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National Prescribing Trends of High-risk Anticholinergic Medications in Older Adults

Taeho Greg Rhee, PhD, MSW[1,2], **Yookyung Christy Choi, PharmD**[3], **Gregory M. Ouellet, MD**[1], and **Joseph S. Ross, MD, MHS**[2,4,5]

[1]Section of Geriatrics, Department of Internal Medicine, School of Medicine, Yale University, New Haven, CT

[2]Center for Outcomes Research and Evaluation (CORE), Yale-New Haven Health System, New Haven, CT

[3]Department of Pharmaceutical Care and Health Systems, College of Pharmacy, University of Minnesota, Minneapolis, MN

[4]Section of General Internal Medicine, Department of Internal Medicine, School of Medicine, Yale University, New Haven, CT

[5]Department of Health Policy and Management, School of Public Health, Yale University, New Haven, CT

Abstract

Objectives—To estimate prescribing tends of and correlates independently associated with high-risk anticholinergic prescriptions among adults aged 65 or older in office-based outpatient visits.

Design—Repeated cross-sectional analysis of the National Ambulatory Medical Care Survey (NAMCS).

Participants—A national sample of office-based physician visits by adults age 65 or older from 2006 to 2015 (n=96,996 unweighted).

Measurements—Prescriptions of high-risk anticholinergics, regardless of indication, were identified. Then, overall prescribing trends were estimated from 2006 to 2015. Stratified analyses of prescribing trends by physician specialty and anticholinergic drug class were also performed. Lastly, we used a multivariable logistic regression analysis to estimate the odds of high-risk anticholinergic prescriptions.

Results—Between 2006 and 2015, 5,876 (6.2%) out of 96,996 visits by older adults, representative of 14.6 million total visits nationally, listed a high-risk anticholinergic prescription. The most common drug classes were antidepressants, antimuscarinics, and antihistamines, which accounted for more than 70% of prescribed anticholinergics. Correlates independently associated with higher odds of receiving high-risk anticholinergic prescriptions included: female sex, the

Corresponding Author: Greg Rhee, PhD, MSW, School of Medicine, Yale University, 333 Cedar Street, PO Box #208025, New Haven, CT, 06520, USA (Phone: +1-773-398-9564; taeho.rhee@yale.edu).

Impact Statement: We certify that this work is novel, as we sought to investigate national prescribing trends of high-risk anticholinergic medications in older adults.

Southern geographic region, specific physician specialties (e.g., psychiatry and urology), receipt of six or more concomitantly prescribed medications, and related clinical diagnoses (e.g., urinary continence) (p<0.01 for all).

Conclusion—The prevalence of high-risk anticholinergic prescriptions was stable over time, but varied by physician specialty and drug class. Promoting quality prescribing is needed as safer alternatives are available.

Keywords

Anticholinergics; older adults; prescribing; outpatient care

INTRODUCTION

Despite a range of clinical indications, medications with anticholinergic properties pose a number of risks to older adults. These agents are commonly prescribed for allergies, obstructive pulmonary disease, and urge urinary incontinence;[1,2] however, they are associated with risks of developing serious adverse events, including cognitive impairment, falls, dementia, and increased mortality in older adults.[3–12] This vulnerability to adverse events is due in large part to a variety of aging-related physiological changes, such as reduced hepatic and renal functions, and increased blood-brain barrier permeability.[13] While some of these medications rely directly on anticholinergic action for their therapeutic effect (e.g., antispasmodics for irritable bowel syndrome and antimuscarinics for urge urinary incontinence),[14] others have anticholinergic side effects separate from their therapeutic action (e.g., antidepressants and antihistamines).

To promote safer prescribing, the recent Beers criteria identified 52 specific strong, high-risk anticholinergic agents in nine major drug classes as potentially inappropriate medications in older adults, and recommends avoidance of 35 of these 52 drugs regardless of indication.[4] In particular, on the basis of a *strong* recommendation grounded on systematic reviews of clinical studies, these 35anticholinergic drugs are to be avoided regardless of indication.[4] Previous studies investigated anticholinergic use at the national level, but relied on self-reported survey questionnaire from civilians, and used old data and older versions of Beers criteria.[11,15] Furthermore, these studies were conducted cross-sectionally such that they did not investigate secular trends of prescribing over time. In light of updated Beers criteria and up-to-date nationally representative survey data collected from physicians from 2006 to 2015, we investigated whether prescribing patterns have changed over time, and whether these patterns vary by physician specialty and anticholinergic class. We also estimated demographic and clinical correlates independently associated with these high-risk anticholinergic medication prescriptions.

METHODS

Data source and study sample

We used data from the 2006–2015 National Ambulatory Medical Care Survey (NAMCS), an annual cross-sectional survey of office-based physician visits. The NAMCS nationally represents ambulatory medical care services, including prescription trends.[16] We limited our

sample to all visits by adults aged 65 or older (n=102,806 unweighted). We excluded observations with any missing covariates (5.7%), which were missing at random by Little's test,[17] leaving a final sample size of 96,996. Using publicly available de-identified data, this study was exempted from the Institutional Review Board (#2000021850) at Yale School of Medicine as no direct human subjects were involved. Further details of the survey, including descriptions, questionnaires, sampling methodology and datasets, are publicly available on the NAMCS website.[16]

Measures

High-risk anticholinergic medications—We examined the first eight medications listed as prescribed for each visit, ensuring consistency across years. Based on Beers criteria and Rudolph *et al.*'s anticholinergic risk scale,[4,18] we characterized use of 35 high-risk anticholinergic medications with recommendations for complete avoidance. These medications included: 1) antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, imipramine, nortriptyline, paroxetine, protriptyline, and trimipramine); 2) antimuscarinics (darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, and trospium); 3) antihistamines (brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, doxylamine, hydroxyzine, meclizine, and triprolidine); 4) skeletal muscle relaxants (cyclobenzaprine and orphenadrine); and 5) antispasmodics (belladonna alkaloids, clidinium-chlordiazepoxide, dicyclomine, hyoscyamine, and propantheline).

Clinical diagnoses—Participating physicians were asked to report patient's reason for visit, physician's diagnosis, and cause of injury and procedures. These indications were then independently coded by SRA International Inc. (Durham, North Carolina)[19] specifically for NAMCS data collection and not for medical billing. The NAMCS provides up to three clinical diagnoses at each visit using the *International Classification of Diseases, 9th edition, Clinical Modification* (ICD-9-CM) diagnostic codes. We constructed several indicator variables for indications potentially relevant to anticholinergic use. These indications consisted of: 1) allergic conditions (287.0, 472.0, 473.0, 473.1, 473.2, 473.3, 473.8, 473.9, 477.0, 477.1, 477.8, 477.9, 536.8, 558.3, 558.9, 579, 691.8, 692.9, 693.1, 708.0, 789.00, 995.0, and 995.3); 2) chronic respiratory diseases (491–496); 3) irritable bowel syndromes (556, except 556.7); 4) overactive bladder (596.51, 788.41, 788.42, and 788.63) or urinary incontinence (388.30–388.36, and 788.91); 5) neuropathic pain (053.1, 250.6, 338.4, 346, 350, 357.2, 729.1, 729.2, and 784.0); 6) parkinsonism, dyskinesia or dystonia (333.71, 333.72, 333.79, 333.81–333.85, 333.89, 333.90, and 333.99); 7) vertigo (386 and 780.4) or motion sickness (994.6); 8) cognitive impairment (331.83) or dementia (290, 294.10, 294.11, 294.20, 294.21, 331.19, 331.82, and 331.0); 9) other psychiatric disorders (290–319, except cognitive impairment and dementia); 10) insomnia (327.00, 327.01, 327.02, 327.09, 780.51, and 780.52); 11) dry mouth (527.7), blurry vision (368.8), fatigue (780.71 and 780.79), hypersomnia (780.54) or tachycardia (785.0); and 12) constipation (564.00–564.02, and 564.09)..

Covariates—Similar to prior work on potentially inappropriate prescriptions, we selected covariates based on the potential for clinically relevant confounding.[20,21] We included the

following demographic variables: age (65–74, 74–85, or 85+), gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), geographic region (Northeast, Midwest, South, or West), primary source of payment (Private, Medicare, Medicaid, or other), reason for visit (acute problem, routine chronic problem, preventive care, or pre- or post-surgery care), and number of repeat visits within the past 12 months (none, 1–2, 3–5, or 6+). For clinical characteristics, variables included:[20,21] physician specialty (primary care, psychiatry, neurology, urology, or other), time spent with a doctor (in minutes), number of chronic conditions (<2 or ≥2), and number of concomitant medications prescribed (<6 or ≥6).

Data analysis

We estimated if demographic and clinical characteristics differed by anticholinergic prescription status using Bonferroni-adjusted bivariate analyses. Second, we assessed overall trends across the 10-year period in the percentage of visits with anticholinergic prescriptions using logistic regression models. Survey year was the main predictor variable, and we combined years into 2-year intervals, assigning values ranging from 1 to 5 (1=2005–2006, 2=2007–2008, etc.). We transformed this variable by subtracting 1 and dividing by 4, resulting in values between 0 and 1, which allowed us to interpret the odds ratio as the change in the odds of anticholinergic prescriptions across the 10-year period. We repeated these analyses, stratified by physician specialty, and anticholinergic class. Lastly, we used a multivariable-adjusted logistic regression analysis to identify demographic and clinical correlates independently associated with high-risk anticholinergic medication prescriptions. We performed all analyses using Stata MP/6-Core version 15.1 (College Station, TX), accounting for the survey sampling design (e.g., unequal probability of selection, clustering, and stratification).[22]

RESULTS

Selected characteristics of the sample

Between 2006 and 2015, 5,876 (6.2%) out of 96,996 visits by adults 65 and older, representative of 14.6 million visits nationally, listed a high-risk anticholinergic prescription. Patient visits in which anticholinergics were prescribed were significantly more likely to be made by women, those with ≥2 chronic conditions, those prescribed ≥6 concomitant medications, and those with related clinical diagnoses, such as overactive bladder or urinary incontinence, neuropathic pain, or vertigo/motion sickness (see Table 1). Among visits in which anticholinergics were prescribed, 53.1% were to primary care, whereas 11.6% were to psychiatry, neurology, or urology.

National trends of high-risk anticholinergic prescriptions

Table 2 shows national trends of anticholinergic prescriptions from 2006 to 2015. Overall, the anticholinergic prescription rate increased from 6.1% in 2006–2007 to 6.8% in 2008–2009, then decreased to 4.7% in 2014–2015. In primary care visits, the rate decreased over time from 8.7% in 2006–2007 to 6.4% in 2014–2015 (OR across 10-year period trends=0.94; 95% CI=0.89, 0.98). The most common drug classes were antidepressants,

antimuscarinics, and antihistamines, which accounted for more than 70% of prescribed anticholinergics in any given time interval.

Multivariable logistic regression analysis

Table 3 presents the results of multivariable-adjusted logistic regression analysis, which estimated the odds of receiving a anticholinergic medication independent of other factors. Older women had 1.88 times greater odds of receiving high-risk anticholinergic prescriptions than older men ($p<0.001$; 95% CI, 1.71–2.06). When compared to visits in Northeast region, visits in the South regions had 1.21 times greater odds of receiving high-risk anticholinergic prescriptions ($p=0.007$; 95% CI, 1.05–1.39). Visits to psychiatry and urology specialists had greater odds of receiving high-risk anticholinergic prescriptions, respectively, compared with primary care visits ($p<0.001$).

Older patients with six or more concomitant medications prescribed had 5.14 times greater odds of receiving high-risk anticholinergic prescriptions when compared to those with <6 medications concomitantly prescribed ($p<0.001$; 95% CI, 4.66–5.68). Among clinical diagnoses, overactive bladder or urinary incontinence, neuropathic pain, vertigo/motion sickness, and insomnia were independently associated with greater odds of having high-risk anticholinergic prescriptions ($p<0.01$).

DISCUSSION

This pharmaco-epidemiologic study investigated predictors of and national prescribing trends in high-risk anticholinergic medications among older adults in a nationally representative sample of office-based outpatient visits from 2006 to 2015. The prevalence of visits with any anticholinergics prescribed was stable over time, increasing minimally from 6.1% in 2006–2007 to 6.8% in 2008–2009, and then decreasing to 4.7% in 2014–2015. These rates are slightly lower than that of the previous study using 2009–2010 Medical Expenditure Panel Survey (MEPS), which reported a prevalence rate of 9.6%.[15] These marginal differences may be due to differences in data collection (e.g., individual- versus visit-level) or which medications were specifically included.

Among the selected medication classes, antidepressants were the most prevalent. This is corroborated by a recent study, which demonstrated a nearly twofold increase in antidepressant prescriptions 2002 to 2012.[21] Furthermore, because safer pharmacologic alternatives with less anticholinergic activity are available for treatments of depression, anxiety, and insomnia, for example, safer prescribing practices should be encouraged. The multivariable logistic regression analysis shows demographic and clinical correlates independently associated with the odds of having strong, high-risk anticholinergic prescriptions. Consistent with previous studies,[15,23] women and patients from the South were more likely to receive high-risk anticholinergic prescriptions. The regional variation may be due to differences in physician practices, patient preferences, and/or formulary structure.

Patients with six or more concomitant medications prescribed at the sampled visit also had a higher likelihood of having high-risk anticholinergic prescriptions. This may pose serious

polypharmacy-related adverse drug events in older adults. Future research is needed to determine if high-risk anticholinergics moderate the relationship between polypharmacy and patient outcomes. Such a finding would further underscore the need for reduction in high-risk anticholinergic prescribing in older adults. In general, visits that had diagnoses often treated by anticholinergics (e.g., urinary incontinence) showed increased likelihoods of receiving high-risk anticholinergic prescriptions. The severity of these indications may justify prescribing anticholinergics in individual patients; however, the heightened risk of these medications merits informed shared decision-making.

There are several limitations to this study. First, NAMCS does not capture visits at hospital-affiliated clinics and emergency departments (about 8.5% of all outpatient visits), and excludes prescription by phone. Second, NAMCS selected information based on a randomly selected visit, which may result in incomplete prescription documentation. For instance, NAMCS does not capture anticholinergic prescriptions given by other clinicians other than the physician at the sampled visit. Third, since only generic names of prescribed medications are provided in data, we excluded some drugs from the analysis (e.g., doxepin) as dosing information is needed to estimate their indications precisely. For these reasons, our findings may underestimate the magnitude of anticholinergic prescribing at all time points.

Despite the limitations, the strengths of our study include generalizability due to the use of nationally representative data. In particular, the NAMCS is one of few datasets, which represents physicians' practice and prescribing patterns in office-based care at the national level. Despite previous studies that divulge the use of strong, high-risk anticholinergic use and negative patient outcomes (e.g., developing cognitive impairment and dementia, or increased mortality) in older adults, the overall prescribing trends of these medications remain stable over time between 2006 and 2015. Our findings highlight that minimizing prescribing of high-risk anticholinergic medications is needed across physician specialty and drug class because safer alternatives are available. The findings from our study lay the foundation for future research to develop and implement better quality of care practices to reduce high-risk anticholinergic prescriptions in older adults.

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Table 1

Selected characteristics (weighted column %) of adults ages 65 and older by anticholinergic prescription status in office-based outpatient visits, 2006–2015.

	Anticholinergic prescription (%)		Total	*P*-value[†]
	No	Yes		
Sample size				
Unweighted sample	91,120	5,876	96,996	
Weighted visits	221,095,517	14,602,357	235,697,874	
Age				
65–74	51.2	49.7	51.1	0.171
75–84	35.8	36.1	35.9	
85+	13.0	14.2	13.0	
Gender				
Female	56.2	70.1	57.0	<0.001
Male	43.8	29.9	43.0	
Race/ethnicity				
Non-Hispanic White	79.1	79.3	79.1	0.639
Non-Hispanic Black	7.9	7.8	7.9	
Hispanic	8.2	8.9	8.3	
Other *a)*	4.8	4.1	4.7	
Region				
Northeast	19.8	17.3	19.6	0.030
Midwest	19.3	20.2	19.3	
South	38.4	41.5	38.5	
West	22.6	21.1	22.5	
Primary source of payment				
Private	15.9	14.0	15.8	0.116
Medicare	79.4	81.0	79.5	
Medicaid	2.6	2.9	2.6	
Other *b)*	2.1	2.0	2.1	
Reason for visit				
Acute problem	25.7	26.7	25.7	<0.001
Routine chronic problem	53.0	56.1	53.2	
Preventive care	12.6	11.5	12.6	
Pre- or post-surgery	8.7	5.7	8.5	
Physician specialty				
Primary care	39.1	53.1	39.9	<0.001
Psychiatry	1.3	2.5	1.4	
Neurology	1.6	2.7	1.7	
Urology	3.7	6.4	3.9	
Other *c)*	54.4	35.4	53.2	

	Anticholinergic prescription (%)		Total	*P*-value[†]
	No	Yes		
Repeat of visits in the past 12 months				
0 visit	6.3	4.6	6.2	<0.001
1–2 visits	35.4	32.5	35.2	
3–5 visits	33.6	33.3	33.6	
6+ visits	24.7	29.5	25.0	
Time spent with doctor				
< 15 min.	18.2	15.9	18.1	0.062
15–20 min.	49.1	49.5	49.1	
21–30 min.	21.0	22.3	21.1	
> 30 min.	11.7	12.2	11.7	
≥2 chronic conditions *d)*	57.7	68.2	58.4	<0.001
≥6 medications	29.5	67.5	31.9	<0.001
Visit diagnosis				
Allergic conditions	3.6	3.6	3.6	0.920
Chronic respiratory diseases	4.1	4.3	4.1	0.659
Irritable bowel syndromes	0.1	0.0	0.1	0.282
Overactive bladder or urinary incontinence	0.5	2.9	0.6	<0.001
Neuropathic pain	1.5	3.3	1.6	<0.001
Parkinsonism, dyskinesia, or dystonia	0.5	0.9	0.5	0.010
Vertigo or motion sickness	0.7	3.7	0.9	<0.001
Cognitive impairment or dementia	0.9	0.9	0.9	0.916
Other psychiatric disorders	3.3	8.3	3.6	<0.001
Other psychiatric disorders (with potential anticholinergic burden)	1.7	2.8	1.8	<0.001
Insomnia	0.5	1.5	0.6	<0.001
Dry mouth, blurry vision, fatigue, hypersomnia, or tachycardia	1.1	1.5	1.1	0.147
Constipation	0.6	0.8	0.6	0.140

Note:

[†] compares proportion differences by anticholinergic prescription using a weight-corrected, Bonferroni-adjusted chi-squared statistic.

a) includes Asians, American Indian/Alaska Natives (AIANs), Native Hawaiian or Other Pacific Islanders (NHOPI), or 2+ reported racial/ethnic groups;

b) includes worker's compensation, self-pay, no charge, and others;

c) includes obstetrics/gynecology, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others; and

d) was based 14 chronic conditions (yes/no) collected by the NAMCS (e.g., arthritis, congestive heart failure, and diabetes).

Table 2

Prevalence of anticholinergic prescriptions (weighted %) in office-based outpatient visits by physician specialty and medication class among US adults ages 65 and older, 2006–2015 NAMCS.

	Years (%)						Trend (2006–2015)		
	2006–2007	**2008–2009**	**2010–2011**	**2012–2013**	**2014–2015**	**Overall**	**OR†**	**95% CI**	***P*-value**
Visits in which any strong anticholinergics prescribed	6.1%	6.8%	6.7%	6.5%	4.7%	6.2%	0.95	0.91 – 0.98	0.004
Stratified by physician specialty									
Primary care	8.7%	8.7%	8.8%	8.2%	6.4%	8.2%	0.94	0.89 – 0.98	0.013
Psychiatry	15.9%	11.9%	10.1%	13.0%	7.6%	11.3%	0.85	0.72 – 1.01	0.058
Neurology	7.9%	10.2%	9.4%	9.0%	13.4%	9.9%	1.11	0.82 – 1.51	0.490
Urology	10.1%	10.0%	11.5%	10.8%	8.8%	10.3%	0.98	0.90 – 1.07	0.670
Other *a)*	3.6%	4.8%	4.6%	4.5%	3.0%	4.1%	0.96	0.90 – 1.02	0.212
Stratified by medication class									
Antidepressants	35.3%	28.7%	31.0%	31.8%	39.0%	32.6%	1.04	0.96 – 1.13	0.340
Antimuscarinics	29.5%	38.6%	30.0%	27.2%	29.6%	31.3%	0.94	0.67 – 1.02	0.117
Antihistamines	22.7%	16.1%	19.2%	17.8%	17.8%	18.6%	0.95	0.87 – 1.03	0.237
Skeletal muscle relaxants	10.5%	13.7%	16.5%	19.0%	11.6%	14.6%	1.09	0.99 – 1.19	0.069
Antispasmodics	7.0%	8.4%	9.1%	9.1%	7.1%	8.3%	1.02	0.93 – 1.12	0.673
Sample Size							Total		
Unweighted sample	899	1,011	1,041	2,063	862		5,876		
Weighted visits	2,759,559	3,461,389	3,242,283	3,064,665	2,074,460		14,602,357		

Note:

† across the 10-year period trends.

a) includes obstetrics/gynecology, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others.

Table 3

Adjusted odds ratios (AOR) of receiving strong anticholinergic prescriptions among adults ages 65 or older in office-based outpatient settings, 2006–2015 NAMCS.

(Reference group in a parenthesis)	AOR	95% CI	*P*-value
Age (65–74)			
75–84	0.96	0.87 – 1.06	0.427
85+	0.95	0.84 – 1.08	0.452
Gender (Male)			
Female	1.88	1.71 – 2.06	<0.001
Race/ethnicity (Non-Hispanic White)			
Non-Hispanic Black	0.92	0.76 – 1.11	0.392
Hispanic	1.07	0.90 – 1.26	0.441
Other *a)*	0.97	0.72 – 1.31	0.848
Region (Northeast)			
Midwest	1.02	0.89 – 1.18	0.748
South	1.21	1.05 – 1.39	0.007
West	1.02	0.88 – 1.19	0.774
Primary source of payment (Private)			
Medicare	1.03	0.90 – 1.17	0.668
Medicaid	1.16	0.87 – 1.53	0.306
Other *b)*	1.11	0.79 – 1.54	0.547
Reason for visit (Acute problem)			
Routine chronic problem	0.96	0.87 – 1.06	0.401
Preventive care	0.87	0.73 – 1.03	0.103
Pre- or post-surgery	0.91	0.74 – 1.11	0.337
Physician specialty (Primary care)			
Psychiatry	1.69	1.12 – 2.55	0.012
Neurology	1.29	0.88 – 1.90	0.193
Urology	2.06	1.75 – 2.44	<0.001
Other *c)*	0.62	0.55 – 0.70	<0.001
Repeat of visits in the past 12 months (Never)			
1–2 visits	1.10	0.91 – 1.33	0.345
3–5 visits	1.01	0.83 – 1.23	0.94
6+ visits	1.11	0.90 – 1.37	0.322
Time spent with a doctor (< 15 min.)			
15–20 min.	0.98	0.86 – 1.12	0.777
21–30 min.	0.99	0.86 – 1.15	0.928
> 30 min.	1.00	0.82 – 1.15	0.713
≥2 chronic conditions (<2)	1.00	0.91 – 1.10	0.987
≥6 medications (<6)	5.14	4.66 – 5.68	<0.001
Visit diagnosis			
Allergic conditions (No)	0.91	0.69 – 1.22	0.538

(Reference group in a parenthesis)	AOR	95% CI	*P*-value
Chronic respiratory diseases (No)	0.83	0.67 – 1.02	0.077
Irritable bowel syndromes (No)	0.36	0.05 – 2.71	0.319
Overactive bladder or urinary incontinence (No)	5.28	3.81 – 7.31	<0.001
Neuropathic pain (No)	1.66	1.26 – 2.18	<0.001
Parkinsonism, dyskinesia, or dystonia (No)	1.37	0.83 – 2.26	0.215
Vertigo or motion sickness (No)	4.96	3.80 – 6.47	<0.001
Cognitive impairment or dementia (No)	0.70	0.47 – 1.04	0.074
Other psychiatric disorders (No)	1.90	1.45 – 2.50	<0.001
Insomnia (No)	2.01	1.28 – 3.15	0.002
Dry mouth, blurry vision, fatigue, hypersomnia, or tachycardia (No)	1.00	0.70 – 1.43	1.000
Constipation (No)	1.29	0.84 – 1.96	0.245
Sample size			
Unweighted sample		96,996	
Weighted visits		235,697,874	
F-statistic		58.75 (p<0.001)	

Note:

a) includes Asians, American Indian/Alaska Natives (AIANs), Native Hawaiian or Other Pacific Islanders (NHOPI), or 2+ reported racial/ethnic groups;

b) includes worker's compensation, self-pay, no charge, and others;

c) includes obstetrics/gynecology, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others; and

d) was based 14 chronic conditions (yes/no) collected by the NAMCS (e.g., arthritis, congestive heart failure, and diabetes).