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Brief Report

Potentially Inappropriate Medication Use in Older Adults With Mild Cognitive Impairment

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Background. Patients with mild cognitive impairment (MCI) may be especially vulnerable to the side effects of potentially inappropriate medications (PIMs), especially those that impair cognition.

Methods. We conducted a cross-sectional study to determine the prevalence of PIM use among 689 patients with MCI. We used the 2003 Beers Criteria for cognitive impairment to identify PIMs. We then determined if certain patients were more likely to use PIMs.

Results. There were 143 (20.8%) patients with MCI taking a PIM: 108 (15.7%) patients were taking one PIM and 35 (5.1%) patients were taking two or more PIMs. The most common PIMs were anticholinergics (35.7%) and benzodiazepines (31.5%). Patients were more likely to be taking PIMs if they were women and were taking a greater number of medications and less likely if they had a history of myocardial infarction.

Conclusions. Patients with MCI are frequently taking PIMs that may negatively affect cognition. Future research is needed to assess whether cognitive impairment symptoms are improved if PIM use is reduced.

Key Words: Mild cognitive impairment—Potentially inappropriate medication—Epidemiology.

CRITERIA for potentially inappropriate medications (PIMs) among the elderly adults have been introduced in order to reduce their use and the associated adverse health consequences (1). Despite recommendations to avoid these medications, PIMs are still prescribed to about a quarter of older adults (1).

Several studies have investigated PIM use among patients with dementia, including Alzheimer's disease (AD), and have reported a high prevalence of PIM use (2,3). Little is known, however, about PIM use among patients with mild cognitive impairment (MCI). This is important because patients with MCI may be receiving PIMs that adversely affect cognition, and it is possible that some cognitive deficits may be a result of PIM use and not a result of neurodegenerative processes (4–7). For example, some PIMs may decrease cholinergic function and lead to attention, memory, and intellectual problems (4,5,7). This in turn may lead to inaccurate assessment of MCI symptoms or inaccurate diagnoses.

The objective of this study was to assess the prevalence of PIMs that impair cognition among patients with MCI. In addition, we determined if certain patients were especially likely to take PIMs.

Methods

Setting

We studied 689 patients from the Alzheimer's Disease Research Centers of California (ARCCs) diagnosed with cognitive impairment but not meeting criteria for dementia between July 2008 and January 2009. The ARCCs consist of 10 clinics located at university medical centers throughout California (8). The Minimum Uniform Data Set (MUDS), a standardized research protocol, is used to collect patient demographic, medical history, and medication data from patients and caregiver informants (9). All sites obtained site-specific Institutional Review Board approval and received informed consent from each patient.

Clinically adjudicated cognitive diagnoses were made at each site during multidisciplinary conferences consisting of neurologists, neuropsychologists, nurses, and psychiatrists. Multisite interrater reliability was measured to ensure uniformity of diagnoses across sites. We classified MCI as a diagnosis of any of the following MUDS cognitive impairment and not dementia diagnosis subtypes: amnestic disorder (10), single mild nonmemory cognitive impairment (10), mild neurocognitive disorder (10), MCI based on

Petersen criteria (11), and MCI based on the Alzheimer's Disease Cooperative Study criteria (12).

Medications

Patient medication data, collected via the MUDS, are recorded in the ARCC database using Multum drug codes and lexicon (13). All patients and caregivers were interviewed at each visit and asked to list all medications currently being taken, including over the counter and prescription. This included drugs that were being taken at the time of the interview on a regular or on an "as-needed" or on a "prn" basis. Duration and frequency of medication use were not collected, and for the purposes of analyses, all medications were considered, including those taken regularly or on a prn basis. Whenever possible, patients and caregivers were encouraged to bring medication containers to the ARCC for documentation.

We defined PIMs as those medications from the 2003 update of the Beers Criteria that are specifically recommended to be avoided in patients with cognitive impairment. This list included barbiturates (i.e., butalbital, phenobarbital); anticholinergics (i.e., oxybutynin, dicyclomine); antispasmodics (i.e., trospium); muscle relaxants (i.e., cyclobenzaprine, baclofen); and the central nervous system (CNS) stimulants dextroamphetamine, methylphenidate, methamphetamine, and pemolin (1). To this list, we added benzodiazepines (i.e., lorazepam, clonazepam) and sedative–hypnotics (i.e., eszopiclone, zolpidem) as they have previously been shown to contribute to cognitive impairment symptoms and adverse drug events in those with cognitive impairment (14,15). These drug categories were not mutually exclusive because some drugs may fall into more than one category. However, each drug only counted once toward total number of PIMs. Information on PIM duration or frequency was not collected.

We also determined current anti-AD medication use and the total number of current medications. We defined total number of medications as all medications currently being taken, including appropriate medications and PIMs, over the counter and prescription; the list for each patient was based on the medications listed by the patient and/or caregiver and confirmed with medication containers whenever possible.

Patient Characteristics

All ARCC patients received a battery of neuropsychological assessments and neurological examinations. Cognitive function was reported with the Mini-Mental State Examination (MMSE; scores range from 0 to 30 with lower scores indicating greater cognitive impairment) (16). The Blessed–Roth Dementia Rating Scale (BRDRS) was used to report functional status (scores range from 0 to 17 with higher scores indicating more functional impairment) (17).

Many patient characteristics were examined as potential predictors of PIM use, including age (continuous), sex, education (≤12 vs >12 years), race (white vs non-white), living situation (living with others vs alone), insurance type (no insurance vs insurance), total number of current medications, current anti-AD medication use, bladder and bowel incontinence (as assessed by the Blessed–Roth; complete control vs incontinence), MMSE score (per *SD* of 3.0 points), and BRDRS score (per *SD* of 2.0 points). Patients and caregivers were interviewed about the patients' history of depression, hypertension, myocardial infarction (MI), stroke or transient ischemic attack (TIA), and diabetes. When possible, diagnoses were verified with patient medical charts.

Statistical Analysis

The total number and type of PIMs taken were determined. To test for bivariate associations between patient characteristics and PIM use, Pearson χ^2, Wilcoxon rank-sum tests, and analyses of variance were conducted for categorical and continuous variables as appropriate. A multivariate logistic regression model was generated to assess the odds of receiving a PIM among patients with MCI and was adjusted for all covariates with $p < .20$ at the bivariate level (sex; education; living situation; number of medications; and a history of stroke, MI, and depression). Statistical analyses were performed using Stata Version 10.0 (StataCorp LP, College Station, TX).

Results

There were 689 patients with MCI. The mean age of the patients was 75.3 ± 9.8 years; 77.4% of patients were white, and 49.5% were women. Mean education was 14.6 ± 4.0 years, with 66.8% of patients reporting more than 12 years of education; the mean MMSE score was 26.5 ± 3.0 points, and the mean BRDRS score was 1.6 ± 2.0 points. Forty-two percent of patients had a history of depression, 63.1% had a history of hypertension, 7.3% had a history of MI, 19.3% had a history of diabetes, and 13.2% had a history of stroke and/or TIA.

One hundred forty-three (20.8%) patients were taking PIMs at the time of the study: 108 (15.7%) were taking one PIM and 35 (5.1%) were taking two or more (Table 1). The most common PIMs were anticholinergics (35.7%), benzodiazepines (31.5%), sedative–hypnotics (22.4%), barbiturates (16.8%), and muscle relaxants (10.5%; Table 1). Thirty-seven patients (25.9%) who were taking a PIM were also taking anti-AD medications. Among patients who were taking a cholinesterase inhibitor, 15 (8.6%) were also taking an anticholinergic medication.

In bivariate analyses, compared with patients not taking PIMs, those taking PIMs had an overall greater number of medications (9.7 ± 3.8 vs 6.8 ± 3.8, $p < .01$), were more likely to be women (64.3% vs 45.6%, $p < .01$), and were more likely to have a history of depression (51.0% vs 37.5%, $p < .01$; Table 2). There was a trend for those patients taking PIMs to be less likely to live alone (68.5% vs 76.0%, $p = .06$; Table 2). In multivariate analyses, women were twice

Table 1. Frequency and Types of Potentially Inappropriate Medication (PIM) Use Among the 689 Patients Diagnosed With Mild Cognitive Impairment*

Number of PIMs	*N* (%)
0	546 (79.2)
1	108 (15.7)
≥2	35 (5.1)
PIM class	*n* (%)†
Anticholinergic	51 (35.7)
Benzodiazepines	45 (31.5)
Sedative–hypnotics	32 (22.4)
Barbiturates	24 (16.8)
Muscle relaxants	15 (10.5)
Central nervous system stimulants	4 (2.8)
Antispasmodics	2 (1.4)

**Notes*: This list was adapted from table 2 of the 2003 update of the Beers Criteria (1) that listed medications contraindicated in patients with cognitive impairment.

†These drug categories were not mutually exclusive as some drugs may fall into more than one category; percentages were calculated out of the 143 total people who were on a PIM, so the percentages sum to greater than 100%.

as likely as men to be taking a PIM (odds ratio [OR]: 2.15; 95% confidence interval [CI]: 1.39–3.32), and each additional medication increased the odds of taking a PIM by 21.0% (OR: 1.21; 95% CI: 1.15–1.28). Patients with a history of MI had a lower prevalence of PIM use (OR: 0.35; 95% CI: 0.13–0.91).

Discussion

In this study, patients with MCI were taking medications with the potential to impair cognition. Women and patients taking a larger number of medications had a higher prevalence of PIM use, and anticholinergics and benzodiazepines were the most commonly prescribed PIMs. Similar to previous findings, patients with MCI were frequently taking anti-AD medications (18), and many of those were also taking a PIM.

Consistent with other studies, our results suggest that taking a large number of medications increases the likelihood of PIM use in older adults and that women have a greater prevalence of PIM use than men (3). The higher prevalence among women could be partially due to a higher frequency of physician visits and medication use than among men (19). Another explanation could be differences in comorbidities that put women at an increased risk for receiving PIMs. Those with MI also had reduced odds of receiving a PIM, but it is unclear why this association exists, and it is possible that it is spurious.

Anticholinergics, the most commonly prescribed PIM class in our cohort, are concerning for several reasons. First, anticholinergics have been shown to be associated with poorer cognitive performance and increased nondegenerative cognitive impairment (4,20). Anticholinergics are also concerning because of the possible concurrent use of cholinesterase inhibitors that are often prescribed to help cognitive impairment (21). It has been shown that dual use of these two drug types may contribute to functional and cognitive decline (21,22). In addition to anticholinergics, it has been demonstrated that barbiturates, benzodiazepines, and other psychoactive drugs may all interfere with cognition (7). Muscle relaxants, benzodiazepines, and barbiturates have also been shown to cause negative cognitive effects and dementia-like symptoms (7,23).

These results should be considered when diagnosing and treating elderly patients with MCI as they are a particularly vulnerable group at an increased risk for continuing cognitive decline and progression to dementia (11,24). In a population of elderly adults where the prevalence of MCI is expected to increase, this is of public health concern because it could mean that MCI diagnosis and symptom assessment are inaccurate. As long as these patients are receiving PIMs that interfere with cognition, the possibility exists that MCI symptoms are in fact not a result of neurodegenerative processes but a result of PIMs (4,5,7).

There were several strengths to this study, including the clinical adjudication of MCI diagnosis. The medication data are also a strength because they were gathered from patients and caregivers and confirmed with medication containers when possible. There were also limitations to the current study, including the heterogeneous MCI definition, but our limited sample size restricted us from performing analyses on each subtype separately. Some of the medications on the Beers Criteria are controversial, for example, CNS stimulants may actually improve cognitive function (25). However, very few participants were taking CNS stimulants, and we doubt our results would have changed appreciably if we removed the controversial medications from our list of

Table 2. Characteristics of the 689 Patients Diagnosed With Mild Cognitive Impairment by Potentially Inappropriate Medication (PIM) Use Group

Characteristic	Taking PIMs (*N* = 143)	Not Taking PIMs (*N* = 546)	*p* Value*
	n (%) or *M* (*SD*)		
Age	74.8 (11.1)	75.4 (9.5)	.98
Women	92 (64.3%)	249 (45.6%)	<.01
Race, white	111 (77.6%)	422 (77.3%)	.89
Education, ≤high school	48 (33.6%)	149 (27.3%)	.15
Living alone	98 (68.5%)	415 (76.0%)	.06
Number of medications	9.7 (3.8)	6.8 (3.8)	<.01
BRDRS (per *SD*)	1.8 (2.3)	1.5 (1.9)	.78
MMSE (per *SD*)	26.5 (2.7)	26.5 (3.0)	.88
No insurance	4 (2.8%)	9 (1.6%)	.49
Hypertension history	92 (64.3%)	343 (62.8%)	.74
Diabetes history	31 (21.7%)	102 (18.7%)	.42
Stroke/TIA history	24 (16.8%)	67 (12.3%)	.16
Myocardial infarction history	6 (4.2%)	44 (8.1%)	.11
Depression history	73 (51.0%)	205 (37.5%)	<.01
Urinary incontinence	6 (4.2%)	15 (2.7%)	.30
Anti-AD drug use	37 (25.9%)	138 (25.3%)	.88

Notes: AD = Alzheimer's disease; BRDRS = Blessed–Roth Dementia Rating Scale; MMSE = Mini-Mental State Examination; TIA = transient ischemic attack.

**p* Values based on Pearson χ^2 or Wilcoxon rank-sum tests for categorical variables and analyses of variance for continuous variables.

PIMs. Finally, the ARCCs are primarily university-affiliated hospitals where patients are seen by specialists, which may limit the generalizability of these results to community clinics with only primary care physicians.

The results of this study indicate that patients with MCI are receiving PIMs that may interfere with cognition. Although we acknowledge that older patients often have numerous comorbidities and medication needs, this highlights the need for close drug monitoring in patients with MCI. If a medication is deemed necessary, the side effects should be closely monitored to assess the development or worsening of any cognitive symptoms. Finally, our results suggest the need for patient and caregiver education to increase awareness of the potential risks and side effects of these medications. Future research should assess if cognitive impairment symptoms are reduced or eliminated in patients with MCI with decreased PIM use.

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Conflict of Interest

The authors have no conflicts of interest and no disclosures.

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