The International Benzodiazepine Symposium: Exploring the Benzodiazepine Opioid Co-prescription Dilemma

Joseph Pergolizzi, M.D.
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Disclosures

Objectives

• Describe the FDA box working for co-prescribing benzodiazepines and ERLA opioids
• Describe the epidemiology of co-prescribing benzodiazepine and opioids
• Describe benzodiazepines as potential analgesic agents
• Describe best in-office practices to address co-prescribing
• Describe alternative non-benzodiazepine sleep aids
Black Box Warning

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate, limit dosages and durations to the minimum required, and follow patients for signs and symptoms of respiratory depression and sedation.
Warnings and Precautions

Risks due to Interactions with Benzodiazepines or Other Central Nervous System Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of BELBUCA® with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. Follow patients closely for signs and symptoms of respiratory depression and sedation.
• Opioid pain relievers and benzodiazepine sedatives are commonly prescribed in the United States. They are frequently prescribed to the same patient.

• Overprescribing of opioid pain relievers (OPR) can result in multiple adverse health outcomes, including fatal overdoses. Interstate variation in rates of prescribing OPR and other prescription drugs prone to abuse, such as benzodiazepines, might indicate areas where prescribing patterns need further evaluation.

https://www.cdc.gov/mmwr/index.html
Prescribing rates per 100 persons (in quartiles), by state and drug type — IMS Health, United States, 2012

https://www.cdc.gov/mmwr/index.html
Vital Signs: Variation Among States in Prescribing of Opioid Pain Relievers and Benzodiazepines — United States, 2012

FIGURE 1. Distribution of state prescribing rates, by drug type — IMS Health, United States, 2012

* State rates are rounded to the nearest 0.25 standard deviation for purposes of presentation.

https://www.cdc.gov/mmwr/index.html
Estimated number of emergency department (ED) visits involving benzodiazepines alone or in combination with opioids or alcohol,* by year and drug combination (patients aged 12 and older): 2005 to 2011

Estimated number of emergency department (ED) visits involving benzodiazepines alone or in combination with opioids or alcohol,* 2005 through 2011, by drug combination and age (patients aged 12 and older)

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Aged 12 to 34</th>
<th>Aged 35 to 44</th>
<th>Aged 45 to 64</th>
<th>Aged 65 or older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines alone</td>
<td>174,998</td>
<td>88,644</td>
<td>150,780</td>
<td>72,575</td>
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<tr>
<td>Benzodiazepines and opioids</td>
<td>90,225</td>
<td>48,471</td>
<td>90,256</td>
<td>20,175</td>
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<tr>
<td>Benzodiazepines and alcohol</td>
<td>63,155</td>
<td>42,783</td>
<td>53,454</td>
<td>4,447</td>
</tr>
<tr>
<td>Benzodiazepines, opioids, and alcohol</td>
<td>16,662</td>
<td>11,098</td>
<td>13,532</td>
<td>1,777</td>
</tr>
</tbody>
</table>

** Predicted risk (in percent) of a more serious outcome* from emergency department (ED) visits involving benzodiazepines alone or in combination with opioids or alcohol,** 2005 through 2011, by drug combination and age (patients aged 12 and older)

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Aged 12 to 34</th>
<th>Aged 35 to 44</th>
<th>Aged 45 to 64</th>
<th>Aged 65 or older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines alone</td>
<td>28%</td>
<td>30%</td>
<td>37%</td>
<td>39%</td>
</tr>
<tr>
<td>Benzodiazepines and opioids</td>
<td>37%</td>
<td>43%</td>
<td>47%</td>
<td>59%</td>
</tr>
<tr>
<td>Benzodiazepines and alcohol</td>
<td>35%</td>
<td>43%</td>
<td>51%</td>
<td>55%</td>
</tr>
<tr>
<td>Benzodiazepines, opioids, and alcohol</td>
<td>39%</td>
<td>47%</td>
<td>57%</td>
<td>70%</td>
</tr>
</tbody>
</table>

* No other drugs were involved.

Wide variation exists from one state to another in prescribing rates for these drugs. For states that prescribe well above the national rate, the need for a change in prescribing practices is urgent.

In 2012, prescribers wrote 82.5 OPR and 37.6 benzodiazepine prescriptions per 100 persons in the United States. State rates varied 2.7-fold for OPR and 3.7-fold for benzodiazepines. For both OPR and benzodiazepines, rates were higher in the South census region, and three Southern states were two or more standard deviations above the mean. Rates for LA/ER and high-dose OPR were highest in the Northeast. Rates varied 22-fold for one type of OPR, oxymorphone.

CDC recommends that states make active use of their prescription drug monitoring programs to calculate current rates of prescribing, examine variations within the state, and track the impact of safer prescribing initiatives.
Benzodiazepines as potential analgesic agents

• Classical belief is that they function at the GABA$_A$ receptor
• Theory of novel receptor subtype-selective compounds
• Benzodiazepines are drugs typically prescribed for the treatment of neurological and/or psychological conditions, including anxiety, insomnia and seizure disorders$^1$.
• Insufficient evidence to support meaningful direct analgesic properties

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm518697.htm
Adverse events of co-prescribing

The U.S. Food and Drug Administration is requiring class-wide changes to drug labeling, including patient information, to help inform health care providers and patients of the serious risks associated with the combined use of certain opioid medications and benzodiazepines.

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm518697.htm
Adverse events of co-prescribing, notably OD

“It is nothing short of a public health crisis when you see a substantial increase of avoidable overdose and death related to two widely used drug classes being taken together,”

*FDA Commissioner Robert Califf, M.D.*

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm518697.htm
Best in-office practices to address co-prescribing
Nocturnal oximetry

• Oximetry, which may be performed over one or several nights in a patient's home (home oximetry), is a simpler, but less reliable or accurate alternative to a formal sleep study (polysomnography).

• If normal overnight oximetry sleep apnea is considered unlikely.

https://en.wikipedia.org/wiki/Sleep_apnea
Specialty referral / communication: Psych, Sleep, Addiction

• Multidisciplinary Team Approach
• Polysomnography
• Psychiatric evaluation
• Addiction Medicine
  • Risk stratification
• Family and Care providers
• Good communication with PCP
• Share decision making
Conduit for Communication

• Conversation skills with patients to problem solve while attempting to keep patients in the practice

“We implore health care professionals to heed these new warnings and more carefully and thoroughly evaluate, on a patient-by-patient basis, whether the benefits of using opioids and benzodiazepines – or CNS depressants more generally – together outweigh these serious risks.”

*FDA Commissioner Robert Califf, M.D.*

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm518697.htm
RESPECT: The communication skills they need for practice, summed up in a catchy acronym

- Rapport
- Explain
- Show
- Practice
- Empathy
- Collaboration
- Technology

Set appropriate expectations and communicate them.

Be clear; be direct!

https://wire.ama-assn.org/education/6-simple-ways-master-patient-communication
A multicentre evaluation of an opioid patient-provider agreement.

Ponglizzi JV¹, Curvo FA², Cui N³, Quade MP⁴, Vena D⁵, Taylor R³, Naftolin F⁷, LeGuang J³⁴.

Author information

Abstract

The role of the patient-provider agreement (PPA) is to set forth respective roles and responsibilities for opioid therapy with the goal of improving outcomes, reducing risks, and improving patient education. The Food and Drug Administration (FDA) Safe Use Initiative Opioid PPA Working Group convened to develop a PPA and test it for acceptability as an educational and shared decision-making tool in opioid therapy. This multicentre study evaluated the utility of the PPA, how readily patients understood it, its ability to educate patients in an unbiased way about opioid treatment and the feasibility of incorporating a PPA in clinical practice. A total of 117 patients and 14 providers at urban centres were included (mean patient age: 56 years) with 85% of patients treated for pain for >3 months. Most patients reported the PPA to be 'somewhat helpful' or 'very helpful' in deciding a course of treatment (96%) and 'easy to understand' (97%). Both patients and prescribers (89% and 92%, respectively) found the PPA was neutral in terms of presenting opioid therapy. Most centres found the PPA could be administered in ≤10 min and 72% of prescribers said this PPA could be readily incorporated into their practice. This PPA was perceived by both patients and prescribers as helpful in deciding a course of treatment and unbiased in terms of presentation of the risks and benefits of opioid therapy.

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KEYWORDS: opioid abuse; opioids; pain management; patient-provider agreement

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Safe Use Initiatives

What to Ask Your Doctor Before Taking Opioids

CAN I HAVE AN Rx FOR NALOXONE?
You should discuss with your doctor whether you should also receive a prescription for naloxone, a drug that can reverse the effects of an opioid overdose and could save lives. In many cases it makes sense to be prepared for potential problems by keeping naloxone in your home.

Play it safe. It doesn't matter who is writing the prescription, ask these questions before taking opioids.

https://www.fda.gov/forconsumers/consumerupdates/ucm529517.htm
Naloxone does not reverse Benzodiazepines

STRATEGY 3: Ensure ready access to naloxone. Opioid overdose-related deaths can be prevented when naloxone is administered in a timely manner. As a narcotic antagonist, naloxone displaces opiates from receptor sites in the brain and reverses respiratory depression that usually is the cause of overdose deaths.⁷

On the other hand, naloxone is not effective in treating overdoses of benzodiazepines (such as Valium®, Xanax®, or Klonopin®), barbiturates (Seconal® or Fiorinal®), clonidine, Elavil®, GHB, ketamine, or synthetics. It is also not effective in overdoses with stimulants, such as cocaine and amphetamines (including methamphetamine and Ecstasy). However, if opioids are taken in combination with other sedatives or stimulants, naloxone may be helpful.
Big picture practices to improve benzodiazepine prescribing in pain management.
What have we learned from opioid efforts

• Board educational awareness is needed

• All stakeholders need to be activity involved when creating safe use initiatives

• Use the KISS Principle

  CDC is committed to an approach that protects the public’s health and prevents opioid overdose deaths.

• Appropriate prescribing and Appropriate consummation

https://www.cdc.gov/drugoverdose/index.html
Legal / regulatory: ? reschedule, ? required REMS?

Unique set of clinical, ethical, and legal dilemmas
Research needs

**Basic science:** the identification of separable key functions of GABAA receptor subtypes and their potential role

**Clinical Science:** The role of benzodiazepines used to self-medicate the consequences of that abuse.

**Practical:** Benzodiazepines suffer from guilt by association?

**Societal:** Co-prescribing with opioids present significant risks.
CDC Guideline for Prescribing Opioids for Chronic Pain: Recommendation #11

• Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.

https://www.cdc.gov/mmwr/index.html
Patient Care Pain Management and Medication Assisted Treatment (MAT)

• FDA’s black box warning of benzodiazepine prescribing and opioid prescribing

• Patients being treated for substance use disorder.
  • Co-prescription of and methadone or buprenorphine and benzodiazepines places patients at extreme risk of overdose.

• Weigh the substantial evidence establishing the considerable risk prior to prescribing either agent in the presence of the other.

• In the rare instance co-prescribing is done then the the patient and their caregivers must be counseled about the increased risk for respiratory arrest and death.
Provider decision support

Patient Resources

RESOURCES FOR PATIENTS

**Benzodiazepine Information**

**Healthy Sleep Tips**
- Harvard University. Twelve Simple Tips to Improve Your Sleep: [healthysleep.med.harvard.edu/healthy/getting/overcoming/tips](http://healthysleep.med.harvard.edu/healthy/getting/overcoming/tips)

**Tips for Managing Anxiety**

**Medication Take-Back Programs**
- New York City Department of Sanitation. SAFE Disposal Events: [www1.nyc.gov/site/dsny/index.page](http://www1.nyc.gov/site/dsny/index.page)

**Treatment for Substance Use Disorder**
- Substance Abuse and Mental Health Services Administration: [www.samhsa.gov/treatment/index.aspx](http://www.samhsa.gov/treatment/index.aspx)

Incentives

• Offer other alternatives
  • Nonbenzodiazepine sleep agents
  • CAM options
  • Counseling
  • Etc....
MYTHS AND FACTS ABOUT BENZODIAZEPINES AND Z-DRUGS

PHYSICAL DEPENDENCE, WITHDRAWAL, SUBSTANCE USE DISORDER, AND MISUSE

**Physical Dependence**
- Physiologic adaptation to a substance requiring the person to take more of the substance to achieve a certain effect.
- Can occur with the chronic use of many drugs—including many prescription drugs, even if taken as instructed.
- Causes drug-specific withdrawal symptoms if drug use is abruptly ceased.
- Benzodiazepine withdrawal syndrome symptoms include:
  - Autonomic hyperactivity (eg, sweating, tachycardia)
  - Hand tremor
  - Insomnia
  - Nausea or vomiting
  - Transient visual, tactile, or auditory hallucinations or illusions
  - Psychomotor agitation
  - Anxiety
  - Grand mal seizures

**Substance Use Disorder**
- Maladaptive pattern of use leading to significant impairment or distress. See DSM-5 diagnostic criteria (Resources for Providers: Screening and Monitoring Tools).

**Benzodiazepine Misuse**
- Using someone else's benzodiazepines or using benzodiazepines in a manner other than prescribed.
- May or may not be associated with physical dependence.
- Signs may include pattern of early refills; prescription problems such as lost, spilled, or stolen medications; and escalating drug use in the absence of a physician’s direction.

HOW TO PRESCRIBE BENZODIAZEPINES JUDICIOUSLY

- Provide appropriate first-line treatment for anxiety and insomnia.
- If benzodiazepines are clinically indicated:
  - fully assess your patient,
  - prescribe the lowest effective dose for the shortest duration—no more than 2 to 4 weeks,
  - talk to your patient about the benefits and risks of benzodiazepine treatment,
  - avoid co-prescribing with opioids or other CNS depressants because of the risk of fatal respiratory depression.
Controlled substance risk management

• Evaluation
• Stratification
• Mitigation
• Monitoring - behavioral aberrancies
• PDMP
• Drug testing
CHECKING THE PRESCRIPTION MONITORING PROGRAM

The New York State Prescription Monitoring Program (PMP) provides quick, confidential, 24/7 access to your patients’ controlled substance prescription history.

1. Consult PMP to determine whether your patient recently filled a prescription for an opioid analgesic, benzodiazepine, or other controlled substance.

2. If the patient has recently filled multiple prescriptions written by different providers and/or filled at different pharmacies:
   • Discuss your concerns with your patient, explaining the risk for overdose when benzodiazepines are used with other agents (especially opioid analgesics and other CNS depressants).
   • Communicate and coordinate with your patient’s other controlled substance prescribers.
   • Avoid abruptly discontinuing benzodiazepines.\(^5,9,10,12,24\)
     • Withdrawal can be severe, causing hallucinations, seizures, and in rare cases has been life-threatening (see page 16).

   • A taper schedule is strongly recommended and clinically appropriate versus refusing continuation of this medication (Resources for Providers: Dose Reduction Plans).
   • Consider that your patient might be misusing controlled substances and/or have a substance use disorder (see page 16).
   • If needed, explain that effective treatments for substance use disorder are available, and treat the patient yourself or refer for treatment (Resources for Providers: Treatment for Substance Use Disorder).
   • For opioid use disorder, discuss and arrange for medication-assisted treatment (eg, buprenorphine or methadone) (Resources for Providers: Treatment for Substance Use Disorder).

As of August 2013, all practitioners are required to review the PMP prior to prescribing any controlled substance listed on schedules II, III, or IV.

See Resources for more information about PMP.

COMMONLY USED BENZODIAZEPINES AND Z-DRUGS

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Elimination half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triazolam</td>
<td>Halcion®</td>
<td>1.5 to 5.5</td>
</tr>
<tr>
<td><strong>Intermediate-Acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Xanax®</td>
<td>11.2 (range: 6.3-26.9)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Klonopin®</td>
<td>12 to 50</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Ativan®</td>
<td>10 to 20</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Serax®</td>
<td>8.2 (range: 5.7-10.9)</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Restoril™</td>
<td>8.8 (range: 3.5-18.4)</td>
</tr>
<tr>
<td><strong>Long-Acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Librium®</td>
<td>24-48</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>Tranxene®</td>
<td>48</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Valium®</td>
<td>Up to 100</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Dalmane®</td>
<td>47-100</td>
</tr>
<tr>
<td><strong>Z-Drugs</strong></td>
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<tr>
<td><strong>Short-Acting</strong></td>
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<td></td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Sonata®</td>
<td>Approx. 1</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Ambien®</td>
<td>5-mg tablets: 2.6 (range: 1.4-4.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-mg tablets: 2.5 (range: 1.4-3.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.5-mg dose: 2.8 (range: 1.62-4.05)</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>Lunesta®</td>
<td>Approx. 6</td>
</tr>
</tbody>
</table>

Consult product prescribing information for detailed warnings, precautions, contraindications, and potential interactions.

DISCONTINUING BENZODIAZEPINE TREATMENT

• Avoid abrupt discontinuation of benzodiazepines because it can lead to severe and potentially life-threatening withdrawal symptoms, especially among patients who have taken benzodiazepines for a prolonged period.

• Take the following measures to taper the dosage safely:
  • Determine and agree on a gradual dose reduction plan with your patient (Resources for Providers: Dose Reduction Plans).
  • Set realistic goals with the patient, based on the dosage and duration of benzodiazepine use.
  • Closely monitor the patient for signs of withdrawal and adjust the taper schedule as clinically indicated.
  • Consider counseling or cognitive behavioral therapy for patients who have a substance use disorder or for whom withdrawal might cause substantial anxiety.
Summary

• Benzodiazepines used with opioids, alcohol, and other CNS depressants can lead to fatal overdose.

• Reduce the risk of preventable overdose deaths by using nonbenzodiazepine treatments, prescribing benzodiazepines judiciously only when clinically indicated, and tapering patients off long-term benzodiazepine treatment