drug event, changes in medication regimens (including acute discontinuations or initiations of medications that might be used to treat a drug-induced event), abnormal laboratory values, and all emergency department transfers and hospitalizations. In addition to periodic reviews, medical records were specially targeted for review based on information derived from selected computer-generated signals including abnormal serum drug concentrations, abnormal laboratory results, and the use of medications considered to be antidotes for adverse drug

effects. Administrative incident reports generated within each participating facility were also reviewed for any indication of a drug-related incident.

Outcome Measures

The primary outcome of the study was an adverse drug event, defined as an injury resulting from the use of a drug. This definition is consistent with definitions used in previous studies.[2,3,11–14] Adverse drug events may have resulted from medication errors (e.g., errors in ordering, dispensing, administration, and monitoring) or from adverse drug reactions in which there was no error.

A pharmacist investigator presented the possible drug-related incidents to pairs of physician reviewers (JHG, JJ, PR, LRH, and CMB). These physician reviewers independently classified incidents using structured implicit review according to the following criteria: whether an adverse drug event was present, the severity of the event, and whether the event was preventable. In determining whether an adverse drug event had occurred, the physician reviewers considered the temporal relation between the drug exposure and the event, as well as whether the event reflected a known effect of the drug. This structured implicit review process has been used in numerous prior studies relating to adverse drug events across various clinical settings.[2,3,11–17] Physician reviewers were not aware of whether a drug-related incident being reviewed had occurred in a resident of an intervention or a control unit.

The severity of adverse events was categorized as less serious, serious, life threatening, or fatal. Adverse drug events categorized as less serious included a nonurticarial skin rash, a fall without associated fracture, hemorrhage not requiring transfusion or hospitalization, and oversedation. Examples of events categorized as serious included urticaria, falls with associated fracture, hemorrhage requiring transfusion or hospitalization but without hypotension, and delirium. Examples of life-threatening events included hemorrhage with associated hypotension, hypoglycemic encephalopathy, and acute renal failure. Adverse drug events were considered to be preventable if they were judged to be due to an error and were preventable by any means available and not just in relation to the clinical decision support system. For the purpose of the analysis of the effect of the intervention, any event characterized as serious or greater in severity, was categorized as *more severe*. All other events were considered *less severe*.

Preventability was categorized as preventable, probably preventable, probably not preventable, or definitely not preventable; results were collapsed into preventable (preventable and probably preventable) and nonpreventable (probably not preventable and definitely not preventable) categories in the analysis.

When the physician reviewers disagreed on the classification of an incident regarding the presence of an adverse drug event, its severity, or its preventability, they met and reached consensus; consensus was reached in all instances in which there was initial disagreement.

Statistical Analysis

Crude rates of events were determined, dividing the number of adverse drug events by the total number of long-term care resident-months in the intervention and control units of the two facilities. Resident-months were estimated from census data for all residents on eligible units and were obtained monthly throughout the course of the project; absences from the facilities (e.g., for hospitalization) were also accounted for when they occurred.

To assess the effect of the intervention, rate ratios comparing rates of all adverse drug events and preventable adverse drug events in the intervention versus control units were estimated using Poisson regression models, adjusting for unit and facility. Additional models were used to estimate adjusted rate ratios for more- and less-severe adverse drug events and preventable more- and less-severe adverse drug events. The study was designed with power of 0.90 to identify a reduction of 20% in the rate of adverse drug events. These power calculations were conservative, because they were based on adverse drug event rates determined in a study of community nursing homes.[2] Subsequent research, employing better methods for event ascertainment, has indicated that actual adverse drug event rates in the long-term care setting are substantially higher.[3]

One of the investigators (JHG) re-reviewed all of the adverse drug events that had been deemed probably preventable or definitely preventable to determine whether it might have been possible for any of the alerts included in the clinical decision support system to lead to the prevention of these adverse drug events. This assessment was performed for events identified on the intervention and control units, although the reviewer (JHG) was unaware of which type of unit the event had occurred on. In a post hoc analysis, which considered only events for which it might have been possible for the alerts to have an effect, the rate ratio comparing the rate of preventable adverse drug events in the intervention versus control units was estimated through a Poisson regression model, adjusting for unit and facility, as was done in the main analysis detailed above.

RESULTS

Across the two study sites and the 29 randomized resident care units, 1,118 long-term care residents had an average age of 87.2, and 71.3% were female. The residents contributed 7,060 months of observation time; there were 3,803 resident-months of observation on the intervention units and 3,257 resident-months of observation on the control units.

Within the intervention units (Table 1), 411 adverse drug events occurred over 3,803 resident-months of observation time. Of the 411 events, 152 (37.0%) were deemed preventable. Within the control units, there were 340 adverse drug events over 3,257 resident-months of observation time. Of the 340 events, 126 (37.1%) were characterized as preventable. There were 10.8 adverse drug events per 100 resident-months and 4.0 preventable events per 100 resident-months on the intervention units. There were 10.4 adverse drug events per 100 resident-months and 3.9 preventable events per 100 resident-months on the control units. The rate ratio estimated using Poisson regression models was 1.06 (95% confidence interval (CI) = 0.92–1.23) for all adverse drug events and 1.02 (95% CI = 0.81–1.30) for preventable adverse drug events.

Table 1. Comparison of Rates of Adverse Drug Events (ADEs) Between Control and Intervention Units

	Intervention Units		Control Units			
ADE	n (%)	Rate/100 Resident-Years	n (%)	Rate/100 Resident-Years	Rate Ratio*	95% Confidence Interval*
All	411 (100)	10.8	340 (100)	10.4	1.06	0.92–1.23
Preventable	152 (37.0)	4.0	126 (30.7)	3.9	1.02	0.81–1.30
More severe†	123 (30.0)	3.2	97 (28.5)	3.0	1.07	0.82–1.40
Preventable more severe	79 (19.2)	2.1	58 (17.1)	1.8	1.15	0.82–1.61
Less severe	288 (70.1)	7.6	243 (71.5)	7.5	1.06	0.89–1.26
Preventable less severe	73 (17.8)	1.9	68 (20.0)	2.1	0.92	0.66–1.28

* Adjusted for unit and facility using Poisson regression models.
† More-severe ADEs include those deemed serious, life-threatening, or fatal.

Results by Severity

In the intervention units, 123 adverse drug events with a severity rating of serious, life-threatening, or fatal occurred over the 3,803 resident-months of observation time (Table 1). Of these events, 79 (64%) were deemed preventable. Within the control units, there were 97 of these more-serious adverse drug events over the 3,257 resident-months of observation time. Of these events, 58 (60%) were characterized as preventable. There were 3.2 of these more-severe events per 100 resident-months and 2.1 preventable events per 100 resident-months on the intervention units. There were 3.0 of these more-severe adverse drug events per 100 resident-months and 1.8 preventable events per 100 resident-months on the control units. The rate ratio estimated through Poisson regression models was 1.07 (95% CI = 0.82–1.40) for all more-serious adverse drug events and 1.15 (95% CI = 0.82–1.61) for preventable more-serious events.

Within the intervention units, there were 288 less-severe adverse drug events. Of these events, 73 (25%) were

Table 2. Frequency of Types of Adverse Drug Events (ADEs)

	Intervention Units		Control Units	
	Total (n = 411)	Preventable (n = 152)	Total (n = 340)	Preventable (n = 126)
ADE	n (%)			
Hemorrhagic	102 (24.8)	22 (14.5)	85 (25.0)	20 (15.9)
Neuropsychiatric*	87 (21.2)	42 (27.6)	71 (20.9)	28 (22.2)
Gastrointestinal	70 (17.0)	17 (11.2)	49 (14.4)	18 (14.3)
Metabolic or endocrine	43 (10.5)	24 (15.8)	32 (9.4)	13 (10.3)
Renal or electrolytic	31 (7.5)	15 (9.9)	47 (13.8)	29 (23.0)
Cardiovascular	20 (4.9)	13 (8.6)	15 (4.4)	8 (6.4)
Dermatological	9 (2.2)	0 (0)	14 (4.1)	1 (0.8)
Fall without injury	14 (3.4)	8 (5.3)	7 (2.1)	2 (1.6)
Extrapyramidal signs or symptoms	12 (2.9)	6 (4.0)	7 (2.1)	1 (0.8)
Syncope or dizziness	7 (1.7)	5 (3.3)	11 (3.2)	4 (3.2)
Infection	12 (2.9)	0 (0)	4 (1.2)	0 (0)
Hematological	4 (1.0)	1 (0.7)	0 (0)	0 (0)
Anticholinergic†	2 (0.5)	2 (1.3)	5 (1.5)	2 (1.6)
Respiratory	2 (0.5)	1 (0.7)	5 (1.5)	3 (2.4)
Anorexia	2 (0.5)	2 (1.3)	4 (1.2)	2 (1.6)
Functional decline‡	2 (0.5)	2 (1.3)	2 (0.6)	2 (1.6)
Fall with injury	2 (0.5)	2 (1.3)	1 (0.3)	1 (0.8)
Ataxia or difficulty with gait	2 (0.5)	2 (1.3)	0 (0)	0 (0)
Hepatic	1 (0.2)	0 (0)	0 (0)	0 (0)

Note: ADEs could manifest as more than one type.
* Neuropsychiatric events include oversedation, confusion, hallucinations, and delirium.
† Anticholinergic effects include dry mouth, dry eyes, urinary retention, and constipation.
‡ ADE manifested only as decline in activities of daily living without any other more-specific type of event. Other types of events may have been associated with functional decline.

Table 3. Frequency of Adverse Drug Events According to Drug Category

	Intervention Units		Control Units	
	Total (n = 411)	Preventable (n = 152)	Total (n = 340)	Preventable (n = 126)
Drug Category	n (%)			
Antiplatelet	66 (16.1)	11 (7.2)	58 (17.1)	11 (8.7)
Antipsychotic	52 (12.7)	25 (16.5)	40 (11.7)	13 (10.3)
Anticoagulant	42 (10.2)	17 (11.2)	39 (11.5)	10 (7.9)
Diuretic	33 (8.0)	18 (11.8)	36 (10.6)	23 (18.3)
Anti-infective	38 (9.3)	1 (0.7)	30 (8.8)	7 (5.6)
Cardiovascular	30 (7.3)	18 (11.8)	38 (11.2)	24 (19.1)
Hypoglycemic	36 (8.8)	19 (12.5)	17 (5.0)	6 (4.8)
Gastrointestinal	39 (9.5)	9 (5.9)	11 (3.2)	5 (4.0)
Antidepressant	25 (6.1)	14 (9.2)	25 (7.4)	9 (7.1)
Opioid	26 (6.3)	11 (7.2)	20 (5.9)	9 (7.1)
Sedative or hypnotic	17 (4.1)	10 (6.6)	23 (6.8)	12 (9.5)
Antiepileptic	17 (4.1)	7 (4.6)	14 (4.1)	9 (7.1)
Nutrient or supplement	9 (2.2)	4 (2.6)	15 (4.4)	8 (6.3)
Steroid	12 (2.9)	1 (0.7)	6 (1.8)	0 (0)
Anti-Alzheimer's	7 (1.7)	4 (2.6)	7 (2.1)	0 (0)
Thyroid	4 (1.0)	3 (2.0)	8 (2.3)	5 (4.0)
Digoxin	5 (1.2)	4 (2.6)	5 (1.5)	2 (1.6)
Anti-Parkinson's	6 (1.5)	4 (2.6)	3 (0.9)	1 (0.8)
Antihistamine	6 (1.5)	3 (2.0)	2 (0.6)	1 (0.8)
Muscle relaxant	5 (1.2)	2 (1.3)	3 (0.9)	2 (1.6)
Topical	3 (0.7)	2 (1.3)	1 (0.3)	0 (0)
Ophthalmic	1 (0.2)	0 (0)	2 (0.6)	0 (0)
Gout	0 (0)	0 (0)	3 (0.9)	2 (1.6)
Antineoplastic	1 (0.2)	0 (0)	1 (0.3)	0 (0)
Respiratory	1 (0.2)	0 (0)	1 (0.3)	1 (0.8)
Osteoporosis	0 (0)	0 (0)	1 (0.3)	0 (0)
Miscellaneous	2 (0.5)	0 (0)	4 (1.2)	3 (2.4)

Note: Drugs in more than one category were associated with some events. Frequencies in each column sum to greater than the total number of events.

deemed preventable. Within the control units, there were 243 less-severe adverse drug events. Of these events, 68 (28%) were characterized as preventable. There were 7.6 of these less-severe events per 100 resident-months and 1.9 preventable events per 100 resident-months on the intervention units. There were 7.5 of these less-severe adverse drug events per 100 resident-months and 2.1 preventable events per 100 resident-months on the control units. The rate ratio estimated through Poisson regression models was 1.06 (95% CI = 0.89–1.26) for all less-severe adverse drug events and 0.92 (95% CI = 0.66–1.28) for preventable less-severe events.

Results According to Adverse Drug Event Type and Drug Category

Table 2 lists the types of adverse drug events in order of overall frequency across the intervention and control units. Types of adverse drug events were generally similar in the intervention and control units. Neuropsychiatric events (e.g., oversedation, confusion, hallucinations, and delirium) constituted the most common type of preventable and the second most common type of nonpreventable events in the intervention and control units. Other frequently identified types of preventable adverse drug events were hemorrhagic (bleeding events), renal or electrolyte (e.g., azotemia, dehydration, hyperkalemia, hypokalemia, and renal failure), gastrointestinal (e.g., abdominal pain, diarrhea, constipation, and impaction), and metabolic or endocrine (e.g., hypoglycemic events, thyroid abnormalities).

Table 3 lists medication categories most frequently associated with adverse drug events in order of overall frequency across the intervention and control units. Antipsychotic agents constituted the most common medication category associated with preventable events in the intervention and control units. Other medication categories frequently associated with preventable adverse drug events were anticoagulants, diuretics, antiplatelet agents, cardiovascular drugs, hypoglycemic agents, and antidepressants. Atypical antipsychotic agents, warfarin, and loop diuretics were the specific drug types most commonly implicated in preventable adverse drug events across the intervention and control units.

Post Hoc Analysis

Overall, there were 152 preventable adverse drug events on the intervention units and 126 such events on the control units. Each of these events was subsequently re-evaluated to determine whether it might have been possible for any of the alerts included in the clinical decision support system to have led to the prevention of the adverse drug event. Of the 152 preventable events on the intervention units, 59 (38.8%) might have been prevented as a result of one or more of the alerts. Of the 126 preventable events identified on the control units, 56 (44.4%) might have been prevented as a result of one or more of the alerts.

In a post hoc analysis limited to events that might have been prevented as a result of one or more of the alerts, the rate was 1.55 preventable adverse drug events per 100 resident-months on the intervention units and 1.72 preventable events per 100 resident-months on the control units, for an adjusted rate ratio of 0.89 (95% CI = 0.61–1.28).

DISCUSSION

Information technology–based interventions, including computerized provider order entry with clinical decision support, have been widely promoted as the most promising approaches for improving medication safety across all clinical settings,[18] but much of the previously published research relating to this particular technology has focused on costs, organizational efficiency, appropriateness of alerts, adherence to guidelines, effect on time for the prescriber, satisfaction, usability, and usage.[19] No previously published study has assessed the effect of computerized provider order entry with clinical decision support on adverse drug events in the long-term care setting.

Previous studies examining the epidemiology of adverse drug events in the long-term care setting have indi-

cated that errors in prescribing and ordering are most commonly associated with adverse drug events[2,3] and that these types of errors may be amenable to computerized provider order entry with clinical decision support, but this study found no effect on the overall adverse drug event rate or the preventable adverse drug event rate.

There are a number of factors specifically related to the clinical decision support system evaluated in this study that probably diminished its effect on adverse drug event rates. The clinical decision support system directly addressed only a minority of the adverse drug events identified in the study. Furthermore, the system must be considered first generation, because it did not offer several important advantages recommended for optimal clinical decision support such as providing alternative orders within alerts that prescribers could directly accept.[20,21] Additionally, it has previously been reported that, on average, there were 2.5 alerts generated per resident-month, and more than half of the alerts displayed to providers were determined to be unnecessary.[10] This was primarily related to the inability of the system to assess the total 24-hour dose of a drug that was already in use and relate it to the recommended dose range and to recognize prior medication orders, leading to unnecessary warnings about drug interactions as well as recommendations for therapies (e.g., laxatives in the setting of opioid use) when they had already been ordered. High signal-to-noise ratios may produce alert fatigue and lead prescribers to click past alerts without considering or even reading them.[22] Finally, the alerts were addressed only to the prescriber and did not consider the efforts of the entire healthcare team, who are particularly important in monitoring the resident for beneficial and adverse effects of drug therapy. Despite these limitations, the study findings remain relevant, because the features of the clinical decision support system are comparable with or exceed those of most commercially available products that long-term care facilities might conceivably implement at the current time. Advanced clinical decision support systems have rarely been disseminated beyond the institutions (mainly hospitals) where they were created.

This study had a number of additional limitations. It focused solely on adverse drug events and did not assess the effect of the intervention on medication errors that did not lead to adverse drug events. There was also potential for contamination by cross-over between intervention and control units, because clinicians exchanged duties and covered for each on many occasions. To assess the possibility that this may have led to changes in prescribing and orders for corollary laboratory tests in the control units, the rate of responses to "unseen" alerts in the control units during the first versus the last quarter of the study year was assessed at one of the study sites.[10] The rate of response was lower in the last quarter, suggesting that prescribers did not adopt new habits due to seeing alerts while caring for residents on the intervention units. This is consistent with a previous study that found that physicians who had received alerts had no better knowledge of the issues highlighted in the alerts at the end of a 1-year period than they had at the beginning.[23]

Over the coming years, it is expected that computerized provider order entry with clinical decision support will play an important role in improving medication safety in the long-term care setting. In addition to improving the efficiencies of these systems with regard to reducing alert burden and offering alternative orders within the alerts, there is a need to increase their scope to address a broader range of drug safety issues. Efforts are also required to further integrate additional clinical and laboratory information into the system. This would include linking newly recognized and documented symptoms (e.g., daytime somnolence, bleeding, edema, cough, dizziness, loose stools) to the use of specific medications.

These findings should not dampen enthusiasm for developing and testing health information technology interventions that may enhance patient safety in the long-term care setting. Such systems are costly and complex to implement, and stakeholders, including payers, providers, facilities, and policy makers, require a clear understanding about their benefits to make decisions about the substantial investments that are required.[6] Formal, rigorous evaluations of these systems are absolutely essential so that they can be improved upon and promoted with confidence for widespread adoption.

ACKNOWLEDGMENTS

We thank Mary Ellen Stansky and Jackie Cernieux, MPH, for their assistance with technical aspects of this study and Bessie Petropoulos for assistance with manuscript preparation.

Conflict of Interest: Dr. Bates is a coinventor on Patent No. 6029138 held by Brigham and Women's Hospital on the use of decision support software for medical management, licensed to the Medicalis Corporation. He holds a minority equity position in the privately held company Medicalis, which develops Web-based decision support for radiology test ordering, and serves as a consultant to Medicalis. He is on the clinical advisory board for Zynx, Inc., which develops evidence-based algorithms, and IntelliDot, which makes barcoding applications for hospitals. He serves as a consultant to Healthgate, which makes tools that allow collaboration on development of decision support. He serves on the board of Care Management International, which is involved in chronic disease management. He is a consultant for Cardinal Health, which makes intravenous drug delivery systems. Supported by grants from the Agency for Healthcare Research and Quality (HS010481 and HS15430). Dr. Bell is the recipient of a Canadian Institutes of Health Research, Institute of Aging New Investigator Award.

Author Contributions: Dr. Gurwitz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis. Study concept and design: Gurwitz, Field, Rochon, Judge. Acquisition of data: Gurwitz, Rochon, Judge, Harrold, Bell, Lee, White. Analysis and interpretation of data: Gurwitz, Field, Reed. Drafting of the manuscript: Gurwitz. Critical revision of the manuscript for important intellectual content: Gurwitz, Field, Rochon, Judge, Harrold, Bell, Lee, White, LaPrino, Erramuspe-Mainard, DeFlorio, Gavendo, Baril, Reed, Bates. Statistical analysis: Field, Reed. Administrative, technical, or material support: LaPrino, Erramuspe-Mainard, DeFlorio, Gavendo, Baril. Study supervision: Gurwitz. Other (intervention implementation): Gurwitz, Field, Ro-

chon, Judge, Harrold, Bell, Lee, White, LaPrino, Erramuspe-Mainard, DeFlorio, Gavendo, Baril, Reed, Bates.

Sponsor's Role: The funding agencies did not contribute to the study design; data collection, analysis, or interpretation; or the decision to submit the manuscript for publication.

REFERENCES

1. National Nursing Home Survey (NNHS) [on-line]. Available at http://www.cdc.gov/nchs/nnhs.htm Accessed September 29, 2008.
2. Gurwitz JH, Field TS, Avorn J et al. Incidence and preventability of adverse drug events in nursing homes. Am J Med 2000;109:87–94.
3. Gurwitz JH, Field TS, Judge J et al. The incidence of adverse drug events in two large academic long-term care facilities. Am J Med 2005;118:351–358.
4. Rochon PA, Field TS, Bates DW et al. Computerized physician order entry with clinical decision support in the long-term care setting: Insights from the Baycrest Centre for Geriatric Care. J Am Geriatr Soc 2005;53:1780–1789.
5. Rochon PA, Field TS, Bates DW et al. Clinical application of a computerized system for physician order entry with clinical decision support to prevent adverse drug events in long-term care. Can Med Assoc J 2006;174:52–54.
6. Subramanian S, Hoover S, Gilman B et al. Computerized physician order entry with clinical decision support in long-term care facilities: Costs and benefits to stakeholders. J Am Geriatr Soc 2007;55:1451–1457.
7. Kuperman GJ, Gibson RF. Computer physician order entry: Benefits, costs, and issues. Ann Intern Med 2003;139:31–39.
8. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decisions support systems on medication safety. Arch Intern Med 2003;163:1409–1416.
9. Wolfstadt JI, Gurwitz JH, Field TS et al. The effect of computerized physician order entry with clinical decision support on the rates of adverse drug events: A systematic review. J Gen Intern Med 2008;23:451–458.
10. Judge J, Field TS, DeFlorio M et al. Prescribers' responses to alerts during medication ordering in the long term care setting. J Am Med Inform Assoc 2006;13:385–390.
11. Gurwitz JH, Field TS, Harrold LR et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003;289:1107–1116.
12. Bates DW, Cullen DJ, Laird et al. Incidence of adverse drug events and potential adverse drug events implications for prevention. ADE Prevention Study Group. JAMA 1995;274:29–34.
13. Leape LL, Bates DW, Cullen DJ et al. Systems analysis of adverse drug events. JAMA 1995;274:35–43.
14. Leape LL, Cullen DJ, Clapp MD et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA 1999;282:267–270.
15. Kaushal R, Bates DW, Landrigan C et al. Medication errors and adverse drug events in pediatric in-patients. JAMA 2001;285:2114–2120.
16. Bates DW, Leape LL, Cullen DJ et al. Effect of computerized physician order entry and a team intervention on prevention on serious medication errors. JAMA 1998;280:1311–1316.
17. Bates DW, Spell N, Cullen DJ et al. The costs of adverse drug events in hospitalized patients. JAMA 1997;277:307–311.
18. Bates DW, Gawande AA. Improving safety with information technology. N Engl J Med 2003;348:2526–2534.
19. Eslami S, Abu-Hanna A, deKeizer NF. Evaluation of outpatient computerized physician medication order entry systems: A systematic review. J Am Med Inform Assoc 2007;14:400–406.
20. Bates DW, Kuperman GJ, Wang S et al. Ten commandments for effective clinical decision support: Making the practice of evidence-based medicine a reality. J Am Med Inform Assoc 2003;10:523–530.
21. Kuperman GJ, Bobb A, Payne TH et al. Medication-related clinical decision support in computerized provider order entry systems: A review. J Am Med Inform Assoc 2007;14:29–40.
22. van der Sijs H, Aarts J, Vulto A et al. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006;13:138–147.
23. Glassman PA, Belperio P, Simon B et al. Exposure to automated drug alerts over time: Effects on clinicians' knowledge and perceptions. Med Care 2006;44:250–256.

Table A1. List of Warning Messages Targeting Prescribing Decisions Associated with the Development of Adverse Drug Events in Long-Term Care

Scenario Description	Warning/Message
Warfarin order in setting of most recent INR of >3 triggers warning message	***WARNING—BLEEDING RISK***
	INR is _____. Current INR is high. Reduce WARFARIN dose and/or monitor closely.
Warfarin interaction with (1) trimethoprim with sulfamethoxazole or (2) amoxicillin with clavulanate	***WARNING—BLEEDING RISK***
	This drug can interact profoundly with WARFARIN. Consider an alternative antibiotic or monitor very closely. Repeat the INR in 3 days and consider reducing warfarin dose.
Warfarin–antibiotic interaction (e.g., amoxicillin)	***WARNING—BLEEDING RISK***
	This drug interacts with WARFARIN. Repeat the INR in 3 days. Consider reducing warfarin dose.
Warfarin–non-antibiotic interaction (e.g., amiodarone)	***WARNING—BLEEDING RISK***
	This drug interacts with WARFARIN. Monitor very closely. Repeat the INR in 3 days.
Risk of bleeding due to overlapping with warfarin (e.g., acetylsalicylic acid)	***WARNING—BLEEDING RISK***
	The use of WARFARIN with NSAIDs and/or ANTIPLATELET AGENTS increases bleeding risk. Re-evaluate need for concomitant therapy.
Risk of bleeding due to overlapping with antiplatelet drugs (e.g., acetylsalicylic acid+naproxen)	***WARNING—BLEEDING RISK***
	ANTIPLATELET AGENTS with NSAIDs increase bleeding risk. Evaluate need for concomitant therapy.
Risk of *worsening* renal insufficiency—any use of NSAIDs, ACE inhibitors, diuretics in resident with BUN or creatinine above certain threshold concentration—laboratory results are the most recent values	***WARNING—RENAL INSUFFICIENCY RISK***
	Current BUN = _____, Creatinine = _____. Worsening renal insufficiency can result from ACE inhibitors, angiotensin receptor blockers (e.g., losartan), diuretics, and NSAIDs. Evaluate medication regimen and monitor BUN and CREATININE closely.
Any drug therapy that can increase potassium concentration (ACE inhibitors, potassium sparing diuretics, potassium supplements, NSAIDs) in setting of most recent potassium concentration of >4.4 triggers warning message	***WARNING—HYPERKALEMIA RISK***

(*Continued*)

Table A1. (Contd.)

Scenario Description	Warning/Message
	Most recent POTASSIUM is ____. HYPERKALEMIA can result from therapy with any of the following: ACE inhibitors, angiotensin receptor blockers (e.g., losartan), potassium sparing diuretics, NSAIDs, and mineralocorticoids. Re-evaluate medication regimen and monitor POTASSIUM concentration closely.
Risk of hypokalemia—any new prescription for thiazide or loop diuretic therapy	***WARNING—HYPOKALEMIA RISK***
	Hypokalemia can result from use of thiazide and loop diuretics. Check POTASSIUM concentration in 7–10 days and continue monitoring.
Multiple psychoactive medications—any three of the following: antidepressant, antipsychotic, sedative, hypnotic, antiseizure medication	***WARNING—OVERSEDATION RISK***
	Use of multiple psychoactive medications increases the risk of oversedation, confusion, delirium, falls, and injury. Evaluate the need for each psychoactive medication. Use the lowest feasible dose.
Antipsychotic drug initiation (also include metoclopramide)	***WARNING—RISK OF PARKINSONIAN SYMPTOMS***
	This drug poses a risk of tremor, rigidity, masked facies, gait problems, and involuntary movements. Use the lowest possible dose and reassess for such effects over the next 2–4 weeks.
Anticholinergic medications—especially high risk for amitriptyline, doxepin, and imipramine	***WARNING—HIGH RISK OF ANTICHOLINERGIC EFFECTS***
	This drug poses a very high risk of dry mouth, constipation, urinary retention, and delirium. Consider alternatives such as desipramine or SSRIs. If absolutely necessary, use the lowest feasible dose and monitor.
Anticholinergic medications (e.g., nortriptyline)	***WARNING—RISK OF ANTICHOLINERGIC EFFECTS***
	This drug poses a high risk of dry mouth, constipation, urinary retention, and delirium. Use the lowest feasible dose. Monitor closely for these effects.
Oxybutynin and tolterodine—urinary retention	***WARNING—RISK OF URINARY RETENTION***
	Order a bladder scan 7 days after initiation of therapy or any change in dose and monitor.
Opioid-induced constipation	***WARNING—CONSTIPATION RISK***
	Opiates can cause constipation. Monitor closely and prevent constipation. Choose a laxative other than docusate sodium. Order a scheduled dose.
Risk of hyperglycemia—concomitant use of prednisone or thiazide diuretic and hypoglycemic agent	***WARNING—RISK OF HYPERGLYCEMIA***
	Oral steroids and hydrochlorothiazide can worsen glucose control. Monitor finger sticks carefully.
Digoxin—any order and any order in excess of 0.125 mg per day	***WARNING—RISK OF DRUG TOXICITY***
	DIGOXIN doses should rarely exceed 0.125 mg per day because of reduced renal clearance in elderly. Recheck digoxin concentration with any change in dose.
Dose suggestions for benzodiazepines, NSAIDs, and antipsychotics	***WARNING—DOSE RECOMMENDATION***
	The recommended initial dose of this drug is __ mg. High doses increase risk of side effects.
Selected Beers criteria drugs (e.g., diazepam, chlordiazepoxide)	***WARNING—RISK OF CNS SIDE EFFECTS***
	Diazepam, clonazepam, chlordiazepoxide, nitrazepam, and bromazepam have a very long half-life increasing risk for CNS side effects. Consider substituting a short-acting benzodiazepine such as oxazepam if appropriate.
Muscle relaxants and antispasmodic drugs: carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, dicyclomine, hyoscyamine, propantheline, belladona alkaloids, clidinium	***WARNING—RISK OF SEDATING EFFECTS***
	Most MUSCLE RELAXANTS AND ANTISPASMODICS are poorly tolerated leading to anticholinergic effects and sedation. Try to avoid their use.
Low TSH in setting of thyroid replacement therapy	***WARNING—OVERTREATMENT***
	Current TSH = _____. A low TSH level in the setting of thyroid replacement therapy may reflect toxicity (even when other thyroid function tests are normal). Reduce dose of thyroid replacement therapy. Recheck TSH in 6 weeks.
Phenytoin initiation	***WARNING—MONITOR DRUG CONCENTRATION***
	Most recent phenytoin concentration: _____. Order phenytoin concentration 5–7 days after initiation of therapy or any change in dose.
Serious drug–drug interaction with amiodarone (e.g., quinidine)	***SERIOUS DRUG–DRUG INTERACTION***

(*Continued*)

Table A1. (Contd.)

(*Continued*)

Table A1. (Contd.)

Scenario Description	Warning/Message
	Amiodarone can increase the concentrations of many drugs. Check for interactions. Monitor closely.
Serious drug–drug interaction with phenytoin (e.g., trimethoprim/sulfamethoxazole)	***SERIOUS DRUG–DRUG INTERACTION***
	This combination can affect phenytoin concentrations. Monitor closely.
Serious drug–drug interaction with lithium (e.g., hydrochlorothiazide)	***SERIOUS DRUG–DRUG INTERACTION***
	In general, the concomitant use of NSAIDs, diuretics or ACE inhibitors with LITHIUM should be avoided due to toxicity risk.
Serious drug–drug interaction with selegiline (e.g., venlafaxine)	***SERIOUS DRUG–DRUG INTERACTION***
	This combination can lead to a serotonin-like syndrome—a potentially life-threatening event.
Serious drug–drug interaction with digoxin (e.g., verapamil)	***SERIOUS DRUG–DRUG INTERACTION***
	This combination can lead to digoxin toxicity. Monitor digoxin concentration closely.
Serious drug–drug interaction with monoamine oxidase inhibitors (e.g., sertraline)	***SERIOUS DRUG–DRUG INTERACTION***
	This combination can lead to serotonin syndrome—a potentially life-threatening event.
Serious drug–drug interaction with theophylline (e.g., ciprofloxacin)	***SERIOUS DRUG–DRUG INTERACTION***
	This combination can lead to theophylline toxicity. Monitor theophylline concentration closely.
Serious drug interaction between phenobarbital and warfarin	***SERIOUS DRUG–DRUG INTERACTION***
	Phenobarbital can reduce the effect of warfarin. Monitor the INR closely.
Serious drug–drug interaction with bromocriptine (e.g., pseudoephedrine)	***SERIOUS DRUG–DRUG INTERACTION***
	This combination can lead to severe hypertension and seizures.
Serious drug interaction between allopurinol and thiazide diuretics (e.g., hydrochlorothiazide)	***SERIOUS DRUG–DRUG INTERACTION***
	This combination can lead to an increased risk of hypersensitivity reactions to allopurinol.
Serious drug interaction between clozapine and risperidone	***SERIOUS DRUG–DRUG INTERACTION***
	This combination may increase the risk of toxicity from risperidone. Monitor closely.
Serious drug–drug interaction with clozapine (e.g., citalopram)	***SERIOUS DRUG–DRUG INTERACTION***
	This combination may increase the risk of toxicity from clozapine. Monitor closely.
Serious drug–drug interaction with tramadol (e.g., paroxetine)	***SERIOUS DRUG–DRUG INTERACTION***
	Avoid this combination—may increase the risk of seizures.
Serious drug interaction between SSRIs and tricyclic antidepressants (e.g., sertraline+nortriptyline)	***SERIOUS DRUG–DRUG INTERACTION***
	Use this combination with extreme caution—this may cause toxic tricyclic concentrations
Serious drug–drug interaction with methotrexate (e.g., phenytoin)	***SERIOUS DRUG–DRUG INTERACTION***
	This combination can increase the risk of methotrexate toxicity.
Serious drug interaction between quinidine and itraconazole	***SERIOUS DRUG–DRUG INTERACTION***
	This combination can increase the risk of quinidine toxicity and should be avoided.
Serious drug–drug interaction which increases ECG QT interval prolongation risk (e.g., haloperidol+erythromycin)	***SERIOUS DRUG–DRUG INTERACTION: ECG QT prolongation risk***
	These agents may produce QT interval prolongation and should not be used together.

INR = international normalized ratio; NSAIDs = nonsteroidal anti-inflammatory drugs; ACE = angiotensin-converting enzyme; BUN = blood urea nitrogen; SSRIs = selective serotonin reuptake inhibitors; CNS = central nervous system; TSH = thyroid-stimulating hormone; ECG = electrocardiogram.

(*Continued*)