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School of Pharmacy

TARGET AUDIENCE: Pharmacists and technicians interested in actions they can take to mitigate this crisis.

EDUCATIONAL OBJECTIVES

After participating in this application-based activity pharmacists and pharmacy technicians will be able to:

- Identify the leading causes of drug overdose fatalities
- Describe the development and effects of the benzodiazepines
- Compare the risks of opioid and benzodiazepine overdose and their co-involvement
- Identify the factors associated with benzodiazepine abuse
- Characterize the approaches to reducing benzodiazepine overprescribing and toxicity

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Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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Law: More Anxiety over Drug Overdose Deaths: Impact of Benzodiazepines

ABSTRACT: Deaths from drug overdoses continue to rise. The primary causes, however, have fluctuated over time. Opioids still remain as the primary factor but over the past two decades, key contributors have changed from prescription drugs to heroin to illegally manufactured fentanyls. Recently, polydrug abuse has surfaced as a significant cause of lethality. In particular, the co-use of opioids with benzodiazepines accounts for up to 30% or more of drug overdose deaths. Benzodiazepines can intensify the dangers associated with opioid overdose. This continuing education activity will review the problem of co-administration and examine some of the influences responsible, notably the high rate of co-prescribing, as well as the efforts by governmental agencies and other stakeholders in trying to alleviate the problem. The pharmacy team's role will also be discussed.

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INTRODUCTION

When a pharmacist learns that a patient is one of the more than 70,000 people who died due to a drug overdose last year, [1] he or she may immediately suspect that this was the result of taking an opioid. There is good reason for this assumption since opioids, especially illegally manufactured drugs like fentanyl, are the leading cause of drug overdose in the U.S.[2] However, opioids are only part of the overdose problem. Pharmacy staff should appreciate that overdose trends are dynamic and that the impact of different classes of drugs may fluctuate with time. In many areas of the U.S., Central nervous system (CNS) stimulants have replaced opioids as the leading cause of overdose deaths.[3] In another example, more than 30% of fatal overdoses involving opioids also involve benzodiazepines, underscoring that poly-drug abuse is becoming particularly troublesome.[4]

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This continuing education (CE) activity will examine trends in drug misuse and overdose with an emphasis on the benzodiazepines' growing contribution. Pharmacy teams are no doubt aware that clinicians frequently prescribe and many people use benzodiazepines. Pharmacists observed an explosive growth of opioid prescribing in the 1990s and 2000s which set the stage for the opioid abuse crisis.[5] Inevitably, increased prescribing of benzodiazepines leads to more misuse and overdose; as the greatest rock band in history recognized more than 50 years ago in *Mother's Little Helper*, "…and if you take more of those, you will get an overdose."[6] As this crisis unfolds, will pharmacists be passive onlookers or active gatekeepers?

OVERDOSE TRENDS

Anyone reading this lesson already knows that the rise in drug overdose deaths has been meteoric, increasing 3.6-fold between 1999 and 2017, with the largest effect occurring in males aged 25-34.[2] In 2017, 70,237 people died from drug overdoses. (In 2018, overdose death rates dropped, the first decline in almost 30 years, only to increase again in 2019.[7]) The problem has become so serious that drug overdose deaths have surpassed traffic accidents to become the leading cause of accidental death in the U.S., especially in people younger than 50 years of age.[8]

While prescription drug overdoses fueled the epidemic in the early part of the Millennium, deaths from prescription opioids stabilized around 2011 and appear to be declining.[2,3] Nationwide, most overdose deaths continue to be linked to opioid drugs, but fentanyl analogs and heroin have replaced prescription drugs as the predominant source of the crisis. While the opioids remain as the primary driver of the drug overdose crisis, other drug classes have emerged as significant contributors.

The CNS stimulant, cocaine has consistently ranked as the second or third most common drug associated with overdose fatalities.[3] Deaths increased almost four-fold between 1999 and 2018, killing more than 14,000 people in 2018. In four regions of the U.S. that include 19 states west of the Mississippi, another stimulant, methamphetamine, was the drug most frequently involved in deaths in 2017.[9]

However, pharmacy staff should realize that lethal drug overdoses go beyond the familiar classes of opioids and stimulants (see **Table 1**). The 2017 Centers for Disease Control and Prevention (CDC) National Center for Health Statistics reported that three benzodiazepines ranked in the top 12 drugs most commonly associated with overdose deaths (alprazolam came in at number 5, ahead of oxycodone which was number six; clonazepam at number 11; and diazepam at number 12).[3] Together, these three drugs were a factor in more than 10,000 deaths.[3]

The U.S. Department of Health and Human Services divides the country into 10 public health regions. Alprazolam was a major

Table 1. Drugs Most Commonly Involved in Drug Overdose Deaths in the U.S. (2016[3])

Rank	Drug	% of Deaths	Category
1	Fentanyl	28.8	Opioid
2	Heroin	25.1	Opioid
3	Cocaine	17.8	Stimulant
4	Methamphetamine	10.6	Stimulant
5	Alprazolam	9.8	Benzodiazepine
6	Oxycodone	9.7	Opioid
7	Morphine	7.9	Opioid
8	Methadone	5.5	Opioid
9	Hydrocodone	5	Opioid
10	Diazepam	3.2	Benzodiazepine
11	Diphenhydramine	3.2	Anti-histamine
12	Clonazepam	2.6	Benzodiazepine
13	Gabapentin	2.4	Other
14	Tramadol	2	Opioid
15	Amphetamine	1.9	Stimulant

contributor to overdose deaths in all 10 regions.[9] Only five other drugs (cocaine, fentanyl, heroin, methadone, and oxycodone) ranked in the top 10 in all 10 regions. Alprazolam was the 4th most common drug in four of the 10 regions (Regions 2, 4, 5, and 6) which included New York and New Jersey, much of the South, the upper Mid-West, and the Southwest. Clonazepam and diazepam were also identified as top 10 drugs in Regions 1 and 2 which comprise the states in the Northeast (clonazepam 6th and 7th, respectively, and diazepam 10th in both).[9]

The appearance of multiple drug classes in the top 15 list underscores the observation that the serious opioid problem has largely evolved into an issue of polydrug abuse, especially the combination of opioids with other substances. The majority of opioid deaths (62.6%) in 2017 co-occurred with one or more of the following: benzodiazepines, cocaine, or methamphetamine, which were each present in 32.5%, 34.0%, and 12.1% of deaths, respectively.[10] These deaths occur across the spectrum of opioid substances. Deaths related to illegally manufactured fentanyls, which have become the leading cause of overdose death in the U.S., are increasingly associated with another drug. Deaths from fentanyl co-involving benzodiazepines, cocaine, and methamphetamine significantly increased from July-December 2017 to January-June 2018 by 11.3%, 14.0%, and 31.0%, respectively. Overdose deaths from fentanyls where no other drug was detected increased at a much lower rate of 6.7%.[10]

Overdose deaths related to benzodiazepines rose more than four-fold between 1996 and 2013.[11] More recently there has been a sharper rise with drug overdose deaths involving benzodiazepines rising from 1,135 in 1999 to 11,537 in 2017, a more

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than 10-fold increase.[4] Emergency department visits related to benzodiazepines increased three-fold over a similar period (2004-2011).[11] Significantly, the number of deaths involving benzodiazepines in combination with synthetic narcotics has increased steadily since 2014, while deaths involving benzodiazepines without any opioids has remained steady.[4] These data point out that abuse of multiple drugs has become more serious than the use of individual drugs.

History of Benzodiazepines

The 1950s ushered in an era of fundamental change in the treatment, diagnosis, and understanding of psychiatric illnesses.[12] Among the many advances was the discovery of the benzodiazepines. A chemist, Leo Sternbach, synthesized the first benzodiazepines to be used in making dyes several decades before their pharmacological properties were recognized.[13] Hoffman-LaRoche embarked on a program to develop "tranquilizers" in the 1950s and among the first products Sternbach synthesized was chlordiazepoxide in 1955. It languished on his lab bench until it was uncovered by a co-worker during a lab cleanup in 1957.[13,14] This research team submitted it for animal testing and found it possessed promising anti-convulsant, muscle relaxant, and sedative properties. Roche marketed chlordiazepoxide as Librium in 1960 and three years later the FDA approved the more potent related compound, diazepam (Valium).[39] Other compounds from numerous manufacturers followed.

As Sternbach acknowledged, researchers had inadequate knowledge about the brain to establish a biochemical hypothesis to guide drug development and the approach took the "low road" of empirical synthetic bench work.[13] The new class of drugs became a phenomenon due in large part to their effectiveness and lower toxicity, especially lacking the respiratory depression possessed by the barbiturates, the drug class which they replaced.[14] By the 1970s, their popularity among clinicians and patients propelled benzodiazepines to the top of the most prescribed drugs lists reaching a peak of 2.3 billion dose units of diazepam prescribed in 1979.[14] Enthusiasm for the drugs began to wane in 1980 as evidence emerged of the risk of abuse and dependence.[14] However, pharmacy teams are quite aware that benzodiazepines are still very frequently prescribed and rates of use are rising (discussed below).

Benzodiazepine Pharmacology

The benzodiazepines act as positive allosteric modulators of $GABA_A$ receptors, increasing the affinity of the receptor for GABA.[15,16] GABA is the most common neurotransmitter in the central nervous system, found in high concentrations in many regions of the brain including the limbic system and other areas involved in emotional and cognitive function. GABA is inhibitory in nature and thus reduces the excitability of nerve cells.[17] There are 3 GABA receptors, designated A, B, and C.[17] $GABA_A$ receptors regulate the function of a ligand-gated chloride-selective ion channel, increasing chloride entry into nerve cells and reducing excitability.[16,17]

Different subtypes of the $GABA_A$ receptor exist depending on the nature of the five subunits which comprise the receptor.[15,18] The different subtypes affect different neuronal functions. Those containing an α_1 subunit mediate sedation and some anti-seizure activity, while receptors containing an α_2 subunit (or possibly α_3) mediate anxiety.[16,18] The traditional benzodiazepines do not discriminate among the subtypes, but the non-benzodiazepine "z" drugs (e.g., zolpidem) are selective for the α_1 type.[18]

Benzodiazepine Toxicity

Overdoses of pure benzodiazepines induce a mild to moderate CNS depression.[19] At high doses, impaired motor coordination, dizziness, vertigo, slurred speech, blurry vision, mood swings, and euphoria can occur, along with erratic behavior and amnesia in some instances.[17,20] When taken in repeated doses over a prolonged period, the slow elimination of benzodiazepines can result in significant accumulation in fatty tissues resulting in the appearance of symptoms of overmedication over time. These may include impaired thinking, disorientation, confusion, and slurred speech. Tolerance, dependence, and withdrawal are also adverse effects associated with long-term use.[17,20]

Benzodiazepines can occasionally induce cardiovascular and pulmonary toxicity in cases of severe overdoses,[19] but deep coma requiring assisted ventilation and death from pure benzodiazepine ingestion is rare.[17,19,20] Then why are benzodiazepines associated with such a significant risk of overdose fatalities? Most lethal adverse effects occur when benzodiazepines are administered with other drugs, especially other CNS depressants, which can cause a deadly interaction.[17,19-21] In addition to lethality, benzodiazepines are also involved in high rates of falls and fractures, motor vehicle crashes, and cognitive impairment and many presentations to emergency departments; these effects also increase when combined with other CNS depressants.[21]

WHAT IS BEHIND THE RISE IN BENZODIAZEPINE-ASSOCIATED OVERDOSE DEATHS?

Opportunity for Misuse

Benzodiazepines are among the most widely prescribed drugs in the U.S. and the number of prescriptions written are rising.[4] Between 1996 and 2013, the number of adults who filled benzodiazepine prescriptions in the U.S. increased 67%, from 8.1 million to 13.5 million. The quantity of benzodiazepines they obtained more than tripled during that period, from 1.1 kg to 3.6 kg lorazepam-equivalents per 100,000 adults.[22,23] Alprazolam, clonazepam, and lorazepam are among the 10 most commonly prescribed psychotropic medications in the U.S.[23] Use of benzodiazepines by middle-aged adults increased nearly 50% from 1996 to 2013 and is especially high among adults 65 or older.[22]

The rate of patient visits to a health care practitioner resulting in a prescription for a benzodiazepine doubled from 3.8% in 2003 to 7.4% of visits in 2015.[21] An estimated 30.6 million adults in the U.S. used benzodiazepines in 2016; these data include both prescribed use and misuse (defined as not prescribed or used by an individual other than the person for whom it was prescribed).[24] Non-Hispanic whites, female gender, older age, and more education were all associated with increased odds of use, with women being prescribed benzodiazepines about twice as often as men.[24,25] Misuse, or abuse/dependence of tobacco, alcohol, marijuana, heroin, prescription opioids, or prescription stimulants were all associated with benzodiazepine use.[24]

In a sign of the times, prescribing of psychotropic drugs has increased during the coronavirus pandemic period. The number of prescriptions for anti-anxiety medications in the U.S. reportedly increased 10.2% from 8.9 million in March 2019 to 9.7 million in November 2020.[26] (Prescriptions for anti-depressants also rose 9.2% over the same period.) Other data suggest an even larger increase; one pharmacy benefit manager reports a 34% increase in anti-anxiety prescriptions between mid-February and mid-November 2020. These increases are attributed to health concerns, social isolation, and the stress of job losses.[26]

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Benzodiazepines' enormous popularity and the high prescribing rate pose risks of unsafe side effects and dependence, and the sheer numbers enable the risk of misuse, deliberate overdose, and diversion. However, the numbers alone do not explain the high incidence of a fatal overdose.

Co-Ingestion: A Major Risk Factor

When used correctly, the benzodiazepines have a relatively low risk of abuse and a low risk of fatal overdose.[19,25,27] However, as noted earlier, co-ingestion of multiple substances markedly increases the risk of fatal drug overdose. A particular area of concern is the co-ingestion of benzodiazepines with opioids.

When opioids are used in combination with benzodiazepines, their respiratory depressant effects on spontaneous ventilation are dramatically enhanced dose-dependently. The combination can also enhance cardiovascular and hemodynamic complications significantly.[17] Concurrent use of benzodiazepines in opioid users is associated with a higher risk of emergency room visits, hospital admissions, and drug overdose death than people exposed only to an opioid.[4] Opioid users exposed to benzodiazepines had a 20% higher chance of experiencing an opioid overdose than those exposed only to opioids. This risk rose to 60% if there was also exposure to non-benzodiazepine sedative-hypnotic.[28] Patients using a benzodiazepine along with an opioid are four times more likely to die from an overdose than patients receiving an opioid alone.[29] A cohort study conducted in North Carolina found that the overdose death rate among patients receiving both opioids and benzodiazepines was 10 times higher than among those only receiving an opioid.[4]

One report found that in 2015, 23% of people who died of an opioid overdose also tested positive for benzodiazepines,[4] while the CDC reported that studies of fatal opioid overdose deaths found evidence of concurrent benzodiazepine use in 31% to

61% of decedents.[30] For the past several years, alprazolam has been found in more overdose autopsies in Kentucky than any specific opioid. Community mental health centers in the state have stopped prescribing alprazolam because it is abused so often and so dangerous in combination with alcohol and opioids.[31]

The incidence of benzodiazepine co-involvement in overdose deaths increased among all types of opioids between 1999 and 2017. In 2017, benzodiazepine co-involvement increased to 17% of deaths involving heroin, 26% of synthetic opioids, 32% of methadone, and 33% of prescription opioids.[32] These values were two to four times higher than the rate seen in 1999.
The combination of an opioid and benzodiazepine can produce both a pharmacokinetic and a pharmacodynamic interaction.[33,34] In terms of *pharmacokinetics*, studies suggest that benzodiazepines are capable of inhibiting the metabolism of some opioids. Benzodiazepines are weak competitive inhibitors of CYP3A4.[33] While this enzyme is the primary metabolizer of fentanyl and oxycodone, other CYP isoforms also play a role and opioid metabolism is influenced by many other factors.[35] Consequently, there is some doubt whether enzyme inhibition is sufficient to produce clinically relevant effects.[33]

It is generally believed that the *pharmacodynamic* interactions are more significant.[33] Preclinical evidence (study in animal models) suggests that benzodiazepines' analgesic, anxiolytic, and rewarding properties are partially mediated by opioidergic mechanisms.[33] Respiratory function is principally controlled through medullary respiratory centers sensitive to chemoreceptor and other signals.[33] These centers are inhibited by opioids acting on μ- and δ-opioid receptors. These areas are also rich in inhibitory GABA receptors,[33] so that both opioids and benzodiazepines are capable of inhibiting respiratory function either separately or in combination. Moreover, benzodiazepines have been shown to eliminate buprenorphine's important protective ceiling effect on respiratory depression, and many heroin users report using buprenorphine with a benzodiazepine.[33] Other CNS depressant drugs, including alcohol, and over-the-counter sleep aids, can also have additive or synergistic effects on the central nervous system and respiratory function.[17,20]

PAUSE AND PONDER: A patient presents a prescription for a powerful opioid and one for alprazolam. What should you do? Does it matter if they are from the same physician? Does it matter if they are from a pain specialist?

Why Are Combinations So Common?

If the connection between co-administration of opioids and benzodiazepines and risk is so strong, why are these combinations seen in overdoses so frequently? Two root causes are related: co-prescribing and addict interest.

Co-Prescribing

Benzodiazepine prescribing rates were found to correlate significantly with benzodiazepine co-involvement in overdose deaths from opioids.[32] The number of prescribed benzodiazepines dosage units have been increasing,[11] and benzodiazepine/opioid co-prescribing rates have quadrupled from 2003 to 2015.[32] More than one-half of the patients received both drugs from the same prescriber, frequently for anxiety or insomnia,[36] and the highest rate of co-prescribing was in the primary care setting.[32]

A study examining patient visits to a health care practitioner between 2014 and 2016 found that when a benzodiazepine was prescribed, roughly one-third of the visits also resulted in an opioid prescription.[37] The rates were higher for women than men and increased with age. The most common reason for visits at which benzodiazepines were co-prescribed with opioids was a problem related to a chronic condition; musculoskeletal system and connective tissue disease was the most frequent primary diagnosis category for visits at which benzodiazepines were co-prescribed with opioids.[37] A different analysis found that the rate of benzodiazepine use among patients with chronic pain are higher than in the general population.[33] The high rate of co-prescribing is likely a causative factor in the rise in overdose deaths.

Pharmacists should note that the risk of overdose may be highest with the initial prescription. A study of Medicare recipients found that there was a five-fold increase in the risk of an opioid-related overdose during the first 90 days of concurrent benzodiazepine use when compared with taking an opioid alone.[34] The risk decreased to 1.87 times on days 91 to 180

and beyond 180 days, patients who had not previously overdosed had no significantly greater risk of opioid overdose. However, the overall risk of an overdose was higher the longer the duration of concurrent use because the increased risk of overdose during each time window would be cumulative.[34] The results, however, point out the importance of being especially vigilant during the early period of co-prescribing. The authors speculated that the diminished risk with time may be due, in part, to the development of tolerance,[34] which creates other problems.

Intentional Co-Ingestion

Co-ingestion of opioids and benzodiazepines may be the result of unintentional overdose related to both types of drugs being prescribed and taken or misused to treat a medical condition. On the other hand, an addict may deliberately seek the combination.

Not all cases of co-ingestion involve co-prescribing. In one study, comparing a national prescription drug monitoring program (PDMP) database with urine drug testing data found that nearly one in five people testing positive for prescribed opioids also tested positive for non-prescribed benzodiazepines.[38] Nearly two-thirds of positive tests revealed the presence of a non-prescribed opioid or benzodiazepine, and more than 4% of people with concurrent use results did not have a prescription for either drug. The authors concluded that analyzing prescription data underestimates the true scope of the problem.[38]

Using benzodiazepines to enhance opioids' effects is widespread among those with opioid use disorder.[11] Most people who intentionally abuse benzodiazepines have other substance abuse problems. Benzodiazepines are usually a secondary drug of abuse—used mainly to augment the high received from another drug or to offset the other drug's adverse effects. A benzodiazepine is the sole drug of abuse in a much smaller number of cases.[25,27,33] The co-abuse of benzodiazepines and opioids is sizeable and has negative consequences for general health, overdose lethality, and treatment outcome.[33] Opioids are only part of the problem; approximately one in five individuals abusing alcohol also abuse benzodiazepines.[25]

Benzodiazepines misuse and abuse is also strongly associated with comorbid psychiatric disorders and personal or family history of substance use disorders.[25] Approximately 40% of benzodiazepine abusers report a comorbid psychiatric disorder which is a higher frequency than is seen in other substance abuse populations. Individuals with a history of alcohol abuse or dependence and antisocial personality disorder appear to be at a particularly elevated risk of benzodiazepine abuse.[25]

Moreover, a study from Norway found that benzodiazepine use may contribute to later opioid use.[39] In the study, benzodiazepine users were seven times more likely to have multiple opioid prescriptions than non-benzodiazepine users. Correcting for pain, the benzodiazepine users were still three times more likely to use opioids later than nonusers. The authors explained that studies have shown patients who take benzodiazepines may have heightened pain and underlying anxiety; these conditions may increase vulnerability to addiction.[39]

These observations suggest that opioid abusers may use benzodiazepines therapeutically to self-medicate pain, anxiety, mania, or insomnia.[33] However, recreational use is also significant. For example, co-users report seeking prescriptions for benzodiazepines for the purpose of enhancing opioid intoxication or "high," and use doses that exceed the recommended therapeutic range. Many drug users believe that benzodiazepines are able to enhance the positive subjective effects of opioids (especially euphoria) and may combine opioids and benzodiazepines in an effort to achieve a greater level of euphoria.[33]

Research also indicates that people who abused benzodiazepines and opioids together were more likely to have used opioids for a longer period of time, and used higher doses of opioids when compared to people who used only opioids to achieve a high,[40] thereby raising their risk of a dangerous overdose. In another example of polydrug abuse, benzodiazepines are also increasingly combined with stimulants (amphetamines, cocaine, "Ecstasy") to lessen some of their undesirable effects (e.g., anxiety, irritation, insomnia).[11]

Significantly, these examples of combining drugs highlight the critical problem of polydrug abuse in general which has been found to be a significant predictor of drug overdose. Reports show that 62% to 72% of patients receiving treatment for a drug overdose had consumed more than one drug class. The percentage is higher when assessing fatal overdoses, reportedly reaching as high as 71% to 98% in some studies.[33] These findings also raise the possibility that drug users have shared or overlapping genetic, family, and environmental vulnerability or susceptibility to abuse different drugs.[41]

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Table 2. Key points from the CMS Guidelines of July 2019[30]	
Problems Associated with Co-Prescribing Benzodiazepines and Opioids	**Central Principles for Co-Prescribing Benzodiazepines and Opioids**
Higher risk of overdose deaths Higher risk of suicide Worsening of treatment outcomes Increased use of health services)	1. Avoid initial combination by offering alternative approaches 2. If new prescriptions are needed, limit the dose and duration 3. Taper long-standing medications gradually and, whenever possible, discontinue 4. Continue long-term co-prescribing only when necessary and monitor closely 5. Provide rescue medication (for example, naloxone) to high-risk patients and their caregivers

Response to the Overdose Problem

A problem of this magnitude usually generates public health efforts to counteract it. Governmental and professional organizations have developed different approaches to try to address the growing benzodiazepine-associated overdose problem.

The problem of combining opioids and benzodiazepines spurred two governmental public health agencies to issue warnings in 2016. The Centers for Disease Control and Prevention (CDC) issued a new guideline for the prescribing of opioids, recommending that clinicians avoid prescribing benzodiazepines concurrently with opioids whenever possible.[30]

A study evaluating the effect of the CDC warning found a significant decrease in the rate of opioid/benzodiazepines co-prescribing in the two years after the guideline release in people using opioids long term. They found with less impact on short term use.[42] The authors point out that there may be many reasons why a prescriber may or may not adhere to clinical guidelines, but the results suggest that guidelines may be benficial.[42]

The FDA issued a boxed warning regarding the dangers of co-prescribing benzodiazepines and opioids.[43] The then-FDA Commissioner, Robert Califf, stated, "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." He added that the FDA implored "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."[43] The FDA expanded the boxed warning in September 2020 to include additional warnings of risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions resulting from benzodiazepine use.[43]

The Centers for Medicare and Medicaid Services (CMS) established guidelines in 2019 to reduce the risk of opioid overdose deaths and reduce co-prescribing of benzodiazepines.[44] The guidelines note negative consequences resulting from co-prescribing these drugs and describe five central principles for co-prescribing benzodiazepines and opioids (see **Table 2**).

CMS also recommends short-term treatments with benzodiazepines defined as seven or fewer days' supply and for no more than two weeks and warns about the risk of tolerance and dependence.[44]

State agencies and medical and public health organizations have also modified and tightened guidelines for prescribing benzodiazepines, especially in combination with opioids. For example, the Maryland Board of Physicians, which licenses physicians and other health care practitioners, has adopted a guidance document on opioid prescribing. It recommends avoiding concurrent prescribing of opioids and benzodiazepines and urges prescribers to consider offering naloxone to patients at high risk of overdose.[45] "High risk" patients include those with concurrent benzodiazepine use.

The Commonwealth of Pennsylvania has a 14-point guideline on "safe prescribing benzodiazepines for acute treatment of anxiety and insomnia," which are "intended to help health care providers improve patient outcomes when caring for these patients and to supplement, but not replace, the individual provider's clinical judgement."[46] The recommendations include these recommendations (among others):

- A thorough medical history should be performed before prescribing benzodiazepines
- Extreme caution should be exercised before prescribing benzodiazepines to a patient with a history of past substance use disorder
- Such prescribing should be associated with careful monitoring, including urine screening; and
- Practitioners must note the FDA's box warning on co-prescribing benzodiazepines and opioids.

PAUSE AND PONDER: What is the pharmacist's role in communicating warnings?

Tech Talk: FAQs and My Role as a Technician

Benzodiazepine use is extremely prevalent. Because technicians have the first and last contact with patients in community settings, it is vital that they understand that this class of drug has high misuse and abuse potential and can contribute to overdose fatalities. If you are a technician, you might be wondering if you can—or should—identify abuse and combat its progression. You need to know a few facts about benzodiazepine abuse because you are, in fact, working most directly with patients.

1. How can I tell if there is benzodiazepine abuse among patients who use my store?
You can't. This kind of information is difficult to discern and abuse rates vary among and within geographic areas. As much as we would like to pinpoint abuse right down to a specific set of patient characteristics, it is almost impossible to do because typically, abuse is hard to prove. Do your best not to judge or stereotype patients who take benzodiazepines, but be aware of the key points in this continuing education lesson. Most important, remember that concurrent benzodiazepine and opioid use increases risk of accidental and lethal overdose.

2. What classifies benzodiazepine use as abuse?
Abuse and dependence differ. You may see aggressive verbal or physical behavior in patients who receive long-term benzodiazepine treatment. Dependent patients need the medication for normal function because their body has become so accustomed to its effect. Abuse goes beyond this. Abuse can be defined as—but definitely not limited to—selling, exceeding the daily dose on the label, recreational use, or simultaneous alcohol or illicit drug use.

3. At what point does the doctor need to be involved when abuse is suspected or risk of a drug overdose is elevated?
In collaboration with the pharmacist, you can contribute to risk assessment and identify abuse potential based on observations you've made; for example, if the patient calls for an early refill and offers flimsy excuses, let the pharmacist know. Make note of trends, too; if the patient often presents right before closing, always calls for early refills, or offers to pay cash if his or her insurance refuses the refill, tell the pharmacist. Tell the pharmacists if the patient has prescriptions for any of the drugs listed in **Table 1**. Pharmacists will generally be vigilant for co-prescription with any of the legal drugs, but may need a "heads up!" if the patient has a prescription for gabapentin or purchases diphenhydramine over the counter. In fact, you work most closely with patiens and should note patients' tendencies.

4. How can a technician work with providers to combat benzodiazepine abuse?
Be ready for problems at the front end. This is your working ground; anticipate that anything can happen. Communicate with the pharmacist, too, because good pharmacists value your opinion to assess whether to notify prescribers about potential problems.

5. Where and how can technicians make note of their observations?
When in doubt, make a note! Make it a habit to document conversations or topics discussed with the patient on the patient's profile. These notes are great to have for future reference and helps the pharmacist to stay in tuned with each patient.

Oregon has issued a powerful admonition against co-prescribing. Advisory guidelines for chronic (greater than 12 weeks) opioid use state "Do not combine opioids with benzodiazepines, muscle relaxants, or sedative hypnotics."

New York City's Department of Mental Health and Hygiene urges "judicious" prescribing of benzodiazepines.[47] Its guidelines advise

- considering non-benzodiazepines for treating anxiety and insomnia,
- prescribing the lowest dose of benzodiazepines for the shortest period of time if a prescription is deemed, necessary (no more than two to four weeks), and
- avoiding co-prescribing benzodiazepines and opioids.

It also encourages consultation with the patient's other prescribers.[47]

Non-governmental organizations have also offered guidance. For example, Oregon Pain Guidance, a diverse group of health care professionals including pharmacists, has published a detailed guide that includes recommendations on proper use of opioids and benzodiazepines.[48]

Some states have taken a stronger stand on limiting prescribing than guidelines and recommendations by imposing regulations.[49,50] Most pharmacists are already familiar with regulations such as mandated e-prescribing, triplicate prescription forms, and prescription drug monitoring programs. These are most often put into place to reduce prescribing and dispensing of opioids. Triple forms have reduced the use of emergency department visits for benzodiazepines and opioids. Many states have also enacted laws that set limits on the prescribing or dispensing of controlled substances either by time (e.g., number of days' supply) or amount of drug (dosage units or total amount).[49,50]

Most states place limits on opioid prescribing, but some have broader application and may limit all controlled substances, and some may restrict drugs from certain schedules. Some states also set refill restrictions (for Schedules III and IV) that are stricter than the federal Law. A few states also have restrictions specifically for pain management clinics and benefit recipients. These are not yet widely applied to benzodiazepines (except for the federal requirements in place for C-IV drugs, such as refill restrictions), but could become more common in the future, especially limiting co-prescribing of benzodiazepines and opioids.

Stanford University researcher and addiction specialist Dr. Anna Lembke says, "We have this whole infrastructure set up now to prevent overprescribing of opioids and address the need for addiction treatment ...We need to start making benzos part of that."[31] State PDMPs are part of the infrastructure. Many states encourage, and a few mandate, that prescribers consult the state's PDMP or equivalent if they co-prescribe benzodiazepines with an opioid drug. Maine, for example, requires prescribers to check PDMP information upon the initial benzodiazepine prescription and every 90 days thereafter.

Recently, Tennessee passed a law that prohibits the dispensing of a prescription for any opioid or benzodiazepine in a quantity greater than a 30-day supply. This restriction also applies to mail order pharmacies mailing drugs into the state. Previously, the state had set a 30-day limit on all Schedule II and III drugs and required practitioners to conduct a urine drug test at least every 30 days if they prescribe a Schedule II or III drug alone or in combination beyond a 30 day period. The law's purpose was to assess patients for substance misuse.

Hawaii limits initial concurrent prescriptions for opioids and benzodiazepines to a maximum of seven days unless it is medically necessary for the treatment of certain specified diseases. New York State limited oral prescriptions for Schedule II and III drugs and benzodiazepines to a five-day supply. Non-benzodiazepine Schedule IV drugs can be prescribed for up to a 30-days' supply or 100 units. Kentucky is an example of less specific regulations. Kentucky's Board of Medical Licensure requires that a physician who is asked to assist a patient in responding to the anxiety or depression resulting from a non-recurring single episode or event, shall prescribe or dispense "the minimum amount of controlled substances to appropriately treat the situation" without a recommended number. Other states can reasonably be expected to enact similar kinds of restrictions in the future. It would be prudent for pharmacist to stay abreast of proposed regulatory changes.

Other Problematic Benzodiazepines

FDA-approved prescription benzodiazepines are not the only drugs in the class that pose problems with abuse.

Flunitrazepam, marketed as Rohypnol, is available in more than 60 countries in Europe and Latin America as a preoperative anesthetic, sedative, and sleep aid. This potent benzodiazepine (approximately 10 times more potent than diazepam) has a rapid onset of action. It came to prominence in the U.S. in the 1990s as an inexpensive recreational sedative and as a "date rape" drug.[51] Also a popular club drug, it is frequently used with other substances. At high doses it produces amnesia, loss of muscle control, and loss of consciousness. Ethanol and other CNS depressants potentiate its effects. It may also precipitate abnormal behavior. The drug has an onset of action of about 30 minutes with peak effects occurring at about two hours and a duration up to 12 hours.[51]

Another growing problem is the development of "designer" benzodiazepines.[52,53] These drugs, originally developed by pharmaceutical companies but never approved for use in the U.S., first surfaced in 2012. They include drugs such as clonazolam, etizolam, diclazepam, flubromazolam, and phenazepam.[52,53] Most are available as traditional oral dosage forms but powdered and smokable forms are also available.[53] Methods for their synthesis, often modifications of approved drugs, are published in the scientific literature and can be found online.[52]

The drugs are most often used in combination with stimulants, hallucinogens, opioids, and alcohol to increase the effects or to facilitate a down cycle after a high dose of the drug.[52,53] People with anxiety disorders may occasionally use them when a prescription product is unavailable.[52] Clonazolam is extremely potent, dosed at the microgram level, and widely and easily available as a "research chemical" sold online.[23] **Table 3** lists these drugs' common adverse effects.[53] They have also been detected in cases of polydrug abuse, especially with opioids and alcohol.[53] One researcher has suggested an analogy of overprescribing benzodiazepines fueling the rise of illicit analogs to the overprescribing of opioids fueling the use of heroin and fentanyl analogs.[23]

Table 3. Common Adverse Effects Associated with Designer Benzodiazepines[53]

Common	At high doses
□ Amnesia □ Ataxia, muscle weakness □ Blurred vision □ Confusion □ Dizziness □ Drowsiness □ Fatigue □ Impaired balance □ Impaired thinking and self-assessment capability □ Lethargy □ Loss of coordination □ Palpitations □ Slurred speech □ Somnolence	□ Auditory and visual hallucinations □ Coma □ Deep sleep □ Delirium □ Seizures

Summary and Concluding Remarks

The drug overdose emergency continues into its third decade and became a crisis long ago.[1-3] Concerns about prescription opioids, which fueled the crisis early in the 2000s, have abated somewhat. Deaths have declined since 2010 in part due to efforts by regulators and health care practitioners to reduce prescribing. However, heroin and fentanyls replaced prescription drugs as the main drivers in the 2010s. Opioids continue to be the main cause of death but other drugs, such as CNS stimulants, are becoming more prominent. However, the most important cause of death now appears to be polydrug abuse. Co-administration of opioids with other CNS depressants, notably the benzodiazepines, is a special concern.

While the benzodiazepines produce few deaths on their own, they can facilitate the respiratory depression produced by the opioids and are a dangerous combination. The sheer number of benzodiazepines prescribed by practitioners, often co-prescribed with opioids and dispensed by pharmacists, provides ample opportunity for dangerous interactions to occur. Dr. Lembke, commenting on the high rate of prescribing stated, "What we're seeing is just like what happened with opioids in the 1990s. It really does begin with overprescribing. Liberal therapeutic use of drugs in a medical setting tends to normalize their use. People start to think they're safe and, because they make them feel good, it doesn't matter where they get them or how many they use."[31]

PAUSE AND PONDER: If we blame overprescribing, should we also blame over-dispensing?

While the prospects are grim, this crisis presents a distinct opportunity for pharmacists to play a major role in abating the problem of overdose deaths. Unlike heroin/fentanyl, methamphetamine, cocaine, or even alcohol, benzodiazepines are largely under health care practitioners' control.[32] Pharmacists dispense nearly all the benzodiazepines involved in overdose deaths and fill many prescriptions for the opioids with which they may be combined. Counseling and other interventions at the time a prescription is dispensed should provide valuable support to other public health efforts. One key instance of intervention would be upon the initial dispensing/use of an opioid/benzodiazepine combination, since the greatest risk of overdose occurs early in the cycle.[34]

Current international prescribing guidelines for benzodiazepines recommend only short-term use, generally two to four weeks even without the addition of opioids.[44,54] Pharmacists should be attentive to instances of longer periods of use as a red flag. The FDA estimates that 50% of patients dispensed benzodiazepines received them for two months or longer.[43] A third key demographic red flag would be dispensing of benzodiazepine combinations to the elderly since this population frequently uses benzodiazepines.[22] Older adults also have elevated risk of impaired cognitive and psychomotor function and mortality from benzodiazepines.[25] In addition, patients co-ingesting benzodiazepines and opioids are generally considered "high risk" and many guidelines recommend providing naloxone, which pharmacists may provide without a prescription in many states.[56]

Pharmacists should recognize that benzodiazepine misuse and abuse is strongly associated with comorbid psychiatric disorders.[25,39] Further, patients with mental health disorders are at increased risk of misuse and overdose of opioids either in an effort to self-medicate or due to overlapping vulnerability.[25,33,39,41] In addition to benzodiazepines, opioid overdose deaths are frequently associated with co-use of antidepressants and antipsychotics.[55] Although less common, antiepileptic and anti-Parkinson drugs are also found in a number of opiate overdose victims[55] and these may also warrant closer monitoring by a pharmacist.[56]

Many unique and useful strategies beyond the familiar role of counseling have also been suggested for pharmacists.[54] These kinds of "multistrategic" approaches, particularly educational efforts, can expand the scope of the pharmacist's involvement in care as part of the pharmacist's expected role in optimizing the use of drugs and minimizing their inappropriate use. Growing evidence indicates that pharmacist intervention has been successful in reducing benzodiazepine use in many different countries.[54]

Finally, if pharmacists are going to assume a crucial role as gatekeepers of optimizing the use of drugs, they also need to be involved in the legislative and regulatory decision-making process, both as knowledge sources and as concerned citizens.

Figure 1 on the next page provides suggestions to step up vigilance and improve safety for patients who take benzodiazepines. **Table 4** on page 12 answers some frequently asked questions for technicians.

Figure 1. Keeping an Eye on Opioid-Benzodiazepine Co-Prescribing

Best

❶ **BE COMMUNITY CHAMPIONS.** Get involved in local efforts to stop accidental,unnecessary drug overdose.
❷ **Follow reports about** accidental, unnecessary drug overdose closely, and know where your community stands in this epidemic**.**
❸ **Let patients know** you're concerned! Simply talking about heightened risk can prompt patients to be careful.

Better

❶ **Recognize that PDMPs only track filled prescriptions**–they don't track other red flags.
❷ **Educate patients about benzodiazepines' risks,** and advise them to avoid concurrent use of opioids.
❸ **Monitor older patients** with prescriptions for benzodiazepines and opioids closely.

Good

❶ **Identify patients who tend to ask for early refills** for benzodiazepines and notify the prescriber.
❷ **Know which benzodiazepines** are most likely to be abused in your area.
❸ **Monitor patients' benzodiazepine use closely!**

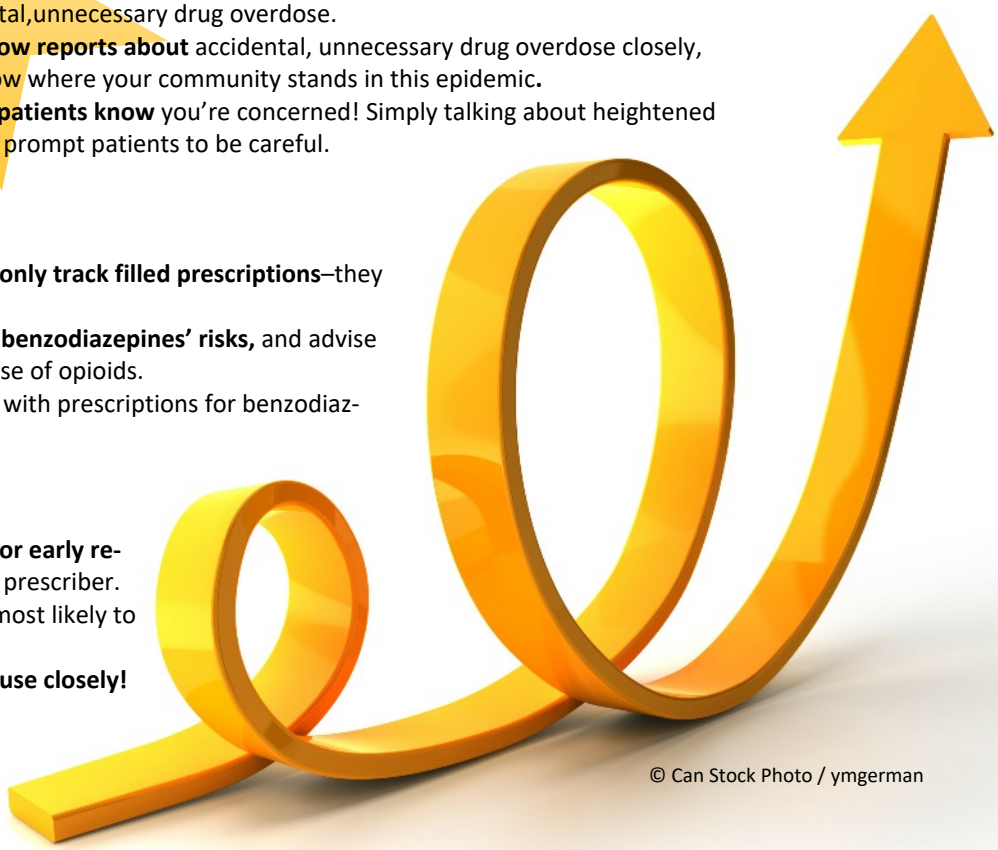

Table 4. A Technician's Guide to Benzodiazepine Prescriptions

Common Problems	What do I do?
How do I know if the medication is a benzodiazepine?	Recognize that ALMOST ALL generic benzodiazepines end in "am." • alprazolam (Xanax) • clonazepam (Klonopin) • chlordiazepo**xide** (Librium)–This is an EXCEPTION! Take note. • diazepam (Valium) • lorazepam (Ativan) • temazepam (Restoril)
Something is missing on the script; what do I do?	Tell the pharmacist or the pharmacy intern. Verify the mistake with them before contacting the provider. Depending on store and state regulations, technicians may not be allowed to make this kind of call. DOCUMENT changes to the script with name of who you spoke with and the date.
The insurer refill was rejected as "too soon to fill." Now what?	Referring to the day's supply, notify the patient of the date that they last filled the prescription and the next available fill date. While most patients are understanding, anticipate that patients who take benzodiazepines routinely might become emotional. Stay calm and explain the rejection. Suggest patients consult with their providers if they need changes to dosing or frequency.
What if this patient always tries to refill too soon?	Bring this to the pharmacist's attention and document each encounter with the patient on the patient's electronic profile. Recognize this as a potential **RED FLAG** for substance misuse or abuse.
What if the patient is going on vacation and needs the fill now?	If the insurance rejects the prescription because it is too soon, the pharmacy cannot bill it until the next available fill date. Process the prescription as cash if the pharmacist approves and the patient agrees. Otherwise the insurance company must confirm an override to fill the prescription. Recognize this as a potential **RED FLAG** for substance misuse or abuse in patients who routinely make excuses.
How do I respond to an angry patient?	Choose your language appropriately. You see many irritated patients on a daily basis, not just patients who refill benzodiazepine prescriptions. With all patients, be respectful, empathetic, and calm. Focus on the problem and what you can do, not what you cannot do. Refer to the pharmacist if you need further assistance.

REFERENCES

1. National Institute on Drug Abuse. Overdose DEATH RATES. Available at https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Accessed October 18, 2020.
2. Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2017. NCHS Data Brief, no 329. Hyattsville, MD: National Center for Health Statistics. 2018. Available at https://www.cdc.gov/nchs/products/databriefs/db329.htm. Accessed October 18, 2020.
3. Hedegaard H, Bastian BA, Trinidad JP, Spencer MR, Warner M. Drugs most frequently involved in drug overdose deaths: United States, 2011–2016. National Vital Statistics Reports; vol 67 no 9. Hyattsville, MD: National Center for Health Statistics. December 12, 2018. Available at https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_09-508.pdf. Accessed October 18, 2020.
4. National Institute on Drug Abuse. Benzodiazepines and Opioids. Revised March 2018. Retrieved from: https://www.drugabuse.gov/drugs-abuse/opioids/benzodiazepines-opioids . Accessed October 18, 2020.
5. Schiller EY, Goyal A, Cao F, Mechanic OJ. Opioid Overdose. Stat Pearls (Internet). Updated August 12, 2020. Available at https://www.ncbi.nlm.nih.gov/books/NBK470415/#article-26226.s3. Accessed October 18, 2020.
6. Richards K, Jagger M. *Mother's Little Helper*. 1966. Available at https://www.songfacts.com/lyrics/the-rolling-stones/mothers-little-helper. Accessed October 18, 2020.
7. Centers for Disease Control and Prevention. Provisional Drug Overdose Death Counts. August 12, 2020. Available at https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm?source=email#nature_sources_of_data. Accessed October 18, 2020.
8. National Safety Council. For the First Time, We're More Likely to Die From Accidental Opioid Overdose than Motor Vehicle Crash. January 14, 2019. Available at https://www.nsc.org/in-the-newsroom/for-the-first-time-were-more-likely-to-die-from-accidental-opioid-overdose-than-motor-vehicle-crash. Accessed October 18, 2020.
9. Hedegaard H., Bastian BA, Trinidad JP, Spencer MR, Warner M. Regional Differences in the Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2017. National Vital Statistics Reports; vol 68 no 12. Hyattsville, MD: National Center for Health Statistics. October 12, 2019. Available at https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_12-508.pdf. Accessed October 18, 2020.
10. Gladden RM, O'Donnell J, Mattson CL, Seth P. Changes in Opioid-Involved Overdose Deaths by Opioid Type and Presence of Benzodiazepines, Cocaine, and Methamphetamine - 25 States, July-December 2017 to January-June 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(34):737-744. Published 2019 Aug 30. doi:10.15585/mmwr.mm6834a2. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6715260/. Accessed October 18, 2020.
11. Votaw VR, Geyer R, Rieselbach MM. McHugh RK. The epidemiology of benzodiazepine misuse: A systematic review. *Drug Alc Depend*. 2019; 200:95-114.
12. Baldessarini RJ. The Impact of Psychopharmacology on Contemporary Psychiatry. *Can J Psychiatry*. 2014; 59(8): 401-405.
13. Sternbach LH. The benzodiazepine story. *J Med Chem*. 1979; 22(1):1-7.
14. Wick JY. The history of benzodiazepines. *Consult Pharm*. 2013; 28(9):538-548.
15. Sigel E, Ernst M. The benzodiazepine binding sites of GABA $_A$ receptors. *Trends Pharmacol*. 2018; 39(7):659 -671.
16. Samardzic J, Strac DS. Benzodiazepines and anxiety disorders: From laboratory to clinic. New Developments in Anxiety Disorders (Durbano F, Marchesi B, eds.) IntechOpen 2016 eBook (PDF) ISBN: 978-953-51-7326-7. Available at https://www.intechopen.com/books/new-developments-in-anxiety-disorders/benzodiazepines-and-anxiety-disorders-from-laboratory-to-clinic. Accessed October 18, 2020.
17. Griffin CE, Kave AM, Bueno FR, Kave AD. Benzodiazepine pharmacology and central nervous system–mediated effects. *Ochsner J*. 2013;13(2):214-223.
18. Rudolph U, Möhler H. GABA-based therapeutic approaches: GABAA receptor subtype functions. *Curr Opin Pharmacol*. 2006;6(1):18-23. doi:10.1016/j.coph.2005.10.003
19. Gaudreault P, Guay J, Thivierge RL, Verdy I. Benzodiazepine poisoning. Clinical and pharmacological considerations and treatment. Drug Safety 1991;6(4):247-265.
20. Kang M, Galuska MA, Ghassemzadeh S. Benzodiazepine Toxicity. *Stat Pearls* (Internet). July 1, 2020. Available at https://www.ncbi.nlm.nih.gov/books/NBK482238/. Accessed October 18, 2020.
21. Agrawal SD, Landon BE. Patterns in Outpatient Benzodiazepine Prescribing in the United States *JAMA Netw Open.* 2019; 2(1): e187399. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6484578/. Accessed October 18, 2020.
22. Bachhuber MA, Hennessy S, Cunningham CO, et al. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996–2013. *Am J Public Health* 2016;106:686-688.
23. Lembke A, Papac J, Humphreys K. Our other prescription drug problem. *New Eng J Med*. 2018;378:693-695.
24. Maust DT, Lin LA, Blow FC. Benzodiazepine Use and misuse among adults in the United States. *Psychiatr Serv*. 2019;70(2):97-106.
25. Schmitz A. Benzodiazepine use, misuse, and abuse: A review. *Mental Health Clinician.* 2016;6(3):120–126. Available at https://meridian.allenpress.com/mhc/article/6/3/120/102755/Benzodiazepine-use-misuse-and-abuse-A-review. Accessed October 18, 2020.
26. Petersen A. More people are taking drugs for anxiety and insomnia, and doctors are worried. *WSJ*. May 25, 2020. Available at https://www.wsj.com/articles/more-people-are-taking-drugs-for-anxiety-and-insomnia-and-doctors-are-worried-11590411600. Accessed October 18, 2020.
27. O'Brien CP. Benzodiazepine use, abuse, and dependence. *J Clin Psychiatry*. 2005;66(suppl. 2):28-33.
28. Cho J, Spence MM, Niu F, Hui RL, Gray P, Steinberg S. Risk of overdose with exposure to prescription opioids, benzodiazepines, and non-benzodiazepine sedative-hypnotics in adults: a retrospective cohort study. *J Gen Intern Med*. 2020;35(3):696-703. doi:10.1007/s11606-019-05545-y
29. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. *BMJ*. 2017;356:j760. Published 2017 Mar 14. doi:10.1136/bmj.j760. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5421443/. Accessed October 18, 2020.
30. Dowell D, Haegerich TM, Chou R. CDC Guideline for prescribing opioids for chronic pain — United States, 2016. *MMWR Recomm Rep*. 2016;65. doi:10.15585/mmwr.rr6501e1er. Available at https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmmwr%2Fvolumes%2F65%2Frr%2Frr6501e1er.htm. Accessed October 18, 2020.

31. Vestal C. These pills could be next U.S. drug epidemic, public health officials say. *Stateline*. July 18, 2018. Available at https://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2018/07/18/these-pills-could-be-next-us-drug-epidemic-public-health-officials-say. Accessed October 18, 2020.
32. Tori ME, Larochelle MR, Naimi TS. Alcohol or benzodiazepine co-involvement with opioid overdose deaths in the United States, 1999-2017. *JAMA Netw Open.* 2020;3(4):e202361. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7146101/. Accessed October 18, 2020.
33. Jones JD, Mogali S, Comer SD. Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug Alc Depen*. 2012;125(2):8-18.
34. Hernandez I, He M, Brooks MM. Exposure-response association between concurrent opioid and benzodiazepine use and risk of opioid-related overdose in Medicare Part D beneficiaries. *JAMA Netw Open.* 2018;1(2):e180919. doi:10.1001/jamanetworkopen.2018.0919 Available at https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2685628. Accessed October 18, 2020.
35. Smith HS. Opioid metabolism. *Mayo Clin Proc*. 2009;84(7):613-624.
36. Hwang CS, Kang EM, Kornegay GM, et al. Trends in the concomitant prescribing of opioids and benzodiazepines, 2002–2014. *Am J Preventive Med.* 2016;51(2):141-160.
37. Santo L, Rui P, Ashman JJ. Physician office visits at which benzodiazepines were prescribed: Findings from 2014–2016 National Ambulatory Medical Care Survey. *National Health Statistics Report*. 2020;137: 1-15.
38. McClure FL, Niles JK, Kaufman HW, Gudin J. Concurrent use of opioids and benzodiazepines: evaluation of prescription drug monitoring by a United States laboratory. J Addiction Med. 2017;11(6):420-426.
39. Webster L. Considering the risks of benzodiazepines and opioids together. *Pain Medicine*. 2010;11(6):801-802.
40. Calcaterra SL, Severtson SG, Bau GE, *et al*. Trends in intentional abuse or misuse of benzodiazepines and opioid analgesics and the associated mortality reported to poison centers across the United States from 2000 to 2014. *Clin Toxicol*. 2018;56(11):1107-1114.
41. Tsuang MT, Lyons MJ, Meyer JM, *et al*. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. Arch Gen Psychiatr. 1998;55(11):967-972.
42. Jeffery MM, Hooten WM, Jena AB, *et al*. Rates of Physician Coprescribing of Opioids and benzodiazepines after the release of the Centers for Disease Control and Prevention Guidelines in 2016. *JAMA Netw Open.* 2019;2(8):e198325. doi:10.1001/jamanetworkopen.2019.8325. Available at https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2740781. Accessed October 18, 2020.
43. U.S. Food and Drug Administration. FDA requires strong warnings for opioid analgesics, prescription opioid cough products, and benzodiazepine labeling related to serious risks and death from combined use. August 31, 2016. Available at https://www.fda.gov/news-events/press-announcements/fda-requires-strong-warnings-opioid-analgesics-prescription-opioid-cough-products-and-benzodiazepine. Accessed October 18, 2020.
44. Centers for Medicare and Medicaid Services. Reduce Risk of Opioid Overdose Deaths by Avoiding and Reducing Co-Prescribing Benzodiazepines. Issued July 1, 2019. Retrieved from: https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/SE19011.pdf. Accessed October 18, 2020.
45. Maryland Board of Physicians. Board Guidance. Available at https://www.mbp.state.md.us/resource_information/res_con/resource_consumer_od_board_guidance.aspx. Accessed October 18, 2020.
46. Commonwealth of Pennsylvania. Safe prescribing benzodiazepines for acute treatment of anxiety & insomnia. Updated May 15, 2017. Available at https://www.health.pa.gov/topics/Documents/Opioids/PA%20Guidelines%20on%20Benzo%20Prescribing.pdf. Accessed October 18, 2020.
47. New York City Department of Health and Mental Hygiene. Judicious prescribing of benzodiazepines. City Health Information. 2016;35(2):13-20. Available at https://www1.nyc.gov/assets/doh/downloads/pdf/chi/chi-35-2.pdf. Accessed October 18, 2020.
48. Oregon Pain Guidance. *Opioid Prescribing Guidelines*. August 2014. Available at https://www.careoregon.org/docs/default-source/providers/manuals-and-formulary/opioid-prescribers-guidelines.pdf?sfvrsn=2672e9e6_0. Accessed October 18, 2020.
49. National Conference of State Legislatures. Prescribing policies: States confront opioid overdose epidemic. Available at http://www.ncsl.org/research/health/prescribing-policies-states-confront-opioid-overdose-epidemic.aspx. Accessed October 18, 2020.
50. Centers for Disease Control and Prevention. Prescription drug time and dosage limit laws. Available at https://www.cdc.gov/phlp/docs/menu_prescriptionlimits.pdf. Accessed October 18, 2020.
51. Gahlinger PM. Club drugs: MDMA, gamma-hydroxybutyrate (GHB), Rohypnol, and ketamine. *Am Fam Physician*. 2004;69(11):2619-2626.
52. Moosmann B, King LA, Auwarter V. Designer benzodiazepines: A new challenge. *World Psychiat*. 2015;14(2):248.
53. Zawilska JB, Wojcieszak J. An expanding world of new psychoactive substances—designer benzodiazepines. Neurotoxicology. 2019;73:8-16.
54. Gallagher HC. Addressing the Issue of Chronic, Inappropriate Benzodiazepine Use: How Can Pharmacists Play a Role? *Pharmacy.* 2013; *1*(2):65-93. Available at https://www.mdpi.com/2226-4787/1/2/65/htm. Accessed October 18, 2020.
55. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *JAMA*. 2013;309(7):657–659. doi: 10.1001/jama.2013.272. https://jamanetwork.com/journals/jama/fullarticle/1653518. Accessed October 18, 2020.
56. National Alliance of State Pharmacy Associations. Pharmacy prescribing: naloxone. January 17, 2019. Available at https://naspa.us/resource/naloxone-access-community-pharmacies/. Accessed October 18, 2020.