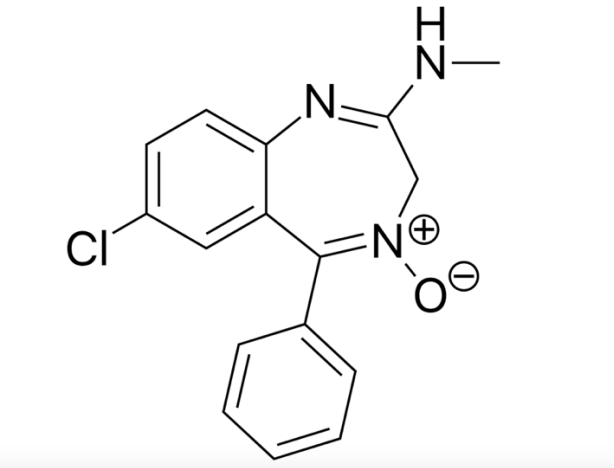
# Benzodiazepine Use in New Mexico and the United States




**New Mexico Statewide Epidemiological Outcomes Workgroup**
**White Paper Series**


Produced by Coop Consulting, Inc.
on behalf of the New Mexico Statewide Epidemiological Outcomes Workgroup
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*The cover image is of the chemical structure of the first benzodiazepine developed in 1955, chlordiazepoxide (Wick, 2003).*
*Image credit: Wikipedia, The Free Encyclopedia. Retrieved 17:21, April 10, 2020*

**Mission** New Mexico's Statewide Epidemiological and Outcomes Workgroup (SEOW) reviews and disseminates data about substance abuse and misuse and their consequences. It also identifies best practice information about evidence-based prevention strategies, policies and practices that can lead to successful outcomes for New Mexicans. The purpose of this two-fold work is to inform communities so that they can better target behaviors and risk factors that can be positively impacted by the implementation of well-chosen, evidence-based prevention approaches that are appropriate for the population. The important work of the SEOW is directed by the Office of Substance Abuse Prevention (Behavioral Health Services Division, Human Services Department) and supported by federal funding from the Center for Substance Abuse Prevention, Substance Abuse and Mental Health Services Administration.

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Abstract:

This SEOW white paper seeks to inform public health efforts surrounding overdoses by exploring benzodiazepine use in the United States and in New Mexico. This paper discusses benzodiazepine's benefits and risks, concomitant use of benzodiazepines with alcohol or opioids, and its role in polysubstance use. This paper highlights national prescribing data, national treatment data, national diversion data, New Mexico's prescribing data, and New Mexico's overdose and treatment data. The paper ends with strategies to prevent benzodiazepine misuse.

## Introduction

Benzodiazepines were co-involved in 21.7% of all opioid overdoses nationally between 2015 and 2017.[i] Benzodiazepines are a type of prescription medication that depress the central nervous system to create a calming effect and slower breathing rate. Benzodiazepines are widely used to treat a wide variety of diagnoses and conditions, including anxiety, seizures, and insomnia. Benzodiazepines are a safe and useful class of medications that also have significant potential for abuse[1], misuse, and physical dependence. The use of benzodiazepines can be problematic because of increased risk of accidents and fatal or non-fatal overdose events. Combinations of benzodiazepines and other central nervous system altering substances, such as opioids or alcohol, pose greater risk of serious or life-threatening problems.

## Background

The first benzodiazepine was developed in 1955 by the Swiss pharmaceutical company Hoffamn-La Roche by chemist Leo Sternbach. The medicine became available to the United States in 1960 as Librium. It was marketed as a safer-to-use anxiolytic than barbiturate drugs, with less risk of dependence and withdrawal. In 1958, Hoffman-La Roche developed the second benzodiazepine, diazepam. In the 1970's benzodiazepines rose to the status of "most frequently prescribed" medicines. In the 1980's, more evidence regarding abuse and dependence of benzodiazepines began producing legislative action. [ii]

Benzodiazepines are a schedule IV substance that are commonly used to treat anxiety disorders, seizure disorders, muscle spasms, insomnia, and alcohol withdrawal. They are also used in anesthesia. (Table 1). According to the DEA, schedule IV substances have "low potential for abuse relative to substances in Schedule I-III". Benzodiazepines depress the central nervous system by promoting activity of the gamma-aminobutyric acid (GABA), a neurotransmitter that suppresses nerve activity.[iii] This slowing of the nervous system and brain produces a calming effect. Another class of medicine called "Z-drugs" differ from benzodiazepines but behave similarly to benzodiazepines. They are used to treat insomnia and carry many of the same risks as benzodiazepines, although this paper does not specifically discuss them.[iv]

Long-term use of benzodiazepines (>120 days) is generally considered risky and is associated with discontinuation issues, such as patients pressuring prescribers to continue

[1] This paper uses the terms "abuse" and "misuse" to preserve distinct medical diagnoses associated with different treatment indicators that are discussed in primary source literature. "Abuse" in the cited literature is generally defined as physical dependence on a substance and engaging in compulsive behaviors that continue despite harmful consequences. "Misuse" in the cited literature is generally defined as engaging in non-medically prescribed use of a substance. Coop Consulting, Inc. recognizes the potential stigmas associated with these terms.

prescribing, and withdrawal. Tolerance and physical dependence on benzodiazepines can develop within weeks of therapeutic use. Therefore, most benzodiazepines are recommended as effective short-term therapies for conditions such as anxiety and insomnia.

Dangers and risks associated with benzodiazepine use include cognitive impairment, impaired motor skills, tolerance, dependence, withdrawal, polysubstance abuse, and overdose. These risks become more pronounced when benzodiazepines are combined with other substances that either influence metabolism or depress the nervous system. Examples of central nervous system depressants are opioids, alcohol, partial and full opioid agonists, muscle relaxers, sedatives, and tranquilizers. Some contraindications for benzodiazepine use include pregnancy, dementia, history of substance abuse, and history of liver disease.

Benzodiazepines are generally dispensed for oral administration in tablets and capsule form. Illicit routes of administration include crushing and nasally inhaling or smoking and dissolving the powder into a solution to inject it. Benzodiazepines differ by speed of onset and duration of action, with faster-acting medications such as alprazolam, commonly marketed under the brand name Xanax, and diazepam under the brand name Valium, posing higher potential for abuse, misuse, and dependence.[v] Route of administration also influences rate of onset.[vi]

Table 1: Common reasons for benzodiazepine prescriptions with the generic and brand benzodiazepine name.

| **Alcohol Withdrawl** | **Insomnia** |
|---|---|
| clordiazepoxide (Librium) | estazolam (Prosom) |
| | flurazepam (Dalmane) |
| **Anesthesia** | quazepam (Doral) |
| midazolam (Versed) | temazepam (Restoril) |
| lorazepam (Ativan) | triazolam (Halcion) |
| diazepam (Valium) | |
| | **Muscle Relaxation** |
| **Anxiety Disorders** | diazepam (Valium) |
| alprazolam (Xanax) | |
| chlordiazepoxide (Librium) | **Seizure Disorders** |
| chlorazepate (Tranxene) | clonazepam (Klonopin) |
| diazepam (Valium) | lorazepam (Ativan) |
| lorazepam (Ativan) | clobazam (Onfi) |
| midazolam (Versed) | diazepam (Valium) |

Created by Coop Consulting, Inc. using information from https://www.rxlist.com/benzodiazepines/drug-class.htm

## Concomitant Use of Benzodiazepines and Alcohol or Opioids

The Substance Abuse and Mental Health Services Administration (SAMHSA) published a study in 2014 that examined 943,032 emergency department (ED) visit outcomes from 2005-

2011 that involved combinations of benzodiazepines and other substances found in national data from the Drug Abuse Warning Network's (DAWN). The results were conclusive that benzodiazepine use is positively associated with risk of serious health outcomes, such as hospitalization or death while in the ED. Serious health outcomes for benzodiazepine use alone posed a greater than 20% risk. Risk increased by 24-55% in patients who whose benzodiazepine use was combined with opioids or alcohol.[vii]

This study illustrates the dangers associated with all benzodiazepine use, as the DAWN data does not differentiate licit prescription use with illicit prescription use. The consequences of adverse outcomes are not limited to non-medical use.

In March 2016, the Center for Disease Control (CDC) published a set of voluntary guidelines for safer prescribing of opioids to mitigate potentially problematic co-prescribing, such as the combination of benzodiazepines and opioids, and to promote the patient's health outcomes.[viii]

The first recommendation is urine drug testing. Urine drug testing is used to screen for potentially dangerous combinations of substances both prior to initiating licit use of a controlled medication, and during a prescription's duration. The practice of drug testing may also allow for identification of patients who are diverting a prescription. Although it is useful, urine drug testing can be easily falsified.

The second recommendation is to check a prescription drug monitoring program, both prior to initiating a prescription and occasionally throughout the duration of the treatment. This practice may allow for the identification of problematic prescription refills and requests patterns of medicine received by a patient, such as obtaining prescriptions from multiple doctors or pharmacies. These screening and monitoring tools help prescribers make clinical decisions about the appropriateness of benzodiazepine treatment.

When benzodiazepines are combined with partial or full opioid agonists, such as buprenorphine and methadone, the risks of abuse and misuse are high. One study in the Journal of Substance Abuse Treatment linked a 60% increase of opioid overdose risk when benzodiazepines are combined with methadone.[ix] Because most patients receiving medication-assisted treatment (MAT) for opioid use disorder with partial or full opioid agonists have histories of benzodiazepine contraindications such as substance use, chronic anxiety, and insomnia, there is not much evidence that short term benzodiazepine treatment is generally an effective therapy. Furthermore, people who use opioid agonists concomitantly with benzodiazepines may be at additional risk of overdose if they relapse into opioid use.

## Tolerance, Withdrawal, Polysubstance Abuse, and Overdose

Increased tolerance risk associated with benzodiazepine use may lead to more frequent use to achieve the desired effect. If patients are using more of a benzodiazepine than directed

by a clinician, they could run out of medication before they can obtain a refill. Abruptly stopping a benzodiazepine prescription generates several issues. Many long-term benzodiazepine users report that "rebound" symptoms, such as difficulty sleeping and increased anxiety with any reduction in dose, are evidence that the medication is working for them, not recognizing that they are becoming physically dependent upon the medicine.[x]

Abruptly discontinuing benzodiazepine use may result in withdrawal symptoms that range from mild to severe to life-threatening. Symptoms may be worse with long term use, short-acting medicines, and high doses. Not all inpatient detox facilities will accept patients with active benzodiazepine use because of the lack of medical resources necessary to manage severe withdrawal.[xi] Because of the risk of more severe withdrawal symptoms of seizures and psychosis, clinicians will generally opt to taper or gradually reduce patients off of benzodiazepines instead of immediately discontinuing prescriptions.

Polysubstance use is a behavior strongly associated with benzodiazepine abuse.[xii] Recreational use of benzodiazepines include intensifying euphoria from opioids, reducing the effects of opioid or alcohol withdrawal, and mitigating insomnia from use of stimulants such as methamphetamine or cocaine.

Benzodiazepines can cause or contribute to fatal and non-fatal overdose from over-depression of the medulla, the part of the central nervous system that controls the body's drive to breath.[xiii] However, when used alone, benzodiazepines don't usually cause overdose. The antidote to a benzodiazepine overdose is an intravenous delivery of flumazenil or its brand name, Romazicon.

Discontinuation of benzodiazepines is generally resisted by patients because of the unpleasant withdrawal symptoms that can follow any decrease in dose. Clinicians have a few strategies they can rely on to reduce or discontinue benzodiazepines. One is gradual dose reduction over weeks to months. Another strategy is to taper and adjunct with anticonvulsant medications such as carbamazepine.[xiv]

## Benzodiazepine Trends in the United States and New Mexico

### *National Prescribing Data*

In 2017, the top 200 prescribed medications in the United States contained four benzodiazepines, which represented 2.15% of the total top 200 prescribed medications. This top 200 prescribed medication list also includes five opioids, which represented 2.92% of the total top 200 prescribed medications.[xv] A serial cross sectional analysis from 2003 to 2015 that examined trends in medical specialties prescribing benzodiazepines revealed stable prescribing rates among psychiatrists and increasing prescribing rates for all other types of physicians from 3.6% to 7.5%.[xvi] Significant increases in associated diagnoses were anxiety and depression

(26.6-33.5%) and back and/or chronic pain (3.6-8.5%). In addition, the rate of co-prescribing benzodiazepines and opioids rose from 0.5% to 2.0%, quadrupling over the twelve-year period of the analysis.

The CDC's National Health Statistics Report from January 2020 describes benzodiazepine prescribing characteristics from 2014-2016 using National Ambulatory Medical Care Survey (NAMCS) data.[xvii] The visit rates at which benzodiazepines were prescribed was highest for females aged 65 years and over, at a visit rate of 62 visits per 100 females. The lowest group for visits at which benzodiazepines were prescribed is with males aged 18-44 years at a visit rate of 9 visits per 100 males. When looking at co-prescribing rates for benzodiazepines and opioids, the trend is maintained. The highest co-prescribing visit rates occurred for females aged 65 years and over at 19 visits per 100 females. Again, the lowest co-prescribing visit rate occurred with males aged 18-44 years at 3 visits per 100 males.

Extensive prescribing of benzodiazepines to females aged 65 and over is troubling because this demographic of patients is already at risk of complications that include dependence, falls, fractures, dementia, and cognitive decline.[xviii] The Beers Criteria, a tool developed by the American Geriatric Society to guide prescribing for geriatric patients, strongly recommends prescribers avoid prescribing benzodiazepines to this patient population because of the associated risks.[xix]

*National Treatment Data*

National Treatment Episode Data Set (TEDS) from 2017 shows a 22% increase between 2015-2017 for individuals seeking tranquilizer abuse treatment, which includes benzodiazepines.[xx] Demographic trends of people who were admitted for tranquilizer abuse treatment in 2017 were unexclusively: 57.8% male, an average age of 33 years old, 76.5% white, 56.2% used daily, 92.5% used oral administration, and most frequently first used tranquilizers at age 30 or later.

Primary and secondary substance analysis from 2017 also shows that tranquilizers such as benzodiazepines were most secondarily used to adjunct primary opiate use. This echoes another TEDS analysis from 2010 that found 48.2% of people admitted for benzodiazepine and narcotic abuse reported the primary substance of abuse choice was narcotics and the secondary was benzodiazepines while 9.9% reported primary abuse of benzodiazepines with secondary abuse of narcotics.[xxi] The other 41.7% of admissions reported another primary substance of abuse with benzodiazepine abuse as a secondary or third substance of choice.

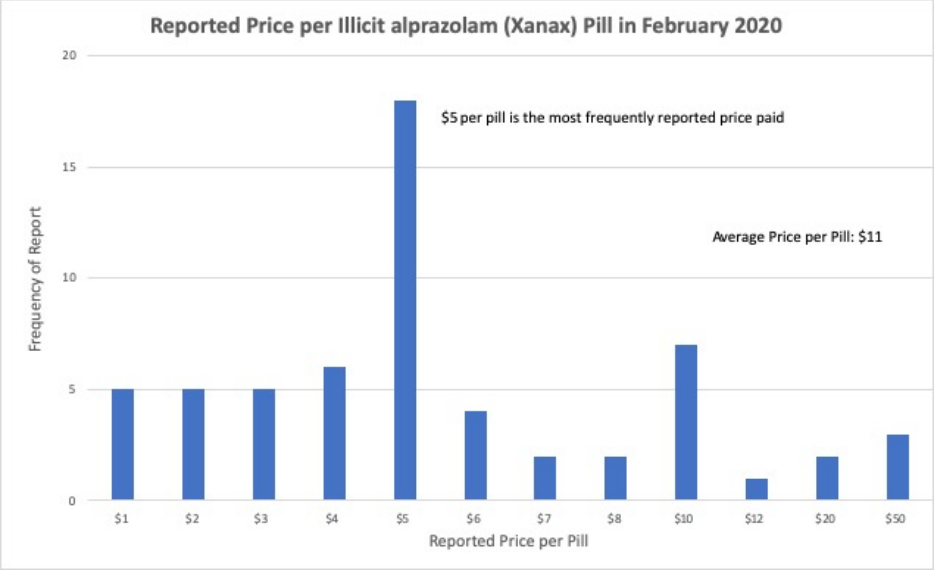
The National Survey on Drug Use and Health estimated that in 2018 2.0% of the United States population (5.4 million) people misused benzodiazepines. For comparison, cocaine's estimated misuse rate was 2.0%, methamphetamines were 0.7%, and opioids were 3.7%.[xxii]

*National Diversion Data*

In 2018, the Drug Enforcement Administration's (DEA) National Forensic Laboratory Information System reported alprazolam as the sixth most diverted substance in the nation, between fentanyl and oxycodone, respectively.[xxiii] Of the benzodiazepines and sedatives, alprazolam accounts for 58% of the diversions, clonazepam 13.78% and diazepam 4.83%. Between 2017 and 2018, reports of alprazolam diversion decreased significantly from 47,160 to 40,195.

According to the nationwide crowdsourced StreetRx platform, an analysis of sixty reports submitted in February 2020 regarding value for an unspecified dose of one generic Xanax pill ranged from $1 to $50, with the median being $5, averaging $11 per pill. There is considerable discrepancy between demographics of who receives the least benzodiazepine prescriptions and demographics of those who seek the most treatment for tranquilizer abuse, both of which are discussed on the previous page. The discrepancy suggests a need to evaluate motivations related to the diversion of benzodiazepine prescriptions. The economic benefit of diverting prescription medicine may motivate patients to use their prescription for income.

Graph 1



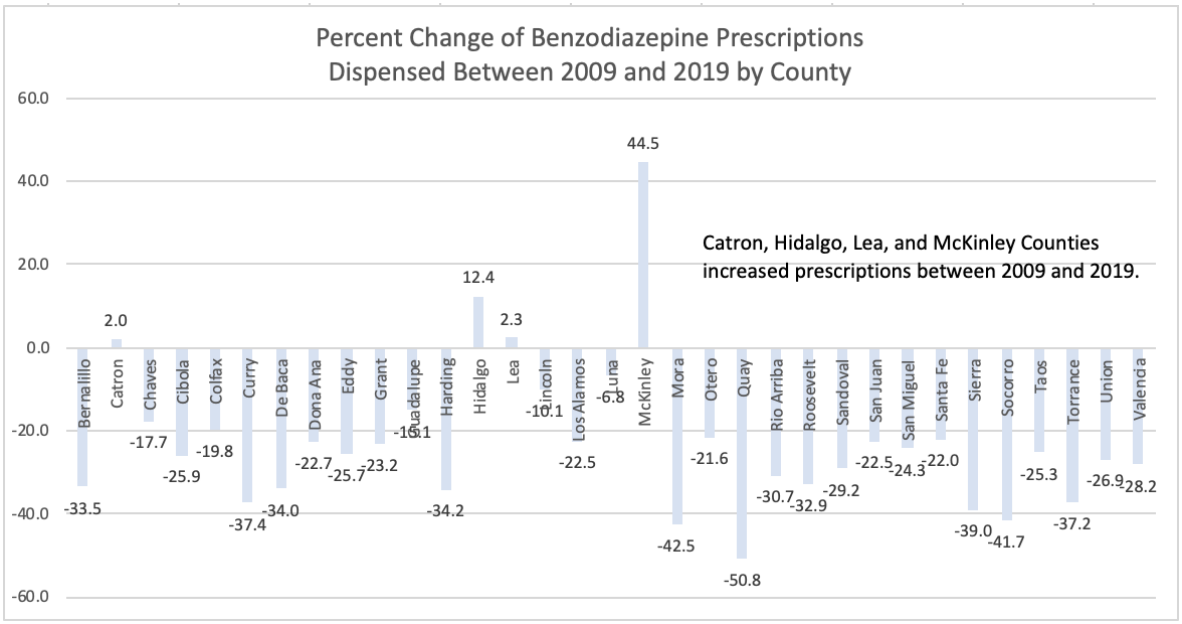

Source: StreetRx.com, retrieved on 3/4/2020, created by Coop Consulting, Inc.

*New Mexico's Prescribing Data*

New Mexico's Prescription Monitoring Program (PMP) shows a decrease of 22.5% between 2009 (197,858) and 2019 (153,408) in patients prescribed benzodiazepines. All but Lea, Mckinley, Catron, and Hildalgo counties have decreased benzodiazepine prescriptions dispensed per 1,000 patients between 2009 and 2019. The counties with the most prescriptions

dispensed per 1,000 patients in 2019 are Lincoln (558), Colfax (552), and Sierra (545). The counties with the least prescriptions per 1,000 patients in 2019 are Catron (153), McKinley (159), and Cibola (183).

Graph 2




Source: New Mexico Board of Pharmacy Prescription Monitoring Program, 2020, created by Coop Consulting, Inc.

A review conducted by the New Mexico Legislative Finance Committee reported in 2020 that 52% of prescribers are adhering to mandatory PMP reviews for routine prescriptions. [xxiv] A PMP prescriber survey conducted by the Pacific Institute of Research and Evaluation in 2019 showed that 83.7% (n=1347) of prescribers in New Mexico prescribed opioids and/or benzodiazepines and that 74.8% of those prescribers were worried or very worried about co-prescribing opioids with benzodiazepines.[xxv]

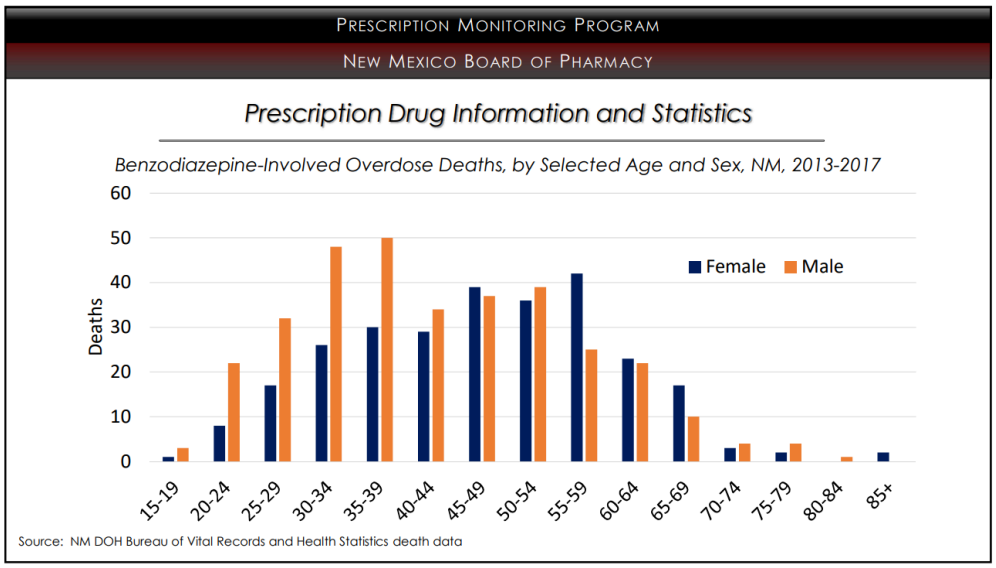
*New Mexico's Overdose and Treatment Data*

In 2018, New Mexico's Department of Health (NM DOH) reported that benzodiazepines caused or contributed to 18% of all overdose deaths in the state.[xxvi] This is a 24% decrease from 2017, when there were 129 deaths associated with benzodiazepines across the state. New Mexico's DEA diversion data is currently unavailable for analysis.

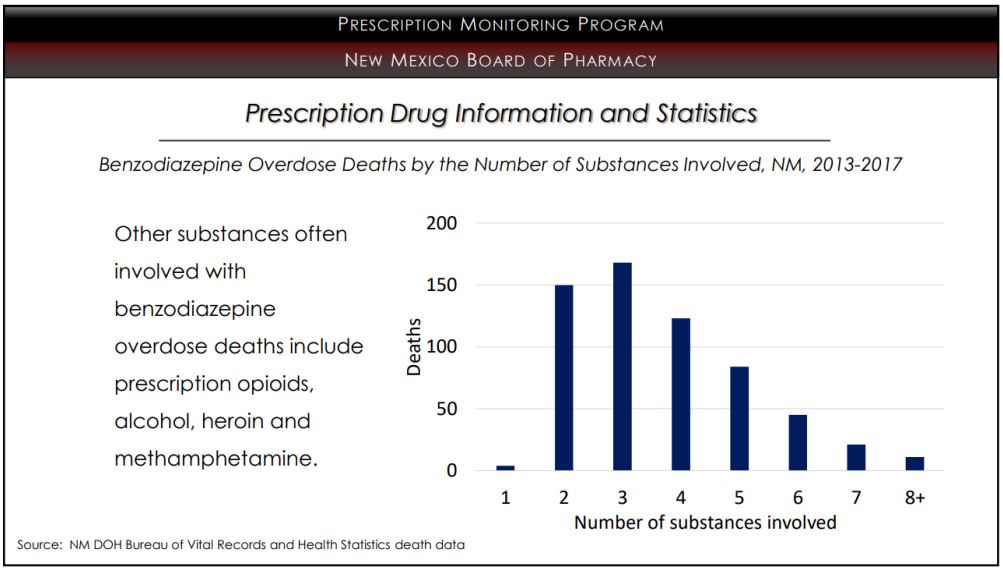
NM DOH's Bureau of Vital Records and Health Statistics death data, as presented by the NM's Board of Pharmacy PMP shows that between 2013-2017, males between 30-39 years and females between 55-59 years old experienced the most deaths from benzodiazepine-involved overdoses (see Graph 3). Additionally, the Board of Pharmacy found that most often there were

three other substances involved in benzodiazepine overdose deaths (see Graph 4). These other substances were most often prescription opioids, alcohol, heroin and methamphetamine.[xxvii]

Graph 3




Graph 4




New Mexico's Substance Use Disorder Gap Analysis of PMP data from 2018 estimates that 15,987 New Mexico residents may have a benzodiazepine use disorder. In 2018, 1,769 New Mexicans received treatment for "sedative hypnotic use disorders", which include benzodiazepines.[xxviii] Benzodiazepines are the second largest gap in treatment availability, after alcohol. Of 308 substance use disorder treatment facilities in New Mexico, 38 substance use

disorder treatment locations deny admission to patients with current benzodiazepine use. Of 31 facilities offering detox services, only 24 locations offer inpatient detox services for sedatives, including benzodiazepines.[xxix]

Prevention

There is a dearth of information on SAMHSA'S Evidence-Based Practices Resource Website regarding evidence-based prevention of benzodiazepine misuse. Considering that benzodiazepines are prescription drugs, some strategies directed to prevent opioid misuse could be transferred to benzodiazepine misuse. Not all of these strategies will translate due to the unique diagnoses associated with benzodiazepine prescribing.

A suitable frontline strategy to prevent misuse is to curb inappropriate prescribing, such as is the case with opioid prevention. The first component of the strategy would be to encourage the use a of prescription monitoring program before initiating prescriptions and continually throughout the treatment duration. This is already the standard practiced in prescribing, but surveys reveal inconsistent PMP reviews associated with benzodiazepine prescribing. High fidelity of PMP checks would reduce prescriptions to patients with problematic behaviors such as receiving prescriptions from multiple prescribers and pharmacies and requesting prescriptions before they are due. The second component of the strategy would be to use urine testing to identify patients who are not using their benzodiazepine prescriptions which is also already standard practice.

Environmental prevention strategies to mirror opioid prevention may include targeting the populations that receive the most prescriptions with an educational message regarding adverse outcomes. Furthermore, shifting the FDA's scheduling from IV to III to control the medicine more tightly may be another national strategy that could impact prescribing practices.

Finally, preventing abuse of primary substances of alcohol, opioids, and stimulants may mitigate benzodiazepine's role in polysubstance abuse. Expanding opioid use disorder treatments and closing the alcohol and benzodiazepine treatment gaps could be a successful strategy to prevent misuse.

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