ORIGINAL RESEARCH

Prevalence and factors associated with off-label antidepressant prescriptions for insomnia

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Background: The primary objective of our study was to investigate the prevalence of off-label antidepressant drug use in insomnia. The secondary objective was to compare prescribing patterns between off-label antidepressants vs hypnotics approved by the US Food and Drug Administration for insomnia, with particular emphasis on socioeconomic characteristics of patients and physicians.

Methods: We undertook a secondary data analysis using the national longitudinal database from the 2006 National Ambulatory Medical Care Survey. Subjects were identified from outpatient visits in which at least one insomnia drug was prescribed. A series of weighted Chi-squared statistics was used to compare drug use for insomnia across various patient and physician characteristics. Multivariate logistic regression was conducted to identify factors associated with off-label antidepressant drug use.

Results: Among 901.95 million outpatient visits that took place in the US in 2006, an estimated 30.43 million visits included at least one drug prescription for insomnia. Off-label antidepressants were prescribed significantly more frequently (45.1%) than nonbenzodiazepine z-hypnotics (43.2%) and benzodiazepines (11.7%). Insomnia prescribing patterns were significantly influenced by physician specialty and physician office settings. Pediatricians (odds ratio [OR]: 65.892; 95% confidence interval [CI]: 5.536–810.564) and neurologists (OR: 4.784; 95% CI: 2.044–11.201) were more likely to prescribe off-label antidepressants than psychiatrists. Self-paying patients were more likely to receive off-label antidepressants as treatment for insomnia than patients with private insurance (OR 2.594; 95% CI: 1.128–5.967).

Conclusion: Our findings indicate significant socioeconomic disparities in the use of off-label antidepressants. Future studies might explore interventional and educational strategies to ensure well informed clinical decisions that can withstand pharmaceutical marketing strategies and diagnostic uncertainties regarding the treatment of insomnia.

Keywords: insomnia, off-label drug use, antidepressants, National Ambulatory Medical Care Survey

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Introduction

Insomnia, defined as difficulty initiating and maintaining sleep, is currently the most prevalent sleep disorder. Approximately 20% of adults examined in a general medical setting experience severe and persistent insomnia.[1] According to the National Sleep Foundation's 2008 "Sleep in America Poll", as many as 65% of adults report one or more sleep difficulties at least several times per week, with 44% experiencing sleep difficulties on a nightly basis.[2] The costs of insomnia, both direct and indirect, range from US$92.5 to US$107.5 billion annually.[3] However, the market for insomnia drugs

is not saturated. There is a potential for increased drug sales and patient awareness of available treatments. Current prescription medications approved by the US Food and Drug Administration (FDA) for insomnia include five benzodiazepines (estazolam, flurazepam, quazepam, temazepam, and triazolam), three nonbenzodiazepine z-hypnotics (eszopiclone, zalepon, and zolpidem),[4] and one selective melatonin receptor agonist (ramelteon).[5] Despite the availability of these drugs, studies consistently show a rise in off-label prescriptions for antidepressants, antipsychotics, and anticonvulsants in the treatment of insomnia.[6,7] Antidepressants accounted for three of the most often prescribed hypnotics, which are trazodone, amitriptyline, and mirtazapine.[8] In other reports, trazodone has contributed to approximately 20% of total insomnia drug sales in the market.[9,10] However, there is growing concern that off-label use of antidepressants may also put patients at higher risk for medication errors, side effects, and unwanted drug reactions.

Off-label prescribing, also called "nonapproved" or "unapproved" use of a drug, is the practice of prescribing medication for purposes different from those indicated by the FDA. Off-label drug use contributes to approximately 21% of prescriptions written annually.[11] The use of off-label drugs is not illegal and is regularly practiced across the country. The FDA does not regulate the practice of medicine, and this translates into freedom of off-label drug use by licensed practitioners.[11,12] Numerous physicians believe it is a privilege accorded to the medical practitioner based on their professional experience under certain circumstances. It has been argued that off-label prescription provides a flexible and experimental platform for fostering the discovery of a new drug indication.[11] Yet, specialists warn that off-label use may be more risky due to lack of safety and efficacy data.[3,7,11]

Amongst off-label drug uses, antidepressant use is one of the most common.[11] Closely related to the issue of off-label antidepressant drug use for insomnia are sociodemographic characteristics of physicians and patients. Physicians may believe erroneously that off-label medications have demonstrated sustained efficacy and are safer. Physicians, as well as patients, may also choose antidepressants over hypnotics because of cost and formulary considerations. This decision-making process involves complicated socioeconomic issues and interactions between the patient and physician. These sociological influences were first considered by John Eisenberg, who identified a series of physician and patient characteristics likely to influence the allocation of a given prescription.[13] Using Eisenberg's findings as a theoretical framework, several insomnia researchers have examined

prescribing patterns across variables such as physician specialty, patient gender, and patient ethnicity.[14–16]

The literature has shown that off-label drug use is widespread but often not supported by strong evidence.[11] To address this concern, the primary objective of our study was to investigate the prevalence of off-label antidepressant drug use in insomnia using a national representative database. The secondary objective was to compare prescribing patterns between off-label antidepressants vs FDA-approved hypnotics for insomnia, with particular emphasis on market-driven patient and physician socioeconomic characteristics.

Methods
Data source
Data were extracted from the National Ambulatory Medical Care Survey (NAMCS). The NAMCS is a national probability sample survey conducted annually by the Division of Health Care Statistics, National Center for Health Statistics, within the Centers for Disease Control and Prevention. The NAMCS sample data are collected from nonfederal office-based clinical practices. The basic sampling unit for the NAMCS is the physician–patient encounter or outpatient visit. For each selected visit, physicians complete an encounter form listing diagnoses, medication, and clinical services that they provided. All records contain patient demographic information, including age, gender, race, ethnicity, and source of payment. Details of the NAMCS sampling design are available to the public online.[17] To enable extrapolation to national estimates, each visit record is assigned an inflation factor called the patient visit weight, which is then used to predict the total number of office visits made in the US. All estimates from the NAMCS are related to the number of patient visits and are subject to sampling variability. An estimate is considered reliable if it has a relative sampling error ≤30% of the estimate, as per NCHS standards. Our study used the 2006 NAMCS data for its timeliness and availability while this project was funded. All data management and analyses described were performed using SAS software (SAS Institute, Cary, NC).

Data extraction and methods
All patient visits to an ambulatory physician office, where at least one frequently used insomnia drug was prescribed, were extracted and categorized into two groups, ie, FDA-approved insomnia prescriptions, including benzodiazepine hypnotics (flurazepam, quazepam, triazolam, estazolam, temazepam), nonbenzodiazepine hypnotics (zolpidem, zaleplon, eszopiclone), and a selective melatonin receptor agonist

(ramelteon), and frequently used off-label antidepressants for insomnia, including amitriptyline, nortriptyline, mirtazapine, doxepin, and trazodone. Up to eight medications can be recorded for each visit in the NAMCS database. Each drug code was assigned a unique "generic drug code" by Multum's Lexicon Plus system, which was used to classify drug entries in the NAMCS. The structure of the Multum database allows multiple-ingredient drugs to be assigned a single generic drug code according to their generic components and therapeutic classifications. Patients who were diagnosed with depression (ICD-9-CM codes 296.20, 296.30, 300.40, 309.00, 309.10, and 311.00) were excluded from the off-label antidepressant group to avoid overestimation of off-label antidepressant use. Using Eisenberg's sociological theory, we also identified several physician and patient characteristics as variables for further analysis, ie, patient age, gender, ethnicity, insurance type, physician's specialty, office setting, and office ownership. The study proposal was approved by the Institutional Review Board of Nova Southeastern University.

Statistical analysis

Each record on the NAMCS data file represents one patient visit. In order to obtain national estimates, the sample weight adjustments and standard error corrections were incorporated in all descriptive and inferential statistical analyses. We first performed a series of descriptive analyses to estimate the national weighted frequency of each drug. Second, we explored bivariate analyses to compare selected predictive variables associated with insomnia prescribing patterns between off-label antidepressants and FDA-approved hypnotics using weight-adjusted Chi-squared analyses. Third, a weighted multivariate logistic regression with SAS PROC SURVEYLOGISTICS application was conducted to predict the maximum likelihood of off-label antidepressant use associated with patient and physician socioeconomic characteristics. Both standard sample design variables (CSTRATM and CPSUM) were included in the SAS PROC SURVEYFREQ program to adjust for the complex sampling design employed by NAMCS. A two-tailed statistic with a P-value less than 0.05 was considered statistically significant.

Results

Prevalence and bivariate analyses

An estimated total of 901.95 million outpatient visits occurred in the US in 2006. There were 30.43 million visits (3.4%) at which at least one frequently used insomnia drug was prescribed. FDA-approved benzodiazepines were prescribed at 3.53 million of these visits (11.6%), whereas FDA-approved nonbenzodiazepine z-hypnotics were prescribed at 12.55 million visits (41.2%). Non-FDA-approved insomnia medications were prescribed at 13.73 million visits (45.1%). The weighted frequency of these drugs is presented in Table 1. The most frequently prescribed drug was zolpidem, which accounted for 32.8% of total prescriptions. This was followed by trazodone (17.9%), amitriptyline (14.5%), temazepam (8.7%), eszopiclone (7.5%), mirtazapine (5.8%),

Table 1 Prevalence of insomnia drugs prescribed at US outpatient visits in 2006

Insomnia drugs	Generic equivalent code	Weighted frequency	Percentage (%)
FDA-approved benzodiazepine hypnotics			
Temazepam (Restoril®)	d00384	2,644,074	8.7%
Estazolam (Prosom®)	d00915	108,135	0.4%
Triazolam (Halcion®)	d00397	535,258	1.8%
Flurazepam (Dalmane®)	d00238	249,686	0.8%
Quazepam (Doral®)	d00917	0	0%
FDA-approved nonbenzodiazepine z-hypnotics			
Zolpidem (Ambien®)	d00910	9,996,496	32.8%
Zaleplon (Sonata®)	d04452	265,363	0.9%
Eszopiclone (Lunesta®)	d05421	2,290,378	7.5%
Selective melatonin receptor agonist			
Ramelteon (Rozerem®)	d05778	614,907	2.0%
Non FDA-approved antidepressants			
Trazodone (Desyrel®)	d00395	5,435,674	17.9%
Amitriptyline (Elavil®)	d00146	4,413,467	14.5%
Mirtazapine (Remeron®)	d04025	1,761,523	5.8%
Nortriptyline (Aventyl®)	d00144	1,424,346	4.7%
Doxepin (Sinequan®)	d00217	695,369	2.3%
Total		30,434,676	100.0%

Note: Insomnia drugs selected according to the National Institutes of Health report[4] and Rozerem® prescribing information.[5]
Abbreviation: FDA, Food and Drug Administration.

nortriptyline (4.7%), doxepin (2.3%), ramelteon (2.0%), triazolam (1.8%), zaleplon (0.9%), flurazepam (0.8%), and estazolam (0.4%). Figure 1 illustrates the prevalence of FDA-approved hypnotic and off-label antidepressant use in the treatment of insomnia.

Table 2 outlines the results from weight-adjusted Chi-squared analyses comparing the off-label antidepressant group and the FDA-approved hypnotic group based on selected patient and physician characteristics. The off-label antidepressant group had a significantly lower mean age than the FDA-approved group (55.8 years vs 58.2 years, $P = 0.0186$). In the off-label antidepressant group, female patients received more insomnia prescriptions than did men (68.2% vs 31.8%). Similar trends were observed in the FDA-approved hypnotic group (62.2% vs 37.8%). In both groups, white patients were more likely to receive insomnia drugs, followed by Hispanics, blacks, and other races. The majority of visits at which insomnia medications were prescribed were paid for by private insurance, Medicare, and Medicaid. This trend was consistent in both groups, but a significant difference was detected in the distribution based on payment mode.

Off-label antidepressant prescribing patterns were significantly influenced by physician specialty ($P < 0.001$) and physician office setting ($P < 0.001$). General practitioners/family physicians prescribed the most insomnia prescriptions (off-label antidepressant group 27.8%, FDA-approved group 24.7%), followed by internal medicine physicians (off-label antidepressant group 22.3%, FDA-approved group 26.0%) and psychiatric specialists (off-label antidepressant group 16.8%, FDA-approved group 16.4%, see Table 2 and Figure 2). The majority of insomnia prescriptions were issued by private solo/group practices (off-label antidepressant group 80.5%, FDA-approved group 92.3%). However, there was a statistically significant difference in the distribution of insomnia prescriptions between the off-label antidepressant group and FDA-approved hypnotic group. Clinics owned by physicians prescribed more insomnia prescriptions (off-label antidepressant group 72.9%, FDA-approved group 80.1%) than other types of physician office ownership, such as a Health Maintenance Organization, community health center, or academic health center. However, no statistically significant difference in physician office ownership was found between the two groups.

Multivariate analysis

Results of multivariate logistic regression presented as odds ratios (OR) and 95% Wald confidence intervals (CI) are shown in Table 3. The adjusted OR represents the increased
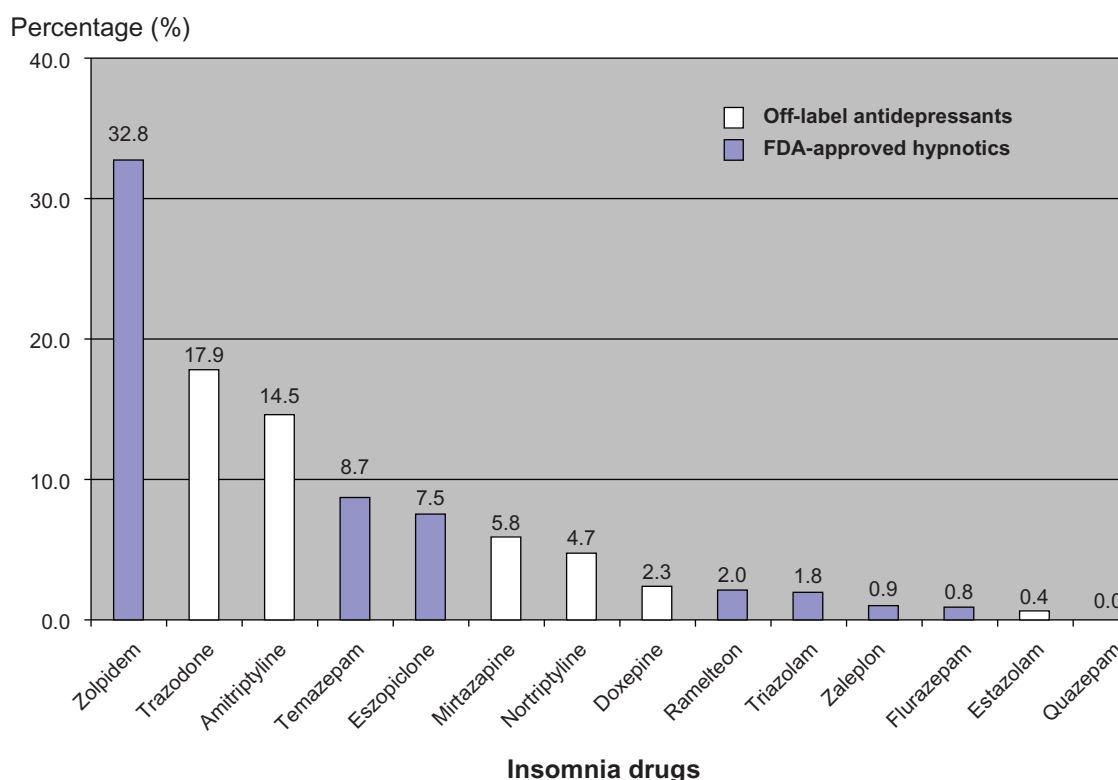

Figure 1 Prevalence of FDA-approved hypnotics and off-label antidepressants use in the treatment of insomnia.
Abbreviation: FDA, Food and Drug Administration.

Table 2 Socioeconomic characteristics of off-label antidepressant group and FDA-approved hypnotic group

Variable	Weighted frequency (%)		P-value*
	Off-label antidepressant group	**FDA-approved hypnotic group**	
Patient age			
Mean (years)	55.775	58.155	0.0186*
Patient gender			
Female	9,274,657 (68.2)	10,423,770 (62.2)	0.2145
Male	4,325,960 (31.8)	6,325,183 (37.8)	
Patient race			
White, non-hispanic	10,286,943 (75.6)	12,557,410 (75.0)	0.4536
Black, non-hispanic	1,281,507 (9.4)	1,435, 060 (8.6)	
Hispanic	1,324,715 (9.7)	2,058,405 (12.3)	
Asian	411,237 (3.0)	573,677 (3.4)	
Native Hawaiian, other Pacific Islander	21,672 (0.2)	35,529 (0.2)	
American Indian/Alaska Native	231,518 (1.7)	88,872 (0.5)	
Multiple races	43,025 (0.3)	0 (0.0)	
Physician specialty			
General/family practice	3,779,358 (27.8)	4,139,900 (24.7)	<0.001*
Internal medicine	3,028,144 (22.3)	4,347,494 (26.0)	
Pediatrics	214,920 (1.6)	4,690 (0.0)	
General surgery	257,555 (1.9)	181,795 (1.1)	
Obstetrics and gynecology	302,143 (2.2)	225,152 (1.3)	
Orthopedic surgery	316,399 (2.3)	678,631 (4.1)	
Cardiovascular diseases	456,555 (3.4)	602,225 (3.6)	
Dermatology	84,648 (0.6)	103,652 (0.6)	
Urology	152,834 (1.1)	149,935 (0.9)	
Psychiatry	2,287,602 (16.8)	2,746,794 (16.4)	
Neurology	881,278 (6.5)	386,081 (2.3)	
Ophthalmology	96,370 (0.7)	0 (0.0)	
Otolaryngology	99,222 (0.7)	104,060 (0.6)	
Other specialties	1,452,388 (10.7)	2,556,955 (15.3)	
Oncology	191,201 (1.4)	521,589 (3.1)	
Physician office setting			
Private solo/group practice	10,941,224 (80.5)	15,463,752 (92.3)	<0.001*
Free standing clinic/urgent center	1,441,709 (10.6)	605,762 (3.6)	
Community health center	391,458 (2.9)	233,423 (1.4)	
Mental health center	272,676 (2.0)	152,946 (0.9)	
Nonfederal government clinic	28,734 (0.2)	0 (0.0)	
HMO or other prepaid practice	499,100 (3.7)	223,104 (1.3)	
Faculty practice plan	25,716 (0.2)	69,966 (0.4)	
Physician office ownership			
Physician or physician group	9,920,331 (72.9)	13,411,483 (80.1)	0.5634
HMO*	573,486 (4.2)	348,105 (2.1)	
Community health center	370,576 (2.7)	228,249 (1.4)	
Medical/academic health center	539,177 (4.0)	378,685 (2.3)	
Other hospital	843,240 (6.2)	819,082 (4.9)	
Other health care corporation	1,071,752 (7.9)	1,270,305 (7.6)	
Other	282,055 (2.1)	211,025 (1.3)	
Blank	0 (0.0)	82,019 (0.5)	
Type of payment			
Blank	396,496 (2.9)	216,360 (1.3)	0.0342*
Private insurance	5,288,962 (38.9)	7,799,779 (46.6)	
Medicare	4,400,684 (32.4)	5,546,188 (33.1)	
Medicaid	2,096,614 (15.4)	1,851,407 (11.1)	
Worker's compensation	18,240 (0.1)	197,141 (1.2)	
Selfpay	740,144 (5.4)	395,585 (2.4)	
No charge	171,981 (1.3)	28,168 (0.2)	
Other	209,478 (1.5)	229,839 (1.4)	
Unknown	278,018 (2.0)	484,486 (2.9)	

Note: *Indicates that weight-adjusted Chi-squared statistic is significant.
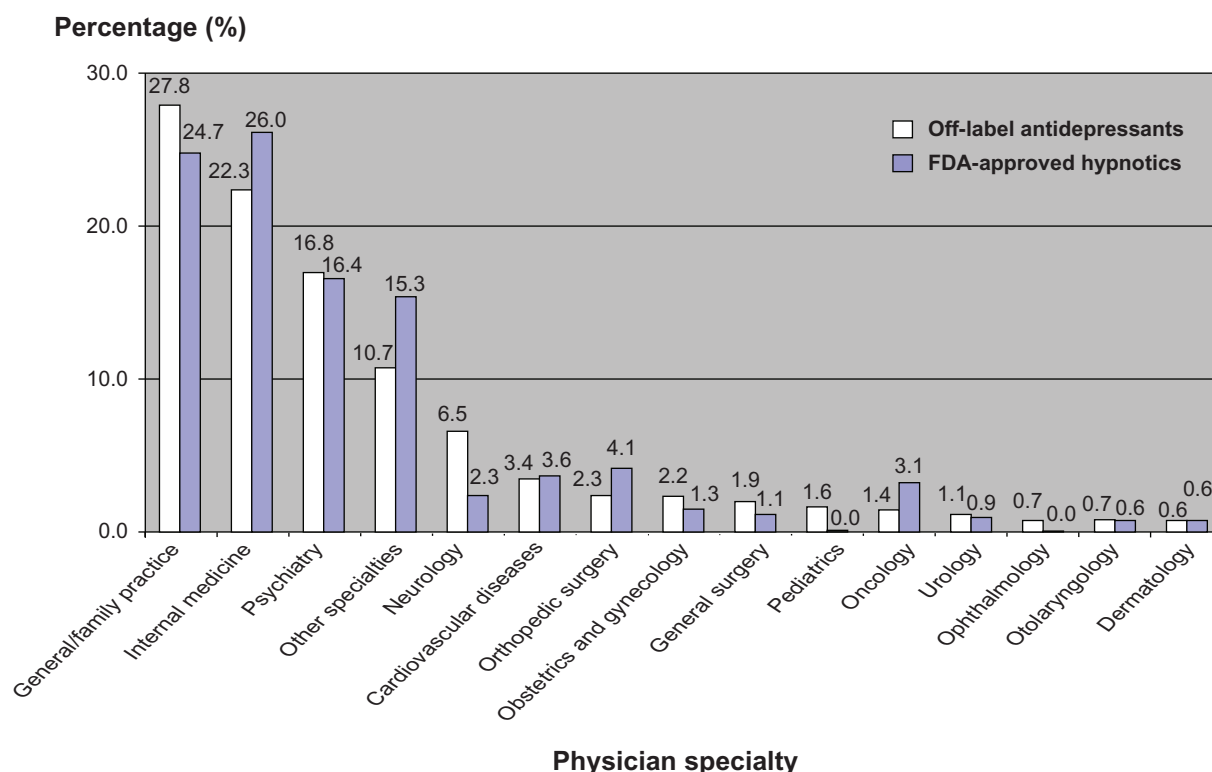**Abbreviations:** HMO, Health Maintenance Organization; FDA, Food and Drug Administration.

Percentage (%)

Figure 2 Distribution of off-label antidepressants and FDA-approved hypnotic prescriptions based on physician specialty.
Abbreviation: FDA, Food and Drug Administration.

likelihood of prescribing off-label antidepressants compared with FDA-approved hypnotics based on each socioeconomic characteristic, using a reference group in each category.

There was no significantly increased likelihood of prescribing off-label antidepressants in relation to patient age, gender, and ethnicity. However, self-paying patients were more likely to receive off-label antidepressants for insomnia than patients with private insurance (OR: 2.594; 95% CI: 1.128–5.967). In contrast, certain physician characteristics significantly increased the likelihood of prescribing off-label antidepressants for treatment of insomnia. Physicians from most specialties did not show an increased likelihood of prescribing off-label antidepressants, except for pediatricians and neurologists. Pediatricians (OR: 65.892; 95% CI: 5.536–810.564) and neurologists (OR: 4.784; 95% CI: 2.044–11.201) were more likely than psychiatrists to prescribe off-label antidepressants. Physicians from freestanding clinics or urgent centers were also more likely to prescribe off-label antidepressants than those from private solo/group practices (OR: 3.26; 95% CI: 1.2–8.9).

Discussion

Of 901.95 million outpatient visits in the US in 2006, at least one insomnia drug was prescribed at 30.43 million visits, representing approximately 3.4% of visits, as opposed to

the estimated 20% of adults reported to experience severe and persistent insomnia.[1] This discrepancy could be due to selective "underprescribing", a phenomenon that has been detected in other chronic diseases.[18,19] However, widespread use of over-the-counter antihistamines might be another reason for this occurrence. According to the National Institutes of Health, alcohol and over-the-counter drugs remain some of the most popular selfcare treatments for insomnia.[4,20]

Off-label antidepressants were prescribed in 45.1% of the prescriptions examined. This is nearly four times the amount of FDA-approved benzodiazepine prescriptions issued. The high prevalent use of off-label antidepressants for insomnia has been reported in other studies.[21,22] Wiegand postulated that physicians favor antidepressants over FDA-approved benzodiazepines due to uninformed perceptions of the safety and nonaddictive advantages of antidepressants over benzodiazepine receptor agonists.[23] It is equally likely that comorbidity with depression and anxiety disorders result in increased use of off-label antidepressants for insomnia treatment.[24] An estimated 40% of all patients with insomnia have a coexisting psychiatric condition,[25] and differences between insomnia and depressive symptoms can be ambiguous.[26] Although the diagnosis of depression was used as an exclusion criterion in our study, the influence of subclinical

Table 3 Likelihood of prescribing off-label antidepressants in the treatment of insomnia

Variable	Adjusted odds ratio	95% Wald confidence interval
Patient age (years)		
<15	0.870	0.153–4.932
15–24	1.853	0.730–4.704
25–44	0.827	0.425–1.609
45–64	1.035	0.567–1.888
65–74	1.019	0.532–1.951
Above 75 years (reference)	–	–
Patient gender		
Female	1.219	0.850–1.750
Male (reference)	–	–
Patient race		
White, non-hispanic (reference)	–	–
Black, non-hispanic	0.816	0.351–1.896
Hispanic	0.706	0.372–1.338
Asian	0.634	0.246–1.629
Native Hawaiian, other Pacific Islander	0.260	0.015–4.385
American Indian/Alaska Native	2.176	0.232–20.424
Physician specialty		
General/family practice	1.811	0.867–3.783
Internal medicine	1.122	0.477–2.638
Pediatrics	65.892	5.536–810.564*
General surgery	3.136	0.817–12.030
Obstetrics and gynecology	2.656	0.770–9.164
Orthopedic surgery	1.406	0.398–4.968
Cardiovascular diseases	1.428	0.572–3.564
Dermatology	1.328	0.243–7.258
Urology	1.552	0.458–5.261
Psychiatry (reference)	–	–
Neurology	4.784	2.044–11.201*
Otolaryngology	2.015	0.611–6.649
Other specialties	1.088	0.460–2.578
Oncology	0.564	0.232–1.368
Physician office setting		
Private solo/group practice (reference)	–	–
Free standing clinic/urgent center	3.255	1.186–8.938*
Community health center	2.970	0.543–16.254
Mental health center	2.880	0.987–8.402
HMO* or other prepaid practice	4.000	0.696–22.994
Faculty practice plan	0.450	0.029–7.013
Physician office ownership		
Physician or physician group (reference)	–	–
HMO	2.217	0.501–9.811
Community health center	1.222	0.183–8.137
Medical/academic health center	2.372	0.756–7.445
Other hospital	2.435	0.633–9.359
Other health care corporation	2.298	0.948–5.570
Other	1.603	0.422–6.090
Type of payment		
Private insurance (reference)	–	–
Medicare	1.433	0.858–2.394
Medicaid	1.617	0.888–2.947
Worker's compensation	0.230	0.024–2.175
Selfpay	2.594	1.128–5.967*
No charge	6.630	0.724–60.713
Other	1.728	0.292–10.229
Unknown	0.745	0.234–2.374

Note: *Indicates adjusted odds ratio with 95% confidence interval is significant.
Abbreviation: HMO, Health Maintenance Organization.

depression in the prescribing of off-label antidepressants cannot be ruled out. Even though prescribing antidepressants in the context of concurrent depression and insomnia is desirable, its use in the treatment of insomnia alone is unclear and arguably weak.[6,23,27] Several randomized controlled trials have investigated the efficacy of antidepressants for insomnia,[28–31] but only a few studies have directly compared its efficacy with that of the benzodiazepine receptor agonists.[32,33] No comparison with z-hypnotics has been conducted to date.

The high prevalence of off-label antidepressant use for treatment of insomnia may also be attributed to its lower cost, given that generic preparations are widely available. However, drug pricing does not fully explain our findings. A recent report cites the economically accessible trazodone as the most frequently prescribed insomnia medication.[34] Our results show that zolpidem accounted for more prescriptions than did trazodone, which is consistent with a report by Roy and Smith.[35] This finding may be explained by the distributor's aggressive marketing efforts, such as direct-to-consumer advertising (DTCA). DTCA spending for zolpidem (Ambien®) was US$11.1 million in 2000 and zolpidem was ranked as the 48th highest DTCA expenditure drug.[36] A subsequent study by Donohue et al showed that this figure increased to US$88 million in 2005, when zolpidem ranked the 14th highest DTCA expenditure drug.[37] This amount has increased eight times within 5 years and DTCA is likely to have helped to secure its widespread usage, despite its reported side effects such as night-time eating, sleepwalking, daytime dizziness, and drowsiness.[38,39] The impact of DTCA is explained by a survey in which 25%–33% of consumers talked to their physicians about the advertised drug they had seen, and 12%–25% of them asked to be prescribed the drug.[40]

It is surprising that there is high consistency in terms of the percentage of patients prescribed off-label antidepressants and FDA-approved hypnotics. This suggests that, despite the availability of FDA-approved hypnotics and their proven efficacy, approximately half of all physicians are still prescribing off-label antidepressants for insomnia. Using logistic regression analysis, we identified pediatricians and neurologists as being more likely to prescribe off-label antidepressants than psychiatrists. The practice of prescribing hypnotics for pediatric insomnia is common among special needs children, particularly those with a depressive disorder. Thus, off-label antidepressants may be a complementary choice for the treatment of insomnia in this population. In addition, concerns over the misuse of benzodiazepines and z-hypnotics in the pediatric population may increase the likelihood of pediatricians prescribing off-label antidepressants. Increased use

of off-label antidepressants may be attributed to concurrent neurological symptoms reported by patients, such as neuropathic pain, that lead to difficulty sleeping.

Our study also found that physicians practicing at freestanding clinics or urgent centers were 3.26 times more likely to prescribe an off-label antidepressant for treatment of insomnia than those practicing at private solo/group practices. There are many freestanding clinics (ie, not associated with a medical institution) that offer off-label treatment for various health conditions. These treatments are usually provided based upon cash payment, which is consistent with our study finding that self-paying patients were 2.59 times more likely to obtain an off-label antidepressant than those with private insurance.

Nevertheless, our study has several limitations. First, we showed that neurologists prescribed 4.8 times more off-label antidepressants than psychiatrists for treatment of insomnia. This finding may be confounded by other off-label antidepressant use, eg, for neuropathic pain, migraine prophylaxis, tension headache, fibromyalgia, and other indications. The presence of these concurrent complaints may increase the likelihood of physicians prescribing off-label antidepressants for treatment of insomnia.[41] On the other hand, the addition of these diagnoses to the exclusion criteria for the off-label antidepressant group may underestimate the likelihood of prescribing off-label antidepressants for insomnia because of the coexistence of these symptoms with insomnia. However, there is also the possibility of overestimating the study effect due to use of ICD-9 codes for the exclusion of patients with depression from the off-label antidepressant group. The tendency to underdiagnose depression may be attributed to ICD coding and, therefore, many patients without an ICD-9 code for depression were prescribed an antidepressant and included in the analysis.

Second, we used drug prescriptions for insomnia without an ICD-9 code because inclusion criteria may erroneously include patients without insomnia, as discussed earlier. Insomnia is frequently perceived as a symptom rather than a disorder, and ambiguity between insomnia and other psychiatric disorders render the use of the ICD-9 code inadequate. It is not uncommon for sedative antidepressants to be used in patients with depression and/or anxiety because of concurrent sleep difficulty. Additionally, our study did not take into account important reimbursement policies and institutional formularies that place restrictions on physicians' prescribing behaviors. Due to the limitations of the NAMCS database, our results did not provide qualitative information on the physician–patient relationship which could be used

to formulate a physician education program in the future. We also did not take into consideration the effect of marital status in our analysis of demographic-based difference in prescribing patterns, as suggested by Brownlee et al.[42]

Conclusion

Our study confirms and expands on the findings of previous research to suggest profound sociodemographic and economic influences on insomnia prescribing patterns. Changing long-established physician prescribing patterns can be difficult, particularly if physicians have specific reasons for prescribing medications to specific populations. Future studies could explore intervention and educational strategies to ensure well informed clinical decisions that can withstand pharmaceutical marketing strategies and diagnostic uncertainties regarding the treatment of insomnia.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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