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Warnings Unheeded: The Risks of Co-Prescribing Opioids and Benzodiazepines

"Opioid analgesics should be used with caution when combined with CNS depressant drugs."[1]

— Prescribing information and package insert for Percocet®, Endo Pharmaceuticals

Despite this common warning found in virtually all opioid product package inserts, reports on prescribing practices suggest that all too often this warning is ignored—with grave consequences. Not only are opioids and benzodiazepines (the most commonly prescribed sedative class) widely prescribed in the United States, they are commonly co-prescribed for patients. Analysis of a commercial database on prescription drugs by the Centers for Disease Control (CDC) indicated that, in 2012, health-care professionals wrote 82.5 opioid prescriptions and 37.6 benzodiazepine prescriptions for every 100 people in the United States.[2] Moreover, of the top 25 medications dispensed from U.S. pharmacies, three opioids and one benzodiazepine made the list (hydrocodone/acetaminophen [#1], tramadol [#20], oxycodone/acetaminophen [#23], and alprazolam [#13]).[3]

Recently released draft guidelines by the CDC[4] for the treatment of chronic pain recommend that "providers should avoid prescribing of opioid pain medication and benzodiazepines concurrently whenever possible." This recommendation is in response to the finding that these drugs are frequently prescribed in combination to patients with pain conditions. For example, one study examining data from a U.S. Veterans Administration (VA) health-care system reported that among patients receiving long-term (i.e., ≥ 3 months) benzodiazepine treatment, those patients receiving the highest dose equivalents (typically exceeding the recommended guidelines) were more likely to be simultaneously receiving a prescription for oxycodone.[5] A large insurance claims analysis reported that patients who are co-prescribed opioids and benzodiazepines for chronic pain are also prescribed opioids at higher doses and for longer.[6] Co-prescribing is not only a problem in patients with pain. Rates of co-prescribing are also high for those enrolled in opioid maintenance therapy for opioid dependence in the VA health-care system, with an estimated 13% and 20% of patients receiving methadone and buprenorphine (respectively) also receiving prescriptions for benzodiazepines.[7]

It is important to note that when discussing "co-prescribing" this does not necessarily mean that the prescriptions are coming from the same physician. Patients often legitimately see multiple doctors for different conditions, and they may have multiple prescribers. In some practice organizations, prescribers may be able to review the full list of prescribed medications, but that is not always the case. Moreover, some patients illegitimately engage in "doctor shopping" in order to obtain controlled drugs by prescription. The broader availability of functional state prescription monitoring programs (PMPs) has provided a new tool for physicians to circumvent both of these hurdles. Regular review of prescribing records from the PMP (whether mandated by the government or not) is recommended when treating patients with controlled substances.

Fatal Consequences: Concomitant Opioid and Benzodiazepine Use

Each year since 2000, overdose deaths from licit and illicit drug use in the general population in the United States

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have increased.[8] The 12-year span from 2001 to 2013 saw a three-fold increase in deaths involving prescription opioids.[9] Although prescription opioids contribute to the highest rates of overdose deaths, benzodiazepines have also been implicated. Data from 2010 suggest that nearly 60% of overdose deaths were due to a prescription drug (rather than illicit drugs), with prescription opioids contributing to the greatest number of deaths at 75%, while benzodiazepines contributed to approximately 29%.[10]

Patients filling both opioid and benzodiazepine prescriptions had a 15-fold increase in the risk of death compared with those filling neither prescription.

In populations of patients taking prescription opioids for the treatment of pain (particularly chronic pain), the risk of overdose is a serious concern.[11] Although several factors may contribute to this risk (e.g., opioid dose, comorbid respiratory conditions), one of the greatest risks is from concomitant use of benzodiazepines. In the United States, deaths from co-prescribed opioids and benzodiazepines increased 14% per year from 2006 to 2011.[12] In one study from West Virginia, filling an opioid prescription in the six months prior to death increased the risk of drug overdose death three-fold, compared with filling a prescription for a non-opioid/non-benzodiazepine controlled drug. Those filling a prescription for a benzodiazepine had a seven-fold increase in death. Critically, patients filling both opioid and benzodiazepine prescriptions had a *15-fold* increase in the risk of death compared with those filling neither prescription.[13]

One alarming study from Canada reported that in a cohort of chronic pain patients who died of a drug overdose with opioids, 85% were co-prescribed a benzodiazepine that was detected in body fluids at death.[11] Similarly, in a population of VA patients being treated with opioids for acute, chronic, or nonterminal cancer pain who died from an opioid overdose, 49% died while they had active prescriptions for both opioids and benzodiazepines, translating to a 3.86 odds ratio increase of death compared with those who were only prescribed opioids. When controlling for opioid dose (which independently and significantly contributes to overdose death rates), the authors found that benzodiazepine dose contributed to risk, with a three-fold increase in risk of death in those receiving the highest benzodiazepines doses (>40 mg diazepam equivalents) compared with those receiving opioids with low doses of benzodiazepines (>0–10 mg).[14] Finally, national data collected from 2003 to 2009 identified oxycodone and alprazolam as the two prescription drugs with the greatest increases in associated death rates (i.e., increases of 265% and 234%, respectively).[15]

Pharmacological Interactions Between Opioids and Benzodiazepines: Potential Mechanisms of Action

Because so few controlled studies have directly examined the nature of the interaction between opioids and benzodiazepines (or other sedatives for that matter), the available data do not clearly define the specific mechanisms of action whereby opioids and benzodiazepines, despite being safe when given alone, lead to untoward outcomes, including death, when taken in combination. Given the many different drugs within both the opioid and benzodiazepine classes, each with a unique structure, pharmacological action (i.e., intrinsic efficacy, potency, receptor binding characteristics), and metabolic pathway, it is likely that multiple factors are at play, both pharmacodynamic and pharmacokinetic, when the drugs are taken in combination. While it is impossible to identify a single mechanism of action that may lead to additive or synergistic actions, it is informative to review the available data and to appreciate the numerous possible mechanisms underlying these potential interactions (see Table 1).

Given the many different drugs within both the opioid and benzodiazepine classes, it is likely that multiple factors are at play when the drugs are taken in combination.

Benzodiazepines have a remarkable safety margin and have rarely been attributed as the sole reason for overdose death (e.g., see review by Gaudreault and colleagues[16]). Mu-opioid agonists reliably reduce respiratory

Table 1
Opioid and benzodiazepine interactions: potential mechanisms of action in overdose

Metabolic drug-drug interactions
Altering parent drug concentrations
Altering active metabolite concentrations
Genetic differences in sensitivity
Changes in drug transport (e.g., p-glycoprotein)
Muscle relaxant effects in throat/airway
Exacerbation of sleep apnea
Loss of tolerance (e.g., interrupted therapy)

Benzodiazepines have a remarkable safety margin and have rarely been attributed as the sole reason for overdose death.

function; this effect is dose-dependent, and tolerance can develop to this effect in patients who take opioids on a chronic basis. Mu-opioid receptors are found in high concentrations in the respiratory control center of the brain in the medulla. These chemoreceptors actively monitor O_2 and CO_2 concentrations circulating in blood and provide a feedback mechanism to modify respiratory function (frequency, depth) to maintain homeostatic oxygen concentrations. Mu-opioid agonist binding essentially dampens or dulls the sensitivity of these chemoreceptors to CO_2, reducing the responsiveness of the system. Thus, low doses of an opioid given to an opioid-naive individual may lead to a modest reduction in respiratory markers (respiratory rate, tidal volume) but have no clinically significant effect. In contrast, supratherapeutic doses given to an opioid-naive individual may lead to respiratory failure, which is typically the assigned cause of death in opioid overdose. The physiology of respiration is obviously more complicated than the simple system described here, and for further discussion we recommend a thorough review by White and Irvine.[17]

Biological Interactions: Enzymes, Transporters, and Channels

One obvious potential mechanism of additive or synergistic action is through a simple pharmacokinetic interaction whereby the presence of one drug increases the concentration of a second agent. We typically think of drug-drug interactions occurring at the point of drug metabolism (usually in the liver), with at least two scenarios that may lead to enhanced drug concentrations and action. The first example would be where Drug 1 acts as an inhibitor of the enzyme responsible for metabolism of Drug 2; thus, in the presence of Drug 1, the metabolism of Drug 2 is decreased or blocked and concentrations of Drug 2 are higher than expected. This scenario is especially problematic when drugs with a long half-life are used (e.g., methadone) and the introduction of an enzyme inhibitor or enzyme competitor may lead to ever-increasing concentrations of Drug 1.

The second example would be where Drug 1 is an inducer of the enzyme responsible for the metabolism of Drug 2 and Drug 2 exerts a significant amount of its activity through a secondary active metabolite. In that instance, the introduction of the enzyme inducer leads to greater concentrations of the active metabolite than expected. As opioids often share structural similarities (with a few exceptions, which are usually the synthetic opioids), many opioids are substrates for the same or overlapping P450 enzymes. The same is true for the benzodiazepines, whereby individual agents share structural similarities within class (and also often share the same long-acting metabolites). In addition, the metabolism of several opioids and benzodiazepines leads to the formation of active metabolites that may exert pharmacodynamic effects. While drug-drug interactions are often revealed through pharmacokinetic studies of drug concentrations in plasma, it is important to recognize that concentrations at the site of action (e.g., the brain) may be quite different and may reflect local metabolism in the brain rather than

the liver (e.g., see review by Pai et al.[18]). However, to understand the potential risk for drug-drug metabolic interactions, it is essential to at least know the specific metabolic pathways for each of the agents prescribed. Table 2 provides an overview (but not an exhaustive list) of commonly prescribed opioids and benzodiazepines along with their known hepatic metabolic pathways and also notes whether their metabolism leads to known active metabolites.

Another pharmacokinetic mechanism that can produce clinically relevant drug-drug interactions is through the superfamily of ATP-binding cassette (ABC) protein transporters of which P-glycoprotein (P-gp) is probably the best characterized. P-gp transporters play a critical role in drug efflux and are found in tissues that act as biological barriers, including the blood-brain barrier and epithelial cells of the liver, kidneys, and intestines (see Silva et al.[19] for a recent interesting review). Thus, P-gp plays a critical role in controlling the movement and concentrations of drugs by limiting both their absorption and their transport out of the brain.

There are at least two compelling illustrative examples of clinically relevant P-gp effects on opioid responses. Loperamide, an opioid used for the treatment of diarrhea, is a substrate for P-gp and is, therefore, largely prevented from crossing the blood-brain barrier (rendering it essentially a peripherally acting opioid). In a study by Sadeque and colleagues,[20] loperamide was administered to healthy adults alone and produced *no respiratory depression* (as expected, given the central mediation of opioid-induced respiratory depression). However, when given in combination with quinidine, a substrate known to inhibit P-gp transport, loperamide produced significant respiratory depression, presumably by quinidine inhibition of P-gp allowing for loperamide entry into the brain.

Table 2
Drug metabolism mediated by cytochrome P450 (CYPs)

Opioid Analgesics	Benzodiazepines
Oxycodone 3A4, 2D6 *oxymorphone (2D6)*	Alprazolam 3A4, 3A5 *α-hydroxyalprazolam (3A4)* *4-hydroxyalprazolam (3A5)*
Hydromorphone 3A4, 2D6	Midazolam 3A4, 3A5, 3A3 *α-hydroxymidazolam (3A4)*
Morphine 3A4, 2C8	Triazolam 3A4
Codeine 3A4, 2D6 *morphine (2D6)*	Diazepam 3A4, 2C19 *desmethyldiazepam (2C19)*
Tramadol 3A4, 2D6 *o-desmethyltramadol (2D6)*	Clonazepam 3A4, 2C19
Methadone 3A4, 2B6, 2D6, 1A2	
Fentanyl 3A4	
Hydrocodone 3A4, 2D6 *hydromorphone (2D6)*	
Buprenorphine 3A4, 2C8 *norbuprenorphine (3A4)*	

Commonly prescribed opioid and benzodiazepine medications are listed along with the P450 CYP enzymes involved in hepatic metabolism of each compound. *Active metabolites are listed in italicized text underneath the parent drug (when applicable).* P450 CYP3A4 is highlighted in blue throughout the table to highlight this common metabolic pathway. This table was adapted from several comprehensive sources.[37-42]

The second illustrative study focused on buprenorphine, a partial opioid agonist that produces a relatively flat dose-response function, even at very high doses.[21] Buprenorphine is recognized for its wide therapeutic window and low risk of opioid overdose when given alone. Buprenorphine also has an active metabolite, norbuprenorphine, which may have limited functional activity in humans with therapeutic dosing but has been demonstrated in preclinical studies to have greater potency as a respiratory depressant compared to the parent drug. A study in mice demonstrated that buprenorphine administration produced limited changes in respiratory function when given alone. However, when given in the presence of a P-gp inhibitor or when given to P-gp knockout mice (i.e., mice genetically engineered to lack the P-gp transporter), buprenorphine caused respiratory depression that was fatal in some cases.[22] The authors demonstrated that inhibition of P-gp precluded norbuprenorphine, the more potent respiratory depressant, from exiting the brain, as evidenced by substantially higher concentrations of norbuprenorphine in the brain compartment after pretreatment with the P-gp inhibitor, as compared with placebo. These studies demonstrate

clearly that changes in drug transport may be a source of significant drug-drug interactions, but one that may be difficult to predict in patients.

A third relevant site for potentially risky drug-drug interactions is the hERG channel (human ether-a-go-go-related gene), a potassium ion channel that is known to play an important role in QTc prolongation and to increase the risk of the rare but often fatal heart arrhythmia known as torsades de pointes. QTc prolongation has received extensive attention in pharmaceutical development because many drugs have been shown to increase the QRS complex on electrocardiogram (ECG); thus, development plans for new drugs commonly require cardiac studies.

With regard to opioids, methadone is probably the most studied and widely reported opioid with documented effects on QTc prolongation,[23] which led to a black box warning related to QTc prolongation and serious arrhythmias. This caveat has led several professional societies to develop new clinical guidelines for the use of methadone and recommend cardiac monitoring,[23,24] although this is not without some controversy (see Krantz et al.[25] and related subsequent published commentary). Importantly, some studies have suggested that the QTc interval prolongation observed with methadone may be prolonged further in the presence of benzodiazepines (e.g., see Peles et al.[26]). Thus, awareness of cardiac risk factors and ECG evaluation prior to initiating treatment or before adding other QTc-prolonging drugs should be considered as a potential preemptive strategy for reducing risks to patients.

Behavioral Risks: Another Pharmacodynamic Concern

Most opioids used for pain management produce their behavioral and pharmacological effects primarily through mu-opioid receptor activation, causing dose-dependent sedation, respiratory depression, and analgesia. Benzodiazepines, which are positive allosteric modulators of GABA-α receptors (ligand-gated chloride channels), produce cognitive and motor impairment, as well as anxiolytic, muscle relaxant, sleep-inducing, and antiepileptic effects.

Each drug, administered alone, produces dose-dependent sedative effects; however, dose combinations, co-prescribed or co-abused, produce enhanced, often synergistic effects of psychomotor impairment, declines in cognitive abilities, increases in sedation, and decreases in arousability. Several controlled studies have examined the behavioral and other interactions of these two drug classes in healthy research participants (e.g., no histories of chronic obstructive pulmonary disease or heart disease). For example, one study[27] explored the pharmacodynamic effects of a single high dose of diazepam (40 mg, a dose 20 times higher than the clinical starting dose) in participants receiving maintenance doses of either methadone or buprenorphine for opioid use disorder. Placebo or diazepam challenges were tested with the normal maintenance dose and 150% of the opioid maintenance dose during each of four sessions. The results indicated that diazepam increased participant ratings of sedation and produced impairment on laboratory measures of psychomotor function, including

Inside the Black Box: Identifying Patients at Risk

- **Does your patient have a history of alcohol use?**
- **Does your patient have a history of drug abuse or misuse?**
  - **If yes: Have you completed a urine drug screen?**
- **Have you tried nonopioid analgesics?**
- **Have you considered nonbenzodiazepine medications for anxiety and/or sleep?**
- **Have you read the package insert for each prescribed drug?**
- **Do you always start at the lowest dose (e.g., start low and go slow)?**
- **Have you accessed the patient's record in a prescription monitoring database?**
  - **If yes: Are any other providers prescribing opioids, benzodiazepines, or contraindicated medications?**
- **Have you counseled your patient about the risks?**

reaction time and speed and accuracy tests.[27] These effects were largely independent of opioid dose, with high-dose diazepam impairment occurring in both methadone- and buprenorphine-maintained subjects. However, these dose combination effects do not appear to be driven by pharmacokinetic interactions. Two controlled studies have examined acute[28] and repeated dose combinations[29] of methadone and diazepam, and both studies found no changes in the plasma levels of the parent drugs or metabolites or their time course-concentration profile.[28] Post-mortem blood samples taken from individuals with fatal overdose have yielded similar findings.[30, 31]

These studies not only have implications for opioid-benzodiazepine overdose, but also raise concerns for increased risk of accidents from daily activities, including risk of falls, workplace accidents, and motor vehicle accidents, as well as increased concern for patients engaging in sports and outdoor activities or caring for children, particularly in patients who have limited experience with the impairing effects of these medications.

Recommendations

There are rational and clinically judicious reasons why opioids and benzodiazepines are co-prescribed. Patients with chronic pain have higher incidence rates of depression, anxiety, and difficulties with sleep, which may explain why these agents are so commonly co-prescribed in this population. However, some of the conditions that warrant treatment with benzodiazepines (e.g., anxiety disorders) are also independent risk factors for opioid overdose.[32] Thus, starting doses should be conservative, and any dose increase should be accompanied by extra monitoring (even if by phone) to assess safety.

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Physicians may consider alternative agents for sleep (e.g., zolpidem or trazodone), but should be aware that most sedatives, regardless of class, have the potential to potentiate opioid sedation, and that few controlled data exist to inform their preferential use and safety. Physicians should be familiar with the risk of drug-drug interactions for the agents they prescribe and should be counseling their patients accordingly so that they and their family members are aware of the signs of potential opioid toxicity (e.g., "nodding" off or oversedation, unusually loud snoring, or behavioral impairment). Patients should be monitored for misuse (e.g., taking higher doses than than prescribed or taking drugs by a different route of administration), and calls for early refills should raise a red flag.

Naloxone overdose kit distribution and overdose prevention training should be considered, as this tool becomes more readily available for prescribing physicians.[33] Although the efficacy of opioids and benzodiazepines for the treatment of their respective indications is likely to encourage their continued widespread clinical use, the decision to start one in the presence of the other should be made with caution and thoughtfulness. Some clinicians recommend never using opioids and benzodiazepines in combination, given the difficulty of weaning should adverse effects arise. Vigilance is warranted if co-prescribing opioids and benzodiazepines, and a cautious and integrated approach should be taken whenever combined therapy is needed for the treatment of comorbid disorders.[34-36]

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