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Prescribing of benzodiazepines and opioids to individuals with substance use disorders

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ABSTRACT

Background: Benzodiazepines are recommended for short-term use due to risk of dependence. This study examined characteristics associated with benzodiazepine and opioid dispensing of 7+ days in a Medicaid population with substance use disorder (SUD).
Methods: Using 2014 MarketScan® data, we performed zero-inflated negative binomial regression to ascertain characteristics associated with longer-term use of these medications.
Results: Nearly 14% of those with SUDs received 1+ fills of benzodiazepines of 7+ days. The highest rates were among those aged 45–64 (IRR = 2.38, $p < 0.0001$) and with non-alcohol SUDs (IRR = 1.12, $p < 0.0001$). Individuals with co-occurring psychiatric disorders, particularly anxiety and depression (IRR = 1.41, $p < 0.0001$), had high rates of benzodiazepine fills. Receiving a 7+ day oral opioid fill (IRR = 1.30, $p < 0.0001$) coincided with increased benzodiazepine dispensing. Similar results occurred for longer-term prescribing of opioids, with higher rates among those with non-alcohol SUDs (IRR = 1.23, $p < 0.0001$).
Conclusions: For many people with SUDs, receiving a benzodiazepine or opioid prescription of 7+ days is not a single occurrence; patients in our sample were more likely to receive 2+ fills than to receive one. Longer-term prescribing is most pronounced among those with co-occurring anxiety disorders. This suggests that anxiety in those with SUD should preferentially not be treated using benzodiazepines. Longer-term polypharmacy with benzodiazepines and opioids coincided. Overdoses among those using both drugs are growing and this study provides evidence that attention to the opioid epidemic should include attention to polypharmacy that includes benzodiazepines.

1. Introduction

Results of the 2015 National Survey on Drug Use and Health (NSDUH) indicated that approximately 20.8 million individuals aged 12 years and older (7.8%) met diagnostic criteria for a substance use disorder (SUD) during the past year (SAMHSA, 2016Substance Abuse Substance Abuse and Mental Health Services Administration [SAMHSA], 2016). A substantial proportion of individuals with a SUD also have a co-occurring mental health disorder. The 2015 NSDUH results indicate that 8.1 million (41.2%) adults aged 18 years or older with a SUD during the past year also had a mental illness (SAMHSA, 2016). It is important to treat both conditions properly in individuals with dual diagnoses (Minkoff, 2001, 2013; Perron et al., 2010; Wisdom et al., 2011).

Benzodiazepines are most commonly prescribed for the short-term treatment of anxiety disorders. Their appropriateness for managing symptoms of alcohol withdrawal is reflected in their labeling as approved by the U.S. Food and Drug Administration (FDA) (e.g., FDA, 2010, 2013). Benzodiazepines are not FDA-approved for managing any other withdrawal syndrome (FDA, 2017). According to American Psychiatric Association guidelines, however, benzodiazepines also have a role in the management of agitation due to intoxication with cocaine or other stimulants (American Psychiatric Association, 2010).

Benzodiazepines have a number of negative side effects and carry warnings regarding drug interactions, fetal harm, dependence, and withdrawal (FDA, 2011). According to the International Clinical Practice Guidelines, treatments involving benzodiazepines should be limited to 4 weeks (Peters et al., 2015). Benzodiazepines can produce both

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physical and psychological dependence (Hood et al., 2014; Uzun et al., 2010), and physical tolerance can develop after only 3–6 weeks of use (Hood et al., 2014). Benzodiazepines are associated with impaired memory and diminished emotional affect (Ashton, 2002), as well as cognitive impairment, delusions, falls, and other morbidities in older adults (American Geriatrics Society, 2015). The safety and effectiveness of these medications have not been established for long-term use or for patients with any form of SUD except alcohol withdrawal (Minkoff, 2001).

Accumulating evidence suggests that benzodiazepine exposure is particularly hazardous for persons with a SUD. Data from the National Institute on Drug Abuse show a 5-fold increase in the number of deaths from benzodiazepine overdose between 2001 and 2014 (National Institute on Drug Abuse, 2015), with benzodiazepines involved in 31% of opioid overdose deaths in 2011 (Chen et al., 2014), suggesting a particular danger associated with concomitant use of opioids and benzodiazepines. SAMHSA has reported increasing admissions for benzodiazepine abuse (SAMHSA, 2011) and noted a high association of benzodiazepine use disorder with opioid use disorder and comorbid psychiatric illness (SAMHSA, 2012). Prescribing benzodiazepines in the presence of known substance use disorder should be undertaken with care.

This study examined the number of outpatient benzodiazepine prescriptions dispensed for a greater than 7-day supply to individuals with a SUD diagnosis. We analyzed this occurrence with and without specific co-occurring psychiatric or pain disorders and looked at dispensing for those with different demographic characteristics. We also examined longer-term benzodiazepine fills with and without receipt of any antidepressant or of an oral opioid dosed in excess of 7 days. On the basis of those findings, we expanded our analysis to include a counterpart examination of predictors of oral opioid fills of 7+ days, including association with demographic and diagnostic variables, as well as receipt of either a longer-term fill of benzodiazepines or antidepressant dispensing. Our objective was to ascertain, among those with a SUD diagnosis, characteristics associated with longer-term use of benzodiazepines and opioids, including the extent to which such use co-occurs.

2. Methods

2.1. Data

We used the Truven Health Analytics MarketScan® Multi-State Medicaid Database for outpatient services and pharmaceutical claims for Medicaid enrollees from multiple states. We included all Medicaid enrollees in the MarketScan data in 2014 aged 13–64 years who had a SUD diagnosis (i.e., an alcohol disorder or any other nontobacco-related SUD). We excluded individuals who were dually eligible for Medicaid and Medicare and those who lacked information related to sex or age. After identifying eligible patients in 2014, we examined the prior year data to determine other diagnoses that these individuals might have received in 2013. This additional information provided a more complete picture of the existing clinical presentation of individuals receiving benzodiazepines. The patient-level deidentified records in the 2014 data files contain Medicaid administrative data for approximately 3.9 million Medicaid enrollees. After the exclusions were applied, 337,095 individuals remained in the sample for this study.

2.2. Variables

The outcomes of interest were the number of benzodiazepine or oral opioid prescriptions greater than a 7-day supply dispensed during 2014. Prescription fills were grouped by number: none, 1, 2–4, and 5+. This allowed us to ascertain characteristics of individuals to whom a 7+ day supply of medications was dispensed. The date of the first prescription for the study medications during 2014 (the index date) triggered a 12-month look-back using the 2013–2014 data to determine whether the patient had a psychiatric or pain diagnosis before or at the time of the prescription.

We used types of diagnoses as primary independent variables in selected analyses, including type of SUD diagnosis (alcohol only, nonalcohol drug only, and both alcohol and drug), type of psychiatric diagnosis (depressive but no anxiety/stress, anxiety/stress but no depressive, both depressive and anxiety/stress, other psychiatric diagnosis only, and no psychiatric diagnosis), and any pain disorder. The MarketScan data are claims data, and the diagnoses used were those provided to patients seen in outpatient clinical settings and billed to Medicaid.

Our analysis of the data by the presence or absence of co-occurring conditions included covariates for any antidepressant fill and for oral opioid or benzodiazepine fills of 7+ days (the latter as appropriate within the relevant model). We included antidepressant use because it is a recommended therapy for the treatment of most chronic anxiety. Other covariates included the demographic variables of age (13–17, 18–44, 45–64 years), sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, all other).

2.3. Analyses

We performed univariate analyses to ascertain demographic and other selected characteristics of the study sample. We conducted bivariate analyses to determine the extent to which those characteristics were associated with benzodiazepine or oral opioid dispensing greater than 7 days and the number of such dispensings during the study year. We used zero-inflated negative binomial regression for multivariate analysis. Negative binominal regression is used for count data that may be overdispersed and Incidence Rate Ratios (IRRs) provide the estimated rate ratio for a one-unit increase in the independent variable (e.g., a 7+ day fill of benzodiazepines), holding other variables constant (Guerrero, 2013). We used zero-inflated versions of the models to address the fact that a large percentage of the sample was never dispensed a benzodiazepine or oral opioid in excess of 7 days.

3. Results

3.1. Descriptives

Of the 3,932,665 enrollees represented in the 2014 MarketScan Medicaid outpatient and pharmaceutical claims, 415,043 had a SUD-related diagnosis. After omitting 18,271 individuals who fell outside the age range of 13–64 years, an additional 59,677 individuals with dual Medicare and Medicaid coverage, and 2410 who were missing data on any of the variables, the sample for this study included 337,095 enrollees.

Table 1 provides frequencies for the sample by selected demographic, diagnostic, and other characteristics. The sample presents with a higher proportion of nonalcohol drug disorders (67.1%) than alcohol disorders (22.5%); those with both constituted 10.4% of the sample. Fifty-four percent of the sample had a co-occurring mental health diagnosis. Only 5.6% presented with depression but not anxiety/stress; 23.3% had anxiety/stress without depression, and 9.7% were diagnosed with both. Sixty-two percent also had a pain-related diagnosis, 40.9% had any antidepressant fill in 2014, 13.6% had a benzodiazepine fill of 7+ days, and 28.0% had an oral opioid fill of 7+ days. Benzodiazepines most frequently filled for 7+ days were alprazolam (58.9%), lorazepam (17.7%), and diazepam (16.5%). Opioids most often filled for 7+ days were acetaminophen/hydrocodone bitartrate (31.3%), acetaminophen/oxycodone hydrochloride (19.6%), and tramadol hydrochloride (17.8%) (neither results shown).