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Outpatient, combined use of opioid and benzodiazepine medications in the United States, 1993–2014

Matthew E. Hirschtritt[a,*], Kevin L. Delucchi[b], Mark Olfson[c]

[a] Department of Psychiatry, University of California, San Francisco, 401 Parnassus Ave, Box 0984-RTP, San Francisco, CA 94143, United States
[b] Department of Psychiatry, University of California, San Francisco, 401 Parnassus Ave, Box 0984, San Francisco, CA 94143, United States
[c] Department of Psychiatry, College of Physicians and Surgeons, Columbia University and New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, United States

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ABSTRACT

The combined use of opioid and benzodiazepine medications increases the risk of hazardous effects, such as respiratory depression. Although recent increases in outpatient use of opioid prescriptions have been documented, there are limited data regarding rates and correlates of combined opioid and benzodiazepines among adults in outpatient settings. Our objective was to examine annual trends in outpatient visits including opioids, benzodiazepines, and their combination among adults as well as clinical and demographic correlates. We used data from the 1993–2014 National Ambulatory Medical Care Survey (NAMCS) among non-elderly (i.e., ages 18–64 years) adults to examine the probability of a visit including an opioid, benzodiazepine, or their combination, in addition to clinical and demographic correlates. From 1993 to 2014, benzodiazepines-with-opioids visits increased from 9.8 to 62.5 (OR = 9.23, 95% CI = 5.45–15.65) per 10,000 visits. Highest-represented groups among benzodiazepines-with-opioids visits were older (50–64 years) (49.1%), white (88.8%), commercially insured (58.0%) patients during their first visit (87.6%) to a primary-care physician (41.9%). We identified a significant increase in the outpatient co-prescription of opioids and benzodiazepines, notably among adults aged 50–64 years during primary-care visits. Educational and policy changes to provide alternatives to benzodiazepine-with-opioid co-prescription and limiting opioid prescription to pain specialists may reduce rates of this potentially hazardous combination.

1. Introduction

In the period between 1993 and 2014, the number of opioid analgesic prescriptions dispensed from retail pharmacies in the United States (US) increased from roughly 113 million to 264 million (Pezalla et al., 2017), with a corresponding increase in opioid-related diversion, abuse, and deaths between 2002 and 2010 (Dart et al., 2015). Similarly, between 1996 and 2013, the percentage of US adults who filled a prescription for a benzodiazepine increased from 4.1% to 5.6%, during which time the rate of deaths attributed to benzodiazepine overdoses increased from 0.58 to 3.07 per 100,000 adults (Bachhuber et al., 2016).

Although rates of outpatient prescription of opioids (Dart et al., 2015) and benzodiazepines (Bachhuber et al., 2016) may be stabilizing or decreasing in the years since 2010, the overall rates remain greatly elevated compared to previous decades. In addition, among adults who are prescribed opioids for daily use, nearly 40% have a concurrent prescription for a benzodiazepine. This is especially concerning given the increased risk of respiratory depression, overdose, and death associated with the co-administration of these two classes of medications (Karaca-Mandic et al., 2017; Saunders et al., 2012; Jann et al., 2014). For instance, in a prospective, outpatient-based study of adult patients prescribed high-dose opioids, those concurrently prescribed benzodiazepines were nearly 10 times more likely to die from overdose (Dasgupta et al., 2016). Similarly, among adults in the Veterans Health Administration who received prescriptions for opioids, nearly half of drug overdose deaths occurred among those concurrently prescribed benzodiazepines (Park et al., 2015). Privately insured, nonelderly adults who received prescriptions for both opioids and benzodiazepines, compared to opioids alone, were more likely to visit the emergency department or have an inpatient admission for opioid overdose (Sun et al., 2017). Furthermore, in the emergency department setting

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; NCHS, National Center for Health Statistics; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; NAMCS, National Ambulatory Medical Care Survey; OR, odds ratio; RFV, reason-for-visit

* Corresponding author.
E-mail addresses: matthew.hirschtritt@ucsf.edu (M.E. Hirschtritt), kevin.delucchi@ucsf.edu (K.L. Delucchi), olfsonm@nyspi.columbia.edu (M. Olfson).

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between 2004 and 2011, the percentage of opioid overdose deaths among adults that also involved benzodiazepine use increased steadily from 18% to 31% (Jones and McAninch, 2015).

In light of these and similar data, the Centers for Disease Control and Prevention (CDC) released revised guidelines (Dowell et al., 2016) for prescribing opioid analgesics for chronic pain in 2016, which recommend that "clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible." However, despite the well-documented risk of death from concurrent administration of opioids and benzodiazepines, less is known about the trends in general, outpatient prescribing patterns of these two classes of medications. Recent analyses of US prescription claims has revealed increased rates of co-prescription of benzodiazepines and opioids among non-elderly adults (Hwang et al., 2016) and adults receiving opioids for musculoskeletal pain (Larochelle et al., 2015). However, these studies have generally limited analyses to the years subsequent to 2001; this excludes the 1990s, which was also marked by a steady increase in rates of opioid prescriptions. In addition, previous studies have either used administrative or claims-level data (Sun et al., 2017; Hwang et al., 2016), which may be associated with validity issues (Strom, 2001), or focused on specific populations of adults (Larochelle et al., 2015).

Therefore, to address this gap in the literature, we sought to examine trends in the outpatient administration of opioids, benzodiazepines, and their combination among nonelderly adults from 1993 to 2014, clinical and demographic correlates of prescription patterns, and likelihood of physicians co-prescribing opioids and benzodiazepines. To achieve these aims, we used prospectively collected, nationally representative data from the National Ambulatory Medical Care Survey (NAMCS). We anticipate that results from these analyses will inform clinical and policy decisions by specifically identifying adults and clinicians who are at highest risk for benzodiazepine and opioid coadministration.

2. Material and methods

2.1. Sample

We used data from the 1993–2014 NAMCS, an annual, cross-sectional, nationally representative probability sample survey of non-federally employed office-based physicians, administrated by National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (National Center for Health Statistics, 2017). We limited our analysis to visits by patients aged 18–64 years (n = 402,027). Physicians specializing in anesthesiology, pathology, and radiology are excluded from the survey, as well as home-based visits or those within institutional settings (e.g., nursing homes). Survey response rates varied from 38.7% in 2014 to 73.1% in 1993 (mean = 61.6%). Within each patient visit, either the physician or a staff member recorded information about patient characteristics and medications that were "ordered, supplied, administered, and continued." Detailed information regarding NAMCS administration and coding can be accessed elsewhere (Centers for Disease Control and Prevention, 2017). Because this research involves use of de-identified data, it was exempt from review by the Institutional Review Board of the University of California, San Francisco.

2.2. Medications

During the years 1993 to 2014, NAMCS forms allowed extraction of five to 30 current medications; to maintain consistency across years, we limited our analyses to the first five medications listed. Starting in 2006, NAMCS medications were coded using Lexicon Plus®, a proprietary database of Cerner Multum, Inc.; medication data from survey years prior to 2006 were recoded into Lexicon Plus® therapeutic classes using syntax developed by the NCHS. Visits were considered benzodiazepine visits if they were included in the Therapeutic Category Level 3, "069 – benzodiazepines" (i.e., alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, oxazepam, prazepam, quazepam, temazepam, or triazolam). Visits were considered opioid visits if they were included in the Therapeutic Category Level 3, "060 – analgesics" (i.e., alphaprodine, codeine, dezocine, diphenoxylate, fentanyl, glutethimide, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, nalbuphine, opium, oxycodone, oxymorphone, pentazocine, propoxyphene, remifentanil, sufentanil, or tapentadolor).

2.3. Demographic characteristics

We classified visits by patient sex, age at time of visit (18–34, 35–49, or 50–64 years), and race (white, black, or other). Because ethnicity was not recorded consistently among the included survey years, this variable was excluded from our analyses.

2.4. Primary source of payment

Following guidelines established by the NCHS, we grouped visits into mutually exclusive payment categories in descending order: (Pezalla et al., 2017) private-pay or commercial, (Dart et al., 2015) Medicare, (Bachhuber et al., 2016) Medicaid and other government insurance (including the Children's Health Insurance Program), or (Karaca-Mandic et al., 2017) other (self-pay, no charge, or "other").

2.5. Reasons for visit and diagnoses

Survey forms included up to three patient-generated reasons-for-visit (RFV) as well as up to three visit diagnoses (using the *International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*]). Pain was classified based on physical location into six categories using RFVs: head or neck, chest, abdomen or pelvis, back or hip, extremities, or unspecified. We also identified visits in which any pain was listed as the primary (i.e., first listed) RFV. Visits were also classified by relevant diagnoses based on *ICD-9-CM* codes: low-back pain (722.10, 722.52, 724.2–724.6, 738.4, 756.11, 839.2, 846.0, 847.2), cancer (140–239, 338.3), anxiety disorders (293.84, 300.0, 300.2–300.3, 308.3, 309.21, 309.81, 313.0), substance use disorders (291–292, 303–305), depressive disorders (296.2, 296.3, 300.4, 311), and insomnia (307.4, 327.00, 327.01, 327.02, 327.09, 780.50, 780.51, 780.52, 780.55, 780.56, 780.59).

2.6. Other visit-level characteristics

We grouped visit status as a first or returning visit by whether the treating physician or anyone in the practice had seen the patient before. In addition, we recoded the specialty of the treating physician as primary care (internal medicine, geriatric medicine, adolescent medicine, pediatrics, family practice, and general practice), psychiatry, or another medical specialty.

2.7. Statistical analysis

We used logistic regression to assess year-by-year time trends in the probability of that visits included any 1 of the 3 medication groups, controlling for patient age and race. We assigned a study-year period variable ([survey year-1993]/22) to examine the strength of association of medication-group prescription from 1993 through 2014. The resultant odds ratios for each medication group estimates the change in odds of a visit containing the medication group relative to a visit in which neither benzodiazepines nor opioids were prescribed over the entire 1993–2014 study period. We compared differences in proportion by visit characteristics using χ^2 tests. Among visits with physician-level weights (2005–2014, n = 6338), we similarly used logistic regression to examine time trends of the 3 medication groups controlling for the