

Can an Algorithm for Appropriate Prescribing Predict Adverse Drug Events?

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Objective: To evaluate whether a medication-appropriateness algorithm applied to pharmacy claims data can identify ambulatory patients at risk for experiencing adverse drug events (ADEs) from those medications.

Study Design: Cohort study.

Methods: We surveyed a random sample of 211 community-dwelling Medicare managed care enrollees over age 65 years who were identified by pharmacy claims as taking a potentially contraindicated medication (exposed enrollees) and a random sample of 195 enrollees who were identified as not taking such a medication (unexposed enrollees). The primary outcome of interest was the prevalence of self-reported events in previous 6 months.

Results: Ninety-nine (24.4% of total sample) respondents reported a total of 134 ADEs during the previous 6 months. Exposed enrollees had a significantly higher number of chronic conditions and were taking more prescription and nonprescription medications. However, the higher rate of self-reported ADEs among exposed enrollees was not statistically significant from that of unexposed enrollees (prevalence odds ratio = 1.42; 95% confidence interval [CI] = 0.90, 2.25). Only 1.5% (2/134) of the self-reported ADEs were attributed to a medication from the potentially contraindicated list. Instead, most ADEs were attributed to medications that are commonly used in older patients, including cardiovascular agents (21.6%), anti-inflammatory agents (12.2%), and cholesterol-lowering agents (7.9%).

Conclusions: A medication-appropriateness algorithm using pharmacy claims data was not able to identify a subgroup of enrollees at higher risk of experiencing an ADE from those medications. The vast majority of ADEs were attributable to commonly prescribed medications.

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Adverse drug events (ADEs) are an important cause of morbidity and hospitalizations among the elderly.^{1,2} Among the 1.6 million US residents of nursing homes, drug-related injuries are estimated to occur at a rate of 350 000 events per year, and more than half may be preventable.³ Using a multimodal assessment of medical records, the prevalence of ADEs in community-dwelling elderly persons was recently estimated to be 50.1 per 1000 person-years, with 27.6% of events considered to be preventable.⁴ A survey of adult primary care patients found a much higher self-reported ADE rate of 27 per 100 patients.⁵ The elderly are considered to be at higher risk for ADEs due to prevalent chronic health conditions, age-related physiologic changes, social isolation, and polypharmacy.⁶⁻⁸

Although not all ADEs are the result of medication error, inappropriate prescribing is a preventable cause of ADEs. In 1991, Beers et al published explicit criteria for inappropriate medication use in institutionalized elderly patients, and the criteria were expanded in 1997.⁹ These and several other criteria have been used extensively in drug utilization review as well as population-based studies to measure the prevalence of inappropriate prescribing.¹⁰⁻¹³ A population survey of older Americans found that 28.7% of those prescribed any medication received at least 1 potentially inappropriate drug.¹¹ When dose and length of therapy were considered, the incidence of inappropriate prescribing rose to 40%.

The objective of the current study is to evaluate whether a medication algorithm based upon inappropriate-prescribing criteria can be used along with managed care pharmacy claims to identify a subset of patients at high risk of suffering an ADE. Administrative-claim algorithms have the potential to be an inexpensive method of identifying patients at risk for ADEs. The study hypothesis is that patients identified as taking a potentially inappropriate medication have a higher likelihood of subsequently suffering a self-reported ADE related to those medications.

METHODS

Algorithms

Historically, Aetna has provided performance reports to physicians that assess pharmaceutical use consistent with nationally accepted guidelines of care. These performance reports were published annually and support-

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ed by administrative-data algorithms. The medications selected for inclusion in the algorithm were taken from medications included in 1 of 2 published consensus recommendations and deemed to be either ineffective or more toxic than equally effective alternatives (see **Appendix**).^{9,12}

Because the algorithm had been adapted from 2 published sets of criteria, secondary analyses using those 2 sets of criteria in their original forms also were performed.^{9,12} The McLeod list was developed by using a modified Delphi approach to arrive at consensus recommendations by an expert panel of clinical pharmacologists, geriatricians, family practitioners, and pharmacists.¹² The McLeod criteria include a broad range of barbiturates and nonsteroidal anti-inflammatory agents. The Beers list was created by a second group of nationally recognized experts in geriatric care and pharmacology who also used a modified Delphi approach to update consensus recommendations.⁹ The Beers criteria include a broad range of potentially inappropriate medications, including muscle relaxants and antispasmodic agents and, in addition, take into account the prescribed strength. For example, selected benzodiazepines are considered appropriate for the elderly population when prescribed at a lower daily dose and inappropriate at a higher daily dose.

Participants

Study participants were managed care Medicare plan members continuously enrolled between July 1, 1999, and June 30, 2000. All participants lived in southeastern Pennsylvania and were aged 65 years or older at the time of enrollment. Pharmacy claims data were used to identify a subgroup of enrollees over age 65 who had a prescription filled for at least 1 of the potentially contraindicated medications during the previous 6 months (exposed enrollees). We identified a second subgroup who according to pharmacy claims were not taking any of those medications (unexposed enrollees). These 2 subgroups were randomly sampled to assemble the study subjects. A power analysis indicated that a sample size of 184 exposed and 184 unexposed enrollees would allow the detection of a difference of 0.15 with a 1-tailed α of .025 and β of .10.¹⁴

Potential participants received an introduction letter via the mail, and a telephone contact was attempted within 2 weeks of the mailing. A single interviewer who was blinded to participants' study group assignment attempted contact both on weekdays and weekends. Contact was attempted a minimum of 6 times before an enrollee was designated as "unable to contact." When contact was established with the potential participants, the interviewer explained the purpose of the study and

obtained oral consent to participate. Enrollees were eligible to participate in the interview if they spoke English or had a translator. Enrollees were excluded from participation if they had a diagnosis of cancer, were hearing impaired, or had an inaccurate telephone number. Both the Emory University Human Investigations Committee and the USQA Center for Health Care Research institutional review board approved the study design.

Data Collection and Analysis

The structured interview consisted of 42 questions regarding general health status; prescription drug use; adherence to medical regimen; source of medication information; ADEs; number of healthcare providers; vitamin, mineral, and herbal supplement use; other over-the-counter medication use; and demographic characteristics. The survey was pilot-tested with 29 participants and subsequently revised. The revised survey had a mean administration time of 16 minutes (range: 4-44 minutes). The interviewer recorded answers on a response sheet and later entered them into an SPSS database.¹⁵ A second member of the research team verified the data entry for accuracy.

The outcome examined for the purpose of this study was prevalence of self-reported ADEs. The interviewer initially asked participants to name all of the prescription medications that they currently were taking. Subsequently, ADEs were measured using an adapted version of a previously published survey.^{16,17} Five questions were asked: (1) whether the participant had experienced an ADE within the last 6 months, (2) which drugs were involved in the ADE, (3) whether a doctor had been notified about the ADE, (4) what changes were made to the treatment regimen because of the ADE, and (5) whether hospitalization was required because of the ADE. All ADEs reported by the study participants were included. A second member of the research team, who was blinded to study group assignment, evaluated all medications reported by the respondents to determine whether the medications were contraindicated according to the algorithm used to identify the cases.

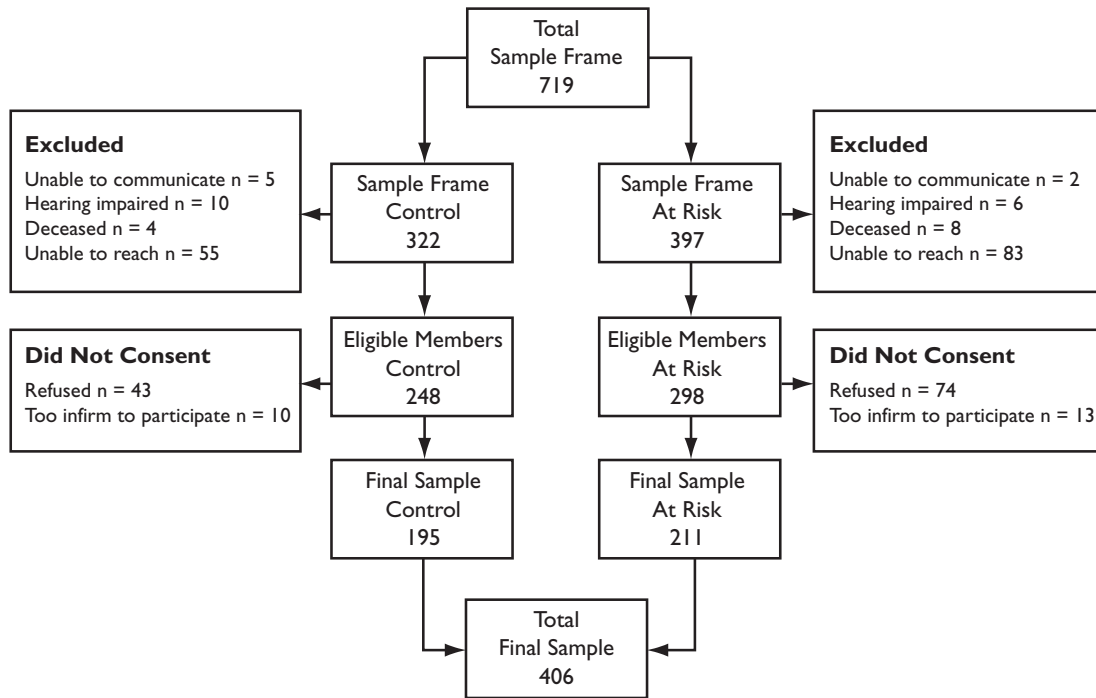
The tested study hypothesis was that the proportion of exposed enrollees reporting an ADE would be higher than the proportion of unexposed enrollees reporting an ADE. This hypothesis was tested by using chi-square tests of categorical data. The prevalence odds ratio of an ADE among exposed enrollees also was calculated. All analyses were conducted using SPSS.¹⁵

RESULTS

Subject Recruitment

Letters were sent to a total of 719 enrollees (**Figure**).

Figure. Subject Recruitment



The telephone interviewer was unable to reach 138 (19.2%) of the participants, 12 (1.7%) participants were deceased, 23 (3.2%) were too infirm to participate, 23 (3.2%) were unable to communicate by telephone, and 117 (16.3%) refused to participate. Thus, the final sample for this study consisted of 406 out of 719 participants (56.5%), 211 exposed and 195 unexposed. Exposed enrollees were less likely to participate in the survey, 211/397 (53.1%) versus 195/322 (60.6%). The characteristics of participants and nonparticipants are shown in

Table 1. Baseline Characteristics of Participants Compared With Nonparticipants

Characteristic	Participants (n = 406)	Nonparticipants (n = 313)	P
Female	266 (65.5%)	182 (58.1%)	.043
Mean age at study entry, y	73.8	75.6	<.001
Mean number of annual inpatient visits	0.3	0.2	.943
Mean number of annual inpatient days	2.3	2.2	.334
Mean number of annual emergency room visits	0.1	0.2	.386
Mean number of annual specialist visits	5.5	5.3	.609
Mean number of annual primary care visits	5.4	5.2	.232

Table 1. Nonparticipants were older and more likely to be male. Physician and hospital utilization rates, however, were similar for participants and nonparticipants.

Demographic Characteristics

Demographic characteristics of the study subjects are shown in Table 2. The mean age, race, marital status, educational attainment, and home ownership were similar in both groups. Women were more likely to be taking a potentially contraindicated medication. The vast majority of respondents (93.6%) were taking at least

1 prescription medication. However, the mean number of prescription medications taken was significantly higher for exposed enrollees (4.7 vs 3.3, P <.001). The prevalence of over-the-counter medication use also was high in both groups, with exposed enrollees taking significantly more over-the-counter medications. The distribution of chronic medical conditions also was significantly different between the 2 groups. Exposed enrollees were significantly more likely to report having hypertension, seasonal allergies, back pain, depression, anxiety, insomnia, or gastrointestinal symptoms.

Active use of potentially contraindicated medications is shown in **Table 3**. Thirty-three percent (70/211) of exposed enrollees and 1.0% (2/195) of unexposed enrollees were taking a potentially contraindicated medication at the time of the telephone interview.

Prevalence of Adverse Drug Events

Overall, 99 respondents reported having experienced at least 1 ADE in the previous 6 months. Exposed enrollees reported more ADEs, but the difference was not statistically significant (27.5% vs 21.0%, $P = .13$). The prevalence odds ratio of reporting an ADE was 1.42 (95% confidence interval [CI] = 0.90, 2.25). Enrollees who were still taking a potentially contraindicated medication at the time of the telephone interview were more likely to report having had an ADE, but this difference also did not reach statistical significance (31.9% vs 22.8%, $P = .10$).

Irrespective of study group assignment, enrollees reporting an ADE were taking an average of 1 more prescription medication (4.7 vs 3.8, $P = .05$) than

enrollees not reporting an ADE. Sixty-two of 201 (30.8%) enrollees taking 4 or more medications reported an ADE, compared with only 36 of 205 (17.6%) enrollees taking 3 or fewer medications. The algorithm did identify a group of enrollees taking more medications and with more chronic conditions; however, this group still did not have a statistically higher rate of ADEs.

Published Prescribing Criteria and Adverse Drug Events

To evaluate the potential effectiveness of the published appropriate-prescribing criteria, active prescription medications were compared with the Beers list⁹ and the McLeod list.¹² Unlike the case for the managed care algorithm, enrollees currently taking a medication on the Beers list were significantly more likely to report an ADE (35.0% vs 20.9%, $P = .004$). Enrollees taking a medication on the McLeod list also were significantly more likely to report an ADE than those not taking a medication on the list (35.1% vs 22.6%, $P = .042$).

Table 2. Demographic Characteristics of Study Group

Characteristic	No. (%)			P
	Exposed (n = 211)	Unexposed (n = 195)	Total (n = 406)	
Mean age, y (range 66-91 y)	74.53	74.45	74.49	.88
Female	155 (73.5)	111 (56.9)	266 (65.5)	<.001
White race (n = 402)	199 (95.2)	178 (92.2)	377 (93.8)	.215
Currently married (n = 401)	132 (63.5)	130 (67.4)	262 (65.3)	.413
Education (n = 399)				
≤ Eighth grade	25 (12.1)	13 (6.7)	38 (9.5)	.066
Ninth grade through high school	109 (52.9)	103 (53.4)	212 (53.1)	.927
> High school	72 (35.0)	77 (39.9)	149 (37.3)	.308
Lives in own home (n = 400)	181 (94.3)	194 (93.3)	375 (93.8)	.679
Taking prescription medication (yes)	207 (98.1)	173 (88.7)	380 (93.6)	<.001
Mean number of prescription medications	4.67	3.30	4.01	<.001
Taking over-the-counter drugs (yes)	203 (96.2)	185 (94.9)	388 (95.6)	.51
Mean number of over-the-counter drugs	3.04	2.43	2.74	<.001
Self-reported medical conditions				
Arthritis	144 (68.2)	111 (56.9)	255 (62.8)	.018
Hypertension	127 (60.2)	97 (49.7)	224 (55.2)	.034
Ulcers/indigestion	76 (36.0)	46 (23.6)	122 (30.0)	.006
Back pain	62 (29.4)	40 (20.5)	102 (25.1)	.039
Anxiety	60 (28.4)	28 (14.4)	88 (21.7)	.001
Seasonal allergies	58 (27.5)	31 (15.9)	89 (21.9)	.005
Depression	54 (25.6)	26 (13.3)	80 (19.7)	.002
Insomnia	53 (25.1)	31 (15.9)	84 (20.7)	.022
Diabetes	37 (17.5)	32 (16.4)	69 (17.0)	.763

Medications Linked to Adverse Drug Events

The medications most commonly reported by enrollees to have resulted in an ADE are shown in **Table 4**. The most common category was cardiovascular agents, followed by anti-inflammatory agents. Anxiolytics and antidepressants, medications commonly cited in published inappropriate-prescribing lists, were infrequently reported by patients as having caused an ADE. Only 2 of the medications associated with a self-reported ADE were on the health plan's list of potentially contraindicated medications. Both were benzodiazepines, and they accounted for a total of 4 reported events. A total of 99 enrollees were taking a benzodiazepine. Forty (40%) were taking it on an as-needed basis and 59 (60%) were taking it at least daily. Only 6 medications from the Beers list of contraindicated medications were reported to have caused an ADE, accounting for only 6.0% (8/134) of the

reported ADEs. Three medications from the McLeod list were reported to have caused an ADE, accounting for only 3.0% (4/134) of the reported ADEs.

Severity of Adverse Drug Events

The most common enrollee-reported symptoms are listed in **Table 5**. A total of 171 symptoms were reported from the 134 ADEs. Gastrointestinal symptoms, fatigue, and dizziness were most common. As a gauge of symptom severity, most episodes (78.9%) were reported to the enrollee's physician, and the physician made a change in prescription medications for the majority (65.7%) of events. Four ADEs (3.0%) resulted in a hospitalization. The 4 patients who reported requiring hospitalization attributed their reaction to 1 of the following medications: verapamil, citalopram, diazepam, or metoprolol. One of the medications, diazepam, is a contraindicated medication according to all 3 lists. The other 3 medications are not on any of the criteria lists.

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DISCUSSION

Adverse drug events are common, with one fourth of the study population reporting an ADE in the previous 6 months. An algorithm using managed care pharmacy claims data to identify potentially inappropriate prescribing practices was not able to identify a subgroup with a higher prevalence of self-reported ADEs from those medications. In fact, the vast majority of ADEs were attributed to commonly prescribed medications. Patients taking a medication from the Beers⁹ or McLeod¹² lists, which include a broader range of medications, were significantly more likely to report having suffered an ADE. However, there was still very little overlap between the medications reported by enrollees to have caused an ADE and the medications listed as potentially inappropriate according to any of the published lists.

Although the appropriate-prescribing algorithm did not identify a significantly higher number of ADEs, the algorithm did identify a subset of patients who were taking significantly more medications, both prescription and nonprescription. This subgroup also had a higher prevalence of chronic

medical conditions, including anxiety and depression. Given the substantial number of enrollees taking benzodiazepines, it is surprising that so few ADEs were

Table 3. Number of Participants Who Reported Taking a Medication on the Health Plan Contraindicated List

Medication on Health Plan Contraindicated List	No. of Cases	No. of Controls
Diazepam	29	0
Clorazepate (dipotassium)	20	0
Chlordiazepoxide	16	0
Flurazepam (hydrochloride)	2	1
Methyldopa + hydrochlorothiazide	2	0
Desmopressin acetate	1	0
Methylothiazide	0	1

Table 4. Medications Reported to Have Caused an Adverse Drug Event

Medication	No. of ADEs (n = 134)
Cardiovascular agents	38 (28.4%)
Calcium channel blockers	12
Beta-blockers	7
Angiotensin-converting enzyme inhibitors	6
Other	13
Anti-inflammatory agents	18 (13.4%)
cyclooxygenase-2 inhibitors	9
nonsteroidal anti-inflammatory drugs	4
Aspirin	2
Steroid preparations	3
Cholesterol-lowering agents	11 (8.2 %)
3-hydroxy-3-methylglutaryl coenzyme A inhibitors	9
Other	2
Antidepressants	8 (6.0%)
Selective serotonin reuptake inhibitors	5
Tricyclics	2
Other	1
Anticoagulants and antiplatelet agents	7 (5.2%)
Anxiolytics	7 (5.2%)
Benzodiazepines	5
Other	2
Antibiotics	7 (5.2%)
Quinolones	4
Other	3
Diuretics	6 (4.4%)
Narcotic pain relievers	5 (3.7%)
Gastrointestinal agents	4 (3.0%)
Unknown	9 (6.7%)
Other	14 (10.4%)

ADE indicates adverse drug event.

Table 5. Commonly Reported Drug Reactions

Drug Reaction(s)	No. (%) (n = 171)
Gastrointestinal symptoms	44 (25.7)
Heartburn/indigestion	18 (10.5)
Constipation/diarrhea	13 (7.6)
Nausea	13 (7.6)
Fatigue/dizziness	31 (18.1)
Limb pain or weakness	19 (11.1)
Medication not effective	14 (8.2)
Mouth/throat symptoms	10 (5.8)
Hemorrhagic	10 (5.8)
Frequent urination/renal	10 (5.8)
Peripheral edema	6 (3.5)
Mood alteration	4 (2.3)
Angina	4 (2.3)
Eye symptoms	3 (1.8)
Hot flashes	3 (1.8)
Other*	13 (7.6)

*Includes breast swelling (2), cold (1), hair loss (2), coughing (2), shortness of breath (2), itching (2), and abnormal laboratory studies (2).

attributed to that class of medication. Polypharmacy is a risk factor for poor adherence as well as medication interactions.¹⁸ The higher rate of ADEs among the exposed enrollees, although not statistically significant, may have been due to polypharmacy rather than the specific use of contraindicated medications. Interventions to reduce polypharmacy, however, have had variable long-term success.¹⁹⁻²¹

Our findings suggest that there are limitations to the use of inappropriate-prescribing algorithms to reduce the prevalence of ADEs. First, many of the medications on the Beers and McLeod lists are no longer widely used.^{10,13} Second, medications that are frequently implicated in preventable events (eg, warfarin) are not on these “bad drug” lists.³ Few medications are absolutely contraindicated in older patients, making these lists extremely narrow. Algorithms have content validity and can identify questionable prescribing, but their predictive validity remains uncertain.²² The Beers criteria have recently been updated to include medications that should generally be avoided in persons aged 65 years or older and medications that should not be used in older persons known to have specific medical conditions.²³ Further research is needed to test this revised tool in older ambulatory populations.

Medications commonly and appropriately prescribed in the ambulatory setting were blamed for the vast

majority of ADEs. This confirms other recent findings.^{4,5,24} Cardiovascular agents are commonly linked to ADEs, in this study representing almost one third of the events. Renal or electrolyte drug events were less frequent than previously reported, probably because our study relied on patient self-report while the previous study used laboratory and medical record review.⁴ A study of recently hospitalized patients reported that antibiotics were the most common drug type linked to an ADE.²⁴ In our community-dwelling elderly, antibiotics were linked to only 5% of ADEs. The overall rate of ADEs identified in this study was very similar to the rate found in an adult ambulatory population that also included self-reported data⁵ and much higher than the rate found in a study that reviewed medical records but gathered no information directly from patients.⁴

These results are subject to several limitations. First, the validity and reproducibility of patient self-report of ADEs have been poorly studied. Drugs can lead to asymptomatic laboratory abnormalities, for example, that a patient may never be aware of. At the same time, attributing symptoms to specific drugs is problematic. Nonspecific symptoms are common among outpatients and may not be related to the specific drug identified by the patient. Another difficulty is distinguishing the expected effects of a drug from an adverse event. To the extent that patients overidentify drug-related symptoms and expected drug events, this study overestimates the ADE rate. Patients and the interviewer were blinded as to study group assignment, so there should not have been a differential effect. Both provider report and medical chart review have been shown to substantially underestimate adverse event rates, and the limitations of implicit chart reviews have been well described.²⁵⁻²⁸ Most episodes were considered serious enough by the patient to be reported to a physician, and in two thirds of cases, the event led to a change in treatment. The study population was Medicare managed care enrollees who were disproportionately well educated and Caucasian and may not be typical of older Americans. As noted above, though, the rate of ADEs was very similar to that found in another study of adult primary care patients.⁵

The initial prescribing event used to identify enrollees in this study was ascertained from pharmacy claims submitted to the health plan for reimbursement. Only one third of the enrollees identified as taking a potentially contraindicated medication by pharmacy claims were still taking that medication at the time of the telephone

survey. The time delay between initial prescription and data evaluation limits the use of claims data as an adverse event–screening tool. More focused algorithms of appropriate prescribing for patients with selected chronic conditions could address some of these limitations. Claims-based algorithms can identify optimal prescribing standards for patients with specific chronic conditions (eg, use of steroid inhalers in asthma patients). Pharmacy claims also can be used to screen for polypharmacy or to identify potentially harmful drug–drug interactions.²⁰ Algorithms also can be used in real time to alert pharmacists to potential drug–drug interactions for new prescriptions. These tools have the potential to fundamentally change the prescribing process for both inpatient and ambulatory medical care, but careful evaluation is needed to ensure that these interventions do in fact improve health outcomes.

CONCLUSION

In this study, an appropriate-prescribing algorithm applied to pharmacy claims data was not helpful for identifying a high-risk group of elderly patients. Nearly one fourth of study participants reported an ADE in the previous 6 months, and the vast majority of reported events were adverse reactions to commonly used medications. More work is needed to develop clinically useful algorithms that can be applied to older ambulatory populations.

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Appendix. Prescription Medications Included in Algorithm as Potentially Contraindicated in Older Patients

Sedatives Propofol	Benzodiazepines Chlordiazepoxide Clorazepate Diazepam Flurazepam Halazepam Prazepam Quazepam	Antihypertensive agents Methyldopa and chlorothiazide Methyldopa and hydrochlorothiazide
Monoamine oxidase inhibitors Isocarboxazid Pargyline Phenelzine Tranlylcypromine		Antispasmodics Dicyclomine/phenobarbital
		Other agents Desmopressin acetate 2-Deoxy-D-glucose Naratriptan