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Concomitant use of buprenorphine for medication-assisted treatment of opioid use disorder and benzodiazepines: Using the prescription behavior surveillance system

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ABSTRACT

Background: Despite clinical guidelines discouraging the practice, it is well-documented that the concomitant use of benzodiazepines and opioid analgesics occurs regularly. Information on concomitant use of buprenorphine for medication-assisted treatment (MAT) of opioid use disorder (OUD) and benzodiazepines, however, is limited. Thus, we aimed to describe real-world drug dispensing patterns for the concomitant use of buprenorphine products approved for MAT and benzodiazepines.

Methods: We examined concomitant use of buprenorphine for MAT and benzodiazepines using the 2013 Prescription Behavior Surveillance System data from eight states. For prescription-level analysis, we estimated the proportion of concomitant buprenorphine and benzodiazepine prescriptions and the proportions of concomitant prescriptions prescribed by the same provider (co-prescribing) and dispensed by the same pharmacy (co-dispensing) for each state. For patient-level analysis, we calculated the proportion of patients with ≥1 buprenorphine therapy episode overlapping with a benzodiazepine episode, i.e., concomitant users, and the proportion of concomitant users who experienced co-prescribing or co-dispensing.

Results: In 2013, 1,925,072 prescriptions of buprenorphine products for MAT were dispensed to 190,907 patients in eight states. Approximately 1 in 8 buprenorphine prescriptions was used concomitantly with ≥1 benzodiazepine prescription(s). Co-prescribing proportions ranged from 22.2 to 64.6% across states, while co-dispensing proportions ranged from 54.7 to 91.0%. Approximately 17.7% of patients had > 1 buprenorphine episode overlapping a benzodiazepine episode for ≥7 cumulative days' supply. Among these patients, 33.1–65.2% experienced co-prescribing, and 65.1–93.3% experienced co-dispensing.

Conclusions: The concomitant use of buprenorphine for MAT and benzodiazepines occurs frequently, with variations by state in co-prescribing and co-dispensing.

1. Introduction

Prescription opioid analgesic abuse is associated with significant morbidity and mortality in the United States (Birnbaum et al., 2011). There were over 17,000 fatal overdoses involving a prescription opioid analgesic in the United States in 2015 (Rudd et al., 2016), and nearly two million Americans aged 12 years or older had opioid use disorder (OUD) in 2013 (Hedden, 2015). Prescription opioid analgesic overdoses kill more Americans each year than heroin and cocaine combined (Paulozzi et al., 2014; CDC, 2011).

One of the responses to the opioid overdose crisis has been greater oversight of prescription opioid analgesics through implementation of Prescription Drug Monitoring Programs (PDMPs) in 49 states and the District of Columbia that track prescribing and dispensing data for controlled substances (Brandeis University, 2017; Haffajee et al., 2015). Depending on the state, prescribers and/or dispensers may be legally required to check the PDMP record prior to prescribing a controlled substance to a patient. A recent study showed that state implementation of PDMPs was associated with a reduction in opioid-related overdose deaths compared to states without PDMPs (Patrick et al., 2016).

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Many overdoses related to prescription opioid analgesics also involve benzodiazepines (Jones et al., 2012). The frequency of concomitant use of benzodiazepines and opioid analgesics, as well as the consequent increased morbidity and mortality, is well-described in the literature (Gomes et al., 2011; Hwang et al., 2016; Jones and McAninch, 2015; Kim et al., 2016; Larochelle et al., 2015; Peirce et al., 2012). However, the study of concomitant use of buprenorphine for medication-assisted treatment (MAT) of OUD and benzodiazepines is less extensive: many studies that examined opioid-benzodiazepine concomitancy excluded buprenorphine for MAT from the analysis (Jones et al., 2012; Kim et al., 2016; Larochelle et al., 2015). MAT is a mainstay of treatment for OUD and has been shown to be effective in reducing opioid use and opioid craving among affected individuals (Connery, 2015; Fiellin et al., 2006; Fudala et al., 2003; Volkow et al., 2014). Additionally, case reports and epidemiologic studies have shown serious morbidity and mortality can occur when buprenorphine is used with benzodiazepines (Faroqui et al., 1983; Hakkinen et al., 2012; Jones et al., 2012; Lintzeris et al., 2007; Nielsen et al., 2007; Schuman-Olivier et al., 2013). Studies have suggested that the concomitant use of buprenorphine and benzodiazepines has been linked to severe respiratory depression, overdose, unconsciousness, and death (Faroqui et al., 1983; Nielsen et al., 2007).

In this study, we used data from the Prescription Behavior Surveillance System (PBSS), a population-based public health surveillance system containing de-identified, longitudinal data from participating state PDMPs, to describe real-world drug dispensing patterns for the concomitant use of buprenorphine products approved for MAT and benzodiazepines.

2. Methods

2.1. Study design and data source

We conducted a cross-sectional study using data from eight states submitting data to PBSS in 2013: California (CA), Ohio (OH), Louisiana (LA), Kentucky (KY), West Virginia (WV), Idaho (ID), Maine (ME), and Delaware (DE) ([dataset]: Kreiner et al., March 14, 2017). These states were selected for this analysis because their PDMPs record prescriptions dispensed to all individuals in the state, including individuals aged 16 years and younger. According to a report by the Centers for Disease Control and Prevention (CDC), five of the eight states included in our analysis were among the top 15 U.S. states with the highest rates of drug overdose deaths in 2013 (WV: 32.2 deaths per 100,000 persons; KY: 23.7 per 100,000; OH: 20.8 per 100,000; DE: 18.7 per 100,000 and LA: 17.8 per 100,000 persons) (Rudd et al., 2016). The other three states had relatively lower rates of drug overdose deaths in 2013 (ID: 13.4 per 100,000; ME: 13.2 per 100,000; and CA: 11.1 per 100,000). At the time of the analysis, the most recent year of complete data for all the analyzed states was 2013. The PBSS is an early warning surveillance and evaluation tool based on de-identified, longitudinal data from participating state PDMPs. It is intended to be used to examine prescribing and dispensing patterns for controlled substances and to identify possible signs of drug misuse and diversion (Morgan et al., 2013). State PDMPs routinely collect information on every prescription for a controlled substance, including those paid for with cash. Participating state PDMPs submit de-identified data quarterly to PBSS, including patient demographics, National Drug Classification (NDC) codes, drug name, fill date, days of supply, pharmacy, and prescriber ID, among other information (Paulozzi et al., 2013). The general characteristics of the PBSS database, methods of data collection, and other data elements are described in more detail in other publications (Finklea et al., 2014; Paulozzi et al., 2013).

We examined the concomitant use of buprenorphine products approved for MAT and benzodiazepines at both prescription- and patient-levels. We used NDC codes to identify prescriptions of all dosage forms of buprenorphine and buprenorphine-naloxone products approved for MAT of OUD (Table S1) as well as benzodiazepine products dispensed in tablets or capsules. We excluded buprenorphine products approved for treatment of pain and benzodiazepines in gel, solution, or suspension forms. The active supply periods of buprenorphine and benzodiazepine prescriptions were defined as fill date plus the days' supply recorded in the database. Patients were excluded from the analysis if their buprenorphine or benzodiazepine prescriptions had missing, 0, or > 90 days' supply, as these represent invalid days' supply.

2.2. Statistical analysis

2.2.1. Prescription-level analysis

We calculated three indicators using different numerators and denominators to assess the concomitant use of buprenorphine for MAT and benzodiazepines: the proportion of overlapping prescriptions (overlapping), the proportion of overlapping prescriptions written by the same provider (co-prescribing), and the proportion of overlapping prescriptions dispensed by the same pharmacy (co-dispensing; Table S2). For a given buprenorphine prescription, if a benzodiazepine days' supply period overlapped with the days' supply of a buprenorphine prescription by one day or more, the buprenorphine prescription was counted as a prescription concomitantly used with benzodiazepines (Fig. S1). These indicators were plotted for assessment of state variation.

2.2.2. Patient-level analysis

To ensure the robustness of concomitant use definition, we also conducted patient-level analysis. Using fill dates and days' supply, we constructed continuous therapy episodes separately for buprenorphine for MAT and benzodiazepines in three steps (Fig. 1):

Step 1: We created the start date and end date of prescription periods by linking consecutive prescriptions for the same patient with continuous days' supply.

Step 2: We counted the total overlapping days' supply in each prescription period. If the total overlapping days' supply was ≤7 days, we added the number of overlapping days to the end of the prescription period. If the total overlapping days of supply was > 7 days, we added 7 days to the end of the prescription period.

Step 3: We created therapy episodes using prescription periods. We permitted a grace period of ≤7 days between the active days' supply of two prescription periods and considered these two prescription periods as parts of the same therapy episode. If the gap between two prescription periods was > 7 days, we considered the two prescription periods as separate therapy episodes.

We defined concomitant users as patients who had at least one benzodiazepine episode that overlapped a buprenorphine episode by ≥7 consecutive days (*numerator)*. In each state, we identified patients dispensed at least one buprenorphine product for MAT (*denominator*). We calculated and plotted the proportion of patients using buprenorphine for MAT and benzodiazepines concomitantly as the first indicator of concomitancy at patient-level.

Among the concomitant users (*denominator*), we then estimated the proportion of those who received at least one buprenorphine and one benzodiazepine prescription from the same prescriber as well as the proportion of those who received at least one buprenorphine and one benzodiazepine prescription from the same pharmacy. We defined the numerator as the number of concomitant users with at least one buprenorphine prescription with overlapping days' supply of a benzodiazepine prescribed by the same prescriber (co-prescribing—second indicator of concomitant use at patient level) and the number of concomitant users with at least one buprenorphine prescription with overlapping days' supply of a benzodiazepine dispensed by the same pharmacy (co-dispensing— third indicator of concomitant use at patient level).

All analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC); maps showing the results for each of the eight states were