Benzodiazepines: Pharmacology to Co-Prescribing Risks and Concerns

Epidemiology of Benzodiazepine Prescribing in Rhode Island

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Estimated time to complete: 60 minutes

There are no prerequisites for participation.

Method of Participation and How to Receive CME Credit.
There are no fees for participating in and receiving credit for this activity.
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- View the CME presentations.
- Complete the CME activity evaluation and post-test at the conclusion of the activity. A passing score of 75% must be achieved in order to receive a credit certificate.

Resources available under the Resources Tab (bottom right of screen).

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Disclaimer
This educational program is designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation.
Learning Objectives

At the conclusion of this session, attendees should be able to:

• Describe who are getting benzodiazepines and what they are getting
• Describe top diagnosis

Target Audience

Physicians, physician assistants, advanced practice pharmacists, APRNs, residents, & fellows who prescribe controlled substances.

CME Accreditation

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Warren Alpert Medical School of Brown University and the Rhode Island Department of Health Academic Center. The Warren Alpert Medical School is accredited by the ACCME to provide continuing medical education for physicians.

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Rhode Island Specific: This program qualifies for 1.0 hours CME Credit in Risk Management and Opioid Pain Management/Chronic Pain Management, two of the required areas of section 6.0; 6.2.1 RI CME re-licensure requirements.

Other Health Professionals: Participants will receive a Certificate of Attendance stating this program is designated for 1.0 hours AMA PRA Category 1 Credits™. This credit is accepted by the AANP, AAPA, and RI Pharmacy re-licensure Board.

Faculty Disclosure/Conflict of Interest

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Epidemiology of Benzodiazepine Prescribing in Rhode Island

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Disclosures - Traci C. Green

- No conflicts of interests to disclose
- My presentation will include discussion of “off-label” use of the following:
  - Naloxone is FDA approved as an opioid antagonist
  - Naloxone delivered as an intranasal spray with a mucosal atomizer device has not been FDA approved and is off-label use
- Funding: CDC National Center for Injury Prevention and Control, 5R21CE001846-02 and 1R21CE002165-01; National Institute on Drug Abuse, 1R21DA029201-02A1; Agency for Healthcare Research and Quality

Learning objectives

- Describe the epidemiology of opioid and benzodiazepine overprescribing in the United States and its consequences
- Overview the epidemiology of opioid and benzodiazepine use in Rhode Island
- Suggest risk mitigation strategies
Opioid Overdose Epidemic

Majority of opioid overdose deaths associated with multiple sources and/or high dosages?

Biology

- Opioids, benzodiazepines operate on different receptors and have synergistic effects on sedation and respiratory depression
  - Mu (μ), Kappa (κ), and Delta (δ) vs. GABA receptors
- Receptors for both opioids and benzodiazepines highly concentrated in the respiratory centers of the medulla
- Animal and human data from clinical studies demonstrate synergistic effects
  - Study in rats demonstrated that while high doses of an opioid (buprenorphine) and a benzodiazepine (midazolam) alone both resulted in mild, but significant increases in PaCO₂, the combined administration of these two drugs resulted in rapid, substantial, and prolonged respiratory depression and hypoxia.
Question

Let's say you learn that your new patient is prescribed benzodiazepines for anxiety. How concerned would you be about dispensing Suboxone (buprenorphine/naloxone) or methadone to them?

• Much more concerned
• A little more concerned
• No more concerned than usual

Question

Let's say you learn that your new patient is prescribed benzodiazepines for anxiety. How concerned would you be about prescribing Percocet to them?

• Much more concerned
• A little more concerned
• No more concerned than usual

Common Risks for Opioid Overdose

- Mixing Substances/ Polypharmacy
  Alcohol, stimulants, marijuana, prescribed and non-prescribed medications
- Social Isolation
  Using alone
- Chronic Medical Illness
  Lung, liver, and kidney compromise
- Opioid Dose and Changes in Purity
- Previous Overdose
- Abstinence
  • Return from incarceration
  • Completion of detoxification
  • Relapse
Prominence of Benzodiazepines in Prescription Opioid Overdoses

- Of the more than 22,000 unintentional pharmaceutical overdose deaths nationally in 2010, 75% involved opioid analgesics, while benzodiazepines were identified in 25% and antidepressants in nearly 20%.
- Opioids are involved in an estimated 75% of the overdose deaths involving benzodiazepines.
- The combination of prescribed opioids and benzodiazepines is the most common cause of poly-substance overdose deaths nationally.


Co-prescription of Benzodiazepine & Opioid confers clear risk of overdose mortality.
Interactions, Polypharmacy

- Sedation, respiratory depression
  - Heroin, opioid analgesics
  - Sedatives, benzodiazepines
    - Act on the same centers in the central nervous system as methadone, buprenorphine, synergistic sedation & respiratory depressing effects

May occur, not will occur
Short term vs. Chronic prescription
Appropriate?, life-saving?
Communication, patient-centered care
Risk mitigation, universal precaution: naloxone

Motivations for misuse

- Studies of patient perception show that benzodiazepines potentiate the intensity, duration of the analgesic, euphoric, and sedative effects of opioids in a dose-response pattern
- Economical: smaller amounts of opioids can be consumed, with similar effects
- Salvage: if heroin, prescription opioid of choice is not as available, can draw out what you have
- Self-medicate: sleep, anxiety
- Street value, supply is consistent: comparatively easy to obtain, “dr. shop/pharmacy shop”

Treatment need skyrocketing

Number of Benzodiazepine and Narcotic Pain Reliever Combination Admissions: 2000 to 2010

45.7% of patients admitted in 2010 for combination opioid-benzodiazepine treatment reported having a co-occurring psychiatric disorder
The View from Rhode Island

- 4th in the nation for benzodiazepine use per capita
- 33% of fatal opioid overdoses from 2014 and 2015 were benzodiazepine-related
- Benzodiazepines were the most common prescription drug dispensed to overdose decedents prior to death
- Overdoses involving benzodiazepines are commonly seen in combinations in prescription opioid overdoses
- Overdoses involving opioid maintenance therapy medications (e.g., buprenorphine, methadone) are rare.

When they do occur, tend to involve a benzodiazepine

Co-Prescribing trends in RI

Nationally, about 13% of all primary care visits involve benzodiazepine or opioid prescriptions.

Among all patients dispensed an opioid in the state in 2015:
- 27% also were dispensed a benzodiazepine at least once within 30 days of receiving an opioid
- Of those dispensed a benzodiazepine:
  - 59% were also dispensed an opioid at least once within 30 days of receiving a benzodiazepine
  - > 2/3rds are prescribed by the same prescriber

Enrollees in RI Substance Abuse Treatment Programs

Note: Monthly admissions are included, and all treatment programs are included.
Note: Includes individuals receiving treatment from mental health programs (i.e., Health Homes, CSP, etc.)
Proposed “Black box” warning

- Citizen’s Petition to the FDA
  - Led by Drs. Alexander-Scott and Wen, co-signed by more than 30 states and cities

Labeling for all Opioid Class Medications should read:
WARNING: CONCURRENT USE WITH BENZODIAZEPINES REDUCES THE MARGIN OF SAFETY FOR RESPIRATORY DEPRESSION AND CONTRIBUTES TO THE RISK OF FATAL OVERDOSE, PARTICULARLY IN THE SETTING OF MISUSE.

Labeling for all Benzodiazepine Class Medications should read:
WARNING: CONCURRENT USE WITH OPIOIDS REDUCES THE MARGIN OF SAFETY FOR RESPIRATORY DEPRESSION AND CONTRIBUTES TO THE RISK OF FATAL OVERDOSE, PARTICULARLY IN THE SETTING OF MISUSE.

MOST OVERDOSES ARE PREVENTABLE

WHAT CAN YOU DO?

CDC Guideline—Concordant Care:
Avoid benzodiazepine/opioid co-prescription, prescribe naloxone as risk mitigation

CDC guidelines for prescribing opioids for chronic pain, March 2016

Recommendation 8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (>50 MME/day), or concurrent benzodiazepine use, are present (recommendation category: A, evidence type: 4).

Recommendation 11. Physicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible (recommendation category: A, evidence type: 3).

- Re-evaluate opioid/benzodiazepine prescription
- Discuss with patient
- Mitigate the co-prescription of taper plan with counseling about risks & a prescription for take-home naloxone
Naloxone: Effective Intervention for Opioid Overdose

- Naloxone (Narcan), an intranasal or intramuscular-administered opioid antagonist used to reverse respiratory depression caused by opioids
- Call 911
- Rescue breathing

How Naloxone Reverses Opioid Poisoning

Naloxone has a stronger affinity to the opioid receptors than the opioid, so it knocks the heroin off the receptors for a short time and lets the person breathe again.

Rationale for Overdose Education and Naloxone Rescue Kits

- Most people who use opioid do not use alone
- Known risk factors:
  - High dose opioids, co-prescription benzodiazepine+opioid, mixing substances, abstinence, using alone, chronic medical illness, starting or tapering MAT
- Opportunity window:
  - Opioid overdoses take minutes to hours
  - Reversible with naloxone
  - Bystanders are trainable to recognize and respond to overdoses
- Fear of public safety
Endorsement for naloxone rescue kits

The AMA has been a longtime supporter of increasing the availability of naloxone to patients, first responders, and bystanders who can help save lives and has provided resources to bolster legislative efforts to increase access to this medication in several states.


APhA supports the pharmacist’s role in selecting appropriate therapy and dosing and initiating and providing education about the proper use of opioid reversal agents to prevent opioid-related deaths due to overdose.

www.pharmacist.com/policy/controlled-substances-and-other-medications-

ASAM Board of Directors

April 2010

Naloxone has been proven to be an effective, fast-acting, inexpensive and non-addictive opioid antagonist with minimal side effects. Naloxone can be administered quickly and effectively by trained professional and lay individuals who observe the initial signs of an opioid overdose reaction.

www.asam.org/docs/public-policy-statements/1naloxone-1-

How to identify an opioid overdose

- Opioids repress the urge to breathe and decrease the body’s brain’s response to carbon dioxide, leading to respiratory depression (decrease rate of breathing) and death

- Respiratory depression (shallow/no breathing)
- Pinpoint pupils
- Blue or grayish lips/fingernails
- No response to stimulus
- Gurgling/heavy wheezing or snoring sound

Occurs within minutes to hours

Naloxone Onset / Duration of Action

- Takes effect in 3-5 minutes
  - If patient is not responding in this time, a second dose may need be administered

- Wears off in 30-90 minutes
  - Patients can go back into overdose if long acting opioids were taken (fentanyl, methadone, extended release morphine, extended release oxycodone)
  - Patients should avoid taking more opioids after naloxone administration so they do not go back into overdose after naloxone wears off
  - Patients may want to take more opioids during this time because they may feel withdrawal symptoms

- Shelf-life is 12-18 months
  - Store at room temperature to minimize degradation
Fatal Opioid Overdose Rates by OEND Implementation

- Naloxone coverage per 100K
- Opioid overdose death rate
- 7% reduction
- 46% reduction
- No coverage
- 1-130 ppk
- 100 ppk


Scotland National Naloxone Program: Opioid-related Death Reduction

<table>
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<tr>
<th>Period</th>
<th>Number of naltrexone kits issued</th>
<th>Number of Scotland's opioid-related deaths (ORDs) with or without antecedent of</th>
<th>Naloxone distribution</th>
<th>Pain relief</th>
<th>Pain or hospital discharge</th>
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<td>2013-11 Naloxone Programme</td>
<td>11 890</td>
<td>3106*570</td>
<td>55%</td>
<td>20%</td>
<td>10%</td>
<td>18%</td>
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<td>2011</td>
<td>3 330</td>
<td>3 400</td>
<td>70%</td>
<td>10%</td>
<td>5%</td>
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<tr>
<td>2012</td>
<td>5 076</td>
<td>6 030</td>
<td>70%</td>
<td>5%</td>
<td>5%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Piper et al. Subst Use Misuse 2008: 43; 858-70.
Walley et al. JSAT 2013; 44:241-7. (Methadone and detox programs)

Increased knowledge and skills

No increase in use, increase in drug treatment

Reduction in overdose in communities

Cost-effective
Naloxone Access Points for Active Drug Users, Family, Friends in Rhode Island

- Long-standing program
- Located in one urban setting, grassroots effort
- Distributes lowest cost formulation, for free, to highest risk individuals

1. Certified Recovery Coaches counsel nonfatal overdose survivors at bedside, train in Nlx, connect to treatment/recovery supports post discharge
2. Hospital service (trauma services, psychiatric hospital) counsels and dispenses at discharge

Pharmacists provide naloxone upon request, initiate prescription

Naloxone distribution has ramped up, reaching target ranges shown to reduce mortality and blunting the epidemic curve. *Sustaining these levels is critical*

Four initiatives to alter an epidemic

239 Rhode Islanders died from accidental opioid-related overdoses last year.
Prevention Initiative:
Targeted Safer Prescribing and Dispensing

- Reduce dangerous prescribing of benzodiazepines through PDMP alerts, provider education & “detailing”
- Guidelines for use of benzodiazepines in MAT and pain

Who in your care should receive OEND? When are they at greatest risk?

- Patients initiating MAT, opioid use
  - Methadone, pain medications: start low, go slow! Risk due to toxicity
  - Buprenorphine: start high, go quick! Risk due to lack of treatment retention (inadequate symptom relief)
- Patients being maintained on MAT, opioids for chronic pain AND prescribed a benzodiazepine
- Patients that have recently concluded MAT or opioid analgesic therapy, patients being tapered
- Patients undergoing abstinence-based treatment
- Patients that have recently concluded abstinence-based treatment

Assess Overdose Risk as part of a patient’s history

- Review medications – Communicate with other prescribers
- Take a substance use, chronic pain history
- Check the prescription monitoring program*
- Personal Overdose history: Where is the patient at as far as overdose?
  - Ask your patients whether they have overdosed, witnessed an overdose or received training
  - Have you ever overdosed?
    - What were you taking?
    - How did you survive?
    - What is your plan to protect yourself from overdose?
    - How do you keep your medications, MAT safe?
    - Are they locked up?
Overdose witness history:
- How many overdoses have you witnessed?
  - Were any fatal?
  - What did you do?
- What is your plan if you witness an overdose in the future?
  - How do you:
    - recognize an overdose?
    - call for help?
    - rescue breathe?
    - give naloxone?
- Do you have a naloxone rescue kit?
- Do you feel comfortable using it?

How to Respond in an Overdose
Steps to teach patients, family, friends, caregivers

1. Recognize the overdose
2. Call 911 for help
3. Rescue breathe
   - Chest compressions if no pulse
4. Administer naloxone
   - If no response, repeat 3 times
5. Stay until help arrives
   - Recovery position if breathing

Prescribe to Prevent:
Overdose Prevention and Naloxone Rescue Kits for Prescribers and Pharmacists
Direct & indirect effects of Prescription Monitoring Programs

- Prescribers
- Pharmacists
- Law enforcement
- Public health/safety dept.
- Target public health measures
- Trend awareness
- Disciplinary actions
- Overdose risk identified, counseled
- Initiate/refer to drug treatment
- Naloxone embedded within PMP
  - “Flag” in Summary
  - Naloxone fills listed in prescriptions, prescribers (standing order prescriber), and dispensers for given date range

PMP-facilitated Naloxone Indicator

3 Best Practice Advisories (BPAs) used to guide care
Morphine Equivalent Value (MEV) BPA
- Appears to providers when an opioid is selected in the discharge med/doc
- Only applies to inpatients on the trauma service
- Response required to continue
- An answer of “Yes – MEV >= 100 mg” contributes to calculated overdose risk

Future Alert Enhancements

Thank you!

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www.prescribetoprevent.org

Free naloxone CME:
www.opioidprescribing.com
Obtain Credits/Certificate

Please complete the Post-Test and Survey upon conclusion. A passing score of 75% is required for credit.

If necessary, please see detailed instructions emailed to you by the CME Office.

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