

PROFESSIONALISM AND COMMENTARY

Benzodiazepines in Long-Term Opioid Therapy

Disclosures:

Dr. Reisfield: Millennium Laboratories (consultant)
Dr. Webster: AstraZeneca, Boehringer Ingelheim, Collegium Pharmaceuticals, Covidien Mallinckrodt, CVS Caremark, Jazz Pharmaceuticals, Nektar Therapeutics, Neura Therapeutik, Nevro Corporation, Orexo, Quintiles, Theravance (consultant/honoraria/advisory board)

Introduction

The prescribing of long-term opioid therapy (LtOT) for chronic noncancer pain (CNCP) gained wide clinical acceptance over the past quarter century. The practice has become increasingly controversial in recent years, however, due both to questions about long-term efficacy and the potential for opioid-related morbidity and mortality [1–3]. Recently, several pain medicine thought leaders have retreated from long-held positions about the wisdom of prescribing LtOT for patients with CNCP [4].

The prescribing of long-term benzodiazepine therapy for anxiety and mood disorders, insomnia, and other indications is also both prevalent and controversial. Advocates for their use point to their rapidity of onset, efficacy, and tolerability, while opponents highlight concerns about sedation, cognitive and psychomotor impairment, abuse and addiction, physical dependence, and the sometimes enormous difficulties in tapering and discontinuing these medications [5–7]. It has been argued that the availability of psychological therapies and selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine uptake inhibitors (SNRIs) for anxiety disorders, and sleep hygiene and melatonin for insomnia have made the long-term administration of benzodiazepines largely avoidable [7–9]. Although a detailed discussion of the safety and efficacy of benzodiazepine therapy is beyond the scope of this commentary, a recent critical appraisal of these agents offered the following conclusions [10]:

- *Anxiety disorders.* The evidence supporting the use of benzodiazepines is drug-, disorder-, and duration-specific. For example, in the management of generalized anxiety disorder and panic disorder, there is robust evidence for the efficacy of these drugs for short-term treatment, but evidence for their long-term efficacy is mostly empirical. In the management post-traumatic stress disorder, there is no evidence to support their short- or long-term use. Moreover, in animal models,

alprazolam administered shortly after stress exposure increased vulnerability to subsequent stress.

- *Mood disorders.* Evidence indicates that benzodiazepines might be useful early in depressive episodes, particularly for the management of associated symptoms, but their long-term efficacy has not been systematically confirmed. Treatment guidelines recommend limiting their use to those patients with primary major depression with symptoms of pronounced anxiety or insomnia that are not adequately controlled with SSRIs or SNRIs.
- *Insomnia.* In general, sedative-hypnotics are US Food and Drug Administration-approved for short-term use and not recommended for long-term use. The risk of falls and confusion make even their short-term use problematic. Significantly, one study found that, among chronic pain patients, those taking benzodiazepines for insomnia continued to report as many problems with sleep as those patients who were not taking these drugs [11].

Benzodiazepines are commonly co-prescribed to patients on LtOT. Evidence indicates that between 20% and 50% of patients who are prescribed LtOT for CNCP also receive prescriptions for benzodiazepines [11–15]. A recent Danish study found that individuals with chronic pain who were managed with LtOT had 12.5 times the odds of being prescribed long-term benzodiazepine therapy than individuals with chronic pain who were not receiving opioids [16]. The co-prescribing of benzodiazepines and opioids appears to be especially prevalent in those patients with substance use disorders. Data from the Consortium to Study Opioid Risks and Trends, which comprised adult enrollees of Kaiser Permanente of Northern California and Group Health Cooperative of Seattle, demonstrated that enrollees on LtOT who had past 2-year substance use disorders—and particularly opioid use disorders—were prescribed higher opioid doses and were more frequent long-term users of benzodiazepines than enrollees without substance use disorders [17].

Individuals with psychiatric diagnoses, chiefly mood and/or anxiety disorders, report a higher prevalence and severity of physical symptoms, including pain. These diagnoses are also predictive of future opioid use. For example, Sullivan and colleagues, in a large, prospective, population-based survey (Healthcare for Communities), found that individuals with mood or anxiety disorders in 1998 were twice as likely as those without these diagnoses to have initiated prescription opioid use by 2001, even after controlling for chronic pain at baseline [18]. A recent

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study of US Veterans of Afghanistan and Iraq found that, compared with those without mental health disorders, those with diagnoses of depression or post-traumatic stress disorder were more likely to receive opioid therapy within 1 year of a pain diagnosis [19]. Furthermore, recent data from the National Epidemiologic Study on Alcohol and Related Conditions indicated that mood and anxiety disorders are strongly associated with—and often precede—nonmedical opioid use and substance (including benzodiazepine and opioid) use disorders [20,21].

This commentary will highlight the actual and potential problems associated with this medication combination and will offer recommendations concerning their co-prescription.

Substance Use Disorder Treatment Admissions

According to the Substance Abuse and Mental Health Administration, the number of substance abuse treatment admissions involving the combination of benzodiazepines and opioids increased by 570% over the most recent decade, from approximately 5,000 admissions in 2000 to more than 33,000 admissions in 2010. In contrast, treatment admissions for all other substances decreased by approximately 10% during the same period. Nearly half of these benzodiazepine-opioid combination admissions occurred in individuals with psychiatric disorders compared with slightly more than a quarter in other drug admissions [22]. This reflects, in part, the fact that benzodiazepines are used to treat anxiety and, to a lesser extent, mood disorders.

Emergency Department Visits

According to the Drug Abuse Warning Network, emergency department visits for nonmedical use of opioid analgesics increased by 111%—from 144,600 to 305,900—from 2004 to 2008. During this same period, visits for nonmedical use of benzodiazepines increased 89%—from 143,500 to 271,700. Benzodiazepines were involved in 26% of opioid-related visits. Of note, alcohol was involved in 15% of opioid-related visits and 23% of benzodiazepine-related visits [23].

Mortality

According to data from the National Vital Statistics System Mortality File, fatal overdoses involving opioids increased nearly 250%—from 4,000 to 13,800—between 1999 and 2006. In more than half of these opioid deaths, at least one additional drug was implicated as contributing to death, with benzodiazepines—involved in 20%—comprising the most frequently specified drug class [24].

In 2010, there were more than 22,000 pharmaceutical overdose deaths in the United States. Opioids (75.2%) and benzodiazepines (29.4%) were the two drug classes most commonly involved in these deaths. Benzodiazepines were involved in 30.1% of opioid deaths—more

than any other drug class. Similarly, opioids were involved in 77.2% of benzodiazepine deaths—again, more than any other drug class [25].

Peirce and colleagues examined data for 1,049,903 individuals who were prescribed controlled medications in West Virginia over a recent 2.5-year period (captured through the state's prescription drug monitoring program) and the subset of 600 who had controlled medication-related deaths (captured through the state's forensic drug database). Those who filled at least one prescription each for an opioid and a benzodiazepine in the 6 months prior to death had greater odds of a drug-related death (odds ratio [OR] 14.9; 7.0–31.8) than those who filled prescriptions for only opioids (OR 3.4; 1.6–7.2) or only benzodiazepines (OR 7.2; 3.3–15.6) [26].

Gomes and colleagues identified 607,156 individuals who were dispensed at least one opioid prescription paid for by the Ontario (Canada) public drug plan between 1997 and 2006. Of this cohort, 1,463 individuals had opioid-related deaths. Following exclusions of individuals with cancer diagnoses or receiving palliative care, without drug coverage in the 180 days prior to death, without overlapping prescriptions, and without matched controls, 498 opioid-related deaths were analyzed. Coroners' toxicological testing found benzodiazepines in 301 (60.4%), more than one opioid in 193 (38.8%), and ethanol in 92 (18.5%) of cases. Compared with matched controls, decedents were more likely to have received benzodiazepines, methadone, antidepressants, or other sedating drugs prior to death. Decedents were also more likely to have a history of alcoholism [27].

Dunn and colleagues examined fatal and non-fatal opioid overdoses among patients in Washington State's Group Health Cooperative between 1997 and 2005. The study cohort comprised patients who initiated opioid therapy for a noncancer pain indication and filled three or more prescriptions in the first 90 days of the pain episode. Higher opioid doses were associated with opioid-related overdoses. Sedative-hypnotic use was included as a covariate. Relative to patients receiving no sedative-hypnotic prescriptions in the 90 days prior to opioid overdose, patients receiving sedative-hypnotics were at increased risk of opioid overdose. Hazard ratios were as follows: 3.4 (1.6–7.2) for a 1- to 22-day supply of sedative-hypnotics, 0.9 (0.2–4.0) for 23- to 44-day supply of sedative-hypnotics, 3.7 (1.6–8.9) for 45- to 71-day supply of sedative-hypnotics, and 2.7 (1.2–6.0) for a 72+ day supply of sedative-hypnotics [28].

Clearly, the combination of opioids and benzodiazepines is potentially lethal. The aforementioned studies, however, were not designed to distinguish medical from nonmedical use of one or both drug classes. However, Hall and colleagues performed a population-based, observational study of West Virginia residents who died of unintentional prescription drug overdoses in 2006, based on medical examiner data, prescription drug monitoring program data, and clinical records. Prescription opioids were

involved in 93.2% of deaths. Most (63.3%) of these deaths involved one or more other prescription drugs, most often benzodiazepines. Of note, 63.1% of decedents had evidence of use of contributory pharmaceuticals without prescription, and 21.4% had received controlled substance prescriptions from five or more providers in the year preceding death [29].

Sleep-Disordered Breathing

Webster and colleagues found an association between combination opioid and benzodiazepine use and sleep-disordered breathing. One hundred and forty patients on long-term, stable doses of opioids (one third on methadone; median daily opioid dose was 266 mg/day of oral morphine equivalents) underwent sleep studies. Abnormal apnea-hypopnea indices were found in 75% of LtOT patients (obstructive sleep apnea in 39%; central sleep apnea in 24%; combination obstructive and central sleep apnea in 8%; and sleep apnea, not otherwise specified in 4%). The study did not include a control group, but the authors noted an estimated prevalence of sleep apnea of 2–4% in the general population. Methadone alone showed a significant dose-dependent relationship with central sleep apnea (the study was not sufficiently powered to exclude other opioids as independent risk factors). Methadone and benzodiazepines showed an additive effect on central sleep apnea. Of note, an inverse relationship was observed with the combination of opioids and (non-benzodiazepine) muscle relaxants [30].

Falls and Fractures in Older Adults

Hip fractures in older adults are associated with substantial morbidity and mortality [31]. Benzodiazepines, both short- and long-acting, have been associated with increased risk of falls and fractures, particularly in older adults [32]. Opioids have also been associated with falls and fractures, with risk diminishing with chronic use [33]. A recent prospective population-based study found that the combination of opioids and benzodiazepines was strongly associated with an elevated age-adjusted fracture risk in men (but not women) at 3-year follow up (relative risk [RR] 7.2; confidence interval [CI] 1.4–37.2; $P = 0.02$) and 6-year follow up (RR 12.0; CI 2.5–58.4; $P = 0.002$) [34].

Motor Vehicle Crashes

Benzodiazepines are among the most represented prescription-controlled substances in several driving under the influence of drugs studies [35,36]. Several recent systematic reviews and meta-analyses have found associations between benzodiazepine use and motor vehicle crashes (MVCs) [37–39].

Gomes and colleagues, in a population-based, nested case-control study of drivers involved in MVC with injury, found a dose-related association between opioid administration and MVC. Compared with individuals prescribed very low dose opioids (<20 oral morphine equivalents/day), those in higher dose categories were associated

with ORs of 1.21–1.42 [40]. Dessanayake et al., in a systematic review of epidemiological studies, reported that opioids were associated with an elevated risk of MVC in young drivers, with conflicting data on risk in elderly drivers [38]. Limited evidence indicates elevated MVC risk at least during the initial 4 weeks of opioid use [40].

We were unable to identify any data on the MVC risk associated with combined opioid and benzodiazepine use.

Discussion

Benzodiazepines and opioids are among the most prescribed medications in the United States. Each drug class possesses strong evidence bases for short-term efficacy in some conditions, but lacking robust scientific evidence, support for their long-term use is mostly empirical.

Benzodiazepines are commonly co-prescribed to patients receiving LtOT, often for comorbid anxiety, mood, or sleep disorders, and—unwittingly—to patients with substance use disorders [41]. Each of these drug classes is associated with falls and fractures in older adults, and the combination is associated with an additive or supra-additive fracture risk, particularly in men. Benzodiazepines are associated with increased MVC risk, whereas opioids are associated with increased risk in young patients (with conflicting data on older patients). The combination is associated with sleep-disordered breathing.

This combination of medications is associated with drug abuse treatment episodes, emergency department visits, and mortality. It seems intuitive that most of this morbidity and mortality is attributable to the misuse of one or both of these medication classes. Indeed, neither opioid misuse nor benzodiazepine misuse is uncommon in pain clinic populations [15,42]. Two studies reported nonprescribed benzodiazepine use in 9–12% of patients on LtOT [43,44]. Moreover, among patients who were prescribed a single benzodiazepine, 10% were found to have a second, nonprescribed, benzodiazepine in their urine [43]. But lacking sufficient data, it is unclear what proportion of this morbidity and mortality is due to use or misuse of only these drugs; to their use or misuse in combination with other central nervous system depressants (including alcohol); to new onset of use or recent dosage escalation of one or both drug classes; or to use of prescribed stable doses in individuals who are vulnerable to the ventilatory depressant effects of these drugs due to sleep-disordered breathing or other medical comorbidities.

Based on the limited evidence for the long-term efficacy of benzodiazepines and opioids, the morbidity and mortality associated with their use in combination, we offer the following recommendations for their co-prescription.

Recommendations

1. Best practices dictate careful consideration of the risks and benefits of combining opioids and

- benzodiazepines in patients with CNCP. Responsible pain physicians are cognizant of the risks, benefits, and alternatives to LtOT but may be less knowledgeable about the corresponding profiles for long-term benzodiazepine therapy. In assessing patient-specific risks associated with LtOT, clinicians must be mindful of the potential additive or supra-additive risks posed by the use—and especially the misuse—of co-administered benzodiazepines.
2. The morbidity and mortality associated with combination therapy in CNCP suggest:
 - a. Near-absolute contraindications to the co-prescription of benzodiazepines and opioids include active misuse, abuse, or addiction to benzodiazepines, opioids, alcohol, and/or other central nervous system depressants. If LtOT is necessary, every attempt should be made to find an alternative to benzodiazepine therapy. In the rare case in which both are determined to be essential, doses of each must be lower than if only one were prescribed. Strong consideration should be given to obtaining addiction medicine or addiction psychiatry consultation, providing more frequent follow ups, and writing small, serial prescriptions with “do not fill before” dates.
 - b. Strong relative contraindications to their co-prescription include:
 - i. History of any substance use disorder. Stronger contraindications apply to patients with shorter periods of remission, absent or poor substance abuse recovery programs, and histories of substance use disorders involving benzodiazepines, opioids, alcohol, or other central nervous system depressants.
 - ii. Unstable mood, anxiety, or thought disorders.
 - iii. Personality disorders, particularly “Cluster B” disorders, which are enduring ways of relating to oneself and others, and are characterized by various combinations of affective instability, impulsivity, failure to conform to social norms, disregard for safety, and suicidality.
 - iv. Relevant medical comorbidities, including morbid obesity, sleep-disordered breathing, chronic obstructive pulmonary disease, and hepatic or renal dysfunction.
 - v. Older adults and others at elevated fall risk.
 3. In cases in which benzodiazepines are being prescribed by a nonpsychiatrist or their new use is anticipated for a psychiatric indication, strong consideration should be given to obtaining psychiatric consultation for the purposes of assessing patient-specific risks and benefits of benzodiazepine-opioid co-administration and evaluating benzodiazepine alternatives. If benzodiazepines are adjudged to be necessary by the treating psychiatrist or the psychiatric consultant, the position of LtOT in the treatment algorithm should be reassessed. If co-administration is determined to be clinically indicated, each drug class should be used at the lowest effective dose and for the shortest effective period of time. Coordination of care between the psychiatrist and the opioid-prescribing physician is imperative.
 4. In cases in which a benzodiazepine is prescribed with an opioid, absent a compelling rationale, the opioid should not be methadone due to its exceptional morbidity and mortality profile [27,30,45].
 5. In cases in which co-prescription is considered, the opioid informed consent discussion should include a discussion of the distinctive risks of benzodiazepines and opioids when used—and misused—in combination.
 6. Further research is necessary to elucidate the nature and magnitude of the risks of opioids and benzodiazepines in combination, particularly when used therapeutically and long-term. Research must account for pharmacological tolerance. Experimental studies tend to involve the acute administration of drugs, and epidemiological studies usually are not designed to distinguish between acute, chronic, and intermittent use of drugs. Development of tolerance to the effects of drugs differs by specific metric (e.g., sedation, ventilatory depression, psychomotor impairment), by specific drug, and by specific individual. Driving under the influence of drug arrests, and serious and fatal MVCs should include toxicological analysis of common drugs of abuse and impairment, including opioids and benzodiazepines.

Acknowledgment

We thank Robert L. DuPont, M.D. for his comments on several drafts of this manuscript.

GARY M. REISFIELD, MD
*Assistant Professor and Director
Pain Management Services
Divisions of Addiction Medicine and Forensic Psychiatry
Department of Psychiatry
University of Florida College of Medicine
Gainesville, Florida, USA*

LYNN R. WEBSTER, MD
*President, American Academy of Pain Medicine,
Medical Director
CRI Lifetree
Salt Lake City, Utah, USA*

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