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Benzodiazepine use during buprenorphine treatment for opioid dependence: Clinical and safety outcomes

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ABSTRACT

Background: Prescribing benzodiazepines during buprenorphine treatment is a topic of active discussion. Clinical benefit is unclear. Overdose, accidental injury, and benzodiazepine misuse remain concerns. We examine the relationship between benzodiazepine misuse history, benzodiazepine prescription, and both clinical and safety outcomes during buprenorphine treatment.
Methods: We retrospectively examined outpatient buprenorphine treatment records, classifying patients by past-year benzodiazepine misuse history and approved benzodiazepine prescription at intake. Primary clinical outcomes included 12-month treatment retention and urine toxicology for illicit opioids. Primary safety outcomes included total emergency department (ED) visits and odds of an ED visit related to overdose or accidental injury during treatment.
Results: The 12-month treatment retention rate for the sample ($N = 328$) was 40%. Neither benzodiazepine misuse history nor benzodiazepine prescription was associated with treatment retention or illicit opioid use. Poisson regressions of ED visits during buprenorphine treatment revealed more ED visits among those with a benzodiazepine prescription versus those without ($p < 0.001$); benzodiazepine misuse history had no effect. The odds of an accidental injury-related ED visit during treatment were greater among those with a benzodiazepine prescription (OR: 3.7, $p < 0.01$), with an enhanced effect among females (OR: 4.7, $p < 0.01$). Overdose was not associated with benzodiazepine misuse history or prescription.
Conclusions: We found no effect of benzodiazepine prescriptions on opioid treatment outcomes; however, benzodiazepine prescription was associated with more frequent ED visits and accidental injuries, especially among females. When prescribing benzodiazepines during buprenorphine treatment, patients need more education about accidental injury risk. Alternative treatments for anxiety should be considered when possible, especially among females.

1. Introduction

Prescribing benzodiazepines during office-based opioid treatment (OBOT) (Gunderson and Fiellin, 2008) with buprenorphine is a practice that evokes intense discussion in clinical settings. Fatal overdoses from mixing benzodiazepines with buprenorphine, especially through concurrent intravenous administration, are a major safety concern (Reynaud et al., 1998b). The Food and Drug Administration required a warning for physicians to use caution when prescribing buprenorphine with benzodiazepines (Reckitt-Benckiser, 2010). Additionally, many clinicians believe that benzodiazepine prescriptions should be avoided because benzodiazepines hinder development of psychological coping strategies (Otto et al., 2005; Soyka, 2010), can be misused (Brunette et al., 2003; Chen et al., 2011) and can contribute to relapse (Brands et al., 2008). In contrast, others argue that use of long-acting benzodiazepine can be helpful in some circumstances, especially to retain people with co-occurring severe anxiety disorders who are receiving treatment for opioid dependence (Bleich et al., 2002; Liebrenz et al., 2010). For instance, 12-month retention in buprenorphine treatment among people with generalized anxiety disorder is low compared to people with major depressive disorder (39% vs. 72%; Gerra et al., 2006) and to the 12-month retention rate reported in

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several buprenorphine treatment samples (43–49%; Alford et al., 2011; Fiellin et al., 2008; Gerra et al., 2006). In the context of this ongoing debate, some OBOT programs avoid both prescribing benzodiazepines and admitting those who already have a prescription. Alternatively, some programs will accept those who already have a benzodiazepine prescription, while encouraging gradual benzodiazepine reduction within a limited time period (Tyrer, 2010), subject to certain conditions aimed at enhancing safety and limiting aberrant drug use behaviors (Lintzeris and Nielsen, 2010). Furthermore, some clinicians prescribe benzodiazepine maintenance to people with co-occurring anxiety disorders during buprenorphine treatment, believing it helps maintain retention and prevents relapse.

Benzodiazepine use is common among patients prescribed buprenorphine for opioid dependence. For example, in a Norwegian prescription database, 30% of patients on buprenorphine received a benzodiazepine prescription during the previous year (Bramness and Kornor, 2007). Early in treatment, patients receiving buprenorphine treatment frequently request a benzodiazepine prescription to mitigate anxiety and insomnia symptoms (Lintzeris and Nielsen, 2010). Misuse of benzodiazepines is also common; in a French sample, 31% of patients on buprenorphine had problematic use of benzodiazepines in the past month (Lavie et al., 2009).

While benzodiazepines and buprenorphine are each safer than their respective alternatives, barbiturates and methadone, the misuse of benzodiazepines with buprenorphine has resulted in dangerous consequences. Benzodiazepines, unlike barbiturates, do not cause respiratory depression when taken alone (Gasser et al., 1975; Murray et al., 1987), although benzodiazepine use has been associated with sedation, psychomotor impairment, and accidental injuries (Oster et al., 1990). Similarly, buprenorphine is safer than methadone when taken by itself; its partial agonism at central mu opioid receptors results in a "ceiling effect" on respiratory depression (Bell et al., 2009).

A French case series reported details of six overdose deaths related to concomitant use of buprenorphine and benzodiazepines (Reynaud et al., 1998a). When buprenorphine and benzodiazepines were co-administered to rats, the protective bell-shaped dose response effect on respiration was eliminated (Nielsen and Taylor, 2005). Human laboratory studies demonstrated that even when buprenorphine is taken at therapeutic doses, co-administration with supra-therapeutic doses of benzodiazepines can remove buprenorphine's "ceiling effect" on respiratory depression in the same pattern as co-administration with methadone (Lintzeris et al., 2006). In Finland, where buprenorphine is the primary opioid of abuse (Yokell et al., 2011), a retrospective analysis of opioid-associated deaths recorded in the national postmortem toxicology database found 1363 opioid-positive cases, of which 182 had buprenorphine poisoning as the cause of death; either a benzodiazepine or alcohol was found in all but one case, and were present in 82 and 58% of cases, respectively (Hakkinen et al., 2012). The median concentrations of buprenorphine and benzodiazepines in these poisonings were in the therapeutic range (Hakkinen et al., 2012). In contrast, a controlled human laboratory study with eight patients prescribed buprenorphine who were orally co-administered diazepam at therapeutic doses ($\leq$20 mg) did not demonstrate an effect of diazepam on oxygen saturation compared with placebo, even though sedation and performance deficits emerged as the dose was increased (Lintzeris et al., 2006). Additionally, in a cross-sectional survey of 250 people with opioid dependence, overdose events from benzodiazepine use were self-reported ten times less frequently during buprenorphine versus methadone treatment (Nielsen et al., 2007). Taken together, these data suggest, even with therapeutic doses of buprenorphine, co-administration of benzodiazepines may result in lethal overdose when used either at supra-therapeutic dosages or at therapeutic dosages through intravenous injection or in combination with sedatives; however, lethal overdose would be unexpected to occur in the context of controlled oral co-administration of therapeutic dosages of benzodiazepines and buprenorphine. Therefore, clinical investigation of the safety of benzodiazepine treatment prescribed at therapeutic doses during buprenorphine treatment is necessary.

Using a chart review with a naturalistic, quasi-experimental design, we attempted to evaluate the relationship between benzodiazepine prescribing and clinical and safety outcomes during buprenorphine treatment, while also evaluating for effects of historical benzodiazepine misuse. We investigated the relationship between past-year benzodiazepine misuse and benzodiazepine prescription in several areas. Our primary clinical outcomes were 12-month treatment retention and number of months without positive urine toxicology screens for illicit opioids. Our primary safety outcomes were emergency department (ED) visits during treatment and ED visits related to overdose and accidental injury. We hypothesized that the best clinical and safety outcomes would occur among those without any benzodiazepine use history. We further hypothesized that there would be more ED visits due to overdose and accidental injuries, more opioid-positive toxicology screens, and poorer treatment retention among those with both a benzodiazepine prescription and history of benzodiazepine misuse as compared with those without either a benzodiazepine prescription or a history of benzodiazepine misuse.

2. Methods

2.1. Sample selection

This sequential-admission retrospective study was conducted with admissions to a collaborative care OBOT program (Alford et al., 2011; Schuman-Olivier et al., 2010) from November 2007 to June 2010. Two nurse care managers collaborated with multiple buprenorphine prescribers, coordinating urine toxicology screening, monitoring treatment adherence, overseeing medication management and facilitating communication with addiction counselors. Prescribers were affiliated with an academic community healthcare system located in five Boston Metro-North cities, sharing an electronic medical record (EMR). The Cambridge Health Alliance human subjects review board approved this protocol. We conducted the chart review using standardized intake forms, quarterly interviews conducted by nurse care managers, and the EMR.

Nurse care managers conducted a brief screening assessment by telephone or in-person to determine treatment program admission eligibility. All newly eligible patients (n = 386) were included in this sequential admission study. Patients were expected to complete an intake process, including: (1) comprehensive urine toxicology, (2) complete OBOT nurse care manager assessment, and (3) buprenorphine prescription from network physician. We excluded those with an incomplete intake process (n = 35, 9%). To enhance external validity, we excluded special populations not commonly treated in standard buprenorphine treatment or whose response to benzodiazepines could be atypical (i.e., psychotic disorder (n = 2, <1%), pregnancy (n = 3, 1%), and intracranial injury (e.g., traumatic brain injury, stroke; n = 18, 4.6%; Fig. 1). All together, we excluded 15% (n = 58) from the analysis, resulting in 328 patients included in the analysis. Records for the final sample (n = 328) were recorded until the date of OBOT program discharge or until 12 months after intake into OBOT treatment.

2.2. Procedure

2.2.1. Treatment. OBOT consisted of buprenorphine maintenance treatment prescribed by program-affiliated physicians from various medical specialties, including internal medicine, family medicine, and psychiatry. Within this program, clinicians encouraged brief inpatient detoxification before starting buprenorphine maintenance for patients with co-occurring substance dependence or significant medical problems; however, detoxification was not required when opioid dependence was the only substance use disorder present. Standard treatment consisted of buprenorphine initiation during a half-day in-office induction. All buprenorphine prescriptions in this study were buprenorphine/naloxone co-formulation sublingual tablets.

Within this abstinence-focused program, patients typically participated in intensive outpatient programming during the first two weeks of treatment and in response to substance use lapses. The program also required patients to step down into weekly relapse prevention groups unless psychiatric needs precluded participation. The program also provided individual therapy and psychopharmacology based on psychiatric need. When an anxiety disorder diagnosis was made by an in-network physician, recommending a benzodiazepine prescription, the medical

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