SEDATIVE-HYPNOTIC PRESCRIBING IN THE UNITED STATES FROM 1993 TO 2010: RECENT TRENDS AND OUTCOMES

by
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Abstract

BACKGROUND: Studies show sedative-hypnotic medications (benzodiazepines [BZDs] and non-benzodiazepine receptor agonists [nBZRAs]) to be associated with adverse outcomes. This dissertation examined prescribing trends of these medications from 1993-2010, and comprised of three studies: study 1 examined trends in prescribing of sedative-hypnotics, study 2 examined physician practice style as a contributing factor for trends seen in study 1, and study 3 examined visits involving sedative-hypnotics in emergency departments (EDs).

METHODS: Data for studies 1 and 2 came from the National Ambulatory Medical Care Survey (NAMCS). Study 1 analyzed trends in the proportion of visits from 1993-2010 where a BZD and/or nBZRA was prescribed. Study 2 examined trends in the proportion of physicians prescribing BZDs and nBZRAs, as well as the predicted number of visits (based on regression models) that a BZD or nBZRA was prescribed among BZD and nBZRA prescribers respectively. Data for study 3 came from the Drug Abuse Warning Network. Analyses used logistic regression to determine the association between ED visits involving BZDs and/or nBZRAs and the seriousness of visit outcomes.

RESULTS: From 1993-2010, we found increases in the proportion of visits resulting in a prescription for a BZD (from 2.6% to 4.4%, $p<0.001$) and a nBZRA (from 0% to 1.4%, $p<0.001$), as well as the co-prescribing of these agents at the same visit (from 0% to 0.4%, $p<0.001$). Over this same period, we observed increases in the proportion of NAMCS physicians each year who prescribed BZDs (from 23.8% to 44.4%, $p<0.001$) and

nBZRAs (from 1.0% to 25.8%, $p<0.001$), and in the predicted number of NAMCS visits that an nBZRA was prescribed among nBZRA prescribers (from 1.33 to 1.72, $p<0.001$). ED visits involving BZDs without nBZRAs and BZDs + nBZRAs were associated with increased odds for more serious outcomes compared to visits involving neither medication (odds ratio [OR]=1.34, 95% confidence interval [CI]=1.20-1.50 for BZDs without nBZRAs; OR=3.15, 95% CI=2.01-4.94 for BZDs + nBZRAs).

CONCLUSIONS: Efforts to encourage safe prescribing of sedative-hypnotics, and greater dissemination of behavioral treatments for insomnia and anxiety disorders, could have the potential to decrease the public health burden attributed to prescribing of these medications.

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Chapter 1: Introduction

Overview of dissertation

Over the past two decades, a number of pharmacological agents have been developed to treat insomnia,[1-3] a condition experienced by an estimated 50-70 million Americans.[4] Benzodiazepines (BZDs) and non-benzodiazepine receptor agonists (nBZRAs), collectively known as sedative-hypnotic medications, induce sleep and lower anxious feelings by acting on the central nervous system. BZDs, developed in the 1950s, are indicated for the treatment of anxiety disorders, insomnia, epilepsy, and alcohol withdrawal symptoms.[5] In recent years, studies have shown that use of BZDs is associated with numerous adverse health outcomes in older adults, including falls[6,7] and hip fractures,[8,9] and decline in functional ability,[10-12] prompting the development of clinical guidelines that strongly discourage the prescribing these medications to older people.[13-17]

The nBZRAs were introduced in the early 1990s,[18-20] and were marketed as safer alternatives to BZDs for the short-term treatment of insomnia. Indeed—early clinical trials showed these agents to be safe and effective.[21-24] However, recent observational studies have shown use of these medications may be associated with the same adverse health outcomes as seen for BZDs.[25-27]

Studies have shown that prescribing of BZDs remained relatively stable,[28,29] and prescribing for nBZRAs increased,[30] up to the early 2000s. There are also studies showing a rise in the number of emergency department (ED) visits involving BZDs and nBZRAs in recent years,[31,32] suggesting that with the growing prescription of BZDs and nBZRAs, there has also been a rise in the occurrence of adverse health outcomes of these agents necessitating emergency treatment. While most research examining trends in

prescribing of BZDs and nBZRAs cover up until the early 2000s, little is known about recent trends in the prescribing of these agents. For example, we know little about how the introduction of nBZRAs in the early 1990s impacted overall prescribing of BZDs in later years, and whether these trends varied across patient groups (e.g., age, gender, and diagnoses of patients). In addition, more research is needed to examine the practice style of physicians who prescribe these medications, and to assess if changes in these styles over time may account for any changes seen in BZD and nBZRA prescribing overall. Finally, in light of studies showing BZDs and nBZRAs to be associated with adverse health outcomes,[7,11,26,27,33] and the increasing trend in BZD- and nBZRA-related ED visits,[31,32] more research is needed to understand the outcomes from these ED visits.

This dissertation examined how the prescribing and use of BZDs and nBZRAs changed between 1993 and 2010, and consists of three studies. The first study examined trends in the prescribing of these medications from 1993-2010, and whether these trends varied among patients with different socio-demographic and clinical characteristics. The second study sought to determine whether changes in prescribing of these medications was driven by changes in the number of physicians prescribing these medications, or the volume of prescriptions among BZD and nBZRA prescribing physicians, and whether these trends varied according to the age of the patients that the physician typically sees and the physician's specialty. Age of the patients is an important characteristic with regard to prescribing BZDs and nBZRAs because much of the clinical evidence regarding the harmful adverse effects of these medications has focused on older age patient groups. Finally, the third study examined the outcomes from a sample of emergency department

visits attributed to use of BZDs and nBZRAs, and assessed variations in these outcomes by age of patient at the visit.

The dissertation drew from data of two large nationally representative datasets: the National Ambulatory Medical Care Survey (NAMCS; studies 1 and 2) and the Drug Abuse Warning Network (DAWN; study 3). NAMCS is a nationally representative annual cross-sectional study that examines the delivery of health services in ambulatory healthcare settings. Physicians or their office staff were asked to report on a random sample of visits during a random one week interval. NAMCS provides data on diagnoses given, form of payment, and medications prescribed, among other variables. DAWN is a public health surveillance system of visits to emergency departments where a substance was the cause of or a contributing factor to the visit. Substances are defined broadly and consist of both illicit substances and pharmacological agents used both medically and non-medically. Data include information on all the substances and medications involved, the reason for the visit, and the disposition after discharge from the emergency department. Together, these large datasets provide unparalleled opportunities to assess trends in prescribing of BZDs and nBZRAs over the past two decades.

The current chapter provides a background for the dissertation's main studies. Specifically, it introduces the pharmacology of BZDs and nBZRAs, and reviews past research on prescribing trends of these agents. Finally, it describes efforts made to discourage the use and prescribing of these medications.

Pharmacology of sedative-hypnotic medications

Sedative-hypnotic medications elicit a calming physiological effect on the central nervous system. The first sedative-hypnotic that found common use was chloral hydrate,

a liquid bromide salt, that was first synthesized in 1832, and was eventually used clinically in the 1870s.[5] With the subsequent development of barbiturates, and later BZDs, a number of medications were made available to induce a sense of calm.

BZDs were first introduced in the 1950s in response to potential dangers in the use of barbiturates.[5,34] BZDs are currently prescribed for a variety of conditions including anxiety, insomnia, muscle spasms, and seizure disorders.[35] Barbiturates provided the same pharmacological effect as BZDs, but were considered to be dangerous because of the potential for dependence, withdrawal and toxicity.[36] BZDs act on the central nervous system by enhancing the effect of the gamma-aminobutyric acid (GABA) neurotransmitter.[35] GABA is an inhibitory neurotransmitter that suppresses central nervous system activity.[1] BZDs bind to GABA receptors and magnify the effect of GABA, resulting in augmentation of GABA's sedating and hypnotic effects. A list of the most commonly prescribed BZDs, their onset of action and elimination half-life is shown in Table 1.1, below.

BZDs vary in their onset of action and elimination half-life. Onset of action is defined by the length of time it takes for the pharmacological agent to elicit the desired effect on the human nervous system.[35] Elimination half-life is defined as the time it takes for the medication to lose half of its physiological effect.[35] Availability of BZDs with different profiles of onset of action and elimination half-life is useful for clinicians when treating specific conditions. For example, to induce a prolonged sense of calm, a physician could prescribe a BZD with a long elimination half-life, in which the effect of the medication will continue to be present for one to three days after administration. To promote sleep, a physician can prescribe a BZD with a rapid onset of action and short

elimination half-life to help the patient fall asleep quickly, with little pharmacological effect when the patient awakes in the morning. For a patient who falls asleep easily but has difficulty remaining asleep, a BZD with a slow onset of action and moderately long elimination half-life may be preferable.

Table 1.1: Benzodiazepines available in the US market

Generic	Brand	Indications	Onset (in hours)	Elimination half-life (in hours)
alprazolam	Xanax	Anxiety and panic disorders	1-2	6.3-26.9
clonazepam	Klonopin	Seizure and panic disorders	1-4	30-40
clorazepate	Tranxene	Anxiety disorders, partial seizures, acute alcohol withdrawal	--	40-50
chlordiazepoxide	Librium	Anxiety disorders, acute alcohol withdrawal	--	24-48
diazepam	Valium	Anxiety disorders	1-1.5	48
estazolam	Prosom	Insomnia	2	10-24
flurazepam	Dalmane	Insomnia	0.5-1	47-100
lorazepam	Ativan	Anxiety disorders	2	12-18
oxazepam	Alepam	Anxiety disorders	3	5.7-10.9
quazepam	Doral	Insomnia	2	39-73
temazepam	Restoril	Insomnia	1.2-1.6	3.5-18.4
triazolam	Halcion	Insomnia	2	1.5-5.5

Note: Table aggregates data collected from the Drug Information Portal (http://druginfo.nlm.nih.gov/drugportal/) from the National Library of Medicine. All data is for the *tablet* or *capsule* version of the medication.

nBZRAs are medications that, similarly to BZDs, bind to GABA receptors to enhance the sedating and hypnotic effects of GABA neurotransmitters. However, while BZDs non-selectively bind to all GABA receptors, the nBZRAs bind specifically to GABA-BZ receptors, and hence more selectively induce a sense of calm.[24] The first nBZRA, zolpidem (brand name: Ambien), was introduced in December 1992.[18] Since then, two other nBZRAs have been introduced: zaleplon (brand name: Sonata) introduced in August 1999,[20] and eszopiclone (brand name: Lunesta) in December 2004.[19] These agents were designed to have a significantly shorter onset of action and elimination half-life than the BZDs.[24] Their rapid onset of action makes them suitable for inducing sleep, and the fast elimination half-life make awaking in the morning easier. Table 1.2 below provides a summary of the three medications in this class available in the US market.

Table 1.2: Non-benzodiazepine receptor agonists available in the US market

Generic	Brand	Indications	Onset (in hours)	Elimination half-life (in hours)
zolpidem	Ambien	Insomnia	1.6	2.6
zaleplon	Sonata	Insomnia	1	1
eszopiclone	Lunesta	Insomnia	1	6

Note: Table aggregates data collected from the Drug Information Portal (http://druginfo.nlm.nih.gov/drugportal/) from the National Library of Medicine. All data is for the *tablet* or *capsule* version of the medication.

Prescribing trends up until the early 2000s

Prior to the 1970s, sedative-hypnotics were the drugs of choice for physicians treating psychiatric conditions.[37,38] Prior to the 1950s, bromide salts and barbiturates were the primary sedative-hypnotics prescribed. In 1955, meprobamate (brand name: Miltown) was introduced as a mild sedative, and quickly became hugely popular—in 1957, nearly a third of prescriptions filled were for the medication.[39] At the same time, BZDs were introduced and replaced use of meprobamate in the 1960s and 1970s when it was found

that meprobamate caused physical dependence.[39] From the 1970s to the early 1990s, there was a substantial decrease in use of sedative-hypnotic prescriptions among the general population.[37,40] Wysowski et al. found that the number of sedative-hypnotic prescriptions dispensed dropped from about 60 million in 1970 to roughly 30 million in 1989.[37] Interestingly, in this time there was a drastic drop in prescribing of barbiturates, and a marked increase in prescribing of BZDs, resulting in the majority of sedative-hypnotics prescribed in 1989 being BZDs.[37]

Studies show that prescribing of BZDs remained relatively unchanged through the 1990s;[28,29] however, there were large increases in prescribing of nBZRAs. Moloney at al. found a nearly 30-fold increase in prescribing of nBZRAs from 1993-2007.[30] Ford et al. also found that prescribing of nBZRAs increased nearly 300% from 1999-2010.[41] There is also evidence showing increases in ED visits related to use of BZDs[32] and nBZRAs[31] in recent years. One study found the number of ED visits involving zolpidem doubled from 2005-2010.[31]

Concerns about BZD and nBZRA safety

Beginning in the 1970s, concerns grew about the safety profile of BZDs. A number of studies showed an association between BZD use and falls[6,7] and hip fractures.[8,9,33] For example, Ray et al. found that use of long-acting BZDs was associated with an 80% increase in the odds of hip fractures compared to those not prescribed BZDs.[33] Studies also show that use of BZDs is associated with functional impairment.[10-12] For example, Gray et al. found that older adults prescribed BZDs were over 20% more likely to develop mobility difficulties, and almost 30% more likely to develop impairment in activities of daily living (ADL) than those not taking these agents.[11]

Physiological studies have also shown that use of BZDs by older adults is associated with impaired balance,[42,43] and lower physical strength and gait speed.[44]

Studies have also shown the use of nBZRAs to be associated with a number of the same adverse health outcomes as those from BZD use.[27,45-48] For example, Wang et al. found that the use of zolpidem was associated with a doubling of the risk for hip fractures among older adults.[27] Studies have also shown associations between the use of nBZRAs and functional impairment and impaired balance.[26,49-51] Most recently, studies showed the use of these medications to be associated with severe next day drowsiness that impair driving abilities,[52-55] increasing the risk of auto accidents.[52,56]

Efforts to discourage BZD and nBZRA prescribing

Due to safety concerns, there have been efforts to discourage the prescribing of these agents. For example, clinical guidelines have provided recommendations on the safe prescribing of these and other potentially dangerous medications.[13-15,17,57,58] The most commonly cited Beers Criteria[15-17] list medications that could potentially lead to adverse health outcomes when used by older adults. The most recently updated version of the Beers Criteria includes both BZDs and nBZRAs.[15] Physician organizations have also developed their own recommendations related to BZD and nBZRA use.[59,60] For example, the American Psychiatric Association in its guidelines for the treatment of panic disorder suggests that BZDs be used only as a short-term treatment.[59] The American Academy of Sleep Medicine guidelines for the treatment of insomnia recommend medications to be used only if behavioral treatments do not provide symptomatic relief.[60]

Monitoring programs have also sought to provide barriers to inappropriate prescribing of these medications. For example, New York state implemented a triplicate

prescribing program for BZDs which resulted in a decline of BZD prescribing by nearly half.[61] Some studies have assessed the efficaciousness of educational visits with prescribers that include discussions on safe prescribing of BZDs and nBZRAs.[62,63] Electronic medical records have also integrated reminders about potential dangers when prescribing BZDs and nBZRAs to patients at risk for adverse outcomes.[64]

Finally, there have been federal legislative efforts to discourage unsafe prescribing of these medications. With the implementation of Medicare Part D in 2006, BZDs were excluded from reimbursement.[65] The Food and Drug Administration has also lowered the recommended dose for prescribing of zolpidem, and later zaleplon and eszopiclone, to women.[66,67]

Unanswered questions

In light of research showing adverse health outcomes associated with the use of BZDs and nBZRAs, and the many efforts to discourage their use, more research is needed to understand trends in the use of these agents. We know little about the impact of the introduction of nBZRAs on prescribing of BZDs, and how these trends differed by different patient groups and different visit types. Further, we know little about the extent to which any change in prescribing of BZDs and nBZRAs is driven by the number of physicians prescribing these medications or the volume in prescribing per physician. Finally, in light of increased ED visits related to BZD and nBZRA use,[68,69] more research is needed to assess the outcomes of these visits. This dissertation addressed these questions to enhance understanding of sedative-hypnotic prescribing in recent years. The findings have potential implications for future policy initiatives aimed at curbing the un-

necessary use of these medications and reducing the adverse outcomes associated with their use.

Chapter 2: Trends in prescribing of benzodiazepines and non-benzodiazepine receptor agonists in the United States: 1993-2010

ABSTRACT

BACKGROUND: Non-benzodiazepine receptor agonists (nBZRAs) were developed as an alternative to benzodiazepines (BZDs) for the treatment of insomnia. However, little is known about how their introduction influenced trends in the use of BZDs. The purpose of this study was to describe trends in the prescribing of BZDs and nBZRAs between 1993 and 2010.

METHODS: Data came from the National Ambulatory Medical Care Survey, which consists of physician-reported information on patient visits. Our study included a total of 516,118 patient visits between 1993 and 2010. We categorized these visits as BZD, nBZRA, and BZD + nBZRA visits based on the medications prescribed during each visit. Linear probability regression models were used to assess trends in the proportion of all visits for the three visit types over the study period.

RESULTS: Between 1993 and 2010, there were increases in the proportion of visits that were BZD (from 2.6% in 1993 to 4.4% in 2010, $p<0.001$) and nBZRA visits (from 0% to 1.4%, $p<0.001$). We also found an increase in visits in which both BZDs + nBZRAs were prescribed (from 0% to 0.4%, $p<0.001$). While there was a large statistically significant increase in nBZRA visits for patients with a sleep disorder (B=0.099, 95% CI=0.045-

0.153), there was also a statistically significant decline in BZD visits for the same type of visit (B=-0.071, 95% CI=-0.128- -0.014).

CONCLUSION: The introduction of nBZRAs as a safer sedative-hypnotic option for treating insomnia likely resulted in declines in prescribing of BZDs for treatment of sleep disorders, but not among other groups of patients. Efforts should be made to encourage the delivery of behavioral treatments for anxiety disorders and insomnia to patients vulnerable to the adverse health outcomes associated with use of BZDs and nBZRAs.

BACKGROUND

As of 2013, it is estimated that 9 million adults in the United States use prescription medication to help them sleep.[70] The most common medications used to treat sleep disorders include benzodiazepines (BZDs) and non-benzodiazepine receptor agonists (nBZRAs).[2] Both are sedative-hypnotics that act on the GABA-A neurotransmitter receptor to induce a sedative effect and to promote sleep.[2] BZDs, the older of the two classes, were discovered in the early 1950s, and are approved by the Food and Drug Administration (FDA) for treatment of a broad range of disorders including anxiety and seizure disorders, as well as insomnia.[5] nBZRAs were introduced in the early 1990s, and are approved by the FDA for the short-term treatment of insomnia.[18-20]

The development of nBZRAs was prompted by concerns about the safety and tolerability of BZDs—which were shown to be associated with a number of unwanted side effects among older adults, including falls,[6,7] hip fractures,[8,9] cognitive impairment,[71] and disability.[10-12] Approved by the FDA in December 1992, zolpidem (marketed as Ambien) was the first nBZRA that entered the US market.[18] Since then, a number of other nBZRAs have been introduced, including zaleplon (brand name: Sonata, approved August 1999)[20] and eszopliclone (brand name: Lunesta, approved December 2004).[19] These nBZRAs were marketed as safer alternatives to the BZDs.[21,22,24]

Little is known about any possible changes in prescription of BZDs after the introduction of nBZRAs. Prior to the introduction of nBZRAs in the mid-1990s, BZDs were among the most common sedative-hypnotic medications prescribed.[72] Since their introduction in the 1950s, prescribing of this class of medications has increased

exponentially.[37] Wysowski et al. found that prescriptions dispensed for BZDs increased from 0.7 million prescriptions in 1970 to 17.9 million in 1989.[37] BZDs have been found to be most commonly used by women[73] and older adults.[74]

The extent to which BZDs and nBZRAs are prescribed together has not been examined. Co-administration of these medications could be dangerous due to the potential for adverse drug interactions.[75] The co-use of BZDs and nBZRAs is especially of concern in light of emerging evidence showing that nBZRAs may be associated with the same harmful side effects as BZDs. There have been a number of high profile cases of car accidents associated with the use of these medications in the popular media,[76,77] and some research indicates an association between use of nBZRAs and falls,[25,26] and hip fractures.[27] As a result, the FDA lowered the recommended doses for zolpidem in 2013, and for zaleplon and eszopliclone in 2014.[67]

The aim of this study was to describe national prescribing trends of both BZDs and NBZRAs from 1993-2010. We examined trends in the prescribing of these medications by patient and visit characteristics. We hypothesized that overall, there was an increase in prescribing of nBZRAs during the study period, coinciding with a decline in prescribing of BZDs among patients with an insomnia diagnosis.

METHODS

Data source

Data for this study came from the 1993-2010 waves of the National Ambulatory Medical Care Survey (NAMCS).[78] NAMCS is an annual cross-sectional survey conducted by the National Center for Health Statistics (NCHS), which examines the use

and delivery of health services in ambulatory healthcare settings in the United States.[79] Each year, a nationally representative sample of physicians is asked to report on a random selection of patient visits in a random week. Physicians are sampled using a multistage probability sampling design based on the American Medical Association Master File. From 1993-2010, the number of visits each year included in our analysis ranged from 20,760 to 36,875, resulting in a total study sample of 516,118 patient visits. Over the past 20 years, the response rates for NAMCS have ranged from 60-70%.

Measures

Prescription medications. For each visit, NAMCS lists all prescriptions and over-the-counter drugs that were "ordered, supplied, administered or continued" at a given patient visit. For the NAMCS 1993-2002 waves, up to 6 medications were recorded for each visit. Starting in 2003, the maximum number of medications recorded was increased to 8. To make the years comparable, we limited the maximum number of medications to 6 in all years (i.e., we only considered the first 6 medications listed). For the purposes of this study, nBZRAs were defined as zolpidem, zaleplon, and eszopiclone; BZDs were defined as alprazolam, clonazepam, chlorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam. We categorized each visit into one of the following four mutually exclusive groups: "no BZD nor nBZRA visits", "BZD visits," "nBZRA visits," and "BZD + nBZRA visits". In this paper we refer to the last three groups as "any sedative-hypnotic visits." Of note, other medications besides BZD and nBZRAs could have been prescribed at any of the visits. Other sedative-hypnotic medications were not examined in this study.

Patient characteristics. NAMCS recorded patients' demographic characteristics, including age (which we categorized as <25, 25-44, 45-64, and 65+ years), gender (female, male), and race/ethnicity (categorized as non-Hispanic white, non-Hispanic black, Hispanic, and other). NAMCS also recorded diagnoses related to the visit including the presence of "chronic conditions," identifying one "primary diagnosis," as well as two "other" diagnoses if applicable. NCHS staff coded diagnoses listed based on ICD-9 codes. Based on these three listed diagnoses, we identified patients as having either a sleep, anxiety, or mood disorder based on ICD-9 codes (sleep disorders: 307.40-307.49, 327.00-327.8, 780.50-780.59; anxiety disorders: 300.00-300.9; mood disorders: 296.00-296.99).

Visit characteristics. NAMCS also recorded whether the visit was by a new patient or an established patient, and whether a follow-up appointment was scheduled at the time of visit. The expected source(s) of payment for the visit was also recorded, which we categorized into private insurance, Medicare, Medicaid, self-pay, or other (including worker compensation, no pay, other, and unknown). Physician's specialty was ascertained from the American Medical Association Master File, and was confirmed with physicians when they were enrolled in the study. We categorized physicians as primary care physicians (including general/family practice and internal medicine), psychiatrists, and other (e.g., pediatrics, general surgery, urology, etc.).

Analyses

Analyses were conducted in three stages. First, we compared the characteristics of any sedative-hypnotic visit to visits where no sedative-hypnotic was prescribed using

bivariate logistic regression. The dependent variable in these analyses was the visit type (e.g., any sedative-hypnotic visit vs. no sedative-hypnotic visit), and the independent variables were the characteristics of the visit. To ascertain differences among the various types of sedative-hypnotic visits (i.e., BZD, nBZRA, and BZD + nBZRA visits), we compared both nBZRA visits and BZD + nBZRA visits to BZD visits using multinomial logistic regression. For example, the characteristics of nBZRA visits were compared to the characteristics of BZD visits, and the characteristics of BZD + nBZRA visits were also compared to the characteristics of BZD visits. These latter analyses were limited to any sedative-hypnotic visits.

Second, we examined trends in the prevalence of different visit types across time (BZD visits, nBZRA visits, and BZD + nBZRA visits) using logistic regression models. As suggested by the NCHS,[80] we binned years into 2-year windows in order to improve the reliability of our estimates, and assigned a number ranging from 1-9 based on these binned groups (e.g., 1 = "1993-1994," 2 = "1995-1996," etc.). Consistent with prior studies using the NAMCS,[81] this time indicator variable was then transformed by subtracting 1 and dividing by 8 (the range of values for the time variable). Thus, this transformed variable ranged from 0 to 1 and the resulting coefficients computed from the regression models represent changes in the odds of each type of visit over the entire study period (e.g., 1993-2010).

Because the prevalence of nBZRA prescriptions in the 1993-1994 period was very low, the logistic regression models produced very large odds ratios for the trends in prescriptions of these medications, limiting our ability to compare trends across medication classes. To represent trends in prescribing that were more comparable across

medication classes, we estimated the absolute change in prescription of these medications over time using linear probability regression models.[82] The outcome for these analyses was the dichotomous variable for the prescription of each medication type. The regression coefficients in the linear probability models represent change in prevalence of prescriptions for each medication type. Because results of statistical tests for the logistic regressions and linear probability models were quite similar, here we report results from linear probability models only.

The analyses were repeated after stratifying the sample based on patient and visit characteristics. Specifically, we stratified results by patient age, gender, race/ethnicity, new- or established-patient status, whether a follow-up was scheduled, main payment source, physician specialty, and diagnoses of sleep, anxiety and mood disorders. Finally, we statistically tested whether the trends in prescribing differed across strata by testing interaction terms of time with indicator variables identifying each stratum compared to all other strata. A statistically significant interaction term suggests that trends differ across strata. These tests adjusted for all patient and visit characteristics examined in our study.

RESULTS

Prevalence and characteristics of BZD and nBZRA visits

Among all patient visits from 1993-2010, there were 17,972 (3.5%, unweighted) BZD visits, 3,042 (0.6%, unweighted) nBZRA visits, and 884 (0.2%, unweighted) BZD + nBZRA visits. Among any visit for which a sedative hypnotic was prescribed (n=21,898), the majority were for patients aged 45 years or older (45-64 years old: 40.5%; 65+ years old: 30.8%), two-thirds involved women, and over four-fifths involved non-Hispanic

white patients (Table 1.1). Over one-fifth of all sedative-hypnotic visits were for patients diagnosed with an anxiety disorder, 11.0% for patients with a mood disorder, and 5.3% for those with a sleep disorder. The majority of any sedative-hypnotic visits were for new patients (92.8%) and involved scheduling a follow-up visit (96.6%). The most common payment sources for these visits were private insurance (48.0%), and Medicare (32.1%). Over half of the visits were with primary care doctors, and 19.1% were with psychiatrists. Compared to visits where no sedative-hypnotic was prescribed, visits where any sedative-hypnotic was prescribed were more likely to be for patients who were older than age 45 (71.3% vs. 51.4%), female (66.6% vs. 58.9%), non-Hispanic white (83.5% vs. 76.2%), diagnosed with a sleep (5.3% vs. 0.6%), anxiety (20.3% vs. 1.3%), or mood disorder (11% vs. 1.0%), to involve new patients (92.8% vs. 86.7%), to include scheduling of a follow-up appointment (96.6% vs. 92.3%), to be paid for by Medicare (32.1% vs. 22.5%) or to be self-pay (7.1% vs. 4.8%), and to involve a primary care physician (53.2% vs. 38.4%) or psychiatrist (19.1% vs. 2.3%). Compared to visits where no sedative-hypnotic was prescribed, visits where any sedative-hypnotics were prescribed were less likely to involve physicians with other specialty (27.7% vs. 59.3%) (all p's<0.001) (Table 2.1).

Compared to BZD visits, nBZRA visits were more likely to be for patients older than age 45 (77.7% vs. 70.2%), male (35.7% vs. 33.1%), of Hispanic ethnicity (8.6% vs. 7.0%) or other race (3.5% vs. 2.1%), and to be diagnosed with a sleep disorder (15.3% vs. 3.1%), and were less likely to be for patients diagnosed with an anxiety (6.1% vs. 22.6%) or mood disorder (7.6% vs. 11.2%), reimbursed by Medicare (31.3% vs. 32.7%), Medicaid (7.1% vs. 9.4%), to be self pay (4.3% vs. 7.7%), or reimbursed by another payment source (2.9% vs. 4.0%), and to involve a psychiatrist (11.2% vs. 19.9%) (all p's

<0.05) (Table 2.2). Compared to BZD visits, BZD + nBZRA visits were more likely to be with patients between age 25-64 (77.7% vs. 64.9%), diagnosed with a sleep (8.3% vs. 3.1%), anxiety (31.0% vs. 22.6%), or a mood disorder (22.0% vs. 11.2%), and to involve a psychiatrist (35.5% vs. 19.9%), and less likely to be reimbursed by Medicare (23.9% vs. 32.7%) (all *p*'s<0.008).

Temporal trends in prescriptions

The percentage of visits involving BZDs rose from 2.6% in 1993 to 4.4% in 2010 (B = 0.019, 95% Confidence Interval [CI] = 0.015-0.024, $p<0.001$) (Figure 2.1). Similarly, the percentage of visits involving nBZRAs increased from 0% in 1993 to 1.4% in 2010 (B = 0.015, 95% CI=0.013-0.016, $p<0.001$). The percentage of visits involving BZDs + nBZRAs increased from 0% in 1993 to 0.3% in 2010 (B = 0.004, 95% CI=0.003-0.004, $p<0.001$).

There were statistically significant increases in BZD visits across most patient and visit characteristics in stratified analyses (Table 2.3). However, there was a statistically significant decrease in BZD visits for patients diagnosed with a sleep disorder (B = -0.071, 95% CI=-0.128- -0.014), and no statistically significant change in BZD visits among patients from the heterogeneous "other" race/ethnicity, visits to psychiatrists, or in visits by patients diagnosed with an anxiety or mood disorder. There were significant interactions with the time variable for age, gender, race/ethnicity, and new patient status. The trend was less pronounced for visits by patients <25 years old compared to other age groups ($F[1, 4624] = 28.45$; $p<0.001$). In contrast, the trend was more pronounced in visits by patients in the 45-64 years age range compared to other age groups (F[1, 4624]

= 13.46; $p<0.001$), for females compared to males (F[1, 4624] = 6.56; $p=0.011$), non-Hispanic blacks compared to all other race/ethnicities (F[1, 4624] = 7.99; $p=0.005$), and for new patients compared to established patients (F(1, 4624) = 4.45; $p=0.035$).

There were increases in nBZRA visits across all patient and visit characteristics, with particularly large increases among visits with patients diagnosed with sleep disorders (B=0.099, 95% CI=0.045-0.153). There were significant interactions with the time variable for age, race/ethnicity, main payment source, physician specialty, and mood disorders. The trend was less pronounced for visits with patients <25 years old compared to other age groups (F[1, 4624] = 107.16; $p<0.001$), Medicaid reimbursement compared to other forms of reimbursement (F[1, 4624] = 5.55; $p=0.019$), and other physician specialty compared to primary care physicians and psychiatrists combined (F[1, 4624] = 28.24; $p<0.001$). The trend was more pronounced for visits with patients aged 45-64 compared to other age groups (F[1, 4624] = 20.88; $p<0.001$), for non-Hispanic whites compared to other race and ethnicities (F[1, 4624] = 6.67; $p=0.010$), for physicians with a primary care (F[1, 4624] = 17.81; $p<0.001$) and psychiatry specialty (F[1, 4624] = 7.20; $p=0.007$) compared to other specialties and for visits of patients with a mood disorder compared to all other visits (F[1, 4624] = 9.38; $p=0.002$).

Finally, there were increases in BZD + nBZRA visits by all patient and visit characteristics, except for visits with patients aged <25 years, with unscheduled follow-ups and those reimbursed by Medicaid. Significant interactions with time were found for age, gender, race, follow-up, main payment source, physician specialty, and all diagnoses. Trends were significantly less pronounced for visits with patients <25 years compared to all other age groups (F[1, 4624] = 42.30; $p<0.001$), for males compared to females (F[1,

4624] = 4.13; p=0.042), for the "other" racial group compared to all Hispanic and non-Hispanic whites and blacks (F[1, 4624] = 3.93; p=0.047), for visits reimbursed by Medicaid (F[1, 4624] = 4.35; p=0.037), and for other physician specialty versus psychiatry and primary care specialties combined (F[1, 4624] = 21.51; p<0.001). The trend was more pronounced for visits with patients aged 45-64 compared to all other age groups (F[1, 4624] = 5.38; p=0.020), for non-Hispanic whites compared to all other racial/ethnic groups (F[1, 4624] = 7.74; p=0.005), for visits with a scheduled compared to unscheduled follow-up (F[1, 4624] = 5.18; p=0.023), for visits with psychiatrists compared to all other physician specialties (F[1, 4624] = 20.82; p<0.001), for visits by patients with an anxiety disorder (F[1, 4624] = 19.46; p<0.001) or mood disorder diagnoses (F[1, 4624] = 13.79; p<0.001) compared to visits without those diagnoses.

DISCUSSION

This study examined trends in prescription of BZD and nBZRA agents overall and in different patient groups between 1993 and 2010. We found that during the study period, prescribing of nBZRAs as well as BZDs each rose, with increases seen in different patient group and visit types. We also found a substantial decline in prescribing of BZDs among patients with sleep disorders, coinciding with a dramatic increase in prescription of nBZRAs in visits involving these patients. This finding suggests that nBZRAs may have partly replaced BZDs in treatment of sleep disorders in this period.

Nevertheless, the introduction of nBZRAs does not appear to have impacted the overall BZD prescribing trend over our study period—rather, we observed a large increase in prescribing of BZDs after 2002. Although nBZRAs are only indicated for

short-term treatment of insomnia and thus unlikely to influence prescription of BZDs for other indications, the growing concerns about adverse health outcomes associated with the use of these medications[6-12,71] and the expanding indications of selective serotonin reuptake inhibitors for treatment of anxiety in addition to mood disorders[59,83] in this period do not appear to have reduced BZD prescriptions. This finding is surprising in light of prior studies in the US and other countries showing either no change or a decline in prescriptions for BZDs between the 1990s and early 2000s.[28,84,85] From our analyses, it appears that from 2002-2010, increases in prescribing of BZDs were particularly pronounced in visits to primary care doctors. This change in prescription patterns for BZDs in the primary care settings is in line with increased prescribing of other psychiatric medications in this setting and may indicate greater recognition or diagnosis of mental health problems.[86] Better understanding of these physicians' prescribing practices would help inform initiatives to improve the prescription of BZDs in this setting.

We also found that an increasing trend of co-prescribing of the two medication classes, with the strongest trend seen among visits to psychiatrists as well as those involving patients diagnosed with sleep, anxiety and/or mood disorders. The finding of increases in co-prescribing of BZDs and nBZRAs during the same visit is disconcerting, but is consistent with research indicating growing polypharmacy in outpatient psychiatry.[81] The risks associated with the use of BZDs are well established.[6-12,71] Evidence regarding the hazards of nBZRAs has also been growing.[25-27,67] The use of both BZDs and nBZRAs together in healthier populations has been shown to modestly increase the medications' sedative properties,[87] but there has been a dearth of studies examining drug-drug interactions in vulnerable population groups such as older adults.

Given that BZDs and nBZRAs act on the same GABA receptors, use of the two medication classes could potentially increase the hazards associated with the use of each. It is plausible that prescriptions for these medications were for different indications (e.g., BZDs for anxiety disorders and nBZRAs for insomnia), which would not be surprising given that anxiety disorders, like many other psychiatric conditions, are often associated with sleep problems.[2] However, given the risk associated with the use of these medications individually, and the lack of information about their possible interaction effects, combining them should be done with caution, especially in vulnerable populations.

Our study also found that prescription of BZDs and nBZRAs was very common among older patients, occurring in just under a third of visits for those aged 65+ years. This finding supports results from previous studies, which show a high prevalence of use of sedative-hypnotics among older adults.[88-92] Our study adds to this literature by showing that this pattern was consistent across BZD, nBZRA, and BZD + nBZRA visits.

In our study, visits reimbursed by Medicaid were less likely to result in prescriptions for nBZRAs, but there was no difference in terms of Medicaid reimbursement for BZD visits. This finding may reflect Medicaid formulary limitations or requirements for pre-authorization in some states. While little is known about the relative safety of nBZRAs, it is of concern that disadvantaged patients may not be receiving medications that may prove to be safer.

As nBZRAs gradually lose their patents, newer sleep-aids have been introduced into the market.[93] For example, zolpidem tartrate (brand name: Intermezzo) was introduced in November 2011, and is approved for treatment of middle of the night

awakenings.[94] Similarly, a new medication to help with regulating circadian rhythm abnormalities in blind patients (tasimelteon, brand name: Hetlioz) was approved by the FDA in January 2014.[95] The most recently approved insomnia medication, suvorexant (brand name: Belsomra) acts by blocking orexin (which promotes wakefulness).[96] Because patients in clinical trials submitted to the FDA are often healthier and younger than typical users of these medications in the real world, it will be important to fully examine the health consequences of these newer sedative-hypnotics in broader population samples.

Over the years, a number of non-pharmacological treatments for anxiety and insomnia have been developed.[97,98] Among these, cognitive behavioral therapy has proven effective in minimizing anxiety and improving overall quality of life.[99] Cognitive behavior therapy for insomnia has been shown to be more effective than the use of sedative-hypnotics in treating insomnia in the long term.[100] Greater efforts should be made to replace sedative-hypnotic prescribing with these non-pharmacological treatments in usual treatment settings.

This study had a number of limitations. First, data for the NAMCS are based on a single office visit. Many individuals, especially those with comorbid conditions, see multiple providers. Our estimates of BZD and nBZRA use may thus be conservative, and sedative-hypnotic prescribing may be even more prevalent than our study suggests. Second, all data on patient visits were reported by physicians or their office staff using medical records. Therefore, the data are prone to reporting and recording errors. It is also possible that data from busier offices with more patients may be less detailed or have more missing data than smaller office settings. Finally, NAMCS limits the number of

medications reported to six, but many individuals, especially older adults, are known to use a greater number of medications.[101]

In the context of these limitations, findings from this study provide a description of temporal trends in prescription of BZDs and nBZRAs over the past two decades. Prescriptions for these medications have been increasing despite concerns about their safety. While the introduction of nBZRAs may have led to fewer prescriptions for BZDs to those with sleep disorders, prescribing of BZDs to other patient groups still increased during the study period. Furthermore, the study recorded a concerning trend of co-prescription of these medication groups. As safer behavioral treatment alternatives are often available for many of the target conditions of these medications, efforts should be made to better educate providers and patients regarding these alternatives.

Figure 2.1: Trends in prescribing of benzodiazepine and non-benzodiazepine receptor agonists between 1993 and 2010, National Ambulatory Medical Care Survey

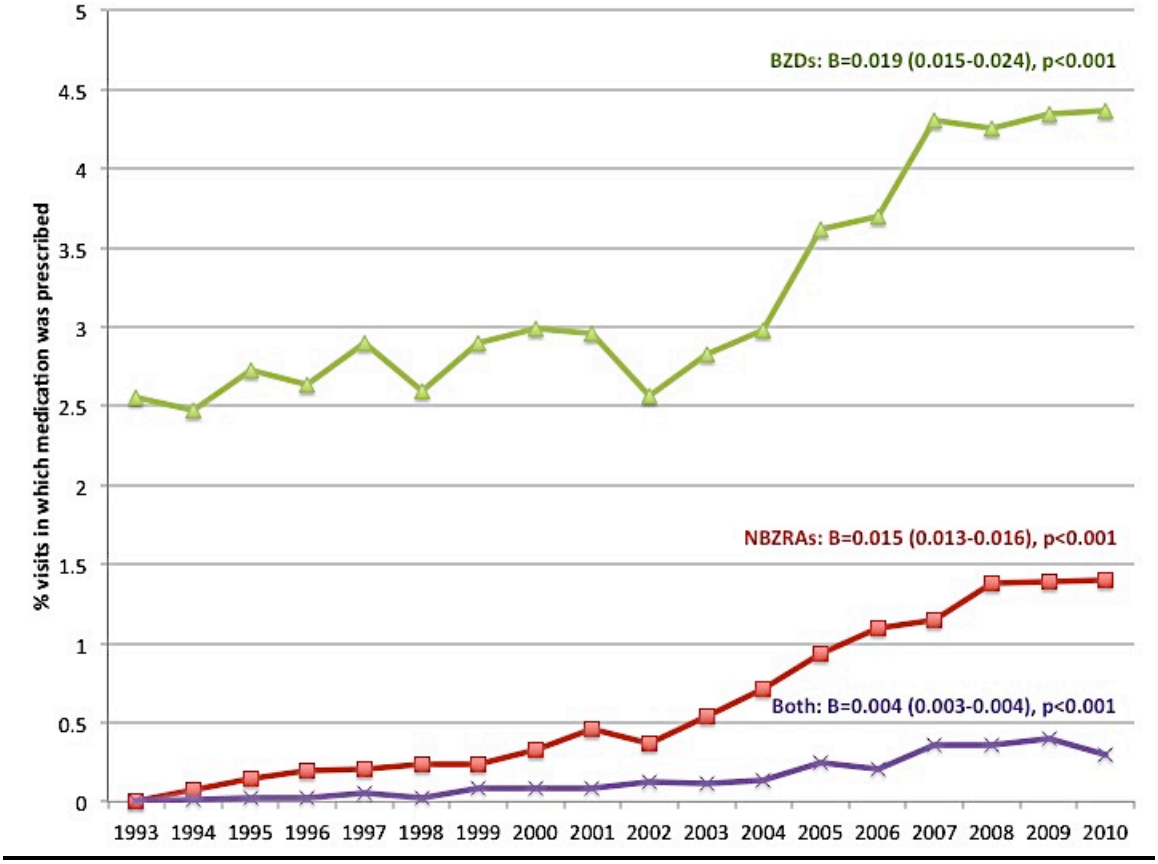


Table 2.1: Patient and visit characteristics of ambulatory healthcare office visits in which any sedative-hypnotic medications were prescribed, National Ambulatory Medical Care Survey 1993-2010

Patient and Visit Characteristic	No BZD[a] nor nBZRA[b] visits n=494,220 n (%[c])	Any sedative-hypnotic visits n=21,898 n (%[c])	Comparison OR (95% CI)
Age			
<25 years	113,595 (25.8)	1,011 (3.6)	Ref.
25-44	114,405 (22.7)	5,864 (25.1)	**7.83 (7.05, 8.69)**
45-64	135,242 (26.4)	8,872 (40.5)	**10.89 (9.81, 12.09)**
65+	130,978 (25.0)	6,151 (30.8)	**8.73 (7.83, 9.73)**
Gender			
Female	282,846 (58.9)	14,331 (66.6)	Ref.
Male	211,374 (41.1)	7,567 (33.4)	**0.72 (0.69, 0.75)**
Race			
Non-Hispanic White	382,100 (76.2)	18,430 (83.5)	Ref.
Non-Hispanic Black	45,667 (9.6)	1,418 (7.0)	**0.66 (0.60, 0.73)**
Hispanic	46,417 (10.0)	1,495 (7.3)	**0.66 (0.59, 0.74)**
Other	20,036 (4.2)	555 (2.3)	**0.50 (0.42, 0.58)**
Diagnosis			
Sleep	3,150 (0.6)	923 (5.3)	**9.21 (8.09, 10.48)**
Anxiety	8,540 (1.3)	4,773 (20.3)	**19.05 (17.69, 20.51)**
Mood	8,270 (1.0)	3,525 (11.0)	**11.82 (10.86, 12.88)**
Patient status			
New	412,100 (86.7)	19,851 (92.8)	Ref.
Established	79,959 (13.3)	1,994 (7.3)	**0.51 (0.47, 0.55)**
Follow-up[d]			
Scheduled	361,704 (92.3)	15,868 (96.6)	Ref.
Unscheduled	26,563 (7.7)	419 (3.4)	**0.42 (0.36, 0.50)**
Main payment source[e]			
Private insurance	188,546 (57.3)	7,950 (48.0)	Ref.
Medicare	83,253 (22.5)	5,170 (32.1)	**1.70 (1.59, 1.81)**
Medicaid	38,348 (10.5)	1,811 (9.0)	1.03 (0.92, 1.15)
Self-pay	19,834 (4.8)	1,651 (7.1)	**1.77 (1.57, 1.99)**
Other[f]	18,489 (4.9)	760 (3.8)	0.92 (0.79, 1.06)
Physician specialty			
Other specialty	347,896 (59.3)	7,955 (27.7)	Ref.
Primary care	125,835 (38.4)	7,152 (53.2)	**2.97 (2.73, 3.24)**
Psychiatry	20,489 (2.3)	6,791 (19.1)	**18.01 (16.18, 20.04)**

Note: All analyses account for the complex sampling design of the NAMCS, and are nationally representative.
[a] Benzodiazepines include: alprazolam, clonazepam, chlorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam.
[b] Non-benzodiazepine receptor agonists include: zolpidem, zaleplon, and eszopliclone.
[c] All percentages are weighted to make results nationally representative.
[d] This item was not assessed in 1997-1998, and 2009-2010.
[e] This item was not assessed in 1993-1996.
[f] Other payment source included worker compensation, no pay, other, and unknown.

Table 2.2: Comparison of patient and visit characteristics of ambulatory healthcare office visits involving benzodiazepines (BZD), non-benzodiazepine receptor agonists (nBZRA), and both classes (BZD + nBZRA), National Ambulatory Medical Care Survey 1993-2010

Patient and Visit Characteristic	BZD[a] visits n=17,972 n (%[c])	nBZRA[b] visits n=3,042 n (%[c])	Comparison nBZRA vs. BZD visits OR (95% CI)	BZD + nBZRA visits n=884 n (%[c])	Comparison BZD + nBZRA vs. BZD visits OR (95% CI)
Age					
<25 years	889 (4.0)	108 (2.4)	Ref.	14 (1.6)	Ref.
25-44	4,923 (25.9)	672 (20.0)	1.31 (0.96, 1.79)	269 (29.4)	**2.87 (1.33, 6.19)**
45-64	7,072 (39.0)	1,363 (46.5)	**2.03 (1.50, 2.75)**	437 (48.3)	**3.14 (1.47, 6.71)**
65+	5,088 (31.2)	899 (31.2)	**1.71 (1.24, 2.35)**	164 (20.7)	1.68 (0.76, 3.70)
Gender					
Female	11,783 (66.9)	1,931 (64.3)	Ref.	617 (69.1)	Ref.
Male	6,189 (33.1)	1,111 (35.7)	**1.12 (1.00, 1.26)**	267 (30.9)	0.90 (0.71, 1.15)
Race					
Non-Hispanic White	15,202 (84.1)	2,471 (80.6)	Ref.	757 (83.1)	Ref.
Non-Hispanic Black	1,148 (6.9)	215 (7.3)	1.11 (0.91, 1.34)	55 (6.9)	1.01 (0.68, 1.52)
Hispanic	1,190 (7.0)	248 (8.6)	**1.28 (1.03, 1.61)**	57 (8.0)	1.15 (0.76, 1.75)
Other	432 (2.1)	108 (3.5)	**1.77 (1.24, 2.52)**	15 (2.1)	1.01 (0.51, 1.98)
Diagnosis					
Sleep	455 (3.1)	408 (15.3)	**5.62 (4.66, 6.79)**	60 (8.3)	**2.83 (1.87, 4.29)**
Anxiety	4,263 (22.6)	248 (6.1)	**0.22 (0.19, 0.26)**	262 (31.0)	**1.54 (1.24, 1.91)**
Mood	2,877 (11.2)	388 (7.6)	**0.65 (0.55, 0.78)**	260 (22.0)	**2.24 (1.80, 2.80)**
Patient status					
New	16,283 (92.8)	2,750 (92.2)	Ref.	818 (93.2)	Ref.
Established	1,638 (7.2)	290 (7.8)	1.09 (0.90, 1.32)	66 (6.8)	0.94 (0.66, 1.35)
Follow-up[d]					
Scheduled	13,251 (96.5)	2,024 (97.1)	Ref.	593 (96.6)	Ref.
Unscheduled	355 (3.5)	55 (2.9)	0.83 (0.57, 1.21)	9 (3.4)	0.99 (0.45, 2.15)
Main payment source[e]					
Private insurance	6,083 (46.2)	1,440 (54.5)	Ref.	427 (53.6)	Ref.
Medicare	4,148 (32.7)	842 (31.3)	**0.81 (0.70, 0.94)**	180 (23.9)	**0.63 (0.48, 0.83)**
Medicaid	1,480 (9.4)	231 (7.1)	**0.64 (0.50, 0.82)**	100 (11.6)	1.07 (0.74, 1.54)
Self-pay	1,373 (7.7)	192 (4.3)	**0.47 (0.37, 0.60)**	86 (7.6)	0.85 (0.57, 1.25)
Other[f]	621 (4.0)	104 (2.9)	**0.60 (0.41, 0.88)**	35 (3.3)	0.71 (0.44, 1.14)
Physician specialty					
Other specialty	6,519 (27.3)	1,220 (31.3)	Ref.	216 (20.3)	Ref.
Primary care	5,756 (52.8)	1,168 (57.5)	0.95 (0.80, 1.12)	228 (44.3)	1.13 (0.87, 1.46)
Psychiatry	5,697 (19.9)	654 (11.2)	**0.49 (0.40, 0.60)**	440 (35.5)	**2.41 (1.82, 3.17)**

Note: All analyses account for the complex sampling design of the NAMCS, and are nationally representative.

[a] Benzodiazepines include: alprazolam, clonazepam, chlorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam.

[b] Non-benzodiazepine receptor agonists include: zolpidem, zaleplon, and eszopliclone.

[c] All percentages are weighted to make results nationally representative.

[d] This item was not assessed in 1997-1998, and 2009-2010.

[e] This item was not assessed in 1993-1996.

[f] Other payment source included worker compensation, no pay, other, and unknown.

Table 2.3: Stratified analyses for temporal trends in prescribing of benzodiazepine and non-benzodiazepine receptor agonists during ambulatory medical office visits, National Ambulatory Medical Care Survey 1993-2010

	Years[a]									Trend[b]	Interaction with Time[c]
	1993-1994	1995-1996	1997-1998	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010		
Patient and Visit Characteristics	%	%	%	%	%	%	%	%	%	B (95% CI),	F-statistic (df), p-value
BZD visits											
Age											
<25 years	0.26	0.32	0.29	0.65	0.46	0.66	0.63	0.62	0.76	**0.005 (0.003, 0.006)**	**F(1, 4624) = 28.45; <0.001**
25-44	2.74	3.03	2.70	3.08	3.33	3.86	4.06	5.06	5.42	**0.027 (0.021, 0.034)**	F(1, 4624) = 0.94; 0.332
45-64	3.79	4.15	3.96	4.13	3.78	4.00	5.30	6.19	5.93	**0.025 (0.017, 0.034)**	**F(1, 4624) = 13.46; <0.001**
65+	3.60	3.57	4.17	3.82	3.44	2.97	4.41	4.93	4.95	**0.013 (0.006, 0.021)**	F(1, 4624) = 0.06; 0.807
Gender											
Female	2.80	2.99	3.12	3.18	3.17	3.35	4.16	4.91	4.92	**0.023 (0.017, 0.029)**	**F(1, 4624) = 6.56; 0.011**
Male	2.08	2.24	2.16	2.61	2.17	2.27	2.95	3.38	3.56	**0.015 (0.010, 0.019)**	
Race											
Non-Hispanic White	2.64	2.73	3.14	3.26	3.01	3.22	4.12	4.84	4.90	**0.024 (0.018, 0.029)**	F(1, 4624) = 1.61; 0.204
Non-Hispanic Black	2.16	2.51	1.39	1.97	2.20	2.29	1.72	2.64	3.87	**0.014 (0.007, 0.021)**	**F(1, 4624) = 7.99; 0.005**
Hispanic	2.01	2.78	1.28	1.76	1.35	2.01	3.12	3.12	2.25	**0.009 (0.000, 0.018)**	F(1, 4624) = 0.72; 0.398
Other	1.38	1.84	1.08	1.55	1.58	1.02	1.31	2.64	1.89	0.007 (-0.002, 0.017)	F(1, 4624) = 1.24; 0.265
Patient status											
New	2.72	2.86	3.00	3.13	2.98	3.10	3.86	4.57	4.65	**0.020 (0.015, 0.025)**	**F(1, 4624) = 4.45; 0.035**
Established	1.41	1.63	1.17	1.87	1.17	1.38	2.23	2.40	2.52	**0.012 (0.006, 0.018)**	
Follow-up[d]											
Scheduled	2.67	2.82	--	3.06	2.92	3.05	3.79	4.36	--	**0.017 (0.011, 0.023)**	F(1, 4624) = 0.84; 0.359
Unscheduled	0.75	1.11	--	1.69	1.15	0.96	1.95	2.87	--	**0.016 (0.008, 0.025)**	
Main payment source[e]											
Private insurance	--	--	2.09	2.30	2.17	2.45	3.03	3.49	3.88	**0.025 (0.019, 0.032)**	F(1, 4624) = 2.33; 0.127
Medicare	--	--	4.68	4.66	4.15	3.71	5.23	5.94	5.64	**0.020 (0.008, 0.033)**	F(1, 4624) = 0.56; 0.454
Medicaid	--	--	2.37	2.69	2.83	2.44	3.36	3.99	3.28	**0.017 (0.003, 0.031)**	F(1, 4624) = 0.05; 0.820
Self-pay	--	--	4.17	5.07	4.36	5.45	6.07	7.17	6.36	**0.036 (0.011, 0.061)**	F(1, 4624) = 0.50; 0.479
Other[f]	--	--	1.64	2.05	2.57	3.51	2.95	3.97	4.85	**0.039 (0.024, 0.055)**	F(1, 4624) = 0.10; 0.753
Physician specialty											
Other specialty	0.98	1.22	1.07	1.22	1.04	1.32	1.84	2.11	2.50	**0.015 (0.010, 0.019)**	F(1, 4624) = 3.84; 0.050
Primary care	3.28	3.68	3.59	3.93	3.98	3.62	4.96	6.18	5.99	**0.029 (0.021, 0.036)**	F(1, 4624) = 2.88; 0.090
Psychiatry	21.98	17.94	23.61	21.09	20.31	21.99	23.45	23.54	22.82	0.027 (-0.018, 0.071)	F(1, 4624) = 0.36; 0.546

Diagnosis											
Sleep disorder	23.47	18.44	13.93	17.94	10.70	11.62	11.50	13.38	10.76	**-0.071 (-0.128, -0.014)**	F(1, 4624) = 1.01; 0.314
Anxiety disorder	32.33	38.02	36.14	34.85	32.18	35.66	34.97	37.82	35.84	0.018 (-0.031, 0.068)	F(1, 4624) = 0.23; 0.633
Mood disorder	25.81	31.85	25.79	24.15	22.90	24.23	26.13	25.67	24.29	-0.024 (-0.078, 0.030)	F(1, 4624) = 0.02; 0.884
nBZRA visits											
Age											
<25 years	0.01	0.01	0.03	0.02	0.06	0.06	0.12	0.09	0.11	**0.001 (0.001, 0.002)**	**F(1, 4624) = 107.16; <0.001**
25-44	0.03	0.17	0.14	0.31	0.31	0.63	1.08	1.43	1.01	**0.013 (0.011, 0.016)**	F(1, 4624) = 1.29; 0.255
45-64	0.04	0.28	0.39	0.54	0.67	0.95	1.67	2.01	2.28	**0.024 (0.021, 0.027)**	**F(1, 4624) = 20.88; <0.001**
65+	0.07	0.23	0.35	0.26	0.58	0.78	1.07	1.38	1.83	**0.017 (0.014, 0.020)**	F(1, 4624) = 0.46; 0.496
Gender											
Female	0.04	0.16	0.25	0.31	0.47	0.67	1.11	1.35	1.55	**0.016 (0.014, 0.018)**	F(1, 4624) = 2.48; 0.115
Male	0.03	0.19	0.18	0.25	0.33	0.55	0.88	1.13	1.18	**0.013 (0.011, 0.014)**	
Race											
Non-Hispanic White	0.04	0.19	0.26	0.28	0.44	0.68	1.04	1.42	1.52	**0.016 (0.014, 0.017)**	**F(1, 4624) = 6.67; 0.010**
Non-Hispanic Black	0.03	0.08	0.15	0.33	0.16	0.33	0.78	0.83	1.26	**0.012 (0.009, 0.015)**	F(1, 4624) = 2.38; 0.123
Hispanic	0.04	0.11	0.06	0.19	0.28	0.57	1.02	0.85	1.03	**0.012 (0.008, 0.015)**	F(1, 4624) = 1.84; 0.175
Other	0.00	0.19	0.07	0.47	0.71	0.49	0.99	0.91	0.62	**0.008 (0.004, 0.012)**	F(1, 4624) = 2.87; 0.090
Patient status											
New	0.03	0.18	0.24	0.32	0.44	0.66	1.05	1.33	1.50	**0.015 (0.014, 0.017)**	F(1, 4624) = 2.99; 0.084
Established	0.04	0.09	0.08	0.12	0.21	0.37	0.76	0.83	0.75	**0.009 (0.007, 0.011)**	
Follow-up[d]											
Scheduled	0.03	0.18	--	0.30	0.44	0.66	1.06	1.29	--	**0.014 (0.013, 0.016)**	F(1, 4624) = 3.71; 0.054
Unscheduled	0.03	0.07	--	0.16	0.13	0.17	0.33	0.83	--	**0.006 (0.003, 0.009)**	
Main payment source[e]											
Private insurance	--	--	0.17	0.31	0.39	0.58	1.05	1.33	1.31	**0.018 (0.015, 0.020)**	F(1, 4624) = 0.67; 0.413
Medicare	--	--	0.41	0.33	0.65	0.81	1.25	1.47	2.01	**0.023 (0.018, 0.028)**	F(1, 4624) = 1.52; 0.218
Medicaid	--	--	0.15	0.23	0.30	0.51	0.68	0.76	0.71	**0.009 (0.005, 0.012)**	**F(1, 4624) = 5.55; 0.019**
Self-pay	--	--	0.30	0.31	0.31	0.63	0.61	1.32	1.53	**0.017 (0.010, 0.023)**	F(1, 4624) = 0.09; 0.765
Other[f]	--	--	0.21	0.21	0.25	0.91	0.73	0.66	0.64	**0.008 (0.004, 0.012)**	F(1, 4624) = 3.30; 0.069
Physician specialty											
Other Specialty	0.02	0.11	0.11	0.08	0.21	0.26	0.56	0.68	0.84	**0.008 (0.007, 0.010)**	**F(1, 4624) = 28.24; <0.001**
Primary care	0.04	0.20	0.29	0.48	0.58	0.96	1.48	1.94	2.15	**0.023 (0.019, 0.026)**	**F(1, 4624) = 17.81; <0.001**
Psychiatry	0.22	1.05	1.53	1.57	2.23	2.87	4.13	4.21	3.52	**0.039 (0.030, 0.047)**	**F(1, 4624) = 7.20; 0.007**
Diagnosis											
Sleep disorder	2.31	5.70	6.58	13.39	10.42	11.94	13.99	16.60	13.72	**0.099 (0.045, 0.153)**	F(1, 4624) = 1.93; 0.165
Anxiety disorder	0.27	0.62	1.30	1.13	1.58	2.05	2.90	3.06	2.82	**0.028 (0.020, 0.037)**	F(1, 4624) = 2.00; 0.158

Mood disorder	0.51	1.85	2.43	2.47	2.58	3.02	5.55	6.19	3.78	**0.042 (0.029, 0.056)**	**F(1, 4624) = 9.38; 0.002**
BZD + nBZRA Visits											
Age											
<25 years	0.00	0.00	0.00	0.03	0.00	0.00	0.01	0.02	0.02	0.000 (0.000, 0.000)	**F(1, 4624) = 42.30; <0.001**
25-44	0.00	0.04	0.05	0.10	0.12	0.15	0.34	0.45	0.57	**0.006 (0.004, 0.007)**	F(1, 4624) = 1.09; 0.296
45-64	0.01	0.02	0.07	0.17	0.16	0.20	0.38	0.62	0.58	**0.007 (0.005, 0.008)**	**F(1, 4624) = 5.38; 0.020**
65+	0.01	0.03	0.03	0.01	0.13	0.11	0.18	0.32	0.23	**0.003 (0.002, 0.004)**	F(1, 4624) = 0.02; 0.882
Gender											
Female	0.01	0.03	0.04	0.08	0.12	0.14	0.28	0.42	0.42	**0.005 (0.004, 0.005)**	**F(1, 4624) = 4.13; 0.042**
Male	0.00	0.02	0.02	0.08	0.08	0.10	0.16	0.28	0.25	**0.003 (0.002, 0.004)**	
Race											
Non-Hispanic White	0.01	0.03	0.04	0.08	0.11	0.13	0.25	0.42	0.40	**0.004 (0.004, 0.005)**	**F(1, 4624) = 7.74; 0.005**
Non-Hispanic Black	0.00	0.00	0.01	0.17	0.01	0.14	0.18	0.19	0.22	**0.002 (0.001, 0.004)**	F(1, 4624) = 2.97; 0.085
Hispanic	0.00	0.00	0.02	0.03	0.19	0.08	0.18	0.24	0.21	**0.003 (0.001, 0.004)**	F(1, 4624) = 2.85; 0.091
Other	0.00	0.01	0.00	0.03	0.00	0.00	0.10	0.15	0.28	**0.003 (0.001, 0.004)**	**F(1, 4624) = 3.93; 0.047**
Patient status											
New	0.01	0.03	0.04	0.09	0.11	0.13	0.25	0.39	0.37	**0.004 (0.003, 0.005)**	F(1, 4624) = 2.22; 0.136
Established	0.00	0.01	0.02	0.01	0.04	0.04	0.11	0.19	0.25	**0.002 (0.002, 0.003)**	
Follow-up[d]											
Scheduled	0.01	0.03	--	0.08	0.11	0.12	0.24	0.37	--	**0.004 (0.003, 0.005)**	**F(1, 4624) = 5.18; 0.023**
Unscheduled	0.00	0.00	--	0.15	0.07	0.05	0.01	0.18	--	0.001 (0.000, 0.003)	
Main payment source[e]											
Private insurance	--	--	0.03	0.07	0.08	0.09	0.23	0.35	0.36	**0.005 (0.004, 0.006)**	F(1, 4624) = 0.01; 0.93
Medicare	--	--	0.06	0.04	0.15	0.12	0.21	0.37	0.32	**0.004 (0.003, 0.006)**	F(1, 4624) = 0.13; 0.718
Medicaid	--	--	0.04	0.33	0.18	0.11	0.19	0.26	0.33	0.002 (-0.001, 0.005)	**F(1, 4624) = 4.35; 0.037**
Self-pay	--	--	0.06	0.07	0.12	0.27	0.24	0.87	0.52	**0.009 (0.004, 0.014)**	F(1, 4624) = 3.48; 0.062
Other[f]	--	--	0.02	0.05	0.05	0.30	0.17	0.24	0.22	**0.003 (0.001, 0.005)**	F(1, 4624) = 0.53; 0.466
Physician specialty											
Other Specialty	0.00	0.01	0.01	0.02	0.03	0.02	0.08	0.12	0.15	**0.001 (0.001, 0.002)**	**F(1, 4624) = 21.51; <0.001**
Primary care	0.01	0.02	0.01	0.12	0.15	0.11	0.20	0.45	0.46	**0.005 (0.004, 0.006)**	F(1, 4624) = 0.02; 0.879
Psychiatry	0.08	0.42	0.92	0.72	0.95	1.94	3.64	4.10	3.37	**0.041 (0.032, 0.051)**	**F(1, 4624) = 20.82; <0.001**
Diagnosis											
Sleep disorder	0.00	1.17	0.00	0.00	0.76	0.61	1.05	3.43	2.70	**0.036 (0.019, 0.052)**	**F(1, 4624) = 4.95; 0.026**
Anxiety disorder	0.09	0.60	0.51	1.02	1.26	1.95	4.25	5.08	3.87	**0.050 (0.037, 0.063)**	**F(1, 4624) = 19.46; <0.001**
Mood disorder	0.20	0.73	1.28	1.29	1.70	1.69	4.47	4.68	3.26	**0.041 (0.030, 0.052)**	**F(1, 4624) = 13.79; <0.001**

Note: Benzodiazepines include: alprazolam, clonazepam, chlorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam. Non-benzodiazepine receptor agonists include: zolpidem, zaleplon, and eszopliclone.

[a] Statistics correspond to the percentage of visits in a specific year that resulted in a prescription for the respective medication within each patient and visit characteristic, and are weighted to make results nationally representative.
[b] Statistics are from linear probability regression models of absolute change in percentage of patient visits resulting in prescription for respective medications across the entire study period (1993-2010); B = beta coefficient for time, 95% CI = 95% Confidence Interval.
[c] *p*-values are from Wald statistics for interaction coefficients of time with the respective patient and visit characteristic vs. all other visits. Adjusted for all patient and visit characteristics.
[d] Inquires of follow-up scheduled was not asked in the NAMCS sample of doctors in 1997-1998, as well as 2009-2010.
[e] Main payment sources was not assessed in the NAMCS sample of doctors in 1995-1996.
[f] Other payment source includes worker compensation, no pay, other, and unknown.

Chapter 3: Changes in physician prescribing of benzodiazepines and non-benzodiazepine receptor agonists between 1993 and 2010

ABSTRACT

BACKGROUND: Prescribing of benzodiazepines (BZDs) and non-benzodiazepine receptor agonists (nBZRAs) has increased over the past two decades, but little is known about the reasons for these increases. The purpose of this study was to investigate whether the increase in prescribing of BZDs and nBZRAs could potentially be attributed to an increase in the number of physicians prescribing these agents, or an increase in prescribing volume per prescribing physician.

METHODS: We used data from 21,860 physicians from the 1993-2010 waves of the National Ambulatory Medical Care Survey. We categorized physicians as BZD prescribers and as nBZRA prescribers separately if they reported prescribing the respective medication during at least one of a series of sampled visits during a randomly selected one-week period. We assessed trends in the proportion of physicians prescribing these agents using logistic regression and trends in the number of visits in which these agents were prescribed per prescribing physician using zero-truncated negative-binomial regression models.

RESULTS: Overall, there was an increase over time in the proportion of all physicians who were BZD prescribers and nBZRA prescribers. The proportion of physicians who were BZD prescribers increased from 23.8% in 1993-1994 to 44.4% in 2009-2010 (Odds

Ratio [OR]=2.51, 95% Confidence Interval [CI]=2.31-2.74) and the proportion of physicians who were nBZRA prescribers increased from 1.0% to 25.8% (OR=16.79, 95% CI=14.38-19.60). Among nBZRA prescribers, the predicted number of visits resulting in a prescription for an nBZRA increased from 1.33 in 1993-1994 to 1.72 in 2009-2010 (Incidence Rate Ratio=2.42, 95% CI=1.70-3.44); there was no change in the predicted number of visits resulting in a BZD prescription per BZD prescribing physicians.

CONCLUSIONS: The increase in prescribing of BZDs is due to an increase in number of prescribers of these medications, but not prescribing volume per prescribing physician. The increase in prescribing of nBZRAs is due to increases in both the number of prescribers and the prescribing volume of individual prescribers. With the growing prescribing of BZDs and nBZRAs, it will be important to educate physicians who prescribe these medications on the potential adverse effects associated with the use of these agents.

BACKGROUND

Pharmacological options for the treatment of insomnia have increased over the past two decades. Currently, a number of pharmacological agents to treat insomnia exist,[1-3] but the most commonly prescribed are benzodiazepines (BZDs) and non-benzodiazepine receptor agonists (nBZRAs).[102,103] BZDs, which were introduced in the 1960s and have a range of indications including anxiety and sleep disorders, were later found to be associated with a number of adverse health outcomes such as falls and hip fractures,[8,9,33] as well as disability, especially in older adults.[10-12,104] The introduction of nBZRAs was in part motivated by concern about the dangers of BZDs; however, research suggests that these medications might have some of the same harmful side effects as BZDs.[27,45,50,105,106]

Despite the concerns regarding adverse side effects, prescribing of BZDs and nBZRAs has increased in the past decade.[41,70,107,108] Ford et al. found nearly a 300% increase in prescriptions for sleep medications from 1999 to 2010.[41] Furthermore, it was estimated that in 2013 nearly 9 million Americans took medications to help induce sleep.[107]

These dramatic increases in prescribing of sleep medications are at odds with studies showing trends in prevalence of insomnia diagnoses over time. While some studies have shown small decreases in the amount of and satisfaction with sleep,[109-111] the changes in sleep quality are not proportional to the increasing rate in prescribing of sleep-aids.[30,41,70,107,108] For example, a recent study by Moloney et al. showed that prescriptions for sleep medications from 1993-2007 far outpaced the rate of diagnosis of insomnia,

suggesting that physicians may perhaps be over treating transient or mild sleep disturbances with these potentially dangerous medications.[30]

More studies about the role of physicians in the increasing prescription rate of these medications are needed. The increase in prescribing of BZDs and nBZRAs can be due to an increase in the number of physicians who prescribe these medications, or an increase in the volume of prescribing among physicians who already prescribe these medications. The different reasons for the prescription trends call for different policy responses and interventions aimed at reducing potentially unnecessary prescription of these hypnotic medications. To explore the potential reasons for recent trends in prescription of BZDs and nBZRAs, we examined trends in the number of prescribing physicians and in the number of visits to prescribing physicians in which these medications were prescribed over the 1993-2010 period. We also explored variations in these trends based on the age of the patients and physician specialty.

METHODS

Data source

Data for this study came from the 1993-2010 waves of the National Ambulatory Medical Care Survey (NAMCS). NAMCS is an annual cross-sectional study conducted by the National Center for Health Statistics (NCHS) that examines the delivery of services in ambulatory healthcare settings in the United States. The study samples physicians using a multi-stage probability sampling design based on the American Medical Association's Master File. Physicians or their staff were asked to report on randomly selected visits to their practices during a random one-week period. The number

of physicians who participated each year between 1993 to 2010 ranged from 2,036 to 3,001, resulting in a combined sample of 21,860 physicians who reported on 516,118 visits. Physicians in our sample reported on an average of 23.6 visits (standard deviation=11.5, range=1-194). The response rates ranged from 60-70% across the years.

Measures

Medications. Physicians were asked to report on any medications that were ordered or prescribed during each of their sampled visits. Between 1993 and 2002, physicians could report on a maximum of six medications per visit. This maximum was increased to eight from 2003 to 2010. We limited the maximum number of medications to six across years to make years comparable. The large majority of visits were prescribed less than six medications (median number=1). To assess the impact of the decision to limit medications prescribed to 6, we compared the proportion of physicians who were categorized as BZD or nBZRA prescribers based on the 6- and 8-medication counts for years 2003-2010. The proportions were very similar for both BZD prescribers (39.4% vs. 40.8%) and nBZRA prescribers (19.6% vs. 21.0%). BZDs for this study comprised alprazolam, clonazepam, chlorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam. nBZRAs comprised zolpidem, zaleplon, and eszopliclone.

Age of patient population. Physicians reported on the age of the patient seen at the visit. Based on this, we calculated the percentage of a physician's sampled visits that were for those aged 65 or older and categorized each physician according to whether or

not they treated mostly older adults (defined as >50% of their sampled patients being age 65 or older).

Physician specialty. Physicians were asked to confirm their specialty listed on the AMA Masterfile. We categorized these specialties as primary care (which included "general/family practice" and "internal medicine"), psychiatry, and other specialty.

Other measures. On induction into the study, physicians reported on the region in which they practiced (i.e., Northeast, Midwest, South, and West) and whether their practice was in an urban or rural environment.

Analyses

Analyses were conducted in two stages. First, we assessed how the proportion of physicians who prescribed BZD and nBZRA medications changed over time. We dichotomized physicians based on whether or not they prescribed each respective medication during at least one of their reported visits. We assessed trends using bivariate logistic regression models with time as the predictor and whether or not the physician was a BZD or an nBZRA prescriber as the outcome. We repeated these analyses stratified by age of the sampled patient population (i.e., ≤50%, >50% over age 65) and by physician specialty (i.e., primary care, psychiatry, and other specialty). To test differences in trends across these groups, we introduced interaction terms between the year variable and the patient age as well as with physician specialty. A statistically significant interaction term would suggest that the trend is different across groups. We then conducted multivariable regression analyses adjusting for patient age and physician specialty in addition to region, and urban vs. rural location of the practice.

Second, limiting our sample to BZD and nBZRA prescribers respectively, we assessed whether the number of visits per prescriber changed over time. Because we limited our sample to prescribers of the respective medications for these analyses, none of the count of visits had a value of 0, making Poisson or negative-binomial regression models inappropriate. We therefore used zero-truncated negative-binomial regression. We set the offset variable for these models as the total number of reported visits in which a medication was prescribed per physician. In addition, based on the bivariate models, we reported at each time point the predicted number of visits in which the medication was prescribed among prescribers of the medication respectively. Similar to above, we stratified results by the age of the sampled patient population and physician specialty, tested for differences in trends across groups using interaction terms, and conducted adjusted analyses controlling for the variables mentioned above.

As suggested by the NCHS,[80] we aggregated time into 2-year bins to enhance stability of the estimates and numbered them with values from 1 to 9 (e.g., 1 = "1993-1994," 2 = "1995-1996," etc.). We then transformed this time variable by subtracting 1 and dividing by 8. The resulting time variable thus ranged from 0 to 1, enabling us to interpret the regression coefficients for this variable as change across the entire study period.

While the NAMCS offers visit-level survey weights to account for the complex sample design and make results nationally representative, we did not weight our analyses because NAMCS does not provide physician-level weights for all years. As a sensitivity analysis, we computed misspecification effects for all statistically significant analyses reported here for years 2005-2010, using physician sampling weights for years 2005-

2010 provided by NAMCS. We multiplied all standard errors from unweighted regression models of the main analyses for years 1993-2010 by these misspecification effects, assuming that the misspecification effects for all included years were similar to those for the 2005-2010 years for which data were available. The results of these sensitivity analyses were for the most part similar to those from the unweighted analyses (see Supplemental Table 3.1)—we therefore report only the unweighted analyses results here. All analyses were conducted in Stata SE version 13 (StataCorp, College Station, TX).

RESULTS

Trends in proportion of physicians who prescribed BZDs and nBZRAs

The proportion of physicians who prescribed BZDs during at least one of their reported visits increased from 23.8% (n=713) in 1993-1994 to 44.4% (n=1,144) in 2009-2010 (Figure 3.1 and Table 3.1, odds ratio [OR]=2.51, 95% Confidence Interval [CI]=2.31-2.74). In stratified analyses, all subgroups saw a statistically significant increase in proportion of physicians who prescribed BZDs. The trend was statistically significantly stronger for physicians in other specialties (OR=2.84, 95% CI=2.53-3.19) and primary care (OR=2.19, 95% CI=1.85-2.59), compared to psychiatry (OR=1.48, 95% CI=1.01-2.16). No trend differences were observed between physicians whose sampled visits included mostly older patients compared to other patients. Similar patterns were seen after adjustment for potential confounders.

The proportion of physicians who prescribed nBZRAs during at least one of their reported visits increased from 1.0% (n=29) in 1993-1994 to 25.7% (n=664) in 2009-2010

(Figure 3.1 and Table 3.1; OR=16.79, 95% CI=14.38-19.60). Increases were seen across all subgroups analyzed. The trend was stronger among other specialty (OR=26.39, 95% CI=20.59-33.83) compared to primary care (OR=16.31, 95% CI=12.50-21.27) and psychiatry (OR=11.79, 95% CI=8.01-17.36). No differences were observed in trends according to the age of patient population. Similar patterns were seen after adjustment for potential confounders.

Trends in number of visits in which a BZD or nBZRA was prescribed among prescribers of respective medications

Overall, the number of BZD visits increased from 1,875 in 1993-1994 to 3,149 in 2009-2010 (Figure 3.1). The predicted number of visits that were BZD visits among BZD prescribers remained virtually unchanged from 1993-2010 (Table 3.2). In zero-truncated negative-binomial regression models, we also observed no increases in this trend among most groups except for other specialty (Incidence Rate Ratio [IRR]=1.29, 95% CI=1.10-1.52) and primary care (IRR=1.63, 95% CI=1.39-1.90). While the trend for primary care was stronger than for "other specialty," no differences were observed in the trends between physicians who mostly saw older patients. After adjustment for confounders, the adjusted incidence rate ratio (AIRR) became positive among all physicians (AIRR=1.35, 95% CI=1.24-1.47), among physicians whose sampled patients were younger (AIRR=1.38, 95% CI=1.26-1.53) as well as physicians most of whose sampled patients were 65+ years old (AIRR=1.22, 95% CI=1.01-1.48). In further analyses, we found that this discrepancy in magnitude of the AIRR was due to a steeper trend in the proportion of BZD prescribing psychiatrists whose sampled patients were

younger (from 41.4% in 1993-1994 to 60.8% in 2009-2010 vs. 72.1% in 1993-1994 to 77.0% in 2008-2010 for psychiatrists overall).

The number of nBZRA visits increased from 32 in 1993-1994 to 1,101 in 2009-2010 (Figure 3.1). The predicted number of visits that were nBZRA visits among nBZRA prescribers increased from 1.33 in 1993-1994 to 1.72 in 2009-2010 (IRR=2.42, 95% CI=1.70-3.44) (Table 3.2). An increasing trend was seen across all subgroups analyzed. Physicians practicing in primary care saw a greater increase in the average number of nBZRA visits (IRR=7.29, 95% CI=4.14-12.83) compared to "other specialty" (IRR=2.76, 95% CI=1.48-5.15). No differences were observed between physicians according to patient age. Results did not change appreciably after adjustment for confounders.

Sensitivity analyses

For the main analyses reported above, we categorized physicians as either BZD prescribers or nBZRA prescribers based on whether they prescribed the medications in at least one visit; however this threshold may have been too low. We therefore conducted two series of sensitivity analyses for the analyses on proportion of physicians who prescribed these medications: (a) by changing the threshold for categorizing physicians as BZD prescribers or nBZRA prescribers to those who prescribed the medications during two or more visits, and (b) limiting the sample to physicians who reported on at least 10 visits. Results from these sensitivity analyses showed a similar positive statistically significant trend in the number of physicians prescribing BZDs and nBZRAs (see Supplemental Table 3.2).

DISCUSSION

A number of studies have found that prescribing of BZDs and nBZRAs have increased over the past two decades.[41,70,107,108] The purpose of this study was to determine whether the increase in prescribing of these agents from 1993 to 2010 reflects an increase in the number of physicians prescribing these medications, or an increase in the number of visits in which these physicians prescribe the medications. Overall, our study had two main findings.

First, we found increases in the proportion of physicians who prescribed BZDs and those who prescribed nBZRAs. It is not surprising to see growth in the number of nBZRA-prescribing physicians given that this medication class was first introduced in 1993. However, the increase in number of BZD prescribers is surprising—particularly in light of greater awareness in recent years about the dangers in use of these agents in some cases and availability of other pharmacological and non-pharmacological treatments for insomnia and anxiety disorders, including nBZRAs for insomnia.[8,10,11,33,104] In stratified analyses, we found that the increase in BZD prescribers was driven by larger increases among physicians in other specialties besides psychiatry, and in primary care. This finding is in line with studies showing increases in psychotropic prescribing in primary care practices.[112-114] Indeed, Olfson, et al. found that prescribing of BZDs to older adults in 2008 was most common among non-psychiatrists.[115] Taken together, these findings call for programs that educate primary care physicians and other non-psychiatrists on the potential adverse effects of these medications.

Second, while we found no overall increase in the number of visits in which a BZD was prescribed among BZD prescribers, there were significant increases for nBZRA

visits among nBZRA prescribers. With the greater acceptance in prescribing of nBZRAs over the past two decades, the frequency of prescribing likely increased as well. The increasing trend was particularly large among doctors in primary care, a finding that confirms previous studies showing an increase in prescribing of psychiatric medications in primary care offices.[114] While we did not see an increase in the number of visits in which a BZD was prescribed among BZD prescribers, we did observe a statistically significant increase among physicians in other specialties and in primary care. This finding suggests that another contributor to the increase in prescribing of BZDs is increased volume in prescribing by non-psychiatry physicians.

It is interesting to note that we did not observe differences in trends for proportion of prescribers and volume per prescriber of BZDs and nBZRAs between physicians according to patient age. With the growing awareness among physicians about the potential adverse effects of these agents in older adults, it is surprising that physicians who saw mostly older adults did not have different trends in prescribing than those seeing mostly younger patients. Numerous clinical guidelines caution against prescribing BZDs and other sedatives to older adults;[15,57,58] for example, the Beer's Criteria[15] lists both BZDs and nBZRAs as potentially dangerous medications that should be avoided when prescribing to older adults.

With the growth in the number of BZD and nBZRA prescribers, it is important that efforts be made to communicate best prescribing practices to physicians. A number of physician organizations and foundations have introduced guidelines for safe prescribing of BZDs and nBZRAs. For example, the American Psychiatric Association provides guidelines on the treatment of Panic Disorder, and suggests that BZDs be used

only for short-term treatment.[116] The American Academy of Sleep Medicine guidelines on the treatment of insomnia suggest that physicians prescribe nBZRAs only as a short-term treatment if behavioral interventions were not effective.[60] Many of these guidelines, however, target physicians with specific specialties, and as our study shows, over the years there has been a growth in prescribing of BZDs and nBZRAs among many physician specialties, including those in primary care and non-psychiatric specialties. It will be important that future guidelines be developed for a broader audience of physicians.

A number of initiatives to encourage safe prescribing practices of BZDs have been introduced.[117-119] These include educational material targeting high-volume prescribers,[62,63] as well as full-fledged audits of medications prescribed by physicians.[119,120] While research on the efficaciousness of these interventions to reducing BZD prescribing is conflicting,[121] the most effective interventions appear to include combining patient education with pharmacy and physician involvement.[120] There have been few initiatives to discourage unsafe prescribing of nBZRAs and the impact of educational efforts and guidelines on prescription of these medications has rarely been examined. Due to emerging evidence showing nBZRAs to be associated with dangerous side effects,[27,45,50,105,106] it will be important to develop such interventions for nBZRAs and to investigate their impact.

There are a number of behavioral treatments for sleep and anxiety disorders that have shown to be as effective, if not more so, than BZDs and nBZRAs.[98,99] One notable example is cognitive behavioral therapy for insomnia (CBT-i), which combines sleep restriction therapy,[122] stimulus control,[123] sleep hygiene education, and relapse prevention in regularly scheduled meetings with clinicians.[98] While these treatments show promise,

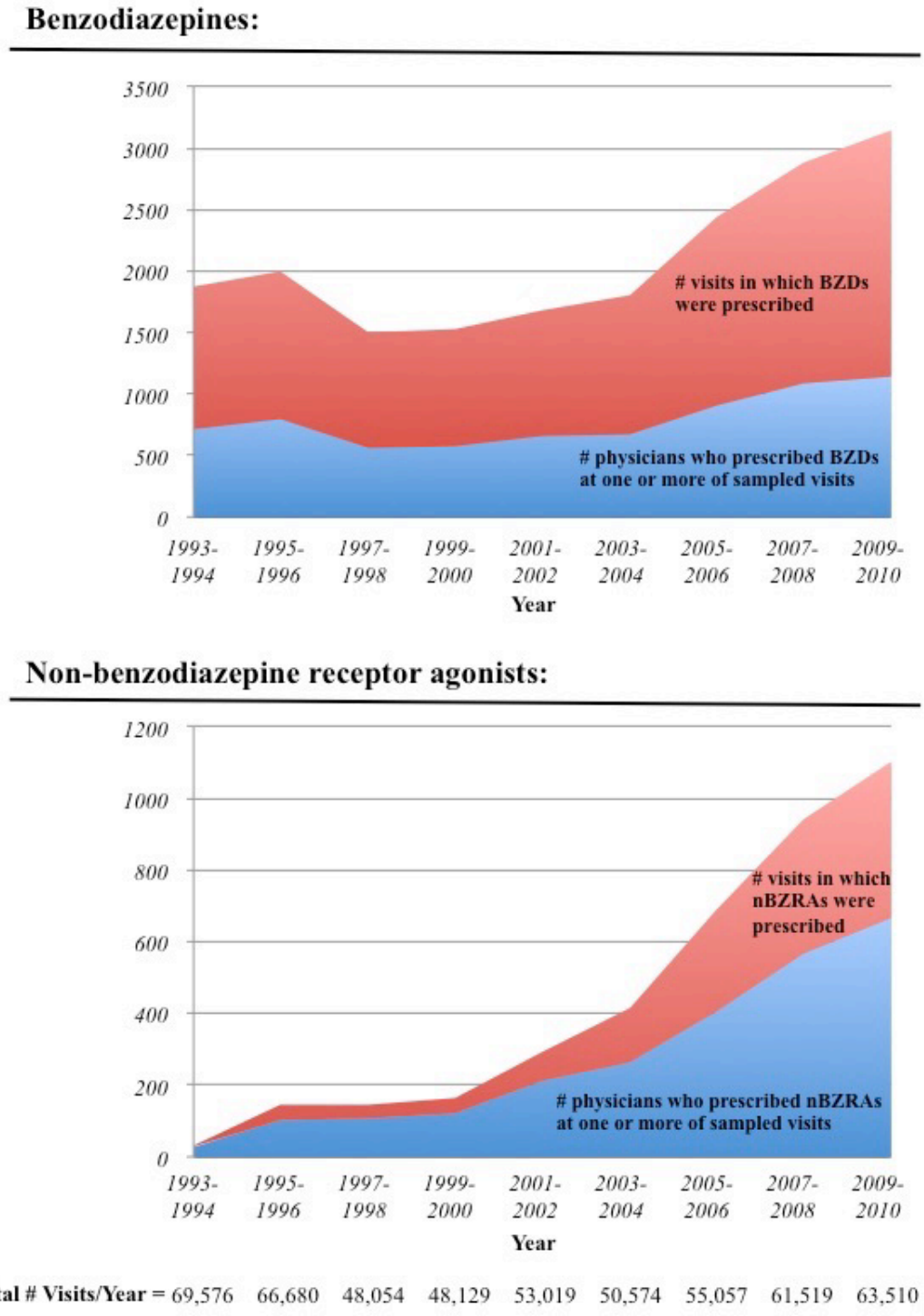
adoption of their use has been slow, and the availability of providers trained in these methods is limited.[124] There are ongoing efforts to implement CBT-i interventions in primary care settings,[97] which in light of our finding of greater adoption in prescribing of BZDs and nBZRAs in primary care will be increasingly important. Furthermore, more work is needed to encourage adoption and dissemination of these interventions. Insurance reimbursement policies, and educating paraprofessionals on the administration of CBT-i could help to address this need.

This study had a number of limitations. First, we categorized physicians as BZD and nBZRA prescribers based on their sampled visits. It is quite possible that the medications prescribed during a physician's sampled visits were not representative of their typical prescribing practices. For example, physicians who did not prescribe BZDs or nBZRAs during the specific sampled visits might have done so in their other visits. Therefore some physicians in our sample may have been misclassified as non-prescribers. Second, the number of visits in which these medications were prescribed per prescriber could have varied over the years. However, past research suggests a remarkable degree of brand loyalty in prescription practices of physicians.[125] Thus, it is quite likely that their prescribing behaviors had remained consistent across sampled and non-sampled visits. Finally, we did not use physician-level survey weights in our analyses as they were not available for all years, and therefore the estimates may not be nationally representative. However, our sensitivity analyses using misspecification effects suggest that our inferences would have changed little if we had used physician-level survey weights.

In the context of these limitations, our study provides a broad overview of the ways in which physician prescribing practices may have contributed to the increasing

trends in prescription of BZDs and nBZRAs. We found that the growth in prescribing of BZDs is due to a greater number of physicians prescribing these medications, particularly among primary care and non-psychiatric specialties; whereas, the growth in prescribing of nBZRAs is due to increases in both the number of nBZRA prescribers and the number of visits in which they prescribe these medications (particularly among primary care physicians). Future research should investigate ways to educate new prescribers of BZDs and nBZRAs on these medications' potential risks and encourage the adoption and dissemination of safer behavioral treatments for sleep and anxiety disorders.

Figure 3.1: Trends in physician prescribing of benzodiazepines and non-benzodiazepine receptor agonists, National Ambulatory Medical Care Survey 1993-2010



Total # Visits/Year =	69,576	66,680	48,054	48,129	53,019	50,574	55,057	61,519	63,510

Table 3.1: Trends in proportion of physicians who prescribed BZDs and nBZRAs from 1993-2010, National Ambulatory Medical Care Survey

	Years[a]									Trend	Trend (Adjusted)
Physician characteristics	1993-1994 %	1995-1996 %	1997-1998 %	1999-2000 %	2001-2002 %	2003-2004 %	2005-2006 %	2007-2008 %	2009-2010 %	OR[b] (95% CI)	AOR[c] (95% CI)
BZDs											
All physicians	23.8	27.9	27.6	28.5	29.6	30.3	39.2	42.7	44.4	**2.51 (2.31, 2.74)**	**2.55 (2.33, 2.80)**
>50% patients age 65+											
No	23.0	26.8	26.5	28.1	28.9	30.4	39.3	41.9	43.1	**2.58 (2.34, 2.83)**	**2.53 (2.28, 2.81)**
Yes	27.9	34.0	33.0	30.9	32.9	30.0	38.6	46.4	50.3	**2.23 (1.82, 2.73)**	**2.56 (2.07, 3.16)**
Specialty											
Other specialty	16.5	16.3	17.8	18.0	18.9	19.2	28.1	31.0	34.5	**2.84 (2.53, 3.19)**	**2.79 (2.48, 3.13)**
Primary care	44.3	47.6	43.0	48.9	49.7	49.6	57.9	61.4	62.3	**2.19 (1.85, 2.59)[d]**	**2.32 (1.96, 2.75)**
Psychiatry	72.1	72.5	73.9	76.2	80.4	78.9	76.2	80.7	77.0	**1.48 (1.01, 2.16)[d]**	**1.49 (1.02, 2.18)[d]**
nBZRAs											
All physicians	1.0	3.6	5.2	6.0	9.3	11.7	17.5	22.2	25.7	**16.79 (14.38, 19.60)**	**19.34 (16.40, 22.80)**
>50% patients age 65+											
No	1.0	3.4	4.9	6.5	9.3	11.7	17.4	21.7	25.1	**16.46 (13.88, 19.51)**	**18.66 (15.54, 22.40)**
Yes	0.8	4.7	6.7	3.8	9.8	11.9	18.5	24.4	28.6	**18.40 (12.71, 26.63)**	**21.29 (14.54, 31.15)**
Specialty											
Other specialty	0.6	1.5	2.5	2.6	5.0	5.7	11.0	15.3	18.3	**26.39 (20.59, 33.83)**	**25.72 (20.02, 33.03)**
Primary care	2.0	5.6	7.2	11.3	14.5	19.6	26.4	32.3	37.1	**16.31 (12.50, 21.27)[d]**	**16.77 (12.82, 21.94)[d]**
Psychiatry	3.7	17.1	25.4	26.2	39.2	44.6	46.4	49.3	59.5	**11.79 (8.01, 17.36)[d]**	**12.04 (8.16, 17.78)[d]**

Note: BZD prescribers include those who prescribed any of the following medications: alprazolam, clonazepam, chlorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam. nBZRA prescribers include those who prescribed any of the following: zolpidem, zaleplon, and eszopliclone; OR=odds ratio, 95% CI= 95% confidence interval.

[a] Statistics correspond to the percentage of physicians in a specific year that had prescribed the respective medication within strata.

[b] Odds ratios come from logistic regression models and correspond to the difference in odds of being a prescriber of the respective medication across the entire study period (i.e., 1993-2010).

[c] Adjusted for >50% sampled patients age 65+, specialty, region, and urban/rural setting.

[d] Statistically significant interaction compared to reference category (i.e., first level) at $p<0.05$.

Table 3.2: Trends in predicted number of prescriptions over sampled visits for physicians who prescribe BZDs and nBZRAs from 1993-2010, National Ambulatory Medical Care Survey

	Years[a]									Trend	Trend (Adjusted)
	1993-1994	1995-1996	1997-1998	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010		
Physician characteristics	Pred. # Visits	Pred. # Visits	Pred. # Visits	Pred. # Visits	Pred. # Visits	Pred. # Visits	Pred. # Visits	Pred. # Visits	Pred. # Visits	IRR[b] (95% CI)	AIRR[c] (95% CI)
BZDs											
All physicians	2.67	2.68	2.69	2.69	2.70	2.71	2.71	2.72	2.73	1.04 (0.91, 1.18)	**1.35 (1.24, 1.47)**
>50% patients age 65+											
No	2.82	2.82	2.83	2.83	2.83	2.84	2.84	2.85	2.85	1.02 (0.88, 1.18)	**1.38 (1.26, 1.53)**
Yes	2.10	2.11	2.13	2.14	2.15	2.17	2.18	2.20	2.21	1.10 (0.90, 1.35)	**1.22 (1.01, 1.48)**
Specialty											
Other specialty	1.86	1.89	1.92	1.94	1.97	2.00	2.03	2.06	2.10	**1.29 (1.10, 1.52)**	**1.26 (1.07, 1.48)**
Primary care	1.93	1.99	2.05	2.12	2.19	2.27	2.34	2.43	2.52	**1.63 (1.39, 1.90)[d]**	**1.75 (1.50, 2.04)[d]**
Psychiatry	5.47	5.53	5.58	5.64	5.70	5.76	5.81	5.87	5.93	1.09 (0.95, 1.26)	1.10 (0.96, 1.27)
nBZRAs											
All physicians	1.33	1.36	1.40	1.44	1.49	1.54	1.59	1.65	1.72	**2.42 (1.70, 3.44)**	**3.83 (2.80, 5.24)**
>50% patients age 65+											
No	1.37	1.41	1.45	1.49	1.53	1.58	1.64	1.69	1.76	**2.20 (1.50, 3.25)**	**3.64 (2.58, 5.14)**
Yes	1.13	1.16	1.19	1.23	1.27	1.33	1.40	1.49	1.59	**4.38 (2.08, 9.23)**	**4.86 (2.27, 10.40)**
Specialty											
Other specialty	1.18	1.21	1.23	1.26	1.30	1.33	1.37	1.42	1.47	**2.76 (1.48, 5.15)**	**2.85 (1.52, 5.35)**
Primary care	1.09	1.12	1.15	1.20	1.26	1.33	1.42	1.55	1.71	**7.29 (4.14, 12.83)[d]**	**6.77 (3.87, 11.87)[d]**
Psychiatry	1.57	1.66	1.76	1.87	2.01	2.16	2.34	2.54	2.77	**3.08 (1.91, 4.98)**	**3.15 (1.96, 5.08)**

Note: BZD prescribers include those who prescribed any of the following medications: alprazolam, clonazepam, chlorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam. nBZRA prescribers include those who prescribed any of the following: zolpidem, zaleplon, and eszopliclone; OR=odds ratio, 95% CI= 95% confidence interval.

[a] Statistics correspond to the predicted number of visits with a prescription for the respective medication within strata, and are estimated from the unadjusted zero-truncated negative-binomial models.

[b] Incidence rate ratios, correspond to the change in incidence of prescriptions of the respective medication across the entire study period (i.e., 1993-2010). Estimated using zero-truncated negative-binomial models.

[c] Adjusted for >50% patients age 65+, specialty, region, and urban/rural setting.

[d] Statistically significant interaction compared to reference category (i.e., first level) at $p<0.05$.

Supplemental Table 3.1: Sensitivity analyses of standard errors for bivariate analyses between 1993 and 2010 accounting for misspecification effects calculated from weighted analyses for the years 2005-2010, National Ambulatory Medical Care Survey

	Proportion of all physicians analyses[a]				Number of prescriptions per physician analyses[b]			
Physician characteristics	Misspecification effects (MEFT)	Unweighted SE	Revised SE[c]	p-value based on revised SE[d]	Misspecification effects (MEFT)	Unweighted SE	Revised SE[c]	p-value based on revised SE[d]
BZDs								
All physicians	1.29	0.11	0.14	**<0.001**	n.s.			
>50% patients age 65+								
No	1.28	0.12	0.16	**<0.001**	n.s.			
Yes	1.30	0.23	0.30	**<0.001**	n.s.			
Specialty								
Other specialty	1.47	0.17	0.25	**<0.001**	1.06	0.11	0.11	**0.004**
Primary care	1.18	0.19	0.22	**<0.001**	1.29	0.13	0.17	**<0.001**
Psychiatry	1.09	0.29	0.31	0.065	n.s.			
nBZRAs								
All physicians	1.33	1.33	1.76	**<0.001**	0.97	0.44	0.42	**<0.001**
>50% patients age 65+								
No	1.26	1.43	1.81	**<0.001**	1.02	0.44	0.44	**<0.001**
Yes	1.34	3.47	4.67	**<0.001**	1.08	1.67	1.80	**<0.001**
Specialty								
Other specialty	1.33	3.34	4.44	**<0.001**	0.92	0.86	0.80	**<0.001**
Primary care	1.23	2.21	2.73	**<0.001**	1.06	2.10	2.23	**<0.001**
Psychiatry	1.06	2.33	2.46	**<0.001**	1.01	0.75	0.76	**<0.001**

Note: Misspecification effects were only computed for statistics for which were statistically significant in main analyses; SE = standard error, n.s. = main analysis not statistically significant; BZD prescribers include those who prescribed any of the following: alprazolam, clonazepam, chlorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam. nBZRA prescribers include those who prescribed any of the following: zolpidem, zaleplon, and eszopliclone.

[a] Analyses correspond to the bivariate analyses seen in Table 3.1.

[b] Analyses correspond to the bivariate analyses seen in Table 3.2; only among BZD prescribers and nBZRA prescribers respectively.

[c] Revised SE is calculated by multiplying the misspecification effect with the unweighted SE.

[d] *p*-value corresponds to significance levels for unweighted analyses accounting for misspecification effects.

Supplemental Table 3.2: Sensitivity analyses for analyses about trends in proportion of physicians who prescribe BZDs and those who prescribe nBZRAs from 1993-2010, National Ambulatory Medical Care Survey

	Years[a]									Trend	Trend (Adjusted)
Sensitivity analyses	1993-1994 %	1995-1996 %	1997-1998 %	1999-2000 %	2001-2002 %	2003-2004 %	2005-2006 %	2007-2008 %	2009-2010 %	OR[b] (95% CI)	AOR[c] (95% CI)
BZDs											
(a) prescribers defined as those who prescribed medication at 2+ visits	7.4	7.8	8.9	9.5	9.2	9.8	12.2	14.9	16.6	**2.49 (2.19, 2.84)**	**2.72 (2.36, 3.15)**
(b) limiting sample to physicians who reported on 10+ visits	23.8	27.9	27.6	28.5	29.6	30.3	39.2	42.7	44.4	**2.57 (2.35, 2.81)**	**2.63 (2.38, 2.89)**
nBZRAs											
(a) prescribers defined as those who prescribed medication at 2+ visits	0.0	0.4	0.4	0.3	0.7	1.3	2.6	3.6	4.5	**34.84 (22.05, 55.03)**	**42.93 (26.38, 69.84)**
(b) limiting sample to physicians who reported on 10+ visits	1.0	3.6	5.2	6.0	9.4	11.7	17.5	22.2	25.8	**17.13 (14.61, 20.07)**	**20.64 (17.40, 24.48)**

Note: BZD prescribers include those who prescribed any of the following medications: alprazolam, clonazepam, chlorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam. nBZRA prescribers include those who prescribed any of the following: zolpidem, zaleplon, and eszopliclone; OR=odds ratio, 95% CI= 95% confidence interval.

[a] Statistics correspond to the percentage of physicians in a specific year that had prescribed the respective medication.

[b] Odds ratios come from logistic regression models and correspond to the difference in odds of being a prescriber of the respective medication across the entire study period (i.e., 1993-2010).

[c] Adjusted for >50% of physician's sampled patients age 65+, specialty, region, and urban/rural.

Chapter 4: Emergency department visits involving benzodiazepines and non-benzodiazepine receptor agonists: results from the Drug Abuse Warning Network

ABSTRACT

BACKGROUND: Benzodiazepines (BZDs) and non-benzodiazepine receptor agonists (nBZRAs) are known to be associated with adverse health outcomes necessitating treatment in emergency departments (EDs). The purpose of the study was to assess outcomes from visits to EDs attributed to use of BZDs and/or nBZRAs.

METHODS: Data came from the 2004-2011 waves of the Drug Abuse Warning Network, a surveillance system that monitors ED visits involving both illicit substances and medications used medically and non-medically. We categorized visits as involving a BZD without an nBZRA, an nBZRA without a BZD, a BZD + nBZRA, or neither drug class. Based on the visit's disposition, we also categorized visits as resulting in a more serious outcome (i.e., hospitalization, patient transfer, or death) or a less serious outcome (i.e., discharge home, release to police/jail, or referral to other treatment). Using logistic regression, we estimated whether the medications involved (with neither BZDs nor nBZRAs as the reference) predicted whether the visit resulted in a more serious outcome (vs. less serious outcome). Results were weighted to be nationally representative of ED visits in the United States involving medications or illicit substances.

RESULTS: Compared to visits involving other substances, visits involving BZDs without nBZRAs had a 34% greater odds of a more serious outcome (odds ratio

[OR]=1.34, 95% Confidence Interval [CI]=1.20-1.50), and visits involving BZDs + nBZRAs had three times the odds of a more serious outcome (OR=3.15, 95% CI=2.01-4.94). Controlling for age, gender, race, the number of reported substances used, whether or not alcohol was involved, and study year did not appreciably change the results.

CONCLUSIONS: ED visits involving BZDs and nBZRAs are associated with a greater odds of more serious outcomes compared to visits involving neither medication. Future research should examine the factors that contribute to patients experiencing adverse health outcomes necessitating emergency treatment.

BACKGROUND

Prescribing of sedative-hypnotic medications has increased over the past two decades.[41,70] Benzodiazepines (BZDs) were developed in the 1950s, and are commonly prescribed for the treatment of anxiety disorders and insomnia.[34] Non-benzodiazepine receptor agonists (nBZRAs) were introduced in the 1990s, and are indicated for the short-term treatment of insomnia.[3] Despite these medications' popularity, their safety has been questioned. Observational studies have shown BZDs to be associated with a number of adverse clinical outcomes, including falls and hip fractures,[6,126,127] and functional decline.[11] For example, Ray et al. found that use of long-acting BZDs was associated with a 70% greater odds of experiencing a hip fracture.[33] Additionally, recent studies have shown nBZRAs to be associated with an increased risk of hip fracture[27,45] and impaired balance.[26,49,51] Older adults are at particularly high risk for adverse health outcomes from BZD use.[11,128]

In addition to studies demonstrating an association between use of BZDs and nBZRAs and adverse clinical outcomes, a number of studies have demonstrated that the use of these agents often leads to injuries necessitating emergency treatment.[46,129] For example, use of BZDs and nBZRAs has been shown to induce severe next-day drowsiness that impairs driving abilities.[52,55,130] In fact, there have been a number of high profile auto accidents in which BZDs and nBZRAs were implicated as a contributing factor.[76,77]

Studies have also shown that the number of emergency department (ED) visits involving BZDs[32] as well as nBZRAs[31] has increased over the past decade. For example, one study showed ED visits involving zolpidem increased 220% from 2005-2010.[31]

However, little is known about outcomes of these visits. EDs see a broad range of cases, both resulting in serious outcomes such as hospitalization or death, and less serious outcomes such as being discharged home, and the nature of these outcomes warrants further investigation. Additionally, given that older adults are at greater risk for hospitalization following ED visits compared to younger people,[31] and the large body of research investigating the association between BZDs and nBZRAs with adverse health outcomes among older people, more research is needed to determine whether any differences in the ED-related outcomes are seen across age groups.

The purpose of this study was to examine outcomes of ED visits involving BZDs and nBZRAs. Specifically, we aimed to determine whether visits involving BZDs without nBZRAs, nBZRAs without BZDs, and BZDs + nBZRAs were associated with more serious outcomes compared to visits involving other substances, and whether these associations differed across age groups.

METHODS

Data source

Data for this study came from the 2004-2011 waves of the Drug Abuse Warning Network (DAWN).[131] DAWN is a surveillance system conducted by SAMHSA that monitors substance involved emergency department visits in a nationally representative sample of hospitals in the United States. For an ED visit to be eligible for DAWN, a substance must have caused or been a contributing factor for the visit. Substances are defined broadly and encompassed both illicit drugs and pharmaceutical agents used both medically and non-medically. Hospitals were not asked to list all medications currently

taken by the patient—only those that were causes of the visit. Based on medical records, staff at participating hospitals reported a number of visit characteristics, including patient demographics, the substances involved, the reason for the visit, and the disposition after discharge (see below). DAWN provides survey design variables and weights to enable researchers to derive nationally representative estimates of ED visits involving substances.

Visits examined in this study

If a visit was deemed eligible for inclusion in DAWN, hospital staff were asked to categorize the reason for each visit. Because visits could have more than one reason, an algorithm was devised to assign a visit type and is described elsewhere.[132] Broadly, visits were classified as being due to a suicide attempt, seeking detox, alcohol involvement (for patients <21 years old), adverse reaction, overmedication, malicious poisoning, accidental ingestion, and "other." To ensure that the visits of our study were due to medical use of a pharmaceutical medication, we limited the sample of visits for our analyses to those that were due to an adverse reaction or overmedication, and that were due to a pharmaceutical agent. We excluded visits involving pharmaceuticals that were taken for non-medical reasons (e.g., opiates for patients seeking detox), and for visits in which the patient was <12 years old. Of the 2,272,434 visits reported to DAWN from 2004-2011, 761,475 (33.5%) met our eligibility requirements.

Measures

Substances. Hospital staff reported the names and route of administration of the substances involved in the ED visit. Staff also reported whether the case involved alcohol.

DAWN categorized each substance using *Multum* Lexicon drug vocabulary modified to include illicit substances. For the purposes of this study, the BZD category included alprazolam, clonazepam, clorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam. nBZRAs consisted of zolpidem, zaleplon, and eszopiclone.

Disposition. Hospital staff also reported the disposition of the visit. Specifically, they recorded whether the visit resulted in the patient being treated and released (i.e., discharged home, released to police, or referred to detox treatment), admitted to this hospital (i.e., ICU/critical care, surgery, chemical dependency/detox, psychiatric unit, or other inpatient unit), and other disposition (i.e., transferred, left against medical advice, died, other, and not documented). Based on a previous study,[133] we categorized visits as resulting in a more or less serious outcome. We considered visits resulting in admittance to any department in the hospital, patient transfer, or death as a "more serious outcome." We considered ED visits resulting in a discharge home, release to police/jail, or referral to other treatment as a "less serious outcome." The remaining dispositions (including left against medical advice, other, and not documented) were not included in our outcome variable.

Other variables. DAWN also collected limited data on patient characteristics, including age (which we categorized as 12-34, 35-44, 45-64, and 65+ years), gender, and race (non-Hispanic white, non-Hispanic black, any Hispanic or Latino, and any other races). DAWN also calculated the number of involved substances reported at the visit.

Analyses

For our analyses we combined DAWN data for years 2004-2011. Each ED visit was categorized as involving one or more BZD without nBZRA, one or more nBZRA without BZD, any BZD + any nBZRA, and any other substance. We first examined demographic characteristics of patients across ED visits, calculating the proportion of patients with each characteristic for visits in the four medication groups. Statistically significant differences across medication groups were determined using chi-squared tests.

Next, we assessed the association between the medications involved in the visit and the visit outcome (more vs. less serious outcome) using logistic regression. The outcome for these analyses was whether the visit resulted in a more or less serious outcome with less serious outcome being the reference. The medication group involved in the visit served as the predictor, with any other substance involved serving as the reference group.

We conducted unadjusted bivariate as well as multivariable analyses adjusting for age, gender, and race of patient, the involvement of alcohol, and number of substances involved. In order to adjust for any possible changes over the 8 years of DAWN, we also adjusted for the year of the study, coded as 7 dummy variables (no dummy included for 2004 which served as the reference). Finally, to determine differences in these trends by age, we stratified our main analyses across age group categories.

RESULTS

Demographic characteristics

Over half of our sample visits were for patients aged 45 years or older (62.3%). Females comprised 62.6% of the sample, and the majority of visits were by non-Hispanic

white patients (76.3%). A small minority of visits involved alcohol (1.4%). Visits involved a mean number of 1.36 substances (standard deviation=1.04, range=1-22). Across our sample of visits, 2.5% involved BZDs without nBZRAs, 0.7% involved nBZRAs without BZDs, and 0.1% involved BZDs + nBZRAs. Across these medication groups (Table 4.1), visits differed by age categories, race, involvement of alcohol, and number of substances (all *p*'s <0.001). There were no differences by gender.

Visits involving BZDs and nBZRAs and severity of outcomes

Twenty three percent of visits in our sample resulted in a more serious outcome (vs. less serious outcome). In unadjusted analyses (Table 4.2), visits involving BZDs without nBZRAs had a 34% increased odds of resulting in a more serious outcome compared to visits involving other substances (odds ratio [OR]=1.34, 95% confidence interval [CI]=1.20-1.50). In addition, visits involving BZDs + nBZRAs had over three times the odds of resulting in a more serious outcome compared to visits involving other substances (OR=3.15, 95% CI=2.01-4.94). In multivariable-adjusted analyses, visits involving BZDs without nBZRAs had a 19% greater odds (AOR=1.19, 95% CI=1.06-1.34), and visits involving BZDs + nBZRAs had more than 2.5 times the odds (AOR=2.63, 95% CI=1.47-4.70) of resulting in a severe outcome compared to visits involving other substances. In these analyses, visits involving nBZRAs without BZDs showed a 31% decrease in the odds of resulting in a more serious outcome (AOR=0.69, 95% CI=0.57-0.83) compared to visits involving other substances.

Across patient age strata, results were somewhat similar (Table 4.3). In bivariate analyses, most age strata had a greater odds of a more serious outcome for visits

involving BZDs without nBZRAs compared to visits involving other substances, but the magnitude of these variations decreased with increasing age strata. Visits involving BZDs + nBZRAs also showed a greater odds of experiencing a more serious outcome across all age strata compared to visits involving neither. While in all age strata, there were odds ratios below 1 for nBZRAs without BZDs, this was statistically significant in the 65+ years age group. In multivariate analyses, the associations described above attenuated but remained in the same direction. Notably in these analyses, the odds ratio for nBZRAs without BZDs for the 45-64 years age group became statistically significant, and the odds ratios for BZDs without nBZRAs and BZDs + nBZRAs in the 45-64 years age group, as well as BZDs + nBZRAs for the 65+ years age group, all lost statistical significance.

Sensitivity analyses

To determine whether the combination of BZDs + nBZRAs during a visit put patients at risk for a more serious outcome beyond the combination of any other medications they were taking, we conducted a sensitivity analysis in which we limited our sample to visits involving two or more substances (Supplemental Table 4.1). The sample size for these analyses was 145,667 visits (19.1% of our original analysis sample). Compared to visits involving other substances, visits involving BZDs without nBZRAs were associated with a 24% greater odds of a more serious outcome (OR=1.24, 95% CI=1.09-1.42), and visits involving BZDs + nBZRAs were associated with more than 2.5 times the odds of a more serious outcome (OR=2.62, 95% CI=1.67-4.12). Visits involving nBZRAs without BZDs had a 36% decline in the odds of resulting in a more

serious outcome compared to visits involving neither (OR=0.64, 95% CI=0.49-0.84). Results were similar after adjustment for confounders.

DISCUSSION

The purpose of this study was to examine the severity of outcomes of emergency department visits involving BZDs and nBZRAs. We found that visits involving BZDs and/or nBZRAs were associated with a greater odds of more serious outcomes, compared to visits involving any other substance. Compared to visits involving other substances, odds for more serious outcomes were greater for visits involving BZDs without nBZRAs, and especially visits including both BZDs + nBZRAs. We also found that these same results were seen across age groups.

The higher odds of a more serious outcome for visits involving BZDs + nBZRAs is particularly concerning. We found that visits involving BZDs + nBZRAs were associated with a greater risk of a more serious outcome, even after accounting for the involvement of alcohol and the number of substances involved. Studies have shown that the involvement of alcohol with other sedating agents is associated with adverse health outcomes.[134] Additionally, polypharmacy has also been shown to be a contributing factor to adverse events.[101] Surprisingly, in sensitivity analyses limited to visits involving two or more substances, the associations we observed remained statistically significant, suggesting that the odds for a more serious outcome associated with the combination of BZDs and nBZRAs (in addition to BZDs without nBZRAs) is greater than the odds due to combination of any two or more other medications. Several studies have observed adverse health outcomes associated with the combined use of BZDs and nBZRAs.[75,135,136]

Our study confirms these findings, and highlights that these outcomes are severe enough to necessitate prolonged health service use.

A plethora of studies show older adults to be at risk for serious outcomes due to medication errors.[137] That we found an elevated odds for more serious outcomes for visits involving BZDs + nBZRAs in the 65+ years age group suggests that the odds of serious outcomes due to these medications is even more elevated in this demographic group. A number of clinical guidelines list medications that should not be used by older adults. For example, the Beers Criteria,[57] most recently updated in 2012,[15] lists both BZDs and nBZRAs as potentially dangerous medications. Given results from our study, these clinical guidelines should also warn against combined use of BZDs and nBZRAs.

It was puzzling that visits involving nBZRAs without BZDs had lower odds of resulting in a more serious outcome compared to visits involving any other substance, after adjustment for confounders. This finding may be due to the greater severity of outcomes associated with other substances that comprised the comparison group (i.e. visits for which neither a BZD nor nBZRA was involved). These comparison substances included prescribed opioids as well as a broad range of other medications associated with severe ED outcomes.

Regardless of the severity of ED outcomes, visits involving BZDs and/or nBZRAs in ED settings highlight the burden these medications place on our healthcare system. Studies have found that adverse events due to medication errors are common[69] and it was estimated that medication errors cost the healthcare system $17.8 billion in 2008.[138] Any measures enacted that prevent excess health service use due to medication errors could have a drastic impact on lowering healthcare costs.

There are promising alternative behavioral treatments for both anxiety disorders and insomnia that have been shown to be as effective, if not more effective, than treatment with BZDs and nBZRAs, and resulting in fewer side effects.[1,2] Examples of behavioral insomnia treatments include sleep restriction,[122] stimulus control therapy,[123] sleep hygiene education,[123] and cognitive behavioral therapy for insomnia.[98,139] Cognitive Behavioral Therapy[99] with and without exposure therapy[140] are also common and effective non-pharmacological treatments for anxiety disorders. Guidelines encourage the use of these treatments,[59,60,83] but they are not widely available.[124] Efforts to encourage adoption of these therapies may help decrease ED use due to use of sedating medications. The broader use of selective serotonin reuptake inhibitors for treatment of anxiety disorders in recent years[141] may also prove to be a safer alternative than long-term BZD use for treatment of anxiety disorders.

Policy initiatives, as well as patient education campaigns, have sought to decrease the prescribing of BZDs and nBZRAs. For example, New York state implemented a triplicate prescription monitoring program that resulted in a decline in prescribing of BZDs by half.[61] Studies have evaluated educational visits to doctors to discuss alternative treatments for sleep disorders[62] and electronic medical record systems have implemented reminders to encourage safer medication alternatives.[64] Pamphlets targeted at patients have also sought to provide education on proper sleep hygene.[142] These efforts need further evaluation.

Our study has several limitations. First, visits reported in DAWN are not representative of all ED visits in the United States—they only represent visits for which substances were causes of or contributing factors for the visit. Consequently, we were

unable to make comparisons to visits in which no medication was involved. Second, data were reported by hospital staff and based on medical records, potentially resulting in useful information not being recorded. For example, we were not able to control for the number of previous ED visits because this was not ascertained. Third, we did not know the indication for the BZD and/or nBZRA use. The indications may be associated with differences in outcomes—for example, ED visits due to BZDs prescribed for transient insomnia may have different outcomes than ED visits due to BZD use for chronic anxiety disorders. Finally, we did not have information on all medications prescribed to the patient—DAWN only reports substances that were involved in the specific visit. DAWN reports depend on ED physicians' recognition that the medication was a contributing factor to the visit.

Despite our study's limitations, the findings highlight the potential dangers in use of BZDs and nBZRAs. The study also highlights the consequences of combining BZDs with nBZRAs. Efforts should be made to reduce combined use of BZDs and nBZRAs. Future studies could also examine the contributing factors that lead patients to experience adverse health outcomes due to use of these agents. By doing so, we could substantially decrease the burden of preventable adverse outcomes from BZD and nBZRA use, potentially resulting in substantial savings on healthcare costs.

Table 4.1: Demographic characteristics of patients during emergency department visits involving benzodiazepines (BZDs) and non-benzodiazepine receptor agonists (nBZRAs), Drug Abuse Warning Network 2004-2011

	Other substances n=737,776	**BZDs w/out nBZRAs** n=17,785	**nBZRAs w/out BZDs** n=5,048	**BZDs + nBZRAs** n=866	
Characteristic	n (%[a])	n (%[a])	n (%[a])	n (%[a])	p-value[b]
Age					<0.001
12-34	186,064 (24.5)	4,183 (21.9)	816 (19.5)	157 (21.7)	
35-44	99,418 (12.7)	2,968 (16.1)	629 (11.2)	142 (12.0)	
45-64	221,071 (28.8)	6,101 (33.2)	1,670 (33.0)	354 (41.1)	
65+	231,223 (34.0)	4,533 (28.8)	1,933 (36.3)	213 (25.2)	
Gender					0.498
Male	275,227 (37.4)	6,754 (36.1)	1,926 (39.3)	278 (34.2)	
Female	462,234 (62.6)	11,020 (63.9)	3,122 (60.8)	588 (65.9)	
Race/ethnicity					<0.001
Non-Hispanic white	367,398 (76.0)	10,964 (83.8)	2,912 (85.6)	574 (90.1)	
Non-Hispanic black	114,985 (14.1)	1,762 (9.4)	407 (6.8)	56 (1.5)	
Hispanic	74,914 (7.8)	1,460 (5.5)	438 (5.9)	62 (7.1)	
All other races/ethnicities	19,072 (2.1)	262 (1.3)	123 (1.8)	12 (1.3)	
Alcohol involved					<0.001
No	727,622 (98.8)	16,007 (91.9)	4,558 (91.6)	793 (93.5)	
Yes	10,153 (1.2)	1,778 (8.1)	490 (8.5)	73 (6.6)	
# substances, mean (SD)	1.30 (0.85)	3.34 (2.87)	2.14 (2.04)	6.56 (3.61)	<0.001

Note: BZDs = benzodiazepines (include alprazolam clonazepam clorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam), nBZRAs = non-benzodiazepine receptor agonists (include zolpidem, zaleplon, and eszopiclone).

[a] All columns report column percentages, unless otherwise reported. All estimates are weighted to account for oversampling and yield nationally representative estimates.

[b] *p*-value from chi-squared tests.

Table 4.2: Severity of outcome following emergency department visits involving benzodiazepines (BZDs) and non-benzodiazepine receptor agonists (nBZRAs), Drug Abuse Warning Network 2004-2011

	Less serious outcome[a]	**More serious outcome[a]**	**Unadjusted comparison**	**Adjusted comparison[b]**
Medications involved	n (Row %)	n (Row %)	OR (95% CI)	AOR (95% CI)
Other substances	521,617 (77.4)	201,666 (22.6)	Ref.	Ref.
BZDs w/out nBZRAs	11,886 (71.8)	5,329 (28.2)	**1.34 (1.20, 1.50)**	**1.19 (1.06, 1.34)**
nBZRAs w/out BZDs	3,581 (79.8)	1,325 (20.2)	0.87 (0.73, 1.04)	**0.69 (0.57, 0.83)**
BZDs + nBZRAs	507 (52.0)	333 (48.0)	**3.15 (2.01, 4.94)**	**2.63 (1.47, 4.70)**

Note: OR=odds ratio, AOR=adjusted odds ratio, 95% CI=95% confidence interval, BZDs=benzodiazepines (include alprazolam clonazepam clorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam), nZBRAs=non-benzodiazepine receptor agonists (include zolpidem, zaleplon, and eszopiclone).

[a] "More serious outcome" defined as the emergency room visit resulting in an admittance to any department in hospital (i.e., intensive critical care unit, surgery, chemical dependence detox/psychiatry, other inpatient unit), transferred, or died. "Less serious outcome" defined as an emergency room visit resulting in a discharge home, release to police/jail, or referred to other treatment.

[b] Adjusted analyses account for age, gender, race of patient, the number of reported substances, whether or not alcohol was involved, and year.

Table 4.3: Emergency department visits involving benzodiazepines (BZDs) and non-benzodiazepine receptor agonists (nBZRAs) and severity of disposition following visit stratified by age group of patients, Drug Abuse Warning Network 2004-2011

	Less serious outcome[a]	More serious outcome[a]	Unadjusted comparison	Adjusted comparison[b]
Medications involved	n (Row %)	n (Row %)	OR (95% CI)	AOR (95% CI)
12-34 years				
Other substances	165,115 (93.0)	17,325 (7.0)	Ref.	Ref.
BZDs w/out nBZRAs	3,362 (86.7)	666 (13.3)	**2.04 (1.54, 2.69)**	**1.57 (1.20, 2.05)**
nBZRAs w/out BZDs	712 (95.2)	81 (4.8)	0.67 (0.34, 1.30)	0.63 (0.30, 1.32)
BZDs + nBZRAs	121 (53.9)	31 (46.1)	**11.41 (2.24, 58.14)**	**6.93 (1.34, 35.75)**
35-44 years				
Other substances	81,624 (88.1)	15,596 (11.9)	Ref.	Ref.
BZDs w/out nBZRAs	2,261 (78.8)	588 (21.2)	**1.99 (1.28, 3.08)**	**1.81 (1.07, 3.05)**
nBZRAs w/out BZDs	499 (89.0)	110 (11.0)	0.92 (0.50, 1.68)	0.81 (0.41, 1.61)
BZDs + nBZRAs	97 (58.9)	38 (41.1)	**5.16 (1.85, 14.37)**	**4.35 (1.34, 14.18)**
45-64 years				
Other substances	154,362 (77.3)	61,736 (22.7)	Ref.	Ref.
BZDs w/out nBZRAs	3,981 (69.6)	1,919 (30.4)	**1.49 (1.27, 1.73)**	1.18 (0.98, 1.44)
nBZRAs w/out BZDs	1,236 (81.5)	386 (18.5)	0.77 (0.55, 1.09)	**0.63 (0.43, 0.91)**
BZDs + nBZRAs	198 (59.4)	145 (40.6)	**2.33 (1.09, 4.97)**	1.49 (0.72, 3.06)
65+ years				
Other substances	120,516 (62.2)	107,009 (37.8)	Ref.	Ref.
BZDs w/out nBZRAs	2,282 (59.3)	2,156 (40.7)	1.13 (0.94, 1.36)	0.93 (0.76, 1.14)
nBZRAs w/out BZDs	1,134 (67.9)	748 (32.2)	**0.78 (0.61, 0.99)**	**0.72 (0.55, 0.95)**
BZDs + nBZRAs	91 (34.6)	119 (65.4)	**3.11 (1.47, 6.57)**	2.02 (0.97, 4.21)

Note: OR=odds ratio, AOR=adjusted odds ratio, 95% CI=95% confidence interval, BZDs=benzodiazepines (include alprazolam clonazepam clorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam), nZBRAs=non-benzodiazepine receptor agonists (include zolpidem, zaleplon, and eszopiclone).

[a] "More serious outcome" defined as the emergency room visit resulting in an admittance to any department in hospital (i.e., intensive critical care unit, surgery, chemical dependence detox/psychiatry, other inpatient unit), transferred, or died. "Less serious outcome" defined as an emergency room visit resulting in a discharge home, release to police/jail, or referred to other treatment.

[b] Adjusted analyses account for gender, race of patient, the number of reported substances, whether or not alcohol was involved, and year.

Supplemental Table 4.1: Emergency department visits involving benzodiazepines (BZDs) and non-benzodiazepine receptor agonists (nBZRAs) and severity of disposition following visit limited to visits involving two or more substances, Drug Abuse Warning Network 2004-2011

	Less serious outcome[a]	**More serious outcome[a]**	**Unadjusted comparison**	**Adjusted comparison[b]**
Medications involved	n (Row %)	n (Row %)	OR (95% CI)	AOR (95% CI)
Other substances	89,013 (74.0)	38,540 (26.0)	Ref.	Ref.
BZDs w/out nBZRAs	7,823 (69.6)	3,942 (30.4)	**1.24 (1.09, 1.42)**	**1.25 (1.07, 1.47)**
nBZRAs w/out BZDs	1,653 (81.7)	685 (18.3)	**0.64 (0.49, 0.84)**	**0.51 (0.39, 0.68)**
BZDs + nBZRAs	507 (52.0)	333 (48.0)	**2.62 (1.67, 4.12)**	**2.62 (1.50, 4.57)**

Note: OR=odds ratio, AOR=adjusted odds ratio, 95% CI=95% confidence interval, BZDs=benzodiazepines (include alprazolam clonazepam clorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam), nZBRAs=non-benzodiazepine receptor agonists (include zolpidem, zaleplon, and eszopiclone).

[a] "More serious outcome" defined as the emergency room visit resulting in an admittance to any department in hospital (i.e., intensive critical care unit, surgery, chemical dependence detox/psychiatry, other inpatient unit), transferred, or died. "Less serious outcome" defined as an emergency room visit resulting in a discharge home, release to police/jail, or referred to other treatment.

[b] Adjusted analyses account for age, gender, race of patient, the number of reported substances, whether or not alcohol was involved, and year.

Chapter 5: Conclusion

The goal of this dissertation was to examine trends in prescribing of BZDs and nBZRAs between 1993 and 2010, and to assess outcomes from emergency department visits associated with their use. The dissertation used data from two large nationally representative datasets—the National Ambulatory Medical Care Survey (NAMCS) and the Drug Abuse Warning Network (DAWN). Overall, we found that prescribing of both BZDs as well as nBZRAs increased over the study period, driven by growth in the number of, and volume of prescribing by, physicians in non-psychiatry specialties. We also found that visits to emergency department settings due to the use of BZDs or nBZRAs were more likely to result in a more serious outcome compared to visits in which neither of these medication groups were involved. This chapter provides a summary of the dissertation's findings, and discusses public health implications and how results may inform future research.

Summary of findings

Study 1. The purpose of the first study was to examine trends in prescribing of BZDs and nBZRAs from 1993-2010 in ambulatory healthcare settings. We found that prescribing of BZDs and nBZRAs increased over the study period. In stratified analyses, there were increases in prescribing across most patient and visit characteristics assessed. Among patients with sleep disorders, however, we observed a large increase in prescribing of nBZRAs coinciding with a decline in prescribing of BZDs. We also found a growing trend in the co-prescribing of BZDs and nBZRAs at the same visit.

Study 2. The purpose of the second study was to explore whether the increasing trend in prescribing of BZDs as well as nBZRAs was due to an increase in the number of physicians who prescribe these medications, or an increase in the number of prescriptions per prescribing physician. Unsurprisingly, we found that the increase in prescribing of nBZRAs was due to both an increase in the number of physicians who prescribe these medications and an increase in the volume of prescribing per physician. We also found that the increase in prescribing of BZDs was due to an increase in the number of prescribers of these medications, but not number of prescriptions per physician. In stratified analyses, the growth in prescribing of BZDs appeared to be driven by increases in prescribing among doctors in primary care and other non-psychiatry specialties.

Study 3. The purpose of the third study was to examine outcomes from visits to emergency departments attributed to BZD or nBZRA use, and to assess differences across age groups. Specifically, the study sought to determine whether visits involving BZDs and/or nBZRAs resulted in a more serious (e.g., hospitalization) or less serious (e.g., discharge home) outcome compared to visits involving other substances. We found visits involving BZDs without nBZRAs, as well as both BZDs and nBZRAs together, were associated with a higher odds of experiencing a more serious outcome compared to visits involving other substances. Notably, visits involving both BZDs and nBZRAs together had nearly three times higher odds of experiencing a more serious outcome compared to visits involving other substances, even after controlling for a number of patient characteristics including age, gender, race, the number of reported substances, and the involvement of alcohol. Additionally, these trends were seen across all age strata examined.

Public health implications

This dissertation found that despite clinical and policy efforts to discourage prescribing of BZDs and nBZRAs in the mid-1990s and early-2000s,[13-15,61,62,143] prescribing of these agents continued to grow up until 2010. Growth in prescribing was seen across most groups of patients assessed (except for patients with sleep disorders for BZDs), and even among older adults, who may be especially vulnerable to adverse side effects. As seen in study 2, growth in prescribing of BZDs and nBZRAs was observed among doctors who saw mostly older adults (i.e., >50% of their patients were age 65+). It is surprising that even with the growing awareness of the potential adverse health outcomes associated with BZD and nBZRA use for older adults, and the published clinical guidelines such as the Beers Criteria,[15,16] prescribing of both medication classes still increased even among physicians who saw mostly older adults. As the results of study 3 suggest, visits to emergency departments involving BZDs and/or nBZRAs were at greater risk of more serious outcomes across the age range.

Study 2 found that one reason for increases in prescribing, in particular for BZDs, was a growth in the number of prescribers in primary care and other non-psychiatry specialties. This finding suggests that growth in prescribing of BZDs and nBZRAs may be attributable to an increase in physicians prescribing these agents who have not historically prescribed psychiatric medications. Over the past decade, there has been growth in prescribing of selective serotonin reuptake inhibitors in primary care settings.[114] The findings from this dissertation show that this trend may be expanding to other psychiatric medication classes including sedative-hypnotics. These findings call for

efforts to educate physicians new to prescribing of these agents on identifying patients who may experience an adverse health outcome attributable to the use of sedative-hypnotics.

In addition to a growth in prescribing of BZDs and nBZRAs in primary care and other non-psychiatric settings, we found a worrisome trend in the co-prescribing of BZDs and nBZRAs. The potential for co-prescribing of BZDs and nBZRAs is conceivable—for example, a patient may be prescribed a BZD for a chronic anxiety disorder and an nBZRA for transient insomnia. However, as BZDs and nBZRAs both act on GABA neurotransmitter receptors, there is a heightened risk for severe over-sedation. Studies from clinical trials have shown an additive effect when these medications are co-administered.[135,136] Epidemiological studies have also shown a greater risk of hip-fractures associated with combining these agents.[75] Findings from study 3 show that ED visits involving the combined use of BZDs and nBZRAs were associated with an increased risk of more serious outcomes compared to visits involving other substances. Guidelines need to be developed to discourage the co-prescribing of these agents.

While prescribing of sedative-hypnotics has increased over the past two or three decades, behavioral therapies for anxiety disorders and insomnia have also been developed.[98,99] Behavioral and other non-pharmacological therapies for insomnia and anxiety disorders are preferable to use of medications because they have been shown to be more effective over time,[1] and do not have the potential for adverse health outcomes. For anxiety disorders, cognitive-behavioral therapy (CBT) draws from principles of cognitive and behavioral psychology and provides a systematic approach for addressing cognitive-distortions that may cause anxiety.[144] Exposure therapy consists of gradually

exposing individuals to fearful experiences to encourage them to confront phobias or other anxieties.[145] For insomnia, a number of behavioral interventions have shown to be quite useful. Sleep restriction therapy limits the time in bed for a patient in order to promote better sleep quality and decrease sleep fragmentation throughout the night.[122] Stimulus control therapy seeks to limit arousal before bed and to encourage patients to associate their bed with sleeping only.[123] Sleep hygiene education can also be used to encourage healthy bedtime rituals (e.g., not eating or drinking alcohol immediately prior to bed time, dimming lights before bed).[1] Formal treatment programs such as CBT for insomnia (CBT-i)[2] draw on these therapies to provide a structured treatment plan that can decrease arousal that interferes with sleep and improve sleep quality overall.[123]

With regards to insomnia treatments, despite CBT-i's demonstrated effectiveness, very few clinicians are trained to deliver the treatment.[124] For example, the Society of Behavioral Sleep Medicine in tandem with the American Board of Sleep Medicine offers a credentialing program in behavioral sleep medicine which involves techniques of CBT-i;[146] however, the costs and the required time investment may be a barrier to training for many clinicians. Additionally, primary care physicians, who are increasingly prescribing sedative-hypnotics, may not have the time to engage their patients in this treatment given the need to meet with so many patients.[147] While fellowship opportunities for training in behavioral sleep medicine do exist, the uptake of this specialty is not particularly high,[124] and more incentives are needed to encourage physicians to go into the field. Efforts to improve the dissemination of CBT-i are ongoing[139] and one line of research is investigating ways to implement CBT-i techniques in primary care settings.[148,149] Additionally, the Veterans Administration is rolling out CBT-i interventions in their

hospitals across the United States.[150] Despite these innovative efforts, more work is needed to disseminate behavioral sleep treatments.

Limitations of studies

The analyses that are the basis for this dissertation had a number of limitations. First, data for both NAMCS and DAWN were extracted from medical records, and consequently our results were open to reporting bias. Busier clinical offices or EDs with a more complex patient load may have been less detailed in their recordings than others. Furthermore, non-response for busier offices may limit the representativeness of the data. Second, data from both NAMCS and DAWN are based on individual visits. For NAMCS, this may be an issue as some patients (especially older adults) see multiple providers; consequently, it is possible that we did not capture all instances of BZDs or nBZRAs prescribed. Our results may thus be a conservative estimate. Third, eligibility for visits in DAWN was dependent on hospital staff recognizing that the ED visit involved a substance. It is possible that visits were not included in DAWN because not enough information was provided on medical records or volunteered by the patient. Fourth, we did not have information on the indication for medication use. While NAMCS provided data on diagnoses given at the visit, we did not know the specific reason for the medication being prescribed. Similarly, DAWN does not report the indication of the use of prescribed medications involved in the visit, only that it was a contributor to the ED visit. Changes in the indications of the prescription of sedative-hypnotics may have resulted in the trends we observed in studies 1 and 2. These changes as well as changes in

the case-mix may have also impacted patterns in the ED visit outcomes observed in study 3.

The future…

Findings from this dissertation show that despite efforts to discourage prescribing of BZDs and nBZRAs, prescribing of these agents has increased over the past two decades. We found that this was in part driven by large increases in prescribing in primary care, and among physicians in other non-psychiatry specialties. We also found that this increased prescribing may be associated with more serious outcomes in EDs.

As BZDs and nBZRAs gradually lose their patents, pharmaceutical companies have developed newer sleep-aid medications. For example, Intermezzo, a zolpidem derivative, was approved by the Food and Drug Administration in 2011 for middle-of-the-night awakenings.[94] Tasimelteon (brand name: Hetlioz) was recently approved for the treatment of irregular circadian rhythm patterns in patients with visual impairments.[95] Suvorexant (brand name: Belsomra), treats insomnia by inhibiting absorption of the neurotransmitter orexin, which promotes wakefulness.[96] It is not clear how these medications will be tolerated when used in the usual care settings and over longer periods of time than commonly used in randomized clinical trials. While clinical trials have shown these medications to be "safe and effective," these studies are based on a smaller number of patients that tend to be healthier than the typical individuals prescribed these medications in usual care settings. Large pharmaco-epidemiological studies are needed to assess the safety of these agents in the general population.

Little is known about how the introduction of these new pharmacological treatments will influence the landscape of prescribing of sleep-aids and other sedative-

hypnotics in the US. Regardless, further efforts should focus on improving the dissemination and acceptability of safer behavioral treatments for sleep disorders. Such efforts could minimize the public health burden of sleep problems and adverse health outcomes from use of BZDs and nBZRAs, as well as improve the quality of life for the 50-70 million Americans who experience insomnia.

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adults. *J Am Geriatr Soc*. 2009;57(6):1000–1006.

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2012;8(2):209–218. doi:10.5664/jcsm.1786.

Curriculum Vitae

Christopher Norfleet Kaufmann

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Date of Birth: August 4, 1983, Boston, Massachusetts

EDUCATION

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Doctor of Philosophy in Mental Health, June 2015
Advisors: Adam Spira, PhD & Ramin Mojtabai, MD, PhD, MPH
Earned *Certificate in Gerontology*, December 2014
Funding support: Individual Ruth L. Kirschstein National Research Service Award, National Institute on Aging

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Masters of Health Science in Mental Health, May 2010

University of Southern California, Los Angeles, CA
Bachelor of Arts in Communication (minor in Performing Arts Studies), May 2006
Annenberg School for Communication and Journalism
Graduated Magna Cum Laude

PUBLICATIONS

18. Canham SL, Mauro PM, **Kaufmann CN**, Sixsmith A. Frequency of alcohol use and loneliness among middle-aged and older adult drinkers in the Health and Retirement Study. *Journal of Aging and Health*, in press.

17. Chen LY, Crum RM, Strain EC, Alexander GC, **Kaufmann CN**, Mojtabai R. Prescriptions, nonmedical use, and emergency department visits involving prescription stimulants. *Journal of Clinical Psychiatry*, in press.

16. Spira AP, Runko VT, Finan PH, **Kaufmann CN**, Bounds SC, Liu L, Buenaver LF, McCauley LM, Ancoli-Israel S, Smith MT. Circadian rest/activity rhythms in knee osteoarthritis with insomnia: A study of osteoarthritis patients and pain-free controls with insomnia or normal sleep. *Chronobiology International*, October 7, 2014 [Epub ahead of print].

15. Spira AP, **Kaufmann CN**, Kasper JD, Ohayon MM, Rebok GW, Skidmore ER, Parisi JM, Reynolds CF (2014). Association between insomnia symptoms and functional status in U.S. older adults. *Journal of Gerontology: Social Sciences*, 69 (Suppl 1), S35-S41.

14. Chen-Edinboro LP, **Kaufmann CN**, Augustinavicius JL, Mojtabai R, Parisi JM, Wennberg AMV, Smith MT, Spira AP. Neighborhood physical disorder, social cohesion and insomnia: Results from participants over age 50 in the Health and Retirement Study. *International Psychogeriatrics*, September 15, 2014 [Epub ahead of print].

13. Wennberg AMV, Gottesman RF, **Kaufmann CN**, Albert MS, Chen-Edinboro LP, Rebok GW, Kasper JD, Spira AP. Diabetes and cognitive outcomes in a nationally representative sample: the National Health and Aging Trends Study. *International Psychogeriatrics*, July 30, 2014 [Epub ahead of print].

12. Chen LY, Crum R, Martins SS, **Kaufmann CN**, Strain EC, Mojtabai R (2014). Patterns of concurrent substance use among nonmedical ADHD stimulant users: Results from the National Survey on Drug Use and Health. *Drug and Alcohol Dependence*, 142, 86-90.

11. Canham SL, **Kaufmann CN**, Mauro PM, Mojtabai R, Spira AP. Binge drinking and insomnia in middle-aged and older adults: The Health and Retirement Study. *International Journal of Geriatric Psychiatry*, May 5, 2014 [Epub ahead of print].

10. Wieland LS, Rutkow L, Vedula SS, **Kaufmann CN**, Rosman L, Twose C, Mahendraratnam N, Dickersin K (2014). Who has used internal company documents for biomedical and public health research and where did they find them? *PLoS One*, 9(5), e94709.

9. Mojtabai R, Chen LY, **Kaufmann CN**, Crum R (2014). Comparing barriers to mental health treatment and substance use disorder treatment among individuals with comorbid major depression and substance use disorders. *Journal of Substance Abuse Treatment*, 46(2), 268-273.

8. **Kaufmann CN**, Chen LY, Crum RM, Mojtabai R. Treatment seeking and barriers to treatment for alcohol use in person with alcohol use disorders and comorbid mood or anxiety disorders. *Social Psychiatry and Psychiatric Epidemiology,* July 31, 2013 [Epub ahead of print].

7. **Kaufmann CN**, Canham SL, Mojtabai R, Gum AM, Dautovich ND, Kohn R, Spira AP (2013). Insomnia and health services utilization in middle-aged and older adults: results from the Health and Retirement Study. *Journals of Gerontology: Medical Sciences,* 68(12), 1512-1517.

6. Chen L, Crum RM, Martins SS, **Kaufmann CN**, Strain EC, Mojtabai R (2013). Service use and barriers to mental health care among adults with major depression and comorbid substance dependence. *Psychiatric Services*, 64(9), 863-870.

5. **Kaufmann CN**, Rutkow L, Spira AP, Mojtabai R (2013). Mental health of protective services workers: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Disaster Medicine and Public Health Preparedness*, 7(1), 36-45.

4. Rutkow L, Vernick JS, Mojtabai R, Rodman SO, **Kaufmann CN** (2012). Legal challenges for substance abuse treatment during emergencies. *Psychiatric Services*, 63, 7-9.

3. Close H, Lee LC, **Kaufmann CN**, Zimmerman A (2012). Co-occurring conditions and change in diagnosis in autism spectrum disorders. *Pediatrics*, 129, e305-e316.

2. Rutkow L, Vernick JS, Wissow LW, **Kaufmann CN**, Hodge, JG (2011). Prescribing authority during emergencies: challenges for mental health care providers. *Journal of Legal Medicine*, 32, 249–260.

1. **Kaufmann CN**, Spira AP, Rae D, West JC, Mojtabai R (2011). Sleep problems, psychiatric hospitalization, and emergency department use among psychiatric patients with Medicaid. *Psychiatric Services*, 62, 1101-1105.

CONFERENCE ABSTRACTS

20. **Kaufmann CN**, Spira AP, Canham SL, Chen LY, Alexander GC, Mauro P, Mojtabai R. Racial/ethnic disparities in US prescribing patterns of sleep medications from 1993-2010. *30th International Conference on Pharmacoepidemiology and Therapeutic Risk Management*, Taipei, Taiwan.

19. **Kaufmann CN**, Canham SL, Mojtabai R, Alexander GC, Bandeen-Roche K, Rutkow L, Spira AP. Association between use of sleep-aids and falls in a population based sample of middle-aged and older adults. *Gerontological Society of America Annual Meeting 2014*, Washington DC.

18. Spira AP, **Kaufmann CN**, Kasper JD, Ohayon MM, Rebok GW, Skidmore ER, Parisi JM, Reynolds CF. Insomnia symptoms and participation in valued activities in U.S. older adults: the National Health and Aging Trends Study. *Gerontological Society of America Annual Meeting 2014*, Washington DC.

17. Canham SL, Mauro PM, **Kaufmann CN**. Alcohol consumption and loneliness in mid- and late-life. *College on Problems in Drug Dependence 2014*, San Juan, Puerto Rico.

16. Chen-Edinboro LP, **Kaufmann CN**, Augustinavicius JL, Mojtabai R, Parisi J, Wennberg AMV, Smith MT, Spira AP. Neighborhood physical disorder, social cohesion and insomnia: results from the Health and Retirement Study. *SLEEP 2014*, Minneapolis, MN.

15. **Kaufmann CN**, Hock RS, Mojtabai R, Thorpe R, Canham SL, Chen L, Spira, AP. Racial/ethnic differences in trajectories of insomnia severity among older adults: results from the Health and Retirement Study. *6th Annual Research on Aging Showcase*, Baltimore, MD.

14. Canham SL, **Kaufmann CN**, Spira AP, Ramsey C, O'Rourke N. Examining the temporal association between substance abuse/dependence and mania in older adults. *Gerontological Society of America Annual Meeting 2013*, New Orleans, LA.

13. **Kaufmann CN**, Chen LY, Spira AP, Canham SL, Alexander GC, Mojtabai R. Trends in the use of non-benzodiazepine sleep-aid medications in the United States, 1996-2010. *29th International Conference on Pharmacoepidemiology and Therapeutic Risk Management*, Montreal, Quebec.

12. Chen LY, **Kaufmann CN**, Alexander GC, Mojtabai R, Martins SS. Correlates of nonmedical use of ADHD-type stimulants versus nonmedical use of other stimulants in a U.S. national sample. *29th International Conference on Pharmacoepidemiology and Therapeutic Risk Management*, Montreal, Quebec.

11. Wieland L, Rutkow L, Vedula S, **Kaufmann CN**, Rosman L, Twose C, Mahendraratnam N, Dickersin K. Getting ahold of internal company documents for research: where are they? *Seventh International Congress on Peer Review and Biomedical Publication*, Chicago, IL.

10. **Kaufmann CN**, Crum R, Chen L, Mojtabai R. Substance abuse treatment-seeking and barriers to care in persons with alcohol use disorders and comorbid mood or anxiety disorders. *College on Problems in Drug Dependence 2013*, San Diego, CA.

9. **Kaufmann CN**, Hock RS, Mojtabai R, Thorpe R, Canham SL, Chen L, Spira, AP. Racial/ethnic differences in trajectories of insomnia severity among older adults: results from the Health and Retirement Study. *SLEEP 2013*, Baltimore, MD.

8. Canham SL, **Kaufmann CN**, Mauro P, Mojtabai R, Spira AP. Binge drinking and insomnia symptoms in older adults: results from the Health and Retirement Study. *SLEEP 2013*, Baltimore, MD.

7. Coryell VT, Spira AP, **Kaufmann CN**, Bounds SC, McCauley LM, Smith MT. Circadian activity patterns in older adults with knee osteoarthritis and/or insomnia. *SLEEP 2012*, Boston, MA.

6. **Kaufmann CN**, Mojtabai R, Canham SL, Gum A, Dautovich N, Kohn R, Spira AP. Insomnia and health service utilization in older adults: results from the Health and Retirement Study. *5th Annual Research on Aging Showcase*, Baltimore, MD.

5. **Kaufmann CN**, Mojtabai R, Canham SL, Gum A, Dautovich N, Kohn R, Spira AP. Insomnia and health service utilization in older adults: results from the Health and Retirement Study. *American Association for Geriatric Psychiatry Annual Meeting 2012*, Washington, D.C.

4. Close H, Lee LC, **Kaufmann CN**. Autism spectrum disorder co-occurring conditions and change of ASD diagnosis. *American Public Health Association Annual Meeting 2011*, Washington, D.C.

3. Vedula S, Mahendraratnam N, Rutkow L, **Kaufmann CN**, Rosman L, Twose C, Dickersin K. A snowballing technique to ensure comprehensiveness of search for systematic reviews: a case study. *19th Annual Cochrane Colloquium*, Madrid, Spain.

2. Rutkow L, Vernick JS, Wissow, LW, **Kaufmann CN**, Hodge, JG. Health care providers' prescribing authority during emergencies: challenges for the management of chronic mental health conditions. *SOPHE/NACDD 2011 Joint Academy and Midyear Scientific Meeting*, Albuquerque, NM.

1. Close H, Lee LC, **Kaufmann CN**. Autism spectrum disorder co-occurring conditions and change of ASD diagnosis. *International Meeting for Autism Research 2011*, San Diego, CA.

GRANTS AWARDED

Ruth L. Kirschstein National Research Service Award (F31), National Institute on Aging.
Title: Sedative-hypnotic use in US older adults: Recent trends and associated outcomes
Grant number: F31AG044052
Role: Principal Investigator
Sponsors: Ramin Mojtabai, MD, PhD, MPH, Adam Spira, PhD, & Joseph Gallo, MD
Dates funded: 8/2013-8/2016

Travel Award, International Society for Pharmacoepidemiology
Awarded a scholarship to attend the International Conference on Pharmacoepidemiology and Therapeutic Risk Management in Taipei, Taiwan.
Date funded: 7/2014

Baltimore Growing Green Design Competition, Chesapeake Bay Trust.
Worked with a team that received funding to build a fruit garden on an abandoned lot in northeast Baltimore with the objective to increase access to fresh food for residents, to educate community members about healthy food choices, and to beautify the neighborhood.
Date funded: 9/2014

Neighborhood Event Grant, Municipal Employees Credit Union (MECU).
Served on a grant-writing team that received funding to organize a community event, entitled "Community R&R: Refresh and Revitalize Our Community." The event aimed to educate members of an East Baltimore community on proper trash disposal.
Date funded: 5/2014

Student Organization Event Grant, Johns Hopkins Alumni Association.
Received funding to organize a career panel for which alumni from Johns Hopkins spoke about their careers in pharmacoepidemiology.
Date funded: 10/2013

TEACHING

Teaching Assistant, "Psychopathology for Public Health," First Term 2014
Instructor: Adam P. Spira, PhD

Teaching Assistant, "Public Health Approach to Psychopathology," First Term 2013
Instructor: Adam P. Spira, PhD

RESEARCH EXPERIENCE

Graduate Research Assistant, *Department of Mental Health*, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, May 2013–Present.
Supervisor: Adam Spira, PhD
Duties: Database management for a number of projects related to sleep disturbances in older adults. Manage and score actigraphy data to examine the sleeping behavior of participants.

Research Assistant, *American Psychiatric Association*, Arlington, VA, June 2012–December 2012.
Supervisor: Eve Moscicki, ScD
Duties: Provided research support for the Practice Research Network team. Responsibilities included data management, database organization, and table and figure creation.

Graduate Research Assistant, *Department of Mental Health*, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, August 2011–August 2012
Supervisor: Ramin Mojtabai, MD, PhD, MPH
Duties: Conducting data analyses using the National Epidemiological Survey of Alcohol and Related Conditions dataset on barriers to treatment for patients with co-occurring substance-use and mood/anxiety disorders.

Senior Research Assistant, *Department of Epidemiology*, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, September 2010–August 2011
Supervisors: Kay Dickersin, PhD, Li-Ching Lee, ScM, PhD
Duties: Assisted with screening articles of randomized controlled trials and creating search strategies for systematic reviews as a part of the Cochrane Collaboration. Conducted data analyses on the epidemiology of autism spectrum disorders as a part of the Center for Autism and Developmental Disabilities Epidemiology.

Research Assistant, *Department of Mental Health*, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, July 2010–August 2011
Supervisor: Ramin Mojtabai, MD, PhD, MPH
Duties: Analyzed data from the National Epidemiological Survey of Alcohol and Related Conditions dataset investigating the prevalence of mental disorders of protective service workers, and describing their mental health care needs and treatment seeking behavior.

Data Manager, *Research Triangle Institute, International*, Baltimore, MD, July 2010–December 2010
Supervisor: Diana Fishbein, PhD
Duties: Assisted in the implementation of the PATHWAYS to Learning Study, an NIH-funded evaluation that examines the mechanisms in differential responses of children to the Promoting Alternative Thinking Strategies (PATHS) school-based intervention.

Research Assistant, *Department of Health Policy and Management*, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, July 2010–September 2010
Supervisors: Lainie Rutkow, JD, MPH, PhD, Jon Vernick, JD, MPH
Duties: Conducted literature reviews about the legal and ethical challenges of providing mental health services to individuals impacted by natural and manmade disasters.

Volunteer Research Assistant, *National Children's Study (SDSU/UCSD)*, San Diego, CA, January 2009–August 2009
Supervisor: Jennifer Zellner, PhD
Duties: Assisted with planning recruitment and community outreach strategies for the National Children's Study, a longitudinal study to examine effects of environmental factors on 100,000 children across the US. Built, designed, and organized Excel database documenting measures for study's initial stages.

Research Analyst, *CBS Television Network*, Los Angeles, CA, October 2006–July 2008
Supervisors: Audrey Chan and Eric Steinberg
Duties: Wrote reports for pilot and episode test screenings. Monitored and analyzed Nielsen ratings for primetime network shows.

LEADERSHIP ACTIVITIES

Co-President, *Johns Hopkins Student Chapter of the International Society for Pharmacoepidemiology*, August 2014–Present
- Coordinate organization of journal club meetings, social activities, and networking events
- Served as vice-President between August 2013-June 2014

Secretary, *Johns Hopkins Chapter of Toastmasters International*, September 2013–Present
- Publish monthly newsletter about club activities and member accomplishments
- Record minutes for biweekly club meetings, and distribute to members

LEADERSHIP ACTIVITIES

Volunteer, *Jane's House of Inspiration*, Baltimore, MD, January 2014–Present
- Jane's House of Inspiration is a non-profit organization that provides substance abuse services to low-income community members in East Baltimore, and promotes community development for the purposes of drug abuse prevention.
- Assist with grant writing, help maintain community garden, distribute donated groceries and clothes to community members, participate in social events (e.g. neighborhood barbeques).

PEER REVIEW ACTIVITIES

Co-reviewed manuscripts submitted to *Social Psychiatry and Psychiatric Epidemiology* (7 reviews), *Health Services Research* (1 review), *Journals of Gerontology Series B: Psychological Sciences* (1 review), *Behavior Therapy* (1 review)

PROFESSIONAL ACTIVITIES AND MEMBERSHIP

2013–present *Toastmasters International*, Member of the Johns Hopkins Chapter
2012–present *Johns Hopkins Center for Drug Safety and Effectiveness*, Center Scholar
2013–present *International Society for Pharmacoepidemiology,* Student Member
2009–present *Department of Mental Health Seminar Series,* Johns Hopkins University
2012–present *Aging and Dementia Works In-Progress Meetings,* Johns Hopkins University
2012–present *Gerontological Society of America*, Student Member

HONORS AND AWARDS

- Paul V. Lemkau Scholarship Award, Johns Hopkins Bloomberg School of Public Health, 2015
- Certificate in Gerontology, Johns Hopkins Bloomberg School of Public Health, 2014
- Trainee, Drug Dependence Epidemiology Training Grant (T32DA007292, PI: Debra Furr-Holden, PhD), Johns Hopkins Bloomberg School of Public Health, 2012-2013
- Department of Mental Health Doctoral Student Scholarship, Johns Hopkins Bloomberg School of Public Health, 2011-2012
- Graduated Magna Cum Laude from the University of Southern California, 2006
- Golden Key Honor Society, 2005
- Lambda Pi Eta Communication Honor Society, 2004
- Alpha Lambda Delta National Freshman Honor Society, 2003

SKILLS

- Stata programming
- Working knowledge of SAS and R statistical packages, and Microsoft Access
- Proficient in analysis of large nationally representative datasets
- Collection of data obtained from actigraphs to measure sleep and wake patterns
- Advanced knowledge of Microsoft Office applications (e.g., writing Excel macros)