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Emergency department visits involving benzodiazepines and non-benzodiazepine receptor agonists

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Abstract

Objective—Sedative-hypnotic medications (e.g., Benzodiazepines [BZDs] and non-benzodiazepine receptor agonists [nBZRAs]) are associated with adverse events, especially in the elderly, that may require emergency department (ED) treatment. This study assessed outcomes from ED visits attributed to BZDs and/or nBZRAs, and variations in these associations by age group.

Methods—Data came from the 2004–2011 waves of the Drug Abuse Warning Network (DAWN). Visits were categorized as involving: (1) BZDs-only, (2) nBZRAs-only, (3) combination of BZDs and nBZRAs, or (4) any other sedative-hypnotic medication. DAWN also recorded the disposition (i.e., outcome) of the visit. Analyses focused on outcomes indicating a serious disposition defined as hospitalization, patient transfer or death. Using logistic regression, the association of BZD and nBZRA use with visit disposition was assessed after applying sample weights so as to be nationally representative of ED visits in the United States involving medications or illicit substances.

Results—Nineteen percent of visits involving other sedative-hypnotics, 28% involving BZDs-only, 20% involving nBZRAs-only and 48% involving a combination of BZDs and nBZRAs resulted in a serious disposition. Compared to visits involving other sedative-hypnotics, visits involving BZDs-only had 66% greater odds (Odds Ratio [OR]=1.66, 95% Confidence Interval [CI]=1.37–2.01), and visits involving a combination of BZDs and nBZRAs had almost four times increased odds of a serious disposition (OR=3.91, 95% CI=2.38–6.41). Results were similar across age groups.

Conclusions—Findings highlight the need for clinical and regulatory initiatives to reduce BZD use, especially in combination with nBZRAs, and to promote treatment with safer alternatives to these medications.

Keywords

sedative-hypnotics; emergency department visits; sleep; anxiety

1. INTRODUCTION

Sedative-hypnotic medications are among the first-line treatments for anxiety disorders and insomnia. Within the past two decades, the U.S. has witnessed a substantial increase in the prescribing of these medications [1,2]. Two commonly prescribed sedative-hypnotic groups are benzodiazepines (BZDs) and non-BZD receptor agonists (nBZRAs). BZDs were developed in the 1950s, and are commonly prescribed for the treatment of anxiety disorders and insomnia [3]. nBZRAs were introduced in the 1990s as safer alternatives to BZDs for the short-term treatment of insomnia [4].

Older adults are at particularly high risk for adverse health outcomes from sedative-hypnotic use [5,6]. Observational studies have shown BZDs to be associated with several adverse clinical outcomes including falls leading to hip fractures [7–9] and functional decline [5]. Studies have also shown nBZRAs to be associated with an increased risk of hip fracture [10,11] and impaired balance [12–14]. Additionally, studies in recent years have suggested that the use of these sedative-hypnotic agents may be associated with serious injuries necessitating emergency treatment [15,16].

Over the past decade, the number of emergency department (ED) visits involving BZDs [17] or nBZRAs [18] has increased. However, little is known about outcomes of these visits. EDs see a broad range of cases, some resulting in serious adverse drug events such as hospitalization or death, and others in benign outcomes such as being discharged to home. It is not clear whether ED visits associated with nBZRAs have less serious outcomes compared to those associated with BZDs. Additionally, given the associations between use of BZDs and nBZRAs with adverse health outcomes in older adults, little is known if the ED visit outcomes for these medications vary according to age. Past research has shown that older adults are at greater risk for hospitalization following ED visits for any reason compared to younger people [18].

Understanding the nature of ED outcomes attributed to sedative-hypnotic use is important for clinical practice due to the high prevalence of their use [19]. 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-only, nBZRAs-only, and combination of BZDs and nBZRAs were associated with more serious ED outcomes compared to visits involving any other sedative-hypnotic, and whether these associations differed across age groups.

2. METHODS

2.1 Data source

Data for this study were drawn from the Drug Abuse Warning Network (DAWN) [20]. DAWN is a surveillance system which monitors substance-involved ED visits in a nationally representative sample of U.S. hospitals. Sponsored by the Substance Abuse and Mental Health Services Administration, the purpose of DAWN is to monitor morbidity and mortality involving use of licit and illicit drugs as well as alcohol in the United States.

Although DAWN has been in operation since the 1970s, the surveillance system underwent a substantial redesign in 2003 in order to yield estimates that were more representative nationally. Consequently, this report only uses data from the years 2004–2011 that used the same methodology. In these years, hospitals were randomly selected based on a universe of hospitals listed in the American Hospital Association's Annual Survey Database, and staff at these hospitals were asked to report on eligible visits. For an ED visit to be eligible for DAWN, a substance must have caused or been a contributing factor to the visit. ED staff reported the names and route of administration of the substances involved in the ED visit. Staff also reported whether the case involved alcohol. Substances are defined broadly and encompass alcohol as well as both illicit drugs and pharmaceutical agents used either medically or non-medically. Hospitals were not asked to list all medications currently taken by the patient; they were only asked to list those substances that contributed to the visit. DAWN provides survey design variables and weights to enable researchers to derive nationally representative estimates of ED visits involving substances. All data were de-identified and publically available, and were therefore exempt from IRB review. For DAWN 2004–2011, there were 2,272,434 reported visits (range 168,841–380,125 per year), contributed by between 205 to 242 hospitals per year.

2.2 Subjects

We limited our sample of visits to only those which involved “anxiolytics, sedatives, and hypnotics” as coded in DAWN's *Multum* Lexicon drug vocabulary (n=246,593). Of these, we further selected visits that were deemed to be due to an “adverse reaction” or an “overmedication.” We then excluded visits that involved a non-medical pharmaceutical agent, illicit alcohol use, visits for patients younger than 12 years, and visits that had a disposition recorded as “not documented,” “left against medical advice,” or “other.” Of the 2,272,434 visits reported to DAWN from 2004 through 2011, a total of 33,044 (1.5%) met our inclusion criteria.

2.3 Variables

Exposure—We categorized each ED visit as involving one or more BZD without nBZRA (BZDs-only), one or more nBZRA without BZD (nBZRAs-only), any BZD + any nBZRA (combination of BZDs and nBZRAs), and any other sedative-hypnotic. For the purposes of this study, BZDs included alprazolam, clonazepam, clorazepate, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam. nBZRAs consisted of zolpidem, zaleplon, and eszopiclone. For the 2004–2008 waves, hospitals could list up to 16 medications for a visit; this number increased to 22 in

subsequent years. In creating categorizations for the exposure variable, we only considered the first 16 medications listed at each visit for all years.

Outcome—ED staff also reported the disposition (i.e., outcome) of the visit. Specifically, they recorded whether the visit resulted in the patient being treated and released (i.e., discharged home; released to police; referred to detox treatment), admitted to that hospital (i.e., ICU/critical care, surgery, chemical dependency/detox, psychiatric unit, or other inpatient unit), or other (i.e., transferred; left against medical advice; died; other; not documented). Based on a previous study [21], we categorized visits based on the seriousness of their disposition. We considered visits resulting in admission to any department in the hospital, patient transfer, or death as a “serious disposition,” and visits resulting in a discharge home, release to police/jail, or referral to other treatment as “other disposition.” The remaining dispositions (including left against medical advice, other, and not documented) were not included in our outcome variable.

Potential confounders—We also considered patient age (which we categorized as 12–34, 35–44, 45–64, and 65+ years), gender (male, female), race/ethnicity (non-Hispanic white, non-Hispanic black, any Hispanic or Latino, and any other races), number involved substances reported at the visit, and the involvement of alcohol (yes, no).

2.4 Analysis

Main analyses—We first examined demographic characteristics of patients across ED visits, calculating the proportion of patients with each characteristic in the four medication groups and comparing using chi-squared tests. Next, we used logistic regression to determine the association between the medications involved in the visit and whether the visit resulted in a serious disposition with other disposition as the reference. The medication group involved in the visit served as the predictor, with any other sedative-hypnotic involved serving as the reference group. We conducted bivariate and multivariable analyses adjusting for age, gender, race/ethnicity, involvement of alcohol, and number of substances involved. To adjust for any possible changes in trends for sedative-hypnotic visits over the 8 years of DAWN, we also adjusted for the year of the study, coded as 7 dummy variables (with 2004 as the reference). While the main analyses compared visits involving BZDs and nBZRAs with visits involving other sedative-hypnotics, we also conducted analyses comparing visits involving (a) BZDs-only vs. nBZRAs-only, (b) combination of BZDs and nBZRAs vs. BZDs-only and (c) combination of BZDs and nBZRAs vs. nBZRAs-only.

Analyses by age group—In order to explore differences by age in associations between visit type and seriousness of outcome, we repeated our main analysis after stratifying by age categories (i.e., 12–34, 35–44, 45–64, and 65+ years). We then tested for interactions for the age by exposure groups in the adjusted and unadjusted analyses.

Sensitivity analyses—To determine whether the combination of BZDs and nBZRAs during a visit put patients at risk for a serious disposition 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.

All analyses were conducted in Stata SE version 13 (StataCorp, College Station, TX) and accounted for the complex sampling design of DAWN using the “svy” command.

3. RESULTS

3.1 Demographic characteristics

Of the 33,044 visits in this study, more than half of visits were for patients aged 45 years or older (60.5%). Females comprised 63.8% of the sample, and the majority of visits were by non-Hispanic white patients (82.2%). Seven percent of visits involved alcohol in addition to the pharmacologic agents under study. Visits involved on average 2.94 substances (standard deviation=2.66, range=1–22). Across our sample of visits, 52.9% involved BZDs-only, 15.1% involved nBZRAs-only, and 3.0% involved a combination of BZDs and nBZRAs. Across these medication groups, visits differed by age categories, race/ethnicity, and number of substances (all p 's <0.001; Table 1).

3.2 Visits involving BZDs and nBZRAs and seriousness of dispositions

Twenty-five percent of visits in our sample resulted in a serious disposition and 75% in an other disposition. In contrast to 19% of visits involving any other sedative-hypnotic resulting in a serious disposition, 28% of visits involving BZDs-only (odds ratio [OR]=1.66, 95% confidence interval [CI]=1.37–2.01), and 48% of visits involving a combination of BZDs and nBZRAs (OR=3.91, 95% CI=2.38–6.41) resulted in a serious disposition (Table 2). In adjusted analyses, visits involving BZDs-only had a 35% greater odds (AOR=1.35, 95% CI=1.11–1.65), and visits involving a combination of BZDs and nBZRAs had almost a tripling of the odds (AOR=2.91, 95% CI=1.70–4.98) of resulting in a serious disposition compared to visits involving other sedative-hypnotics.

In further analyses, visits involving nBZRAs-only had lower odds of a serious disposition compared to visits involving BZDs-only both in unadjusted and adjusted analyses (OR=0.65, 95% CI=0.52–0.80; AOR=0.60, 95% CI=0.48–0.75). Furthermore, visits involving a combination of BZDs and nBZRAs were associated with higher odds of a serious disposition compared to visits involving nBZRAs-only (OR=3.64, 95% CI=2.27–5.82; AOR=3.29, 95% CI=1.90–5.69) or BZDs-only (OR=2.35, 95% CI=1.52–3.63; AOR=2.19, 95% CI=1.39–3.46).

3.3 Results across age groups

Across patient age strata, results were similar (Table 3). In bivariate analyses, in most age strata, visits involving BZDs-only were associated with a greater odds of a serious disposition compared to visits involving other sedative-hypnotics, but the magnitude of these variations decreased with increasing age strata. Visits involving a combination of BZDs and nBZRAs were also associated with a greater odds of experiencing a serious disposition across all age strata compared to visits involving other sedative-hypnotics. In multivariable analyses, the associations described above attenuated but remained in the same direction. Notably, the odds ratio for BZDs-only for the 35–44 years age group, and the combination of BZDs and nBZRAs for the 45–64 years age group was no longer statistically significant. Of note, there were no statistically significant interactions for the age by exposure groups

(Adjusted Wald test for joint interactions: $F_{(9, 1425)}=0.74$, $p=0.676$ for unadjusted analyses, and $F_{(9, 1425)}=0.72$, $p=0.696$ for adjusted analyses).

3.4 Sensitivity analysis

To determine whether the combination of BZDs and nBZRAs during a visit put patients at risk for a serious disposition 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 (Table 4). The sample size for these analyses was 20,544 visits (62.2% of our original analysis sample). Compared to visits involving other sedative-hypnotics, visits involving a combination of BZDs and nBZRAs were associated with more than 3.5 times the odds of a serious disposition (OR=3.63, 95% CI=2.17–6.08).

Furthermore, consistent with the results of the main analyses, visits involving BZDs-only were associated with a 72% greater odds of a serious disposition (OR=1.72, 95% CI=1.33–2.23). Results were similar after adjustment for potential confounders, except that the odds ratio for nBZRAs-only became significant.

4. DISCUSSION

We examined the severity of outcomes of ED visits involving BZDs and nBZRAs. Visits involving BZDs and those involving combination of BZDs and nBZRAs were associated with statistically and clinically significantly greater odds of a serious disposition, compared to visits involving other sedative-hypnotics. Results were similar across age groups.

Our finding that almost half of visits involving a combination of BZDs and nBZRAs resulted in a serious disposition is especially noteworthy. Although the absolute number of BZD and nBZRA combination visits was low, this trend is concerning. Even after accounting for the involvement of alcohol and the number of substances involved, visits involving combination of BZDs and nBZRAs still had substantially greater odds of resulting in a serious disposition compared to visits involving other sedative-hypnotics. Studies have shown that the involvement of alcohol with other sedating agents is associated with adverse health outcomes [22]. Additionally, polypharmacy has been shown to be a contributing factor to adverse events [23]. Surprisingly, in the sensitivity analysis limited to visits involving two or more substances, the associations we observed remained statistically significant, suggesting that the odds for a serious disposition associated with the combination of BZDs and nBZRAs is greater than the odds due to combination of any other two or more medications. Several studies have observed adverse health outcomes associated with the combined use of BZDs and nBZRAs [24–26]. Our study confirms these findings, and suggests that these outcomes are severe enough to necessitate more intense health service use.

Older adults are at greater risk for adverse drug events [27–30], and our study confirms these findings, particularly with BZD and nBZRA use. A number of clinical guidelines list medications that should not be used by older adults. For example, the Beers Criteria [31], most recently updated in 2015 [32] lists both BZDs and nBZRAs as potentially dangerous medications. Given results from our study, these clinical guidelines might be modified to also warn against combined use of BZDs and nBZRAs.

It was puzzling that visits involving nBZRAs-only had a lower odds of resulting in a serious disposition compared to visits involving any other sedative-hypnotic, after adjustment for potential confounders. This finding may be due to the greater severity of outcomes associated with other sedative-hypnotics that comprised the comparison group (i.e. visits involving older and potentially less safe agents such as barbiturates).

There are promising 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 [33,34]. Guidelines encourage the use of these treatments [35,36], but with the exception of CBT for anxiety, they are not widely available [37]. Efforts to encourage dissemination of these therapies, especially in older adults, may help decrease ED visits due to the use of sedating medications. The broader use of selective serotonin reuptake inhibitors for treatment of anxiety disorders in recent years [38] may also prove to be a safer alternative than long-term BZD use.

Policy initiatives, as well as patient education campaigns, have sought to decrease the prescribing of BZDs and nBZRAs. For example, the state of New York implemented a triplicate prescription monitoring program that resulted in a decline in prescribing of BZDs by half [39]. Studies have evaluated educational visits to doctors to discuss alternative treatments for sleep disorders [40], and electronic medical record systems have implemented alerts and reminders to encourage prescription of safer medication alternatives [41]. Educational materials targeted at patients have also provided information on proper sleep hygiene [42]. These efforts need further evaluation.

Our study has several limitations. First, data were reported by ED 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. Second, indications for medication use were not recorded. The indications may be associated with differences in outcomes. Finally, all medications used by the patient were not recorded—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.

Our findings highlight the potential dangers in use of BZDs and nBZRAs, and the importance of using clinical judgment in determining the appropriateness of prescribing one of these agents in patients who may be at risk for adverse outcomes (especially older adults). The study also highlights the potential consequences of combining BZDs with nBZRAs. Efforts should be made to reduce combined use of these medications. Increasing awareness of the potential public health consequences of BZDs and nBZRAs may substantially decrease the burden of adverse health outcomes associated with these drugs and lead to improved care for patients across all age groups.

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References

1. Bertisch SM, Herzig SJ, Winkelman JW, Buettner C. National Use of Prescription Medications for Insomnia: NHANES 1999–2010. *Sleep*. 2014; 37:343–9. DOI: 10.5665/sleep.3410 [PubMed: 24497662]
2. Ford ES, Wheaton AG, Cunningham TJ, Giles WH, Chapman DP, Croft JB. Trends in Outpatient Visits for Insomnia, Sleep Apnea, and Prescriptions for Sleep Medications among US Adults: Findings from the National Ambulatory Medical Care Survey 1999–2010. *Sleep*. 2014; 37:1283–93. DOI: 10.5665/sleep.3914 [PubMed: 25083008]
3. Lader M. Benzodiazepines revisited—will we ever learn? *Addiction*. 2011; 106:2086–109. DOI: 10.1111/j.1360-0443.2011.03563.x [PubMed: 21714826]
4. Taylor SR, Weiss JS. Review of insomnia pharmacotherapy options for the elderly: implications for managed care. *Popul Health Manag*. 2009; 12:317–23. DOI: 10.1089/pop.2008.0047 [PubMed: 20038257]
5. Gray SL, LaCroix AZ, Hanlon JT, Penninx BWJH, Blough DK, Leveille SG, et al. Benzodiazepine use and physical disability in community-dwelling older adults. *J Am Geriatr Soc*. 2006; 54:224–30. DOI: 10.1111/j.1532-5415.2005.00571.x [PubMed: 16460372]
6. Puustinen J, Lähteenmäki R, Polo-Kantola P, Salo P, Vahlberg T, Lyles A, et al. Effect of withdrawal from long-term use of temazepam, zopiclone or zolpidem as hypnotic agents on cognition in older adults. *Eur J Clin Pharmacol*. 2014; 70:319–29. DOI: 10.1007/s00228-013-1613-6 [PubMed: 24337417]
7. Landi F, Onder G, Cesari M, Barillaro C, Russo A, Bernabei R, et al. Psychotropic medications and risk for falls among community-dwelling frail older people: an observational study. *J Gerontol a Biol Sci Med Sci*. 2005; 60:622–6. [PubMed: 15972615]
8. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc*. 1999; 47:30–9. [PubMed: 9920227]
9. Rossat A, Fantino B, Bongue B, Colvez A, Nitenberg C, Annweiler C, et al. Association between benzodiazepines and recurrent falls: a cross-sectional elderly population-based study. *J Nutr Health Aging*. 2011; 15:72–7. [PubMed: 21267523]
10. Berry SD, Lee Y, Cai S, Dore DD. Nonbenzodiazepine sleep medication use and hip fractures in nursing home residents. *JAMA Intern Med*. 2013; 173:754–61. DOI: 10.1001/jamainternmed.2013.3795 [PubMed: 23460413]
11. Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Zolpidem use and hip fractures in older people. *J Am Geriatr Soc*. 2001; 49:1685–90. [PubMed: 11844004]
12. Allain H, Bentué-Ferrer D, Polard E, Akwa Y, Patat A. Postural instability and consequent falls and hip fractures associated with use of hypnotics in the elderly: a comparative review. *Drugs Aging*. 2005; 22:749–65. [PubMed: 16156679]
13. Berlin I, Warot D, Hergueta T, Molinier P, Bagot C, Puech AJ. Comparison of the effects of zolpidem and triazolam on memory functions, psychomotor performances, and postural sway in healthy subjects. *J Clin Psychopharmacol*. 1993; 13:100–6. [PubMed: 8463441]
14. Frey DJ, Ortega JD, Wiseman C, Farley CT, Wright KP. Influence of zolpidem and sleep inertia on balance and cognition during nighttime awakening: a randomized placebo-controlled trial. *J Am Geriatr Soc*. 2011; 59:73–81. DOI: 10.1111/j.1532-5415.2010.03229.x [PubMed: 21226678]
15. Wadsworth EJK, Moss SC, Simpson SA, Smith AP. Psychotropic medication use and accidents, injuries and cognitive failures. *Hum Psychopharmacol*. 2005; 20:391–400. DOI: 10.1002/hup.709 [PubMed: 16106487]

16. Chung SD, Lin CC, Wang LH, Lin HC, Kang JH. Zolpidem Use and the Risk of Injury: A Population-Based Follow-Up Study. *PLoS ONE*. 2013; 8:e67459.doi: 10.1371/journal.pone.0067459 [PubMed: 23826304]
17. Licata SC, Rowlett JK. Abuse and dependence liability of benzodiazepine-type drugs: GABA(A) receptor modulation and beyond. *Pharmacol Biochem Behav*. 2008; 90:74–89. DOI: 10.1016/j.pbb.2008.01.001 [PubMed: 18295321]
18. Mitka M. Zolpidem-related surge in emergency department visits. *Jama*. 2013; 309:2203.doi: 10.1001/jama.2013.6289 [PubMed: 23736709]
19. Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. *Arch Gen Psychiatry*. 2010; 67:26–36. DOI: 10.1001/archgenpsychiatry.2009.175 [PubMed: 20048220]
20. Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network. 2011: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
21. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. The DAWN Report: Benzodiazepines in Combination with Opioid Pain Relievers or Alcohol: Greater Risk of More Serious ED Visit Outcomes. Rockville, MD: Dec 18. 2014
22. Wilkinson CJ. The acute effects of zolpidem, administered alone and with alcohol, on cognitive and psychomotor function. *J Clin Psychiatry*. 1995; 56:309–18. [PubMed: 7615484]
23. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother*. 2007; 5:345–51. DOI: 10.1016/j.amjopharm.2007.12.002 [PubMed: 18179993]
24. Zammit G. Comparative tolerability of newer agents for insomnia. *Drug Saf*. 2009; 32:735–48. DOI: 10.2165/11312920-000000000-00000 [PubMed: 19670914]
25. Saano V, Hansen PP, Paronen P. Interactions and comparative effects of zopiclone, diazepam and lorazepam on psychomotor performance and on elimination pharmacokinetics in healthy volunteers. *Pharmacol Toxicol*. 1992; 70:135–9. [PubMed: 1508840]
26. Zint K, Haefeli WE, Glynn RJ, Mogun H, Avorn J, Stürmer T. Impact of drug interactions, dosage, and duration of therapy on the risk of hip fracture associated with benzodiazepine use in older adults. *Pharmacoepidemiol Drug Saf*. 2010; 19:1248–55. DOI: 10.1002/pds.2031 [PubMed: 20931664]
27. Chrischilles EA, VanGilder R, Wright K, Kelly M, Wallace RB. Inappropriate medication use as a risk factor for self-reported adverse drug effects in older adults. *J Am Geriatr Soc*. 2009; 57:1000–6. [PubMed: 19507293]
28. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. *Ann Intern Med*. 2007; 147:755–65. [PubMed: 18056659]
29. Hanlon JT, Schmadre KE, Koronkowski MJ, Weinberger M, Landsman PB, Samsa GP, et al. Adverse drug events in high risk older outpatients. *J Am Geriatr Soc*. 1997; 45:945–8. [PubMed: 9256846]
30. Field TS, Gurwitz JH, Harrold LR, Rothschild J, DeBellis KR, Seger AC, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. *J Am Geriatr Soc*. 2004; 52:1349–54. DOI: 10.1111/j.1532-5415.2004.52367.x [PubMed: 15271125]
31. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med*. 2003; 163:2716–24. DOI: 10.1001/archinte.163.22.2716 [PubMed: 14662625]
32. The American Geriatrics Society. 2015 Beers Criteria Update Expert Panel, American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2015; 63:2227–2246. [PubMed: 26446832]
33. Bain KT. Management of chronic insomnia in elderly persons. *Am J Geriatr Pharmacother*. 2006; 4:168–92. DOI: 10.1016/j.amjopharm.2006.06.006 [PubMed: 16860264]

34. Costa e Silva JA. Sleep disorders in psychiatry. *Metab Clin Exp*. 2006; 55:S40–4. [PubMed: 16979426]
35. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008; 4:487–504. [PubMed: 18853708]
36. American Psychiatric Association. Practice guideline for the treatment of patients with panic disorder. n.d. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf (accessed August 13, 2014).
37. Vitiello MV, McCurry SM, Rybarczyk BD. The future of cognitive behavioral therapy for insomnia: what important research remains to be done? *J Clin Psychol*. 2013; 69:1013–21. DOI: 10.1002/jclp.21948 [PubMed: 23348150]
38. Pirraglia PA, Stafford RS, Singer DE. Trends in Prescribing of Selective Serotonin Reuptake Inhibitors and Other Newer Antidepressant Agents in Adult Primary Care. *Prim Care Companion J Clin Psychiatry*. 2003; 5:153–7. [PubMed: 15213776]
39. Wagner AK, Ross-Degnan D, Gurwitz JH, Zhang F, Gilden DB, Cosler L, et al. Effect of New York State regulatory action on benzodiazepine prescribing and hip fracture rates. *Ann Intern Med*. 2007; 146:96–103. [PubMed: 17227933]
40. de Burgh S, Mant A, Mattick RP, Donnelly N, Hall W, Bridges-Webb C. A controlled trial of educational visiting to improve benzodiazepine prescribing in general practice. *Aust J Public Health*. 1995; 19:142–8. [PubMed: 7786939]
41. Weber V, White A, McIlvried R. An electronic medical record (EMR)-based intervention to reduce polypharmacy and falls in an ambulatory rural elderly population. *J Gen Intern Med*. 2008; 23:399–404. DOI: 10.1007/s11606-007-0482-z [PubMed: 18373136]
42. Meisler JG. Patient education: getting enough sleep. *J Womens Health*. 1998; 7:1203–1204. [PubMed: 9929851]

Demographic characteristics of patients during emergency department visits involving sedative-hypnotic medications, Drug Abuse Warning Network 2004–2011

Characteristic	Other sedative-hypnotic		BZDs-only		nBZRAs-only		Combination of BZDs and nBZRAs		p-value ^b
	n=10,099	% ^a (95% CI)	n=17,199	% ^a (95% CI)	n=4,906	% ^a (95% CI)	n=840	% ^a (95% CI)	
Age									<0.001
12–34	32.1 (29.4, 34.9)		21.7 (18.8, 25.0)		18.1 (14.4, 22.5)		21.9 (12.0, 36.5)		
35–44	16.5 (14.4, 18.9)		16.2 (14.4, 18.2)		11.1 (8.9, 13.7)		12.1 (7.0, 20.0)		
45–64	29.8 (27.6, 32.1)		32.9 (30.6, 35.2)		33.9 (29.2, 38.8)		41.5 (33.7, 49.8)		
65+	21.7 (19.4, 24.1)		29.2 (26.8, 31.7)		37.0 (32.3, 41.9)		24.6 (16.8, 34.6)		
Gender									0.494
Male	35.1 (31.7, 38.6)		36.2 (33.9, 38.6)		39.1 (34.7, 43.8)		33.5 (24.6, 43.8)		
Female	64.9 (61.4, 68.3)		63.8 (61.4, 66.2)		60.9 (56.2, 65.3)		66.5 (56.2, 75.4)		
Race/ethnicity									<0.001
Non-Hispanic white	75.7 (71.2, 79.7)		84.2 (80.9, 87.0)		85.6 (82.1, 88.5)		90.0 (81.7, 94.7)		
Non-Hispanic black	11.7 (9.1, 14.9)		8.9 (6.8, 11.6)		6.7 (4.8, 9.2)		1.5 (0.8, 3.0)		
Hispanic	11.2 (8.3, 14.8)		5.5 (4.2, 7.2)		5.9 (4.1, 8.4)		7.2 (3.3, 15.2)		
All other races/ethnicities	1.5 (1.0, 2.2)		1.4 (0.8, 2.3)		1.9 (1.0, 3.5)		1.3 (0.4, 4.5)		
Alcohol involved									0.267
No	94.4 (91.4, 96.4)		92.3 (90.9, 93.5)		91.4 (88.4, 93.8)		93.4 (85.7, 97.1)		
Yes	5.6 (3.6, 8.6)		7.7 (6.5, 9.1)		8.7 (6.2, 11.7)		6.6 (2.9, 14.3)		
# substances, mean (SD)	2.27 (1.94)		3.32 (2.84)		2.17 (2.07)		6.60 (3.59)		<0.001
Year									0.140
2004	6.9 (4.7, 10.0)		3.8 (2.5, 5.7)		5.0 (2.5, 9.8)		2.1 (0.7, 6.7)		
2005	8.7 (6.1, 12.2)		7.1 (4.7, 10.5)		6.8 (4.3, 10.6)		4.9 (2.2, 10.5)		
2006	10.1 (6.9, 14.6)		9.3 (6.0, 14.2)		7.3 (4.8, 10.9)		8.8 (4.2, 17.6)		
2007	11.4 (8.0, 15.9)		13.4 (8.8, 19.9)		12.9 (8.0, 20.1)		10.3 (4.7, 21.1)		
2008	15.5 (10.9, 21.5)		17.3 (11.5, 25.1)		15.7 (9.9, 23.8)		21.4 (7.8, 46.7)		
2009	15.2 (10.9, 20.8)		17.1 (11.6, 24.5)		18.2 (12.1, 26.6)		22.6 (13.3, 35.8)		
2010	15.6 (10.8, 22.1)		16.2 (11.3, 22.5)		19.7 (13.6, 27.9)		16.0 (9.7, 25.2)		

Characteristic	Other sedative-hypnotic n=10,099	BZDs-only n=17,199	nBZRAs-only n=4,906	Combination of BZDs and nBZRAs n=840	p-value ^b
2011	% ^a (95% CI) 16.6 (11.5, 23.5)	% ^a (95% CI) 16.0 (10.5, 23.5)	% ^a (95% CI) 14.4 (9.5, 21.1)	% ^a (95% CI) 13.9 (5.4, 31.2)	

Note: BZDs = benzodiazepines (include alprazolam, clonazepam, lorazepam, diazepam, estazolam, flurazepam, lorazepam, oxazepam, and triazolam), nBZRAs = non-benzodiazepine receptor agonists (include zolpidem, zaleplon, and eszopiclone), 95% CI = 95% confidence interval.

Number of missing values: gender=13, race/ethnicity=6,551

^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 for categorical variables; F-test for continuous

Table 2

Serious dispositions following emergency department visits involving sedative-hypnotic medications, Drug Abuse Warning Network 2004–2011

	Other disposition ^a	Serious disposition ^a	Unadjusted comparison	Adjusted comparison ^b
Medications involved	Row % (95% CI)	Row % (95% CI)	OR (95% CI)	AOR (95% CI)
Other sedative-hypnotic	80.9 (78.1, 83.4)	19.1 (16.6, 21.9)	Ref.	Ref.
BZDs-only	71.8 (69.4, 74.1)	28.2 (25.9, 30.6)	1.66 (1.37, 2.01)	1.35 (1.11, 1.65)
nBZRAs-only	79.8 (76.5, 82.7)	20.2 (17.3, 23.5)	1.07 (0.87, 1.33)	0.82 (0.64, 1.04)
Combination of BZDs and nBZRAs	52.0 (40.8, 63.1)	48.0 (36.9, 59.3)	3.91 (2.38, 6.41)	2.91 (1.70, 4.98)

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), nBZRAs=non-benzodiazepine receptor agonists (include zolpidem, zaleplon, and eszopiclone). All analyses are weighted to account for oversampling and yield nationally representative estimates.

^a“Serious disposition” 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. “Other disposition” defined as an emergency room visit resulting in a discharge home, release to police/jail, or referred to other treatment.

^bAdjusted analyses account for age, gender, race of patient, number of reported substances, whether or not alcohol was involved, and year.

Table 3

Emergency department visits involving sedative-hypnotic medications and serious dispositions following visit stratified by age group of patients, Drug Abuse Warning Network 2004–2011

Medications involved	Other disposition ^a	Serious disposition ^a	Unadjusted comparison	Adjusted comparison ^b
	Row % (95% CI)	Row % (95% CI)	OR (95% CI)	AOR (95% CI)
12–34 years				
Other sedative-hypnotic	90.3 (85.0, 93.9)	9.7 (6.1, 15.1)	Ref.	Ref.
BZDs-only	86.7 (83.2, 89.6)	13.3 (10.4, 16.8)	1.43 (0.82, 2.50)	1.20 (0.61, 2.38)
nBZRAs-only	95.2 (90.7, 97.6)	4.8 (2.4, 9.3)	0.47 (0.19, 1.13)	0.46 (0.17, 1.27)
Combination of BZDs and nBZRAs	53.9 (18.5, 85.8)	46.1 (14.2, 81.5)	8.00 (1.77, 36.17)	4.60 (1.17, 18.02)
35–44 years				
Other sedative-hypnotic	87.0 (82.1, 90.8)	13.0 (9.3, 17.9)	Ref.	Ref.
BZDs-only	78.8 (70.7, 85.1)	21.2 (14.9, 29.3)	1.81 (1.03, 3.16)	1.67 (0.96, 2.89)
nBZRAs-only	89.0 (81.6, 93.6)	11.0 (6.4, 18.4)	0.83 (0.44, 1.57)	0.70 (0.35, 1.43)
Combination of BZDs and nBZRAs	58.9 (34.2, 79.8)	41.1 (20.2, 65.8)	4.68 (1.64, 13.38)	4.36 (1.67, 11.38)
45–64 years				
Other sedative-hypnotic	79.5 (75.0, 83.4)	20.5 (16.6, 25.0)	Ref.	Ref.
BZDs-only	69.6 (65.6, 73.3)	30.4 (26.7, 34.4)	1.69 (1.25, 2.30)	1.51 (1.09, 2.08)
nBZRAs-only	81.5 (75.8, 86.1)	18.5 (13.9, 24.2)	0.88 (0.56, 1.38)	0.84 (0.51, 1.35)
Combination of BZDs and nBZRAs	59.4 (40.9, 75.5)	40.6 (24.5, 59.1)	2.65 (1.16, 6.07)	1.81 (0.81, 4.02)
65+ years				
Other sedative-hypnotic	64.2 (57.6, 70.3)	35.8 (29.7, 42.4)	Ref.	Ref.
BZDs-only	59.3 (55.1, 63.4)	40.7 (36.6, 44.9)	1.23 (0.87, 1.73)	1.11 (0.79, 1.57)
nBZRAs-only	67.9 (62.2, 73.0)	32.2 (27.0, 37.8)	0.85 (0.61, 1.18)	0.84 (0.60, 1.18)
Combination of BZDs and nBZRAs	34.6 (20.0, 52.8)	65.4 (47.2, 80.0)	3.39 (1.50, 7.63)	2.45 (1.03, 5.79)

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), nBZRAs=non-benzodiazepine receptor agonists (include zolpidem, zaleplon, and eszopiclone). All analyses are weighted to account for oversampling and yield nationally representative estimates.

^a“Serious disposition” 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. “Other disposition” 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, number of reported substances, whether or not alcohol was involved, and year.

Table 4

Emergency department visits involving sedative-hypnotic medications and serious dispositions following visit limited to visits involving two or more substances, Drug Abuse Warning Network 2004–2011

	Other disposition ^a	Serious disposition ^a	Unadjusted comparison	Adjusted comparison ^b
Medications involved	Row % (95% CI)	Row % (95% CI)	OR (95% CI)	AOR (95% CI)
Other sedative-hypnotic	79.7 (75.9, 83.1)	20.3 (16.9, 24.1)	Ref.	Ref.
BZDs-only	69.6 (66.6, 72.4)	30.4 (27.6, 33.4)	1.72 (1.33, 2.23)	1.50 (1.14, 1.96)
nBZRAs-only	81.7 (77.2, 85.4)	18.3 (14.6, 22.8)	0.88 (0.63, 1.23)	0.66 (0.46, 0.94)
Combination of BZDs and nBZRAs	52.0 (40.8, 63.1)	48.0 (36.9, 59.3)	3.63 (2.17, 6.08)	3.08 (1.74, 5.44)

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), nBZRAs=non-benzodiazepine receptor agonists (include zolpidem, zaleplon, and eszopiclone). All analyses are weighted to account for oversampling and yield nationally representative estimates.

^a“Serious disposition” 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. “Other disposition” defined as an emergency room visit resulting in a discharge home, release to police/jail, or referred to other treatment.

^bAdjusted analyses account for age, gender, race of patient, number of reported substances, whether or not alcohol was involved, and year.