Clinical and Economic Outcomes Associated With Potentially Inappropriate Prescribing in the Elderly

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Objective: To evaluate the risk of adverse events (AEs) and the healthcare costs for elderly patients receiving specific potentially inappropriate medications (PIMs).

Study Design: Retrospective cohort study.

Methods: Patients 65 years and older who started 1 of 23 PIMs were matched with control subjects who were not receiving PIMs. The following 4 AEs and PIMs were evaluated: delirium or hallucinations with Beers high-severity (BHS) anticholinergics, delirium or hallucinations with BHS narcotics (meperidine hydrochloride or pentazocine lactate or pentazocine hydrochloride), extrapyramidal effects with trimethobenzamide hydrochloride, and falls or fractures with BHS sedative hypnotics. The risk of having the AE of interest within 360 days and the annual healthcare costs were examined.

Results: Patients receiving BHS sedative hypnotics were significantly more likely to have a fall or fracture than controls (hazard ratio, 1.22; 95% confidence interval [CI], 1.10-1.35). Patients receiving BHS anticholinergics did not have higher risk of delirium or hallucinations than controls (hazard ratio, 1.03; 95% CI, 0.91-1.16). Delirium or hallucinations occurred at a higher rate among patients receiving BHS narcotics, and extrapyramidal effects occurred at a higher rate among patients receiving trimethobenzamide; however, too few events occurred to assess statistical significance. For all PIMs evaluated, annual adjusted medical and total healthcare costs were significantly higher for patients exposed to PIMs than for controls.

Conclusion: The use of certain BHS PIMs in the elderly may increase AEs or healthcare costs.

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Developed in 1997 to improve the quality of pharmaceutical care, criteria by Beers[1] have been widely used to identify potentially inappropriate medication (PIM) use in the elderly. In 2002, the Beers criteria were updated to incorporate new information from scientific literature.[2] Severity ratings (high vs low) were assigned to each of the medications. Because some medications listed in the Beers criteria may be justified for certain patients, Zhan et al[3] convened an expert panel to classify the Beers criteria into the following 3 categories: (1) drugs that should always be avoided by the elderly, (2) drugs that are rarely appropriate for the elderly, and (3) drugs that have some indications but are often misused.

Clinicians and managed care organizations (MCOs) have adopted the Beers criteria to help identify and target elderly members who may be at risk of adverse events (AEs) due to their use of PIMs. Starting in 2006, the National Committee for Quality Assurance[4,5] has included a Healthcare Effectiveness Data and Information Set (HEDIS) performance measure for MCOs to evaluate the percentage of elderly members who received PIMs. The specifications for this HEDIS measure are based on the Beers criteria.

Despite the wide adoption of the Beers criteria within managed care, outcomes data associated with using these PIMs in the elderly are limited. While MCOs are tasked with developing clinical programs to decrease the use of PIMs in the elderly, it is unknown which specific PIMs are most beneficial to target to improve clinical outcomes and reduce healthcare costs. Because the Beers criteria were developed solely based on an expert consensus panel and have not been studied in controlled clinical trials, it has not been proven that reducing PIM use in the elderly prevents adverse clinical outcomes. Although retrospective claims analyses have examined healthcare expenditures or AEs among elderly patients receiving PIMs in the community setting,[6-9] these studies grouped together patients with different types of PIMs and did not thoroughly examine outcomes associated with specific PIMs. Because outcomes may vary for different PIMs, studies evaluating specific PIMs are necessary to build stronger evidence that the use of PIMs leads to adverse outcomes in the elderly.

We tested the hypothesis that the use of specific Beers high-severity (BHS) medications designated as "always avoid" or "rarely appropriate" in the elderly would

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Take-Away Points

Despite widespread adoption of the Beers list of potentially inappropriate medications (PIMs) in the elderly, outcomes data are limited. Clinical and economic outcomes associated with the use of specific PIMs in the elderly were evaluated.

- Patients using Beers high-severity sedative hypnotics had increased risk of falls or fractures.
- Increased risk of delirium or hallucinations was not observed for patients using high-severity anticholinergics.
- Beers high-severity narcotics and trimethobenzamide hydrochloride may increase the rate of adverse events.
- For all PIMs evaluated, medical costs were significantly higher for patients exposed to PIMs than for control subjects.

result in increased AEs and healthcare costs. Using retrospective claims data, we evaluated the risk of selected AEs and healthcare costs for elderly patients receiving specific BHS PIMs versus comparable elderly patients not receiving PIMs.

METHODS

This was a retrospective cohort study using electronic pharmacy and medical claims from an MCO based in the western United States. To focus the analysis on a limited number of medications that would have a higher likelihood of causing AEs, medications were evaluated if they had a severity rating of "high" using the Beers criteria[2] and were classified as "always avoid" or "rarely appropriate" by Zhan et al.[3] Based on potential adverse outcomes that could occur in the elderly as reported in the Beers criteria[2] or other literature sources,[10,11] these medications fell within the following 5 AE categories: delirium or hallucinations related to BHS anticholinergic use, delirium or hallucinations related to BHS narcotic use, extrapyramidal AEs related to trimethobenzamide hydrochloride use, falls or fractures related to BHS sedative hypnotic use, and hypoglycemia related to chlorpropamide use. Because only 40 patients receiving chlorpropamide were identified, the last category was not included in the evaluation. A total of 23 medications and 4 AE categories were evaluated (Table 1).

Patient Identification and Matching

Patients 65 years and older were identified if they started 1 of 23 PIMs listed in Table 1 (with no prior use during the 180-day preperiod) during the identification period from January 2003 through June 2005. The date of the first prescription of the PIM during the identification period was defined as the index date. Patients 65 years and older who were not receiving the PIM or another PIM within the same AE category were selected as potential control subjects. For controls, an index date was randomly selected within the identification period. Table 2 gives additional inclusion and exclusion criteria that were applied for the different cohorts.

The final cohorts were obtained by matching controls with patients exposed to a PIM on a 1:1 basis using the propensity score method.[12] Independent variables used to calculate the propensity score for matching are given in Table 2. Matching was performed in a stepwise fashion; pairs were matched using the lowest window (propensity score, 0.0000001), and then the window was gradually extended by a factor of 10 until reaching 0.1.

Outcomes Variables

The primary outcome was the risk of having the AE of interest during a postperiod of up to 360 days for exposed patients versus controls. The AEs of interest were delirium or hallucinations for the BHS anticholinergics, delirium or hallucinations for the BHS narcotics, extrapyramidal effects for trimethobenzamide, and falls or fractures for the BHS sedative hypnotics. Patients were designated as having the AE of interest if they had an inpatient hospitalization, an emergency department visit, or 2 medical claims with a primary diagnosis code representing the AE (Table 1).

Patients were followed up from the index date until the first date when one of the following conditions occurred: (1) the patient discontinued the index medication (defined as a gap of ≥30 days past the end of supply date for the last prescription for the index medication and the end of the postperiod), (2) the patient in the anticholinergic or narcotic medication evaluation filled a BHS anticholinergic or narcotic other than the index medication, (3) the patient in the control group for trimethobenzamide filled trimethobenzamide, (4) the patient in the sedative hypnotic evaluation filled a BHS sedative hypnotic other than the index medication, (5) the patient reached the end of the 360-day postperiod, or (6) the patient had an AE of interest.

Pharmacy ingredient costs, medical charges, and total healthcare costs (pharmacy plus medical) were measured for exposed patients versus controls over the 360-day postperiod. Adjusted costs were estimated for the cohorts after controlling for potential confounding factors.

Statistical Analysis

Propensity scores were estimated using logistic regression analysis. Proportional hazards regression was used to analyze the relative risk of having the target AE for exposed patients versus controls. Patients who did not have the target AE were censored at their end of follow-up.

Costs were evaluated using *t* tests for means, Wilcoxon rank sum tests for medians, and generalized linear models (GLMs) with a log link and gamma distribution for adjusted

Table 1. "High-Severity, Always Avoid" or "High-Severity, Rarely Appropriate" Medications Stratified by Adverse Event Category

Adverse Event Category	BHS Medications	Adverse Event *ICD-9-CM* Diagnosis Codes
Delirium or hallucinations related to BHS anticholinergic use	Dicyclomine hydrochloride Hyoscyamine hydrobromide or hyoscyamine sulfate Propantheline bromide Belladonna alkaloids Atropine sulfate Scopolamine hydrobromide Methocarbamol Carisoprodol Chlorzoxazone Metaxalone Cyclobenzaprine hydrochloride Orphenadrine citrate or orphenadrine hydrochloride	Delirium or hallucinations 290.xx 292.xx 293.xx 294.xx 295.xx 296.xx 297.xx 298.xx 331.0x 331.1x 331.2x 331.82 780.1 300.29
Delirium or hallucinations related to BHS narcotic use	Pentazocine lactate or pentazocine hydrochloride Meperidine hydrochloride	Delirium or hallucinations 290.xx 292.xx 293.xx 294.xx 295.xx 296.xx 297.xx 298.xx 331.0x 331.1x 331.2x 331.82 780.1 300.29
Extrapyramidal adverse events	Trimethobenzamide hydrochloride	Extrapyramidal effects 332.1 333.72 333.85 333.90 333.99 781.0x
Falls or fractures related to BHS sedative hypnotic use	Flurazepam hydrochloride Meprobamate Barbiturates (excluding phenobarbital sodium) Clonidine hydrochloride Diazepam Quazepam Halazepam Clorazepate dipotassium	Falls or fractures 780.2 E880.x to E888.x 800.xx to 829.xx

BHS indicates Beers high-severity; *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.*

costs. Adjustment variables included in the GLMs were age, sex, health plan type, geographic state, Charlson Comorbidity Index[13] (calculated during the preperiod using a method adapted for electronic claims databases[14]), and preperiod costs. Statistical analysis was performed using SAS version 9.1 (SAS Institute, Inc, Cary, NC). All comparisons were 2-sided with a .05 level of significance.

RESULTS

BHS Anticholinergics

Among 37,358 pairs of patients exposed to BHS anticholinergics and controls, baseline characteristics were similar except that exposed patients filled more days supply for anticholinergics during the preperiod (Table 3). Ex-

Table 2. Inclusion, Exclusion, and Matching Criteria Applied for Each Cohort

Variable	BHS Anticholinergics		BHS Narcotics		Trimethobenzamide Hydrochloride		BHS Sedative Hypnotics	
	Exposed Patients	Controls	Exposed Patients	Controls	Exposed Patients	Controls	Exposed Patients	Controls
Inclusion Criteria								
Age ≥65 y	X	X	X	X	X	X	X	X
Prescription claim for the PIM of interest	X		X		X		X	
Claim for any medication on index date or during preperiod (180 days before index date)	X	X	X	X	X	X	X	X
Continuous enrollment for preperiod and 360 days after index date	X	X	X	X	X	X	X	X
Exclusion Criteria								
Preperiod claim for the PIM of interest or another PIM within the same adverse event category	X	X	X	X	X	X	X	X
Preperiod claim for a medication to treat psychosis or dementia	X	X	X	X				
Preperiod claim for a BHS potentially inappropriate narcotic or anticholinergic medication	X	X	X	X				
Preperiod medical claim for mental or central nervous system disorder	X	X	X	X				
Preperiod medical claim for delirium or hallucinations	X	X	X	X				
Preperiod claim for an antiparkinson agent					X	X		
Preperiod medical claim for a movement disorder					X	X		
Preperiod medical claim for a fall or fracture							X	X
Matching Criteria (Propensity Scoring Variables)								
Demographics	X	X	X	X	X	X	X	X
Health plan type (Medicare vs commercial)	X	X	X	X	X	X	X	X
Charlson Comorbidity Index	X	X	X	X	X	X	X	X
No. of distinct BHS medications other than index medication during preperiod	X	X	X	X	X	X	X	X
Sum of days supply for other anticholinergics (anticholinergics not designated as high-severity potentially inappropriate) during preperiod	X	X	X	X				
Preperiod claim for specific medications with potential to cause cognitive impairment[a]	X	X	X	X				
Days supply for opioid agonists or partial agonists other than index medication during preperiod		X	X	X				
Preperiod claim for specific medications with potential to cause extrapyramidal effects[b]					X	X		
Preperiod claim for specific medications with potential to cause sedation[c]							X	X
Preperiod claim for specific hypotensive medications with potential to increase risk of fall or fracture[d]							X	X
Preperiod medical claim for specific conditions that may increase the risk of fall or fracture[e]							X	X

BHS indicates Beers high-severity; PIM, potentially inappropriate medication.
[a]Specific medications with potential to cause cognitive impairment included antiepileptic agents, antiparkinson agents, barbiturates, benzodiazepines, cimetidine, propranolol hydrochloride, indomethacin, opioid agonists or partial agonists, tricyclic antidepressants, and clonidine hydrochloride.
[b]Butyrophenones, benzisoxazoles, clozapine, olanzapine, quetiapine fumarate, molindone hydrochloride, phenothiazines, prochlorperazine edisylate or prochlorperazine maleate, aripiprazole, thioxanthenes, ziprasidone hydrochloride or ziprasidone mesylate, loxapine hydrochloride or loxapine succinate, metoclopramide hydrochloride, methyldopa, and reserpine.
[c]Muscle relaxants, tricyclic antidepressants, urinary antispasmodics, antiparkinson anticholinergics, other anticholinergics, antiepileptic agents, sedating antihistamines, phenobarbital, benzodiazepines, nonbenzodiazepine γ-aminobutyric acid receptor modulators or melatonin receptor agonists, opioid agonists and partial agonists, central adrenolytics, and other sedative hypnotic agents.
[d]Diuretics, short-acting nifedipine, reserpine, alpha-1 antagonists, and other peripheral adrenolytics.
[e]Epilepsy, osteoporosis or osteomalacia, hypotension, overactive bladder or incontinence, Parkinson's disease, and stroke.

posed patients also had higher preperiod medical costs than controls.

Patients exposed to BHS anticholinergics experienced 15.60 cases of delirium or hallucinations per 1000 person-years compared with 15.18 cases per 1000 person-years for controls (Table 4). The risk of delirium or hallucinations was not significantly different between patients exposed to BHS anticholinergics compared with controls (hazard ratio, 1.03; 95% confidence interval [CI], 0.91-1.16).

Compared with controls, exposed patients had lower adjusted pharmacy costs ($773 vs $796) but higher adjusted medical costs ($17,154 vs $15,214) and higher adjusted total healthcare costs ($18,398 vs $16,482) during the postperiod (P <.001 for all). These results are given in Table 5.

BHS Narcotics

The 395 patients who met the identification criteria for exposure to BHS narcotics were matched with controls having similar characteristics (Table 3). Exposed patients had higher preperiod medical costs than controls.

Delirium or hallucinations occurred at a rate of 16.07 cases per 1000 person-years among exposed patients and 10.75 cases per 1000 person-years among controls (Table 4). However, the number of events (5 for exposed patients and 4 for controls) was too few to assess whether there were statistical differences between cohorts.

While adjusted postperiod pharmacy costs were similar between cohorts, adjusted postperiod medical costs and adjusted postperiod total healthcare costs were significantly higher for exposed patients than for controls ($26,370 vs $20,952 for medical costs and $27,447 vs $22,471 for total healthcare costs; P = .03 for both). These results are given in Table 5.

Trimethobenzamide Hydrochloride

There were 1085 patients exposed to trimethobenzamide and 1085 controls. Clinical characteristics were well matched between the 2 cohorts (Table 3). Patients exposed to trimethobenzamide had higher preperiod medical costs than controls.

Four patients exposed to trimethobenzamide and 1 control experienced extrapyramidal effects (4.09 vs 0.93 cases per 1000 person-years) (Table 4). Statistical testing and regression analysis were not performed because the number of events was too few to make meaningful comparisons.

Compared with controls, exposed patients had similar adjusted pharmacy costs ($907 vs $916; P = .86) and significantly higher adjusted medical costs ($27,722 vs $16,647; P <.001) and adjusted total healthcare costs ($29,144 vs $18,034; P <.001) during the postperiod (Table 5).

BHS Sedative Hypnotics

For 13,542 pairs of patients receiving BHS sedative hypnotics and controls, most of the clinical variables were similar; however, the exposed cohort had a higher percentage of patients with a medical condition that may increase the risk of falls or fractures than controls (17.3% vs 16.0%) (Table 3). Exposed patients also had higher preperiod medical costs than controls. Exposed patients had more cases of fall or fracture per 1000 person-years (69.10 vs 56.36) and were significantly more likely to have a fall or fracture than controls (hazard ratio, 1.22; 95% CI, 1.10-1.35; P <.001). These results are given in Table 4.

Adjusted pharmacy costs were similar for patients exposed to BHS sedative hypnotics compared with controls (Table 5). However, exposed patients had significantly higher adjusted medical and total healthcare costs than controls ($20,537 vs $15,835 for adjusted medical costs and $21,807 vs $17,154 for adjusted total healthcare costs; P <.001 for both).

DISCUSSION

In this evaluation of BHS PIMs categorized as "always avoid" or "rarely appropriate" for the elderly, the risk of developing an AE was different depending on the category of PIM. Patients receiving BHS sedative hypnotics were 22% more likely to have a fall or fracture than controls. In contrast, patients receiving BHS anticholinergics were not found to have a higher risk of delirium or hallucinations than controls. While delirium or hallucinations occurred at a higher rate among patients receiving BHS narcotics compared with controls and extrapyramidal effects occurred at a higher rate among patients receiving trimethobenzamide compared with controls, too few events occurred to assess statistical significance. For all 4 types of BHS PIMs, annual adjusted medical and total healthcare costs were significantly higher for exposed patients than for controls.

While these results are consistent with other retrospective claims analyses that have shown an association between PIM use in the elderly and increased adverse clinical outcomes[6-8] or increased healthcare costs,[8,9] this study adds to the current literature because it examines patients receiving specific PIMs instead of a heterogeneous mix of patients receiving different types of PIMs. In an era of limited healthcare resources, these results may help MCOs prioritize which specific medications and patients to target for interventions designed to reduce the use of PIMs in the elderly.

The fact that elderly patients receiving BHS sedative hypnotics had an increased risk of falls or fractures is not surprising because the use of sedative hypnotics has long been implicated as contributing to falls and fractures among the el-

Table 3. Baseline Demographics, Clinical Characteristics, and Costs

Variable	BHS Anticholinergics		BHS Narcotics	
	Exposed Patients (n = 37,358)	Controls (n = 37,358)	Exposed Patients (n = 395)	Controls (n = 395)
Age, mean (SD), y	75.0 (6.3)	75.0 (6.3)	74.3 (5.9)	74.2 (5.8)
Female sex, No. (%)	24,910 (66.7)	24,883 (66.6)	273 (69.1)	274 (69.4)
Health plan type, No. (%)				
Commercial	1390 (3.7)	1393 (3.7)	28 (7.1)	16 (4.1)
Medicare	35,968 (96.3)	35,965 (96.3)	367 (92.9)	379 (95.9)
Geographic state, No. (%)				
California	25,732 (68.9)	25,742 (68.9)	105 (26.6)	103 (26.1)
Texas	6782 (18.2)	6869 (18.4)	93 (23.5)	89 (22.5)
Oklahoma	1504 (4.0)	1497 (4.0)	103 (26.1)	107 (27.1)
Washington	2256 (6.0)	2184 (5.8)	68 (17.2)	68 (17.2)
Oregon	1084 (2.9)	1066 (2.9)	26 (6.6)	28 (7.1)
Charlson Comorbidity Index, mean (SD)	0.87 (1.45)	0.86 (1.44)	1.27 (1.99)	1.11 (1.62)
No. of distinct BHS medications, mean (SD)	0.04 (0.21)	0.04 (0.20)	0.06 (0.23)	0.06 (0.25)
Days supply for anticholinergic medications, mean (SD)	10.30 (37.65)	9.43 (36.81)	12.37 (39.50)	12.48 (38.39)
Days supply for opioid medications, mean (SD)	NE	NE	23.88 (45.35)	23.88 (51.76)
Prior use of a medication with potential to increase risk of, No. (%)				
Cognitive impairment	17,238 (46.1)	17,255 (46.2)	246 (62.3)	245 (62.0)
Extrapyramidal effects	NE	NE	NE	NE
Sedation	NE	NE	NE	NE
Hypotension	NE	NE	NE	NE
Medical condition likely to increase risk of fall or fracture, No. (%)	NE	NE	NE	NE
Preperiod costs, mean (SD), $				
Pharmacy costs	482 (614)	489 (645)	571 (602)	608 (669)
Medical costs	9393 (30,434)	8837 (33,987)	18,016 (37,829)	11,708 (29,741)
C statistic for the propensity scoring model	0.663		0.745	

BHS indicates Beers high-severity; NE, not evaluated for this study.

derly.[15-17] Additional analysis of 790 patients within this study who were exposed to a BHS sedative hypnotic and who had a fall or fracture found that the mean (SD) event-related medical costs per patient over the 3-month period was $10,339 ($22,406) (median, $1821). These findings lend support to the current Medicare Part D design in which certain sedative hypnotics (eg, benzodiazepines) are a benefit exclusion. For non–Part D plans, these results justify the need to conduct interventions to minimize the use of BHS sedative hypnotics among the elderly and help prevent high medical costs associated with falls or fractures.

With such a large sample size (37,358 pairs), it is surprising that patients receiving BHS anticholinergics did not have increased risk of developing delirium or hallucinations. While delirium or hallucinations would be expected with BHS anticholinergics in theory, perhaps the way that patients actually take these medications in the real-world setting minimizes the number of observed events. Patients may take these medications intermittently or at low doses and, as a result, may never experience such events. Another possible explanation is that delirium or hallucinations may be overlooked by patients or caregivers and may never be reported to the patient's physi-

Trimethobenzamide Hydrochloride		BHS Sedative Hypnotics	
Exposed Patients (n = 1085)	Controls (n = 1085)	Exposed Patients (n = 13,542)	Controls (n = 13,542)
76.3 (7.0)	76.1 (6.6)	75.2 (6.4)	75.2 (6.4)
803 (74.0)	800 (73.7)	9338 (69.0)	9458 (69.8)
47 (4.3)	42 (3.9)	490 (3.6)	426 (3.1)
1038 (95.7)	1043 (96.1)	13,052 (96.4)	13,116 (96.9)
966 (89.0)	968 (89.2)	9750 (72.0)	9786 (72.3)
47 (4.3)	47 (4.3)	1859 (13.7)	1845 (13.6)
33 (3.0)	33 (3.0)	480 (3.5)	471 (3.5)
28 (2.6)	27 (2.5)	945 (7.0)	938 (6.9)
11 (1.0)	10 (0.9)	508 (3.8)	502 (3.7)
1.15 (1.93)	1.15 (1.90)	0.97 (1.58)	0.94 (1.53)
0.17 (0.44)	0.17 (0.44)	0.12 (0.36)	0.11 (0.35)
NE	NE	NE	NE
NE	NE	NE	NE
NE	NE	NE	NE
94 (8.7)	95 (8.8)	NE	NE
NE	NE	7484 (55.3)	7456 (55.1)
NE	NE	5090 (37.6)	4991 (36.9)
NE	NE	2341 (17.3)	2164 (16.0)
553 (602)	515 (560)	532 (675)	540 (658)
14,470 (43,392)	11,104 (51,541)	12,122 (43,610)	8901 (30,410)
0.702		0.639	

cian. It is also possible that these events were reported but the provider did not code them in the encounter. Delirium and hallucinations may be underrecognized or undercoded in the claims database.

Although patients receiving BHS anticholinergics did not seem to have an increased risk of delirium or hallucinations, they had higher total postperiod healthcare costs. The disparity between AEs and healthcare costs for the BHS anticholinergics may be owing to these medications causing other AEs that were not evaluated in this analysis. While this study focused on evaluating the risk of delirium and hallucinations, which was the primary AE of concern as reported in the literature,[10] it is possible that BHS anticholinergics could increase the risk of other costly events (eg, falls and fractures) that were not studied within this analysis. Further evaluation of different AE outcomes among patients exposed and not exposed to BHS anticholinergics may help explain some of the factors contributing to increased healthcare costs.

Although the few patients identified as receiving BHS narcotics is reassuring from the health plan's perspective, the small sample size (395 pairs of exposed patients and controls) did not allow for an adequate evaluation of the risk of AEs with these medications. With trimethobenzamide, the number of patients identified was higher (1085 matched pairs), but the occurrence of extrapyramidal events was so infrequent that an adequate evaluation of the risk of extrapyramidal events could not be performed. While the rates of AEs for both of these analyses were higher among exposed patients than among controls, these results must be interpreted with caution because of the few AEs detected. Furthermore, because there were large differences in preperiod medical costs for exposed patients versus controls in the BHS narcotics and trimethobenzamide analyses, the cost results may not be reliable for these medication categories even though preperiod costs were controlled for in the analysis.

Because only BHS "always avoid" or "rarely appropriate" medications were evaluated, it is possible that other Beers PIMs for the elderly could have a greater or lesser effect on AEs and healthcare costs. It is unlikely that medications rated as "low severity" by the Beers panel of experts would have a greater effect than the BHS medications evaluated in the present study; however, there are additional BHS medications that were not studied because they were classified as having "some indications" by Zhan et al.[3] Further research is necessary to evaluate the additional medications that are contained within the Beers and HEDIS drug lists.

Despite matching on numerous clinical variables, exposed patients in all 4 PIM categories had higher baseline medical costs than controls. This suggests that patients who are prescribed PIMs tend to be higher utilizers of healthcare resources than patients not prescribed PIMs. The analysis of postperiod costs adjusted for baseline (preperiod) costs; however, it is

Table 4. Rate and Risk of Adverse Events of Interest During Follow-up

Variable	Delirium or Hallucinations With BHS Anticholinergics		Delirium or Hallucinations With BHS Narcotics		Extrapyramidal Effects With Trimethobenzamide Hydrochloride		Falls or Fractures With BHS Sedative Hypnotics	
	Exposed Patients (n = 37,358)	Controls (n = 37,358)	Exposed Patients (n = 395)	Controls (n = 395)	Exposed Patients (n = 1085)	Controls (n = 1085)	Exposed Patients (n = 13,542)	Controls (n = 13,542)
Sum of patients' follow-up years	31,213	36,421	311	372	977	1,069	11,505	12,969
Acute inpatient hospitalization for event of interest								
No. of cases	63	70	2	1	0	0	238	245
No. of cases per 1000 person-years	2.02	1.92	6.43	2.69	0	0	20.68	18.89
Emergency visit for event of interest								
No. of cases	116	109	0	0	3	1	510	474
No. of cases per 1000 person-years	3.72	2.99	0	0	3.07	0.93	44.32	36.55
2 Medical claims for event of interest								
No. of cases	415	482	4	4	1	1	622	569
No. of cases per 1000 person-years	13.30	13.23	12.86	10.75	1.02	0.93	54.06	43.87
Acute inpatient hospitalization, emergency visit, or 2 medical claims for event of interest								
No. of cases	487	553	5	4	4	1	795	731
No. of cases per 1000 person-years	15.60	15.18	16.07	10.75	4.09	0.93	69.10	56.36
Risk of hospitalization, emergency visit, or 2 medical claims for event of interest								
Hazard ratio (95% CI)	1.03 (0.91-1.16)		NE		NE		1.22 (1.10-1.35)	
P	.67						<.001	

BHS indicates Beers high-severity; CI, confidence interval; NE, not evaluated for this study.

possible that this statistical adjustment could not completely adjust for differences between the cohorts. It cannot be ruled out that the increased costs among exposed patients are a continuum of the increased preperiod costs and are not necessarily representative of costs associated with AEs related to a PIM.

Another consideration possibly contributing to cost differences between the cohorts is the fact that the Charlson Comorbidity Index, the case mix adjustment measure used in this analysis, does not account for mental health diagnoses. Prior research has found that mental health comorbidity is a predictor of receiving Beers and HEDIS 2006 high-risk drugs among the elderly.[18,19] To evaluate whether mental health conditions were equally represented among the exposed patients and controls in the present study, we performed a post hoc analysis to determine the percentage of patients in each cohort with a diagnosis code for an organic psychotic condition (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 290-294) or for other psychoses, including schizophrenia, depression, and bipolar disorder

Table 5. Healthcare Costs Over the 360-Day Postperiod

Variable	BHS Anticholinergics			BHS Narcotics			Trimethobenzamide Hydrochloride			BHS Sedative Hypnotics		
	Exposed Patients (n = 37,358)	Controls (n = 37,358)	P[a]	Exposed Patients (n = 395)	Controls (n = 395)	P[a]	Exposed Patients (n = 1085)	Controls (n = 1085)	P[a]	Exposed Patients (n = 13,542)	Controls (n = 13,542)	P[a]
Pharmacy Costs, $												
Mean (SD)	976 (1319)	1068 (1372)	<.001	1169 (1534)	1302 (1456)	.21	1172 (1536)	1155 (1342)	.78	1091 (1419)	1134 (1410)	.01
Median	593	691	<.001	721	878	.08	740	755	.51	667	736	<.001
Adjusted cost estimate[b]	773	796	<.001	1022	1043	.77	907	916	.86	889	880	.24
Medical Costs, $												
Mean (SD)	20,855 (57,282)	19,138 (56,462)	<.001	26,684 (39,536)	21,999 (48,903)	.14	34,764 (83,481)	22,431 (75,787)	<.001	24,163 (64,500)	18,287 (52,151)	<.001
Median	4578	3441	<.001	12,320	4462	<.001	7829	3743	<.001	6205	3659	<.001
Adjusted cost estimate[b]	17,154	15,214	<.001	26,370	20,952	.03	27,722	16,647	<.001	20,537	15,835	<.001
Total Healthcare Costs, $												
Mean (SD)	21,831 (57,506)	20,207 (56,680)	<.001	27,853 (39,830)	23,301 (49,360)	.15	35,937 (83,913)	23,586 (76,022)	<.001	25,254 (64,719)	19,421 (52,418)	<.001
Median	5606	4602	<.001	13,974	5441	<.001	9212	4933	<.001	7196	4931	<.001
Adjusted cost estimate[b]	18,398	16,482	<.001	27,447	22,471	.03	29,144	18,034	<.001	21,807	17,154	<.001

BHS indicates Beers high-severity.
[a]Represents the level of significance for the comparison of exposed patients versus controls. *P* values were estimated using *t* tests for mean costs, Wilcoxon rank sum tests for median costs, and generalized linear models with a log link and gamma distribution for adjusted costs.
[b]Estimated using generalized linear models with a log link and gamma distribution adjusting for age, sex, health plan type, geographic state, Charlson Comorbidity Index, and preperiod costs.

(*ICD-9-CM* codes 295-299), during the preperiod. Because of the restrictive inclusion and exclusion criteria, there were no patients with these diagnoses in the evaluations of the BHS anticholinergics, BHS narcotics, or trimethobenzamide. For the BHS sedative hypnotic analysis, the percentage of patients with an organic psychotic condition was similar between exposed patients and controls (1.9% vs 1.8%; $P = .50$), but the percentage of patients with other psychoses was higher for the exposed patients versus controls (2.2% vs 1.7%; $P = .003$). Because we cannot rule out the possibility that patients exposed to BHS sedative hypnotics might have had a greater mental comorbidity that contributed to their higher overall preperiod and postperiod costs, further research is warranted on the role of mental health comorbidity in contributing to costs associated with PIM use in the elderly.

Consistent with other claims analyses, this study is subject to limitations that include potential errors in diagnosis coding, incomplete medical claims, and unobservable factors that may have influenced the outcomes. In addition, outcomes within this population of elderly western US MCO patients may not be representative of elderly patients within a larger or more diverse demographic region.

Despite these limitations, the study findings help differentiate the level of risk associated with using specific PIMs in the elderly. Patients using BHS sedative hypnotics had an increased risk of costly falls and fractures, while an increased risk of delirium or hallucinations was not observed for patients using BHS anticholinergics. Less frequently used medications such as the BHS narcotics and trimethobenzamide may increase the rate of AEs, but results are inconclusive because of the small sample size. For all PIMs evaluated, annual adjusted medical and total healthcare costs were significantly higher for patients exposed to PIMs than for controls. For MCOs conducting or deciding whether to conduct clinical programs to reduce PIMs in the elderly, these findings provide evidence that the use of certain BHS PIMs in the elderly may increase AEs or healthcare costs.

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