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**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology Review (OSE)**
**Office of Pharmacovigilance and Epidemiology (OPE)**

# Integrated Drug Utilization, Epidemiology and Pharmacovigilance Review: Benzodiazepine Use, Misuse, Abuse, Dependence, Withdrawal, Morbidity, and Mortality

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| Drug Names: | alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam |
| Subject: | Review of benzodiazepine use, misuse, abuse, dependence, withdrawal, morbidity, and mortality |
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****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

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## GLOSSARY

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| AAPCC | American Association of Poison Control Centers |
| AE | adverse event |
| CDC | Centers for Disease Control and Prevention |
| CNS | central nervous system |
| CSA | Controlled Substance Act |
| CSS | Controlled Substance Staff |
| DEA | Drug Enforcement Administration |
| DEPI | Division of Epidemiology |
| DP | Division of Psychiatry |
| DPV | Division of Pharmacovigilance |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition |
| ED | emergency department |
| FAERS | FDA Adverse Event Reporting System |
| ICD-10 | International Classification of Diseases, Tenth Revision |
| IDV | Symphony Health Integrated Dataverse® |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCHS | National Center for Health Statistics |
| NEISS-CADES | National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance |
| NPDS | National Poison Data System |
| NPA | IQVIA National Prescription Audit™ |
| NSDUH | National Survey on Drug Use and Health |
| NSP | IQVIA National Sales Perspectives™ |
| NVSS-M | National Vital Statistics System - Mortality |
| OSE | Office of Surveillance and Epidemiology |
| PCC | poison control center |
| PLR | Physician Labeling Rule |
| PT | Preferred Term |
| PTSD | posttraumatic stress disorder |
| SAMHSA | Substance Abuse and Mental Health Services Administration |
| SMQ | Standardised MedDRA Query |
| SUD | substance use disorder |
| TEDS | Treatment Episode Data Set - Admissions |
| TPT | IQVIA Total Patient Tracker™ |

## EXECUTIVE SUMMARY

### Background

The purpose of this review is to inform potential class labeling changes for benzodiazepines (b) (5) The Division of Epidemiology II (DEPI) and the Division of Pharmacovigilance (DPV) undertook a review of available data to describe benzodiazepine use, abuse, misuse, dependence, withdrawal, and associated adverse events (AEs), including death. Specifically, the objectives of this review are to: describe the current scope, trends, and patterns of benzodiazepine prescribing, misuse, abuse, and morbidity and mortality in the U.S.; stratify outcomes by the involvement of benzodiazepines alone vs. concomitantly with opioids and other substances (e.g., alcohol, marijuana, stimulants); review published epidemiologic studies on the risks of abuse, misuse, addiction, dependence, and overdose associated with long-term use of benzodiazepines, as well as to identify potential predictors of long-term use and dependence; identify vulnerable populations and risk factors for misuse, abuse, dependence, addiction, and overdose; provide a high-level overview of all reports of benzodiazepine abuse, dependence, or withdrawal received in the FDA Adverse Event Reporting System (FAERS), including distribution by age, sex, outcome, geographic location, and frequency of AEs reported; and conduct a report-level analysis of direct reports of benzodiazepine abuse, dependence, or withdrawal retrieved from FAERS in order to describe characteristics of these cases in more detail, including specific symptoms and time to onset of dependence, as well as reported duration and specific symptoms of withdrawal.

### Data Sources and Methods

DEPI accessed proprietary drug utilization databases available to the FDA and examined data from national surveys, substance use disorder (SUD) treatment admissions, calls to U.S. poison control centers, emergency department (ED) visits, and death certificates. DEPI also searched the published literature for articles on risks of misuse, abuse, and addiction associated with benzodiazepine use, factors associated with long-term benzodiazepine use and dependence, and social factors influencing preferences for abuse of specific benzodiazepine drugs. DPV conducted a search of FAERS and described characteristics of and outcomes involved in benzodiazepine reports of drug abuse, dependence, and withdrawal.

I. Drug Utilization

Nationally estimated sales distribution and dispensed prescription data from the following proprietary databases available to the FDA were used to conduct analyses of drug utilization for benzodiazepines

- IQVIA, National Sales Perspectives™ database, 2018
- IQVIA, National Prescription Audit™ database, 2014-2018
- IQVIA, Total Patient Tracker™ database, 2014-2018
- Symphony Health, Integrated Dataverse®, 2015-2018

II. Epidemiologic data

The epidemiologic review included information on benzodiazepine use, misuse, abuse, addiction, morbidity, and mortality from the following data sources:

- National Survey on Drug Use and Health (NSDUH), 2015-2018
- Monitoring The Future (MTF), 2007-2018
- National Poison Data System (NPDS) exposure calls to Poison Control Centers (PCC), 2009-2017
- National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) Project, 2016-2017
- National Vital Statistics System, Mortality (NVSS-M), 2000-2017
- Treatment Episodes Data Set- Admissions (TEDS), 2017
- Published epidemiologic literature (literature search)

III. Spontaneous reports - FAERS

DPV searched the FAERS database for all benzodiazepines to identify postmarketing case reports through June 30, 2019 to describe characteristics of and outcomes involved in benzodiazepine reports of drug abuse, dependence, and withdrawal.

**Review Findings**

I. Use, Misuse, and Abuse of Benzodiazepines and Associated Morbidity and Mortality

Drug Utilization Data

The estimated number of benzodiazepine prescriptions and tablets dispensed from U.S. outpatient pharmacies has decreased in recent years; however, benzodiazepines remain a widely prescribed class of drugs in the U.S., with approximately (b) (4) tablets dispensed in 2018 alone. The estimated number of benzodiazepine prescriptions dispensed increased from approximately (b) (4) prescriptions in 2006 to (b) (4) prescriptions in 2013, and then decreased to (b) (4) prescriptions in 2018[1]. Solid oral formulations of benzodiazepines were predominantly dispensed to adult female patients. An estimated (b) (4)% of patients appeared to be on benzodiazepine therapy for 2 months or longer based on prescription claims data from the outpatient retail setting. From 2014 through 2018, alprazolam, diazepam, lorazepam, and clonazepam were the most frequently dispensed benzodiazepines.

Epidemiologic data

Our examination of available data suggest that benzodiazepine misuse, abuse and associated morbidity and mortality are substantial but primarily occur in the context of polysubstance use.

[1] Estimates of dispensed prescriptions were affected by a methodology change in the underlying data source to account for prescription voids and reversals, resulting in a trend break in estimates prior to 2017. Estimates for 2017 and 2018 were approximately (b) (4) due to the change in methodology.

- Annually from 2015 to 2018, approximately 5.4 million (2.0%) U.S. individuals aged 12 and older are estimated to have misused or abused benzodiazepines. The highest prevalence was in the 18-25 year-old age group, in which almost half of past-year benzodiazepine users reported misusing or abusing the drugs. The most commonly reported reasons for benzodiazepine misuse or abuse were to "relax or relieve tension" (46.3%), "help with sleep" (22.4%), "get high or [respondent] was hooked" (11.8%), "help with emotions" (10.5%), and "experiment or to see what the drug is like" (5.7%).
- Among 12th graders, estimated nonmedical use of several commonly used benzodiazepines has declined over the past decade, paralleling downward trends in use of multiple other prescription and illicit drugs in this group.
- In 2016, the nationally estimated number of ED visits due to nonmedical use of benzodiazepines (n=167,845), was higher than the corresponding estimate for prescription opioids (n=129,863), although a relatively small proportion of visits involved benzodiazepines alone—13.9% (n=23,335) compared to 31.2% (n=40,499) for visits due to prescription opioid nonmedical use.
- There was a high frequency of exposure calls to U.S. poison centers involving benzodiazepine misuse or abuse, and trends were generally consistent with prescribing trends. The annual number of exposure calls involving a benzodiazepine misuse or abuse increased from 10,156 in 2009 to 10,738 in 2011, then decreased to 8,761 in 2017. However, the observed declines in benzodiazepine exposure calls were driven by calls with minor clinical effects, whereas benzodiazepines exposure calls with more severe medical outcomes increased across the study period. Approximately 63% of benzodiazepine misuse/abuse calls in 2017 involved multiple substances—most commonly prescription opioids, alcohol, or stimulants—and medical outcomes in these cases are more severe than in cases involving benzodiazepines alone. The distribution of medical outcome severity in single-substance misuse/abuse calls was similar across the five most commonly prescribed benzodiazepines.
- Upon analysis of 15,779 single-substance benzodiazepine exposure calls reported to U.S. poison centers specifically involving abuse between 2009-2017, 15% (n=2,394) reported moderate-to-severe medical outcomes in patients with clinical effects related to the exposure. The most commonly reported related clinical effects and corresponding frequency in these exposures included drowsiness/lethargy (76%), slurred speech (24%), confusion (14.1%), tachycardia (13.3%), hypotension (13.3%), and ataxia (13.1%).

- Benzodiazepine-involved poisoning deaths increased from 1,298 in 2010 to 11,537 in 2017. The proportion of deaths due to benzodiazepines alone was small and decreased over this period, from 8.6% in 2000 to 2.7% in 2017. From 2013-2017, 55.4% of benzodiazepine-involved fatal poisonings also involved prescription opioids, but only 9.7% involved benzodiazepines and prescriptions opioids without mention of any additional substances.

- We identified no high-quality longitudinal studies assessing the risk of addiction associated with benzodiazepine use. However, in 2017, 1.2% of admissions (n=10,316) to publicly-funded substance use disorder treatment programs indicated that benzodiazepines were the primary drug of abuse, compared to 3.1% for opioid analgesics. An additional 7.3% and 9.8% of admissions indicated benzodiazepines as the secondary and tertiary drug of abuse, respectively. In one published analysis of NSDUH data from 2015-2016, an estimated 0.5 million people ages 18 and older annually reported misuse or abuse of benzodiazepines, did not report misuse or abuse of other sedatives, hypnotics, or anxiolytics, and met the criteria for Sedative, Hypnotic, or Anxiolytic Use Disorder, per the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Although these data cannot be used to estimate the risk of benzodiazepine addiction associated with use of these medications, they indicate that both primary benzodiazepine use disorders and polysubstance addiction involving benzodiazepines do occur.

FAERS Data: High-level Overview

The high-level overview of FAERS reports revealed that, after exclusion of those reports also included in NPDS to avoid duplicate counts with DEPI's NPDS analysis, almost 44,000 reports related to benzodiazepine abuse, dependence, or withdrawal were reported to FDA from the time of approval through June 30, 2019, of which approximately 24% involved a concomitant opioid. The most frequently reported PTs across the top four most frequently reported benzodiazepines (in descending order: alprazolam, diazepam, lorazepam, clonazepam) were similar and mostly related to overdose, abuse, dependence, or withdrawal. There were slight differences in distribution of PTs across the four drugs, but no major differences were noted. Sixty percent of all fatal reports involving a benzodiazepine also involved a concomitant opioid, with approximately 3% of fatal reports involving a benzodiazepine as a single drug substance. The remaining fatal reports involved a benzodiazepine along with one or more of the following, listed in decreasing order of frequency: alcohol, various antidepressants, acetaminophen, zolpidem and various antipsychotics (See **Section 3.9.1** and **Table 3.17** for additional details). The FAERS findings were congruent with the epidemiologic data, which demonstrated high levels of benzodiazepine abuse and increased severity of clinical effects when benzodiazepines abuse involved other drugs.

II. Dependence and Withdrawal

Epidemiologic Data

From 2009 to 2017, the number of calls to U.S. poison centers for benzodiazepine withdrawal increased from 263 to 372. A small number of published longitudinal studies described risk factors for long-term or high-dose benzodiazepine use or dependence. These included female sex, older age, mental health conditions, and concomitant use of certain medications (e.g., antidepressants). However, most of these studies were conducted in non-U.S. populations and had other limitations.

FAERS Data: Report-level Review

The report-level review of 104 FAERS cases of benzodiazepine as single drug substance submitted directly to FDA from patients and healthcare providers (i.e., direct reports)

mostly consisted of reports of dependence or withdrawal occurring with use of a benzodiazepine as prescribed, rather than abuse. Because we limited our search to direct reports only, there is likely a bias against identifying cases of abuse or illicit use, especially because most cases in this case series (n=82, 79%) were submitted by the patients themselves.

We identified dependence and subsequent withdrawal, in some cases with high morbidity, that developed during therapeutic use of benzodiazepines (clonazepam, alprazolam, lorazepam, diazepam, triazolam, or oxazepam). Approximately 80% of the cases in this case series described symptoms associated with withdrawal from benzodiazepines that included mainly central nervous system effects (e.g., insomnia, increased anxiety or panic attacks, memory impairment, depression), cardiovascular effects (e.g., heart rate or rhythm fluctuations), and gastrointestinal effects (e.g., abdominal pain, nausea, diarrhea). The median time to onset of dependence or tolerance was within two weeks of initiating use, ranging from one day to four years. The majority of cases reported a duration of use ranging from months to years, rather than the short-term use of no more than several weeks currently recommended in some benzodiazepine product labeling. The median duration of withdrawal symptoms for all benzodiazepines was approximately 9.5 months and ranged from two weeks to eight years. An important limitation in the assessment of these cases was the difficulty in differentiating withdrawal symptoms from potential re-emergence or continuation of symptoms for which the benzodiazepine was being used. The Drug Abuse and Dependence Section of the current Xanax product labeling also acknowledges the difficulty of distinguishing withdrawal and recurrence, especially in patients undergoing dose reduction.

Our analysis of the FAERS dependence and withdrawal cases, coupled with the findings of prevalent longer-term use and increasing numbers of poison center calls for benzodiazepine withdrawal, suggest a need for enhanced communication about these risks and the appropriate management of patients treated with benzodiazepines. Although benzodiazepine product labeling includes varying recommendations for dosing, duration of use, and tapering schedules, we noted FAERS cases from patients and prescribers who described the need for increased prescriber education about the risk of dependence and withdrawal even when the drugs are used at therapeutic doses for short periods of time, including the lowest available dosages. In addition, the series includes cases from patients and prescribers who specifically requested additional or more prominent warnings in benzodiazepine product labeling with respect to the potential for dependence and subsequent withdrawal, suggesting that additional emphasis on these serious AEs in the product labeling may be warranted. Based on the cases described in **Section 3.9.2.1**, it is possible that if the patients had been managed by the providers according to recommendations in the product labeling, the serious symptoms of dependence and subsequent withdrawal may have been lessened or avoided altogether.

**Conclusions**

In this review, we describe substantial morbidity and mortality associated with benzodiazepine use, misuse, and abuse, most often in the context of polysubstance use

that includes but is not limited to prescription opioids. We also describe potentially preventable harms from benzodiazepine dependence and withdrawal. Below, we provide considerations and recommendations for addressing these risks to improve the benefit-risk balance of this class of drugs.

**Considerations for Regulatory Action**

Findings from this review suggest that benzodiazepines confer substantial risks and public health burden, although some measures suggest a modest decline in recent years as dispensing has decreased. Some harms could potentially be mitigated by enhanced communication of risks and recommended prescribing practices. FDA has a number of regulatory and non-regulatory options worth considering to achieve this goal and optimize the benefit-risk balance for this drug class. These include changes in product labeling, public communications (e.g., drug safety communications), (b) (5)

The FDA Guidance for labeling states that a Boxed Warning may be used when there is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation [1]. A Boxed Warning to alert prescribers to the risk of abuse, misuse, addiction, dependence and withdrawal could increase awareness of risks, improve the safety of use, and improve the benefit-risk balance of benzodiazepines. The epidemiologic data reviewed in this document provide evidence of substantial morbidity and mortality associated with benzodiazepine misuse and abuse, predominantly in the setting of polysubstance use that includes, but is not limited to, opioids. The FAERS data reviewed provide some evidence that there is a lack of awareness or misconceptions among prescribers about appropriate management of patients taking benzodiazepines, including the requirement for careful patient selection and close monitoring to identify a pre-existing or emergent substance use disorder; the risks of developing dependence and subsequent withdrawal with benzodiazepine use, even at therapeutic doses for relatively short periods of time; and the need for dose tapering to prevent or lessen serious withdrawal symptoms. We identified cases where serious dependence and withdrawal symptoms may have been lessened or avoided altogether had the prescriber followed prescribing and dose reduction recommendations in the product labeling.

The review team also identified inconsistencies in current benzodiazepine product labeling. For example, some benzodiazepines are lacking language related to risk of withdrawal, while others have entire sections devoted to this risk. These inconsistencies may give the perception of a differential risk of abuse, dependence and withdrawal among the different benzodiazepines. Therefore, there is an additional need to harmonize language in all sections of the product labeling related to abuse, dependence, and withdrawal across the benzodiazepine class.

These (b) (5) tools to enhance risk communication should be considered, (b) (5)

These could include a drug safety communication (DSC) in conjunction with labeling changes, (b) (5)

(b) (5)

(b) (5)

For example, a boxed warning could cause some prescribers to substitute other, less safe medications (e.g., barbiturates) or to suddenly discontinue benzodiazepines, resulting in serious withdrawal symptoms and possibly patients turning to illicit sources of benzodiazepines, some of which may be counterfeit or adulterated with lethal synthetic opioids. (b) (5)

**Recommendations**

(b) (5)

Foremost, we recommend consideration of the following actions:

1. Harmonize the benzodiazepine class labeling by making the following additions to all benzodiazepine product labels in which they are currently lacking. (b) (5)

(b) (4), (b) (5)

(b) (4), (b) (5)

2. Consider a Boxed Warning for all benzodiazepines describing the risks of misuse and abuse, dependence, withdrawal, addiction, and overdose, and the need for gradual dose tapering. Suggested language is included as an example below, (b) (5)

(b) (4), (b) (5)

3. Issue a DSC to accompany any labeling changes

4. (b) (5)

# 1 INTRODUCTION

The Food and Drug Administration (FDA) identified the need to review postmarketing data on abuse and dependence associated with all benzodiazepines (b) (5), (b) (4)

- (b) (5)
- (b) (4)

In June 2019, the Controlled Substances Staff (CSS) consulted the Division of Epidemiology II (DEPI) and the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE) to provide current information on benzodiazepine abuse, misuse, mortality, and associated adverse events (AEs) from long-term use of benzodiazepines, including dependence and withdrawal. Specifically, CSS requested that DEPI and DPV assist in answering the following question from the Division of Psychiatry (DP):

> "Is alprazolam associated with a substantially increased risk of abuse or dependence compared to other marketed benzodiazepines? If the risk is comparable, is a class labeling action indicated? If so, please provide recommendations for class labeling language."

In their consult, CSS asked several questions of OSE to assist in answering the above question from DP. Specifically, CSS requested that OSE:

1. review abuse and dependence data of alprazolam vs. that of other benzodiazepines (See **Section 1.1**)
2. evaluate abuse potential and dependence of Xanax vs. Xanax XR(See **Section 1.1**)
3. search the FDA Adverse Event Reporting System (FAERS) using the Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) for abuse, dependence, and withdrawal, and the following specific terms: euphoria, high, mania, hypomania, derealization, depersonalization, hallucinations, paranoia, psychotic disorder, amnesia (See **Section 3.9.1**)

Subsequently, extensive discussions occurred between DEPI, DPV, DP, and CSS to refine the consult question and the scope of the OSE review, in particular to inform potential class labeling language changes. All parties agreed that DEPI and DPV would complete an OSE Integrated Review of the available data to describe benzodiazepine use, abuse, misuse, dependence, withdrawal, and associated adverse events (AEs), including death using drug utilization databases, and epidemiologic and postmarketing AE

reporting data, understanding that a recently completed DEPI review by Dr. Alex Secora et. al. [2] would assist with the comparative analysis of alprazolam and other benzodiazepines (See **Section 1.1**). It was also determined that OSE would not be able to address Question #2 above due to trivial utilization of Xanax XR relative to Xanax and the difficulty reliably distinguishing Xanax XR from immediate-release Xanax in epidemiologic databases.

## 1.1 BACKGROUND

The purpose of this review is to inform potential class labeling changes for benzodiazepines (b) (5) related to this drug class. The review objectives are:

- To describe the current scope, trends, and patterns of benzodiazepine prescribing, misuse, abuse, and morbidity and mortality in the U.S.
- To stratify outcomes by the involvement of benzodiazepines alone vs. concomitantly with opioids and other substances (e.g., alcohol, marijuana, stimulants).
- To review published epidemiologic studies on the risks of abuse, misuse, addiction, dependence, and overdose associated with long-term use of benzodiazepines, as well as to identify potential predictors of long-term use and dependence.
- To identify vulnerable populations and risk factors for misuse, abuse, dependence, addiction, and overdose.
- To provide a high-level overview of all reports of benzodiazepine abuse, dependence, or withdrawal received in FAERS, including distribution by age, sex, outcome, geographic location, and frequency of AEs reported.
- To conduct a report-level analysis of direct reports of benzodiazepine abuse, dependence, or withdrawal retrieved from FAERS in order to describe characteristics of these cases in more detail, including time to onset of dependence, duration of use, as well as reported duration and specific symptoms of withdrawal.

*Previous Review of Postmarketing Data on Benzodiazepines*

DEPI completed a review in June 2019, providing postmarketing data on the utilization and abuse of alprazolam and other commonly prescribed benzodiazepines. Specifically, DEPI accessed proprietary drug utilization databases available to the FDA, as well as data on calls to U.S. poison control centers (PCC) and emergency department (ED) visits due to pharmaceutical drug exposures. DEPI also reviewed the published literature on alprazolam abuse and associated mortality. In brief, the review concluded that the totality of epidemiologic data suggested that the public health burden from alprazolam misuse and abuse and associated morbidity and mortality was substantially greater than from other benzodiazepines. After adjusting for prescription availability (tablets dispensed), alprazolam's higher rates of abuse and related adverse outcomes persisted in some, but not other data sources. The availability of counterfeit alprazolam products further complicated direct comparisons of abuse rates across benzodiazepine drugs. Abuse and

related adverse outcomes were also widely observed with other benzodiazepines, and the review recommended a comprehensive review of abuse and related outcomes for the entire benzodiazepine class. This review also noted that more than (b)(4)% of alprazolam prescriptions dispensed were for the immediate release formulation. Therefore, analyses of abuse-related data were not stratified by immediate-release versus extended-release alprazolam products, even in the few data systems that collect data at the product level, as these comparisons would not be interpretable.

DPV conducted a search of FAERS and completed a pharmacovigilance memorandum in January 2018 in response to an observed increase in benzodiazepine AE reports submitted by patients describing prolonged symptoms after benzodiazepine withdrawal and failed attempts at discontinuation of benzodiazepines [3]. DPV found that this increase in reporting was likely due to an online call to action by the Benzodiazepine Information Coalition soliciting all patients injured by benzodiazepines to report their experiences to the FDA. However, DPV also identified several themes in the FAERS reports, including: lack of physician education/knowledge regarding benzodiazepine prescribing, lack of patient education by the physician at the time of prescribing, or a prescribed tapering schedule that did not prevent withdrawal symptoms (i.e. taper was too rapid). DPV reviewed the product labeling of benzodiazepines in conjunction with writing this memo and found that, although inconsistent across drugs, they did adequately convey the risks of abrupt discontinuation of benzodiazepines. Based on analysis of the FAERS reports and medical literature at the time of this memo, DPV did not recommend regulatory action.

### 1.2 REGULATORY HISTORY AND PHARMACOLOGY

The first U.S. approval of a benzodiazepine occurred in 1960 for chlordiazepoxide, followed by diazepam in 1963. Since then, more than a dozen other benzodiazepine molecules, in multiple formulations, have been approved for use in the U.S. All are currently classified as schedule IV drugs under the CSA (**Table 1.1**). Indications for these benzodiazepines include anxiety and panic disorder, seizure disorder, insomnia, and sedation. The exact mechanism of action for benzodiazepine is unknown but it is presumed that binding occurs at several stereospecific receptor sites within the central nervous system (CNS), specifically enhancing the activity of gamma-aminobutyric acid. CNS depression occurs with all benzodiazepines [4].

**Table 1.1: Benzodiazepine Products**

| Active Ingredient (Brand Name) | Application number | Initial U.S. Approval | Formulations | Indications |
|---|---|---|---|---|
| Alprazolam (Xanax) | 018276 | 10/16/1981 | Oral tablet, Oral liquid | Anxiety disorder |
| Chlordiazepoxide (Librium, others) | 012249 | 02/24/1960 | oral tablet oral capsule | Anxiety disorder |
| Clobazam (Onfi) | 202067 | 10/21/2011 | oral tablet oral suspension oral film | Seizure disorder (adjunct treatment of seizures associated with Lennox-Gastaut syndrome) |
| Clonazepam (Klonopin) | 017533 | 06/4/1975 | Oral tablet | Seizure and panic disorder |
| Clorazepate (Tranxene) | 017105 | 06/23/1972 | oral tablet | Anxiety disorder |
| Diazepam (Valium, others) | 013263 | 11/15/1963 | Oral tablet Oral liquid, injection, rectal | Anxiety disorder |
| Estazolam (Prosom) | 019080 | 12/26/1990 | oral tablet | Insomnia |
| Flurazepam (Dalmane) | 016721 | 04/07/1970 | oral capsule | Insomnia |
| Lorazepam (Ativan) | 017794 | 09/30/1977 | Oral tablet Oral liquid, injection | Anxiety disorder |
| Midazolam (Versed, others) | 018654 | 12/20/1985 | injectable nasal spray oral syrup | Sedation Anxiolysis Amnesia |
| Oxazepam (Serax) | 015539 | 06/04/1965 | oral capsule | Anxiety disorder |
| Quazepam (Doral) | 018708 | 12/27/1985 | oral tablet | Insomnia |
| Temazepam (Restoril) | 018163 | 02/27/1981 | Oral capsule | Insomnia |
| Triazolam (Halcion) | 017892 | 11/15/1982 | oral tablet | Insomnia |

Source: Drugs@FDA.com. Accessed: December 2019
"Others" indicate an active ingredient that has more than one brand name product.

The occurrence of benzodiazepine withdrawal symptoms is related in part to the pharmacologic properties of the drug, dose, duration of use, and abruptness of discontinuation. While increased use of benzodiazepines may result in increased risk of withdrawal, there is no known dose or duration that increases the risk or duration of

withdrawal symptoms. The time of onset of withdrawal varies relative to the half-life of the benzodiazepine in question, resulting in delayed onset for long-acting benzodiazepines and rapid onset within 24 to 48 hours of discontinuation of short-acting benzodiazepines. The duration of withdrawal may be affected by many factors, including the duration of benzodiazepine use, length of taper used at the time of discontinuation, and the pharmacokinetics of the particular drug [5].

**Table 1.2** displays the pharmacokinetic properties (time to peak effect, elimination half-life for parent drug and active metabolites, CYP3A4 interactions) for the following benzodiazepines: alprazolam, clonazepam, diazepam, lorazepam, triazolam, and oxazepam.

**Table 1.2. Comparison of Benzodiazepine Pharmacokinetics**

| Drug* | $T_{max}$, hours | Elimination half-life, hours | Active metabolite | CYP Interactions |
|---|---|---|---|---|
| **Short-acting** | | | | |
| **Alprazolam** | 1 to 2 | 11.2 (6.3 to 26.9) | Inactive | CYP3A4 |
| **Oxazepam** | 2 to 4 | 8.2 (5.7 to 10.9) | Inactive | No |
| **Triazolam** | 0.7 to 2 | 1.5 to 5.5 | Inactive | Yes |
| **Intermediate-acting** | | | | |
| **Lorazepam** | 2 to 4 | 12† to 18‡ | Active; lorazepam glucoronide | No (Hepatic metabolism via conjugation) |
| **Long-acting** | | | | |
| **Clonazepam** | 1 to 4 | 30 to 40 | Inactive | Limited CYP3A4 |
| **Diazepam** | 0.5 to 1 | Up to 48†; Up to 100‡ | Active; N-demethyldiazepam | Limited CYP3A4; 2C19 |

*Information based on oral, immediate-release formulations.
† Elimination half-life for parent compound.
‡ Elimination half-life for active metabolite.
$T_{max}$ = time to peak concentration or peak effect

## 1.3 PRODUCT LABELING

While all benzodiazepine product labels contain some language related to abuse, misuse, dependence, and withdrawal, the product labeling is not consistent across the class. In addition, the product labeling does not yet follow the Physician Labeling Rule (PLR) format, with the exception of Doral (quazepam), Halcion (triazolam), and Onfi (clobazam). (b) (4)

**Table 1.3** below provides a comparison of the labeling statuses and location in the product labeling for abuse, misuse, dependence, and withdrawal for benzodiazepines, noting the inconsistencies across the class [4] [6] .

| Table 1.3. Comparison of Benzodiazepine Product Labeling of Abuse, Misuse, Dependence, and Withdrawal | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Product Info** | | **WARNINGS** | | | | **PRECAUTIONS** | | **Other Sections** | | | | |
| **Drug** | **RLD or RS Product (A)NDA (Applicant)** | **General‡** | **Physical and Psychological Dependence** | **Dependence and Withdrawal Reactions, Including Seizures** | **Withdrawal Symptoms** | **Information for Patients** | **General** | **DRUG ABUSE AND DEPENDENCE** | **AR** | **Post-introduction reports or 6.2 PME** | **D&A** | **MG (Y/N)** |
| **Alprazolam*** | Xanax N018276 (Pharmacia and Upjohn) | | | X (Additional section on Interdose Symptoms and Risk of Dose Reduction) | | X (Additional section on Advice for Panic Disorder) | | X | X | hypomania, mania | X | Y |
| **Alprazolam XR** | Xanax XR N021434 (Pharmacia and Upjohn) | | | X | X | X | X | X | | hypomania, mania | X | Y |
| **Chlordiazepoxide** | Librium A085475 (RS Valeant) | X | | | | X | | X | | | | Y |
| **Clobazam (PLR format)†** | Onfi N202067 (RS Lundbeck) | | X (5.6) | | X (5.4) | | | X | | | X | Y |
| **Clonazepam*** | Klonopin N017533 (Genentech) | | X | | X | X | X (focus on seizure risk) | X | | | | Y |
| **Diazepam*** | Valium N013263 (Roche) | | | | | X | | X | | | | Y |
| **Estazolam** | Prosom A074921 (RS Mayne Pharma LLC) | X | | | | | | X | | | | Y |

| Table 1.3. Comparison of Benzodiazepine Product Labeling of Abuse, Misuse, Dependence, and Withdrawal | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Product Info** | | **WARNINGS** | | | | **PRECAUTIONS** | | **Other Sections** | | | | |
| **Drug** | **RLD or RS Product (A)NDA (Applicant)** | **General‡** | **Physical and Psychological Dependence** | **Dependence and Withdrawal Reactions, Including Seizures** | **Withdrawal Symptoms** | **Information for Patients** | **General** | **DRUG ABUSE AND DEPENDENCE** | **AR** | **Post-introduction reports or 6.2 PME** | **D&A** | **MG (Y/N)** |
| **Lorazepam*** | Ativan N17794 (Bausch) | X | X | | | X | | | | | | Y |
| **Oxazepam** | Oxazepam A072253 (RS Actavis) | | X | | | X | | | | | | Y |
| **Quazepam (PLR format)†** | Doral N018708 (Galt Pharms) | X (W/P) | | | X (5.3) | | | X (9) | | | | Y |
| **Temazepam** | Restoril N018163 (SPECGX LLC) | X | | | | | | X | | | | Y |
| **Triazolam (PLR format)†** | Halcion N017892 (Pharmacia and Upjohn) | | | X (5.8 Tolerance/ Withdrawal Phenomena) | | | | X (9) | | | | Y |

*Top 4 reported benzodiazepines in FAERS as of June 30, 2019
† In the PLR format, benzodiazepine withdrawal syndrome is in W/P
‡ "X" in the General column denotes there is no specifically named section for abuse, misuse, dependence or withdrawal in the Warnings section, but there is some mention of these events in an unstructured manner in that same section
Note: Midazolam excluded because not for outpatient use
AR = Adverse Reactions; D&A = Dosage and Administration; MG = Medication Guide; PLR = Physician's Labeling Rule; PME = Postmarketing Experience; RLD = Reference label drug; RS = Reference standard; W/P = Warnings and Precautions

The most prominent warning in the product labeling for all benzodiazepines is a Boxed Warning for the risks of using benzodiazepines with opioids that may result in profound sedation, respiratory depression, coma, and death. As summarized in **Table 1.3,** there is variable language describing risks of dependence and withdrawal signs and symptoms in the Warnings Section of all benzodiazepines, except for diazepam, estazolam, and temazepam, which contain such language in the Drug Abuse and Dependence Section only. Lorazepam and oxazepam are the only two benzodiazepines that do not have a Drug Abuse and Dependence Section in their respective product labeling.

We note that the Drug Abuse and Dependence Section of the Xanax product labeling warns of the risk of withdrawal in patients taking high doses and with longer duration of treatment, as well as those who received "brief therapy with Xanax at doses within the recommended range for the treatment of anxiety." While the labeling identifies risk factors for psychological dependence including patients with history of alcohol or drug abuse, or "addiction-prone individuals" who should be under careful surveillance when receiving Xanax, it also recommends that "all patients on XANAX who require a dosage reduction be gradually tapered under close supervision," not only those with the aforementioned risk factors.

The Dosage and Administration Section of the Xanax product labeling includes detailed instructions on how to initiate and discontinue alprazolam. It also includes a warning to avoid abrupt discontinuation of treatment due to the danger of withdrawal. It further recommends that "dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage" for all patients.

See below for additional language related to recommended dosage and administration, dose reduction, and warnings for abuse, misuse, dependence, and withdrawal in the labeling for Xanax as an example [7]. As noted above, this language is not consistent across all benzodiazepine product labels.

**Selected Sections from the Xanax Product Labeling**

**WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS**

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[*see *Warnings, Drug Interactions]*.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

**WARNINGS**

**Risks from Concomitant Use with Opioids**

Concomitant use of benzodiazepines, including XANAX, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks,

reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe XANAX concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of XANAX than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking XANAX, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when XANAX is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined [see Drug Interactions].

**Dependence and Withdrawal Reactions, Including Seizures**

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to XANAX. These include a spectrum of withdrawal symptoms; the most important is seizure (see DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at the doses recommended for the treatment of transient anxiety and anxiety disorder (ie, 0.75 to 4.0 mg per day), there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of XANAX greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

*The importance of dose and the risks of XANAX as a treatment for panic disorder:* Because the management of panic disorder often requires the use of average daily doses of XANAX above 4 mg, the risk of dependence among panic disorder patients may be higher than that among those treated for less severe anxiety. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder showed a high rate of rebound and withdrawal symptoms in patients treated with XANAX compared to placebo-treated patients.

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

**Interdose Symptoms**

Early morning anxiety and emergence of anxiety symptoms between doses of XANAX have been reported in patients with panic disorder taking prescribed maintenance doses of XANAX. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound or withdrawal symptoms over the entire course of the interdosing interval. In these situations, it is recommended that the same total daily dose be given divided as more frequent administrations (see DOSAGE AND ADMINISTRATION).

**Risk of Dose Reduction**

Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also inadvertent reduction of dose (eg, the patient forgets, the patient is admitted to a hospital). Therefore, the dosage of XANAX should be reduced or discontinued gradually (see DOSAGE AND ADMINISTRATION).

**PRECAUTION**

**Information for Patients**

*For all users of XANAX:*

To assure safe and effective use of benzodiazepines, all patients prescribed XANAX should be provided with the following guidance.

1. Advise both patients and caregivers about the risks of potentially fatal respiratory depression and sedation when XANAX is used with opioids and not to use such drugs concomitantly unless supervised by a health care provider.
2. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined [see Drug Interactions].
3. Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.
4. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
5. Inform your physician if you are nursing.
6. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
7. Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.
8. Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.

*Additional advice for panic disorder patients:*

The use of XANAX at doses greater than 4 mg/day, often necessary to treat panic disorder, is accompanied by risks that you need to carefully consider. When used at doses greater than 4 mg/day, which may or may not be required for your treatment, XANAX

has the potential to cause severe emotional and physical dependence in some patients and these patients may find it exceedingly difficult to terminate treatment. In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 7 to 29% of patients treated with XANAX did not completely taper off therapy. In a controlled postmarketing discontinuation study of panic disorder patients, the patients treated with doses of XANAX greater than 4 mg/day had more difficulty tapering to zero dose than patients treated with less than 4 mg/day. In all cases, it is important that your physician help you discontinue this medication in a careful and safe manner to avoid overly extended use of XANAX.

In addition, the extended use at doses greater than 4 mg/day appears to increase the incidence and severity of withdrawal reactions when XANAX is discontinued. These are generally minor but seizure can occur, especially if you reduce the dose too rapidly or discontinue the medication abruptly. Seizure can be life-threatening.

**ADVERSE REACTIONS**

To discontinue treatment in patients taking XANAX, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAX be decreased by no more than 0.5 mg every three days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

**DRUG ABUSE AND DEPENDENCE**

**Physical and Psychological Dependence**

Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following discontinuance of benzodiazepines, including XANAX. The symptoms can range from mild dysphoria and insomnia to a major syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. Distinguishing between withdrawal emergent signs and symptoms and the recurrence of illness is often difficult in patients undergoing dose reduction. The long term strategy for treatment of these phenomena will vary with their cause and the therapeutic goal. When

necessary, immediate management of withdrawal symptoms requires re-institution of treatment at doses of XANAX sufficient to suppress symptoms. There have been reports of failure of other benzodiazepines to fully suppress these withdrawal symptoms. These failures have been attributed to incomplete cross-tolerance but may also reflect the use of an inadequate dosing regimen of the substituted benzodiazepine or the effects of concomitant medications.

While it is difficult to distinguish withdrawal and recurrence for certain patients, the time course and the nature of the symptoms may be helpful. A withdrawal syndrome typically includes the occurrence of new symptoms, tends to appear toward the end of taper or shortly after discontinuation, and will decrease with time. In recurring panic disorder, symptoms similar to those observed before treatment may recur either early or late, and they will persist.

While the severity and incidence of withdrawal phenomena appear to be related to dose and duration of treatment, withdrawal symptoms, including seizures, have been reported after only brief therapy with XANAX at doses within the recommended range for the treatment of anxiety (eg, 0.75 to 4 mg/day). Signs and symptoms of withdrawal are often more prominent after rapid decrease of dosage or abrupt discontinuance. The risk of withdrawal seizures may be increased at doses above 4 mg/day (see WARNINGS). Patients, especially individuals with a history of seizures or epilepsy, should not be abruptly discontinued from any CNS depressant agent, including XANAX. It is recommended that all patients on XANAX who require a dosage reduction be gradually tapered under close supervision (see WARNINGS and DOSAGE AND ADMINISTRATION).

Psychological dependence is a risk with all benzodiazepines, including XANAX. The risk of psychological dependence may also be increased at doses greater than 4 mg/day and with longer term use, and this risk is further increased in patients with a history of alcohol or drug abuse. Some patients have experienced considerable difficulty in tapering and discontinuing from XANAX, especially those receiving higher doses for extended periods. Addiction-prone individuals should be under careful surveillance when receiving XANAX. As with all anxiolytics, repeat prescriptions should be limited to those who are under medical supervision.

## DOSAGE AND ADMINISTRATION

The lowest possible effective dose should be employed and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment.

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction.

Dose Titration

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an

acceptable therapeutic response (ie, a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained.

Dose Reduction

Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided (see WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE).

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.

In any case, reduction of dose must be undertaken under close supervision and must be gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be reinstituted and, only after stabilization, should a less rapid schedule of discontinuation be attempted. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every 3 days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

# 2 REVIEW METHODS AND MATERIALS

## 2.1 OVERVIEW AND FRAMEWORK

In this integrated review, pharmacovigilance data and epidemiologic data were complementary for understanding the risks from benzodiazepine misuse, abuse, and dependence. Furthermore, drug utilization data provided context. We examined several data sources to describe the utilization, abuse, misuse, and related adverse outcomes, associated with benzodiazepines. These data sources collect information from various populations: the general population, people filling prescriptions in the outpatient retail setting, people seeking medical treatment for adverse effects of non-medical use, and individuals entering or being assessed for substance use disorder (SUD) treatment. We present major features of each data source in **Table 2.1**. We provide a more detailed description of each data source and our analytic approach in the sections below. Unless otherwise indicated, we used standard regulatory definitions of misuse and abuse. [8]

> Misuse: Intentional use, for therapeutic purposes, of a drug in a way other than prescribed or by an individual for whom it was not prescribed
> Abuse: the intentional, non-therapeutic use of a drug product or substance, even once, for its desirable psychological or physiological effects

**Table 2.1 Overview of data sources to assess the current landscape of benzodiazepines misuse, abuse, dependence, and withdrawal.**

| Characteristic assessed | Population and data sources used | Use of data source(s) |
|---|---|---|
| Drug Utilization | The IQVIA, National Sales Perspectives™ (NSP) database, 2018 | Estimated number of benzodiazepine units from manufacturers to all U.S. channels of distribution |
| | The IQVIA, National Prescription Audit™ (NPA) database, 2014-2018 | Estimated number of prescriptions and tablets dispensed from outpatient retail/mail order pharmacies |
| | The IQVIA, Total Patient Tracker™ (TPT) database, 2014-2018 | Estimated number of unique patients, stratified by molecule, and age groups who received prescriptions dispensed from outpatient retail pharmacies |
| | The Symphony Health Integrated Dataverse (IDV), 2015-2018 | Determined utilization patterns by duration of use estimated from dispensed prescription claims data from retail pharmacies |
| Scale and relative frequency of benzodiazepine misuse, abuse, dependence, and withdrawal | General population<br>National Survey on Drug Use and Health (NSDUH), 2015-2018 | Estimated number of individuals in the general U.S. population reporting misuse or abuse of benzodiazepines |
| | Secondary school students<br>Monitoring The Future (MTF), 2007-2018 | Estimated number of students in U.S. secondary schools reporting misuse or abuse of benzodiazepines |
| Routes of abuse for benzodiazepines | Calls for advice after misuse/abuse<br>National Poison Data System (NPDS) exposure calls to Poison Control Center (PCC), 2009-2017 | Routes of abuse for single-substance exposure calls |
| Morbidity and mortality associated with benzodiazepine misuse, abuse, | People seeking care for adverse effects of pharmaceutical exposures<br>National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES), 2016-2017 | Assess outcomes such as need for healthcare intervention associated with benzodiazepine misuse and abuse |

| Characteristic assessed | Population and data sources used | Use of data source(s) |
|---|---|---|
| dependence, and withdrawal | Calls for medical assistance after pharmaceutical exposures<br>NPDS exposure calls to PCCs, 2009-2017: benzodiazepines | Quantify calls involving benzodiazepine misuse or abuse<br>Assess severity of medical outcomes for drug exposures from calls to PCCs by specific benzodiazepines |
| Mortality associated with benzodiazepine use | Drug overdose deaths<br>National Vital Statistics System, Mortality (NVSS-M), 2000-2017 | Assessed deaths involving benzodiazepines, by decedent characteristics and co-involved drug substances |
| | General population, prescribers, and patients<br>FAERS, All reports through June 30, 2019 | Described characteristics of and outcomes involved in benzodiazepine reports of drug abuse, dependence, and withdrawal |
| Occurrence of Sedative, Hypnotic, or Anxiolytic Use Disorder related to benzodiazepine use | People entering treatment for substance use disorder (SUD)<br>Treatment Episode Data Set (TEDS), 2017 | Proportion of admissions for treatment for SUD in which patients endorse benzodiazepines as primary, secondary, and tertiary drugs of abuse |
| | General population<br>National Survey on Drug Use and Health (NSDUH), 2015-2016 (published analysis of NSDUH [9]) | Estimated number of individuals in the general U.S. population who reported misuse or abuse of benzodiazepines, did not report misuse or abuse of other sedatives, hypnotics, or anxiolytics, and met the criteria for Sedative, Hypnotic, or Anxiolytic Use Disorder, per Diagnostic and Statistical Manual of Mental Disorders, 4th Edition |
| Longitudinal risk and risk factors for benzodiazepine misuse, abuse, addiction, dependence, and long-term use | PubMed, Embase and Web of Science databases, 2000-2009 | Conducted literature search for<br>• Longitudinal studies of the risk of misuse, abuse, addiction, and dependence from benzodiazepine use<br>• Studies of factors associated with benzodiazepine dependence or long-term use;<br>• Studies of social factors affecting preferences and patterns of abuse and misuse of specific benzodiazepine products |

## 2.2 DRUG UTILIZATION ANALYSES

Proprietary drug utilization databases available to the Agency were used to conduct these analyses; see **Appendix A.2** for detailed descriptions and limitations of the databases. The focus of this analysis is on oral formulations of benzodiazepines, unless otherwise noted. Also, different analyses had differing age groups or time frames studied based on factors such as database capabilities and limitations.

To determine the various settings of care where benzodiazepines are distributed, the IQVIA, National Sales Perspectives™ (NSP) database was used to obtain the estimated number of benzodiazepine units (e.g., number of tablets, milliliters of liquid) sold from manufacturers to U.S. retail and non-retail channels of distribution in 2018. The sales distribution data do not necessarily reflect what is being directly sold or administered to patients; rather, these data provide an estimate of units sold from the manufacturers into various channels of distribution.

The IQVIA, National Prescription Audit™ (NPA) database was used to obtain the nationally estimated number of prescriptions and tablets dispensed from U.S. outpatient retail/mail order pharmacies for oral benzodiazepines from January 2014 through December 2018, annually. In addition, the NPA Extended Insights (NPA EI) and New to Brand (NPA NTB) databases was used to estimate the number of prescriptions and tablets dispensed stratified by age groups (0-9,10-19,20-39,40-64,65+), formulation, and gender.

The IQVIA, Total Patient Tracker™ (TPT) database was used to obtain the estimated number of unique patients, stratified by molecule, and age groups (0-11,12-17,18-25,26-39,40-64,65+) who received a dispensed prescription for oral benzodiazepines from U.S. outpatient retail pharmacies, from 2014 through 2018, annually.

The Symphony Health Integrated Dataverse® (IDV) was used to determine U.S. estimates of utilization patterns by duration of use for top benzodiazepines, stratified by age groups (0-11,12-17,18-25,26-39,40-64,65+), annually from 2015 through 2018. Duration was calculated using the days' supply values for prescription dispensings, typically entered by dispensing pharmacy staff. Episodes of therapy were created using an allowable gap of 50% of the previous dispensing's days' supply to link to a subsequent dispensing. For example, a dispensing for a 30-day supply was allowed an extra 15 days from the dispensing end date to link to the next dispensing.

## 2.3 THE NATIONAL SURVEY ON DRUG USE AND HEALTH

NSDUH is an annual survey funded by the Substance Abuse and Mental Health Services Administration (SAMHSA) designed to provide nationally representative estimates of illicit and prescription drug misuse/abuse in the general U.S. population: non-institutionalized residents of the U.S. who are aged 12 years and above. Population subgroups not covered by the survey include individuals residing within institutional facilities (e.g., jails, nursing homes), as well as those without a permanent address (e.g., homeless individuals). The survey is conducted in a face-to-face manner, and during the year 2018, the interview final response rate was 66.5% for a total of 67,791 completed interviews [10].

Since 2015, NSDUH has elicited information on any use of benzodiazepines, as well as misuse/abuse, in the past year. NSDUH defines *misuse* of a drug as the following: "use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told." Since NSDUH's definition of misuse includes intentional, non-therapeutic use of a drug to obtain a desired psychological or physiological effect (i.e., abuse), this review labels it *misuse or abuse*. NSDUH defines "any use of benzodiazepines" as any use of benzodiazepines for any reason, either use of one's own prescription benzodiazepine as directed by a physician, or misuse or abuse.

We extracted available data from reports and detailed tables from the 2016-2018 NSDUH posted publicly on the SAMHSA website [11]. We reported national estimates in terms of numbers of individuals, percent of the total population, and percent of past-year any-users. To give some context to the estimates of misuse or abuse of benzodiazepines, we also extracted the corresponding estimates for misuse or abuse of prescription pain relievers and prescription stimulants, respectively. Also, we abstracted statistics on the primary reason for benzodiazepine misuse or abuse and on the prevalence of past-year benzodiazepine use disorder[2], from a peer-reviewed publication of an analysis of 2015-2016 NSDUH data [9], written by personnel from the National Institute of Drug Abuse and SAMHSA.

### 2.4 MONITORING THE FUTURE

Supported by the National Institute on Drug Abuse (NIDA) and conducted by the University of Michigan, MTF is a nationally representative, annual cross-sectional survey of adolescent, college, and adult high school students and graduates, intended to monitor emerging substance abuse problems and understand the effectiveness of policy and intervention efforts designed to address the. The survey captures self-reported information on drug use behaviors among students in the 8$^{th}$, 10$^{th}$, and 12$^{th}$ grades, and has been conducted continuously since 1975. This school-based survey asks about use of a wide variety of substances, including alcohol, tobacco, and other over-the-counter, prescription, and illicit drugs. Specifically, the survey asks about nonmedical use of several stimulants and other prescription drugs, that is, use "not under a doctor's orders."

Results reported in this review are from the 2018 report [12]. Trends in specific tranquilizers and sedatives are determined by branching questions in the 12$^{th}$ grade questionnaire. Questions about the use of specific drugs are not asked of 8$^{th}$ and 10$^{th}$ graders. Twelfth grade respondents are asked to report use of a general type of drug such as sedative or tranquilizer in the last 12 months. For those indicating the use of a general type of drug, they are given follow-up questions, including "what tranquilizer have you taken during the last year without a doctor's orders? (Mark all that apply.)" Because endorsing a benzodiazepine in response to this question may indicate misuse or abuse, as FDA defines them, this review labels it *misuse or abuse.*

[2] The study classified participants as meeting criteria for benzodiazepine use disorder if they reported misuse or abuse of benzodiazepines, did not report misuse or abuse of other sedatives, hypnotics, or anxiolytics, and met the criteria for Sedative, Hypnotic, or Anxiolytic Use Disorder, per DSM-IV.

We report results from 2007-2018, however, as seldom-used drugs were dropped and more commonly used drugs were added, not all years are available for all drugs. It is also important to note that the survey structure requires the individual to indicate that they misused or abused a sedative or tranquilizer before they are provided the option of the individual benzodiazepines; some individuals may not be aware that the benzodiazepine they misused or abused is contained under these general classes. Additionally, we are unable to report overall benzodiazepine misuse and abuse since this question is not asked and because the selected benzodiazepines in this survey are included among other non-benzodiazepines within larger classes of drugs.

## 2.5 AMERICAN ASSOCIATION OF POISON CONTROL CENTERS, NATIONAL POISON DATA SYSTEM

**Data Source**

NPDS is a database managed by the American Association of Poison Control Centers (AAPCC), and derived from a nationwide network of PCCs that receive calls from individuals, healthcare professionals, and other interested persons in the general U.S. popoulation regarding exposures to prescription drugs and other substances. [13] PCC healthcare professionals systematically follow up on reported exposures to document their medical outcome. Quality control measures are used to ensure data accuracy and completeness. Note that exposures do not necessarily represent a poisoning or overdose, as the AAPCC does not completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs. [13]

In 2017, there were over 2.6 million calls to PCCs, the majority of which (2.1 million) were human exposure calls. Of these human exposure calls, 60% were for individuals under the age of 20. Almost 19% were for intentional exposures, and the remainder for other reasons (e.g., adverse reaction, withdrawal).

**Data Analysis**

We searched NPDS for closed cases of human exposure to benzodiazepines, 2009-2017, by using the AAPCC generic code for *benzodiazepines* and excluding cases that had medical outcome classified as "confirmed non-exposure." We identified the generic code for benzodiazepines using MicroMedex® Solutions and the 2019 AAPCC Pharmaceutical and Non-Pharmaceutical Generic Code List – February 2019 version (**See Appendix B Table B1).** At the time of extraction, AAPCC had completed its standard processes for outcome adjudication and quality control for all these data and had locked the data to ensure reliability.

Using these data, we conducted further analysis on selected cases from 2013-2017 with reported exposure to one of five, commonly prescribed benzodiazepine molecules: alprazolam, clonazepam, diazepam, lorazepam, and temazepam. We used MicroMedex® product codes to identify these cases. (Product codes are included in **Appendix B Table B2**.)

Search parameters used for benzodiazepines and selected benzodiazepine molecules are summarized in **Table 2.2.**

| Table 2.2. NPDS Search parameters- benzodiazepines | |
|---|---|
| Report name | Case Log (Generic Code) |
| Month/year of query | 8/2019 |
| Date range for query (benzodiazepines) | 1/1/2009- 12/31/2017 |
| Date range for query (selected benzodiazepines: alprazolam, clonazepam, diazepam, lorazepam, and temazepam) | 1/1/2013- 12/31/2017 |
| Call type | Exposure |
| Case status | Closed |
| Species | Human |
| Minimum Age | 0 (years) |

Analysis of NPDS consisted of three components:

1. Trends in exposure calls, 2009-2017

Data were stratified by reason of exposure (intentional: abuse, misuse, suicide, unknown; unintentional: adverse reaction, withdrawal, unknown; and other) and severity of related medical outcomes (minor effect, moderate effect, major effect, and death). A sub-analysis was conducted for abuse/misuse calls to examine the number of calls, stratified by single and multiple-substance.

2. Reason for exposure by age group

Data were aggregated for the nine-year period and stratified by age group (0-5, 6-12, 13-19, 20-39, 40-64, 65 and older, and unknown).

3. Cases of abuse and misuse

We analyzed data from calls involving exposure to benzodiazepines that had been classified as either of two, mutually exclusive AAPCC categories for reason for exposure: “intentional abuse” or “intentional misuse.” We evaluated the calls using categories defined by AAPCC (variable definitions are included in **Appendix B Table B3**).

a. Co-exposures: prescription opioids, heroin/illicit fentanyl analogue, alcohol, marijuana, and stimulants (both prescription and illicit)
b. Route of abuse/misuse: oral, nasal/inhalation, injection, other, and unknown. In the NPDS data, multiple routes can be reported for a single substance. For these cases, we counted each route mentioned by the caller separately. As a result, the totals for each individual route may exceed the total number of exposures for that product. Also, route of administration cannot be mapped to a specific drug in multiple-substance exposures.
c. Severity of medical outcomes for cases with related clinical effects:
    i. All abuse/misuse cases

ii. By selected benzodiazepine molecule (alprazolam, clonazepam, diazepam, lorazepam, and temazepam)

d. Frequency of related clinical effects reported in exposures with moderate to severe medical outcomes (moderate effect, major effect, death/death, indirect report)

Analyses were performed independently by two analysts to optimize accuracy of results, with any discrepancy resolved by detailed review of processes.

## 2.6 National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance

**Data Source**

Cases and national estimates of the number of ED visits for drug-related AEs were based on data from the NEISS-CADES project, a national stratified probability sample of approximately 60 hospitals with a minimum of 6 beds and a 24-hour ED in the U.S. and its territories. The NEISS-CADES project, which has been described in detail elsewhere, is a joint effort of the Centers for Disease Control and Prevention (CDC), the U.S. Consumer Product Safety Commission, and the FDA. [14] [15] [16] [17]

In brief, trained data abstractors located at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed drug related AEs attributed to medications used for any reason. Abstractors record up to four medications implicated in each AE and systematically document clinical features of the incident, including intent of drug use, clinical diagnoses and clinical manifestations. Clinical manifestations are coded based on MedDRA(MedDRA, version 9.1). Cases of AEs involving non-therapeutic medication use (e.g., non-medical use and self-harm) were collected systematically starting in 2016.

**Definition**

*Nonmedical use* includes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and overdoses without indication of intent. [18] [19] (**Table 2.3**). Of note, NEISS-CADES excludes cases involving inadequate therapy, drug withdrawal, detoxification treatment, harms from ED treatment, and deaths.

**Table 2.3. Definition of nonmedical use** [18] [19]

| Category | NEISS-CADES Definition |
|---|---|
| Abuse | Clinician diagnosis of abuse (for current ED visits) or documented recreational use (e.g., "to get high") |
| Therapeutic misuse | Documented therapeutic intent, but the pharmaceutical was not as directed (e.g., taking someone else's prescription medication for pain, intentionally taking larger doses than prescribed or recommended) |
| Overdoses without indication of intent | Cases of overdose without indication of intent have insufficient documentation to categorize the case as |

| Category | NEISS-CADES Definition |
|---|---|
| | abuse, therapeutic, or self-harm (e.g., patients found unresponsive by paramedics and patients unable or unwilling to provide description of circumstances or intent). |

**Search Strategy and Analysis**

We abstracted information on ED visits that involved nonmedical use of benzodiazepines, 2016-2017, including concurrent exposures, clinical manifestations, and rate of ED visits by age group, from a peer-reviewed publication of NEISS-CADES data written by Center for Disease Control and Prevention (CDC) personnel. [20] To put the benzodiazepine data into context, we also abstracted the respective numbers of ED visits involving benzodiazepines, prescription opioids, prescription stimulants, and muscle relaxants in 2016, from an earlier study by the same group of investigators. [18] Note that the study using 2016 NEISS-CADES [18] did not exclude additional cases in which benzodiazepines were identified by a positive laboratory test.

## 2.7 TREATMENT EPISODE DATA SET - ADMISSIONS

Treatment Episode Data Set-Admissions (TEDS) is a national data set comprising publicly-funded admissions to substance abuse treatment programs, plus data from some admissions that were privately funded. SAMHSA compiles TEDS from mandated data reporting by substance abuse treatment facilities to state agencies. Also, some states collect data on privately-funded admissions from facilities that receive public funding. Using the TEDS 2017 annual report [21], we extracted data on the number of substance abuse treatment episodes in which the patient endorsed benzodiazepines as the primary, secondary, or tertiary drug of abuse. To provide context, we also extracted these numbers for opioid analgesics, and for the most frequently-reported primary drugs of abuse.

## 2.8 NATIONAL VITAL STATISTICS SYSTEM-MORTALITY

NVSS-M are death certificate data available as both public use and restricted use data files. Data are currently available for 2017 and previous years. Public use data are accessible though the CDC WONDER online database [22] and through the National Center for Health Statistics (NCHS) website [23]. For this review, we used the publicly accessible databases available through the NCHS website and limited the data to U.S. residents. For calculating rates, we used the population-level denominators files also provided through the NCHS website [24].

For this review, we focused on drug-induced cause of death, i.e., drug poisoning (overdose) deaths. Each death certificate contained a single underlying cause of death, up to twenty multiple causes, and demographic data. The underlying cause of death indicated the injury intent (e.g., accident, suicide, undetermined) and whether the cause was drug-induced. Consistent with previous literature [25], drug overdose deaths were identified using *International Classification of Diseases, Tenth Revision* (ICD-10) underlying cause-of-death codes X40–X44 (drug poisonings (overdose) unintentional), X60–X64 (drug poisonings (overdose) suicide), X85 (drug poisonings (overdose) homicide), and Y10–Y14 (drug poisonings (overdose) undetermined intent) (**Table 2.4**).

Specific multiple-cause-of-death codes identified the drug categories involved in overdose deaths. Benzodiazepines were uniquely identified by the ICD-10 code T42.4. Other drugs involved were identified through multiple-cause-of-death ICD-10 codes T36.0 to T50.9. Of note, the ICD-10 codes, T36.0 to T50.9, do not include alcohol. We stratified drug overdose deaths by alcohol involvement, which was defined using the ICD-10 code T51.0 ("ethanol"), a sub-category of T51 ("toxic effect of alcohol"). Prescription opioids were defined using the conservative definition proposed by Seth, et al. [26] (ICD-10: T40.2 to T40.3). Synthetic opioids were defined using the ICD-10 code T40.4. Heroin was defined using the ICD-10 code T40.1. Stimulants were defined using the ICD-10 code T43.6 ("psychostimulants with abuse potential").

**Table 2.4. Underlying Cause of Death and Multiple Cause of Death ICD-10 codes**

| Category | ICD-10 code |
|---|---|
| **Underlying Cause of Death** | |
| Drug Poisoning (overdose) [a] | |
| Unintentional | X40-X44 |
| Intentional/ suicide | X60-X64 |
| Homicide | X85 |
| Undetermined | Y10-Y14 |
| **Multiple Cause of Death** | |
| Poisoning by drugs, medicaments and biological substances [b] | T36.0 to T50.9 |
| Benzodiazepine | T42.4 |
| Prescription opioids [c] | T40.2 to T40.3 |
| Other opioids | T40.2 |
| Methadone | T40.3 |
| Synthetic opioids | T40.4 |
| Heroin | T40.1 |
| Stimulants (psychostimulants with abuse potential) | T43.6 |
| Alcohol (ethanol) | T51.0 |

Source: CDC WONDER. Multiple Cause of Death (Detailed Mortality) www.wonder.cdc.gov [22]
[a] Underlying cause of death, drug poisonings [25]
[b] Does not include alcohol (ICD-10: T51.0)
[c] Conservative definition according to Seth et al (2018) [26]

## 2.9 LITERATURE REVIEW

We conducted two literature searches for this review.

We focused the first literature search on identifying longitudinal studies evaluating the risk of misuse, abuse, dependence, and addiction as outcomes of long-term benzodiazepine use and studies examining predictors of long-term benzodiazepine use or benzodiazepine dependence. We created search strings individualized for the PubMed, Embase and Web of Science databases and conducted these database searches on July 26, 2019 and July 30, 2019. Search strings for each database are included in **Appendix E Table E1**. Briefly, search strings selected articles with *benzodiazepine* or a specific

benzodiazepine molecule in the title; abuse, misuse or dependence related terminology; and epidemiologic study designs, especially longitudinal cohorts or studies involving follow-up time. The search string excluded articles with terminology indicating clinical, laboratory or animal study designs. We selected articles for a full-text screen by first reading titles and abstracts. Based on the full-text screen, we included articles in the review if they described the risk of misuse, abuse and addiction from long-term benzodiazepine use and risk factors for benzodiazepine dependence and long-term benzodiazepine use. Studies reporting on risks of concomitant use of benzodiazepines with prescription opioids were not considered within the scope of this review since this had been previously described [27]. We also excluded articles reporting on studies conducted prior to 2000 and conference abstracts.

We identified 1,688 articles from searching PubMed, Embase, and Web of Science. After removing duplicate articles, 1,152 articles remained for title screening. We then screened these articles based on information in the title and abstract and 182 articles remained for full text screening. Finally, 6 articles met our inclusion criteria and were included in this review **(Appendix F Table F1)**. The most common reasons why we excluded articles based on the full-text screen were cohorts which included patients using Z-drug, opioids, or other drugs in addition to benzodiazepines and lack of an assessment of abuse, dependence, or long-term use outcome.

For the second literature search, we identified studies describing social factors associated with preferences and patterns of abuse and misuse of benzodiazepines, focusing on specific benzodiazepine products. This search was conducted on November 13, 2019. For this search, we searched PubMed, Embase and Web of Science. The search string selected articles with *benzodiazepine* or a specific benzodiazepine molecule in the title, quantitative and qualitative epidemiologic studies, terminology for abuse and misuse, and terminology for social influence and behaviors. As with the first literature search, we excluded articles with terminology indicating clinical, laboratory or animal study designs, and we excluded conference abstracts. Search strings for this literature search are included in **Appendix E Table E2.**

We identified 129 records from PubMed, Embase, and Web of Science for the second literature search. After deleting duplicates, 107 articles remained for title and abstract screening. The majority, 105 articles, were excluded during the title and abstract screening. The two remaining articles both included qualitative data analysis of youth and young adults **(Appendix F Table F2)**.

## 2.10 FDA ADVERSE EVENT REPORTING SYSTEM

### 2.10.1 Definitions

In addition to the standard regulatory definitions of misuse and abuse in **Section 2.1**, we provide additional definitions and examples of drug abuse, misuse, dependence, and withdrawal for use in the FAERS portion of this review.

**Table 2.5** provides definitions for drug abuse, misuse, dependence, and withdrawal. **Table 2.6** provides examples of clinical manifestations associated with abuse, misuse, and withdrawal of sedatives or anxiolytics, such as benzodiazepines.

| **Table 2.5. Definitions and Examples of Drug Abuse, Misuse, Dependence, Tolerance, and Withdrawal in FDA Guidances** [28] | | |
|---|---|---|
| | **Definition** | **Examples** |
| **Drug abuse** | Intentional, nontherapeutic use of a drug product or substance even once, to achieve a desired psychological or physiological effect | • Additional doses to achieve euphoria<br>• Administration via an unapproved route |
| **Drug misuse** | Intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse | • Additional dose of pain medication to alleviate pain<br>• Additional dose of weight loss medication to achieve greater or faster weight loss<br>• Taking a sleeping pill for insomnia from a friend |
| **Drug dependence** | Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. | • Caffeine<br>• Clonidine<br>• Amphetamines |
| | Psychological dependence is a state in which individuals have impaired control over drug use based on the rewarding properties of the drug (ability to produce positive sensations that increase the likelihood of drug use) or the psychological distress produced in the absence of the drug. | • Opioids |
| **Tolerance** | Tolerance is a state that develops as a result of physiological adaptation characterized by a reduced response to a specific dose of drug after repeated administration of the drug (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). | • Opioids<br>• Clonidine |
| **Withdrawal** | Withdrawal is defined as a characteristic withdrawal syndrome for that drug occurring in response to 1) abrupt discontinuation or a significant dose reduction of that drug or 2) administration of an antagonist or taking the drug itself to alleviate withdrawal symptoms. | • Opioids<br>• Beta-blockers |

| **Table 2.6. Examples of the Clinical Manifestations Associated with Drug Abuse, Misuse, and Withdrawal** [29] | | |
|---|---|---|
| **Drug Class** | **Drug Abuse or Misuse** | **Withdrawal** |
| **Sedatives/Anxiolytics (i.e., benzodiazepines)** | Slurred speech, incoordination, unsteady gait, nystagmus, impaired cognition, mood changes, impaired judgement, impaired memory, stupor, or coma | Anxiety, insomnia, autonomic hyperactivity (e.g., sweating, pulse rate greater than 100 beats per minute) hand tremor, transient visual, tactile, or auditory hallucinations or illusions, psychomotor agitation, nausea/vomiting, grand mal seizures |

### 2.10.2 FAERS Search Strategy

DPV conducted two searches of FAERS to retrieve reports of benzodiazepine abuse, dependence, or withdrawal. We used the search strategy in **Table 2.7** to provide a high-level overview of trends in reporting over all time; a report-level analysis was not completed on the results of this search.

| **Table 2.7. FAERS Search Strategy – High-Level Overview*** | |
|---|---|
| Date of Search | July 1, 2019 |
| Time Period of Search | All reports through June 30, 2019 |
| Search Type | Drug Safety Analytics Dashboard Quick Search |
| Product Terms | Product active ingredient: alprazolam; bromazepam; brotizolam; clobazam, chlordiazepam; chlordiazepoxide; chloridazepoxide hydrochloride; clonazepam; clotiazepam; cloxazolam; delorazepam; diazepam; estazolam; flubromazepam; flubromazolam; flutazolam; loprazolam; loprazolam mesilate; lorazepam; lormetazepam; medazepam; midazolam hydrochloride; midazolam maleate; nitrazepam; nitrazolam; nordazepam; oxazepam; phenazepam; quazepam; temazepam; tetrazepam; triazolam |
| MedDRA Search Terms (Version 22.0) | *Drug abuse dependence and withdrawal* (SMQ) Broad search[†] |
| *See Appendix G1 for a description of the FAERS database.<br>[†] See Appendix G2 for a list of the preferred terms (PTs) in *Drug abuse dependence and withdrawal* (SMQ) Broad search<br>MedDRA=Medical Dictionary for Regulatory Activities; SMQ=Standardised MedDRA Query | |

We used the search strategy in **Table 2.8** to target a subset of FAERS reports to characterize cases of abuse, dependence, or withdrawal. During DPV's routine pharmacovigilance activities, we noted that direct reports provide significant detail with respect to dependence and withdrawal; therefore, we limited the search strategy in **Table 2.8** to direct reports only, i.e., those submitted to the FDA directly from consumers and healthcare professionals**.** We further limited these search results to only reports with a benzodiazepine as a single drug substance to prevent confounding by concomitant medications.

| **Table 2.8. FAERS Search Strategy – Benzodiazepine as Single Drug Substance Report-Level Analysis*** | |
|---|---|
| Date of Search | July 1, 2019 |
| Time Period of Search | All reports through June 30, 2019 |
| Search Type | Drug Safety Analytics Dashboard Quick Search |
| Product Terms | Product active ingredient: alprazolam; bromazepam; brotizolam; clobazam, chlordiazepam; chlordiazepoxide; chloridazepoxide hydrochloride; clonazepam; clotiazepam; cloxazolam; delorazepam; diazepam; estazolam; flubromazepam; flubromazolam; flutazolam; loprazolam; loprazolam mesilate; lorazepam; lormetazepam; medazepam; midazolam hydrochloride; midazolam maleate; nitrazepam; nitrazolam; nordazepam; oxazepam; phenazepam; quazepam; temazepam; tetrazepam; triazolam |
| MedDRA Search Terms (Version 22.0) | *Drug abuse dependence and withdrawal* (SMQ) Narrow search[†] |
| Case Type | Direct |
| Other Limitation | A benzodiazepine is the only coded product for the report or mentioned in the narrative (i.e., single drug substance) |

* See Appendix G1 for a description of the FAERS database.
[†] See Appendix G2 for a list of the preferred terms (PTs) in *Drug abuse dependence and withdrawal* (SMQ) Narrow search
MedDRA=Medical Dictionary for Regulatory Activities; SMQ=Standardised MedDRA Query

### 2.10.3 Case Definition for Report-Level Analysis of Benzodiazepine as Single Drug Substance [28]

We used the following inclusion and exclusion criteria to assess the FAERS reports retrieved with the search criteria described in **Table 2.8**.

*Inclusion criteria:*
Cases that report one or more of the following criteria:

- The term(s) "drug abuse," "drug misuse," "drug dependence," "drug tolerance," or "drug withdrawal" was stated in the narrative with or without clinical manifestations associated with drug abuse, misuse, dependence, tolerance, or withdrawal of the drug of interest (see **Table 2.6** in **Section 2.10.1** for examples specific to sedatives/anxiolytics, e.g. benzodiazepines).

  OR

- Clinical assessment by the reviewer of drug abuse or misuse based on the provided case details (e.g., reported unapproved route of use, drug intake without a prescription, intentionally taking higher than prescribed doses, self-treatment of

withdrawal symptoms with another agent, pathological or toxicological screening, clinical diagnosis of substance use disorder by a health care provider).

*Exclusion criteria:*

Reports will be excluded from further analysis for the following reasons:

- Reports that do not provide enough clinical information to assess the presence of drug abuse, misuse, dependence, or withdrawal
- Reports describing intentional overdose
- Reports describing a problem with a generic product as reason for symptoms
- Reports describing AEs not related to abuse, misuse, dependence, or withdrawal, or those cases with no AE described
- Reports describing more than one suspect medications
- Illegible and duplicate reports

# 3 REVIEW RESULTS

## 3.1 DRUG UTILIZATION ANALYSES

### 3.1.1 Benzodiazepine Sales Distribution Data

The IQVIA, National Sales Perspectives™ (NSP) database was used to determine the various settings of care where benzodiazepines were distributed by the manufacturers. Sales data in 2018 showed that approximately (b)(4)% of benzodiazepine units (e.g. tablets, milliliters) were sold to U.S. outpatient retail settings, (b)(4)% to non-retail pharmacies, and (b)(4)% to mail-order/specialty pharmacies.[3] For the following analyses, only outpatient retail and mail order pharmacy utilization patterns were examined unless otherwise noted.

### 3.1.2 Benzodiazepine Dispensed Prescription Data

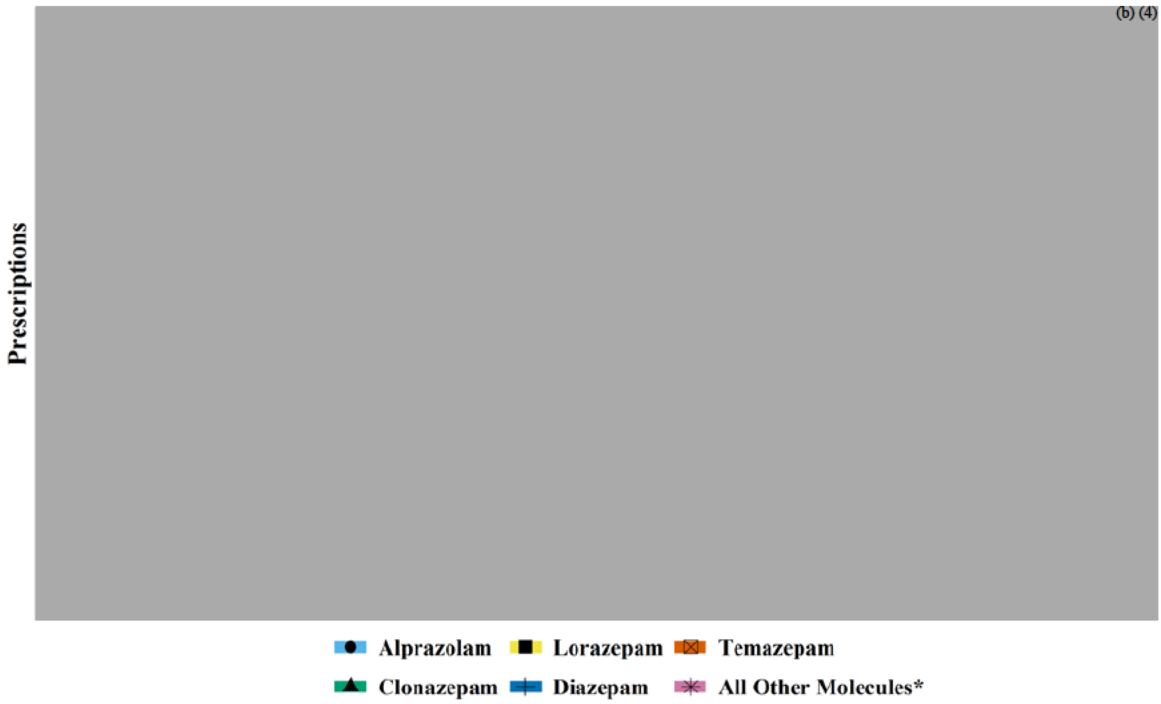
**Figure 3.1 below and Table A.1 in Appendix A.1** provide the estimated number of oral benzodiazepine prescriptions dispensed from U.S. outpatient retail and mail-order pharmacies, stratified by molecule, from 2006 through 2018, annually. Overall, the estimated number of benzodiazepine prescriptions dispensed increased from approximately (b)(4) prescriptions dispensed in 2006 to a peak of (b)(4) in 2013 and then decreased to (b)(4) in 2018.[4] In 2018 approximately (b)(4)% of prescriptions were dispensed for alprazolam, (b)(4)% for clonazepam, (b)(4)% for lorazepam, (b)(4)% for diazepam, (b)(4)% for temazepam, and (b)(4)% for all other benzodiazepine molecules.

[3] Source: IQVIA. National Sales Perspective™ (NSP). January 2018 – December 2018. Data Extracted October 2019. File: 2019-800 NSP benzo current.csv

[4] Estimates of dispensed prescriptions were affected by a methodology change in the underlying data source to account for prescription voids and reversals, resulting in a trend break between estimates prior to 2017. Estimates for 2017 and 2018 were (b)(4) approximately (b)(4) due to the change in methodology.

**Figure 3.1**

**Estimated number of oral benzodiazepine prescriptions dispensed from U.S. retail/mail order pharmacies, 2006 – 2018****




Source: IQVIA, National Prescription Audit™ (NPA). January 2006 – December 2018. Data Extracted October 2019.Files: 2019-800 NPA benzo current.csv; 2019-800 benzo static 2006-2011.csv; 2019-800 benzo static 2012-2015.csv

*All Other Molecules include: chlordiazepoxide, clobazam, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam

****There was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided and/or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017, data prior to January 2017 have not been adjusted to the new methodology, therefore, the dotted line represents a trend break and any changes over time must be interpreted in the context of the changes in methodology. Overall, estimates using this new methodology were approximately (b) (4) compared with estimates using legacy estimation methodology. Changes in the projection methodology do not affect prescription volumes dispensed from the mail-order/specialty pharmacies.**

**Figure 3.2 below and Table A.2 in Appendix A.1** provide the estimated number of oral benzodiazepine units (tablets) dispensed from U.S. outpatient retail and mail-order pharmacies, stratified by molecule, from 2006 through 2018, annually. Overall, the estimated number of benzodiazepine units dispensed appeared to increase from approximately (b) (4) units in 2006 to a peak of approximately (b) (4) units in 2013 before a decrease to (b) (4) units in 2018. Over the examined time period approximately (b) (4)% of units dispensed were for alprazolam, (b) (4)% for clonazepam, (b) (4)% for diazepam, (b) (4)% for diazepam, (b) (4)% for temazepam, and (b) (4)% for all other benzodiazepine molecules.

**Figure 3.2**

**Estimated number of units (tablets) for oral benzodiazepines dispensed from U.S. outpatient/mail order pharmacies, 2006 – 2018****


Source: IQVIA, National Prescription Audit™ (NPA). January 2006 – December 2018. Data Extracted October 2019.Files: 2019-800 NPA benzo current.csv; 2019-800 benzo static 2006-2011.csv; 2019-800 benzo static 2012-2015.csv

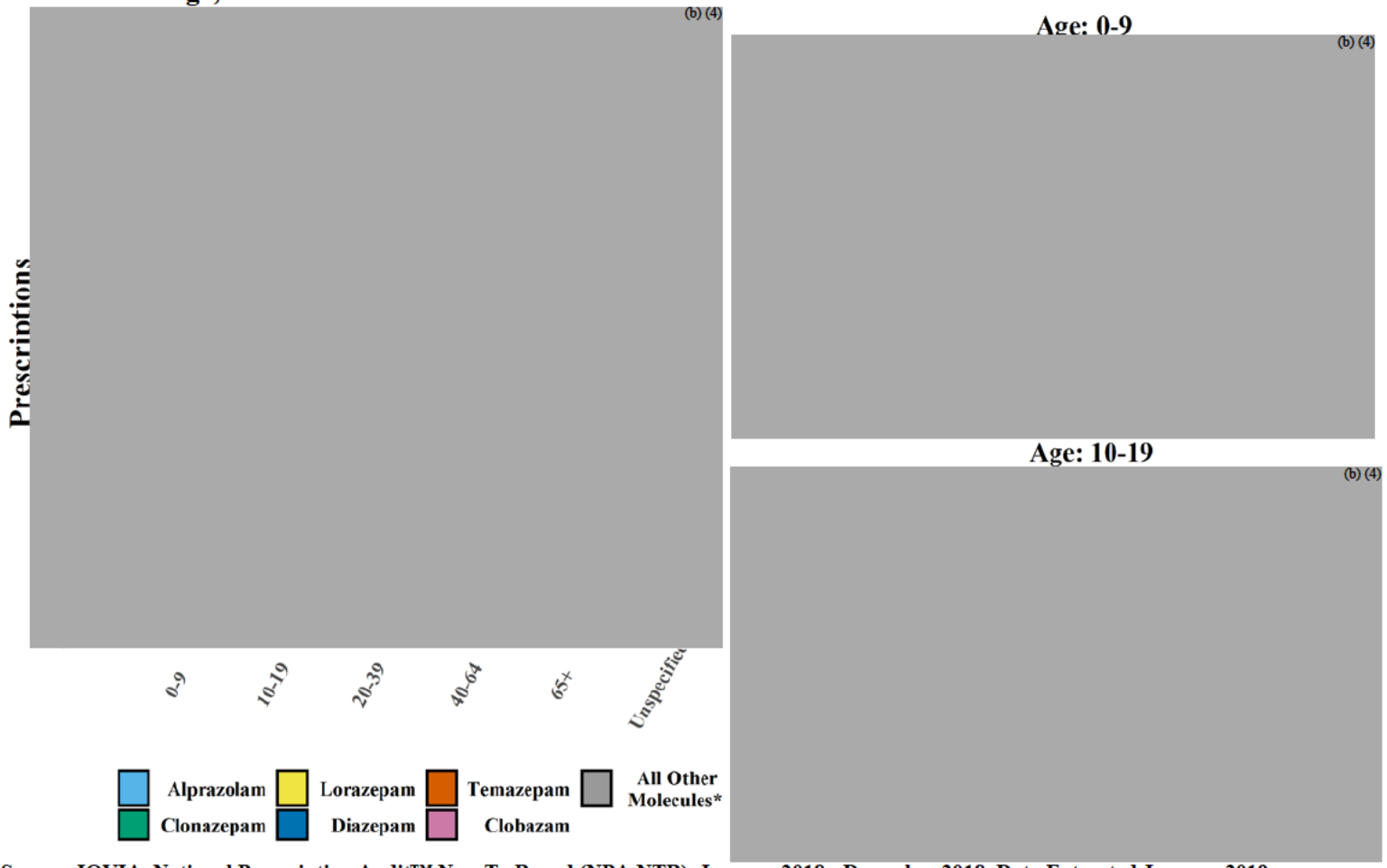
*All Other Molecules include: chlordiazepoxide, clobazam, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam

****There was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided and/or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017, data prior to January 2017 have not been adjusted to the new methodology, therefore, the dotted line represents a trend break and any changes over time must be interpreted in the context of the changes in methodology. Overall, estimates using this new methodology were approximately (b) (4) compared with estimates using legacy estimation methodology. Changes in the projection methodology do not affect prescription volumes dispensed from the mail-order/specialty pharmacies.**

**Figure 3.3 below and Table A.3 in Appendix A.1** provide the estimated number of benzodiazepine prescriptions dispensed from U.S. outpatient retail/mail order pharmacies in 2018, stratified by molecule, age and formulation. Of note, alprazolam, clonazepam, and lorazepam were the most frequently dispensed benzodiazepines in the adult population. The most frequently dispensed benzodiazepine differed between pediatric age groups. Approximately (b) (4)% of clobazam prescriptions dispensed to patients 0-9 years old were for liquid formulations of clobazam.

**Figure 3.3**

**Estimated number of oral benzodiazepine prescriptions dispensed from outpatient retail/mail order pharmacies, stratified by molecule and age, 2018**



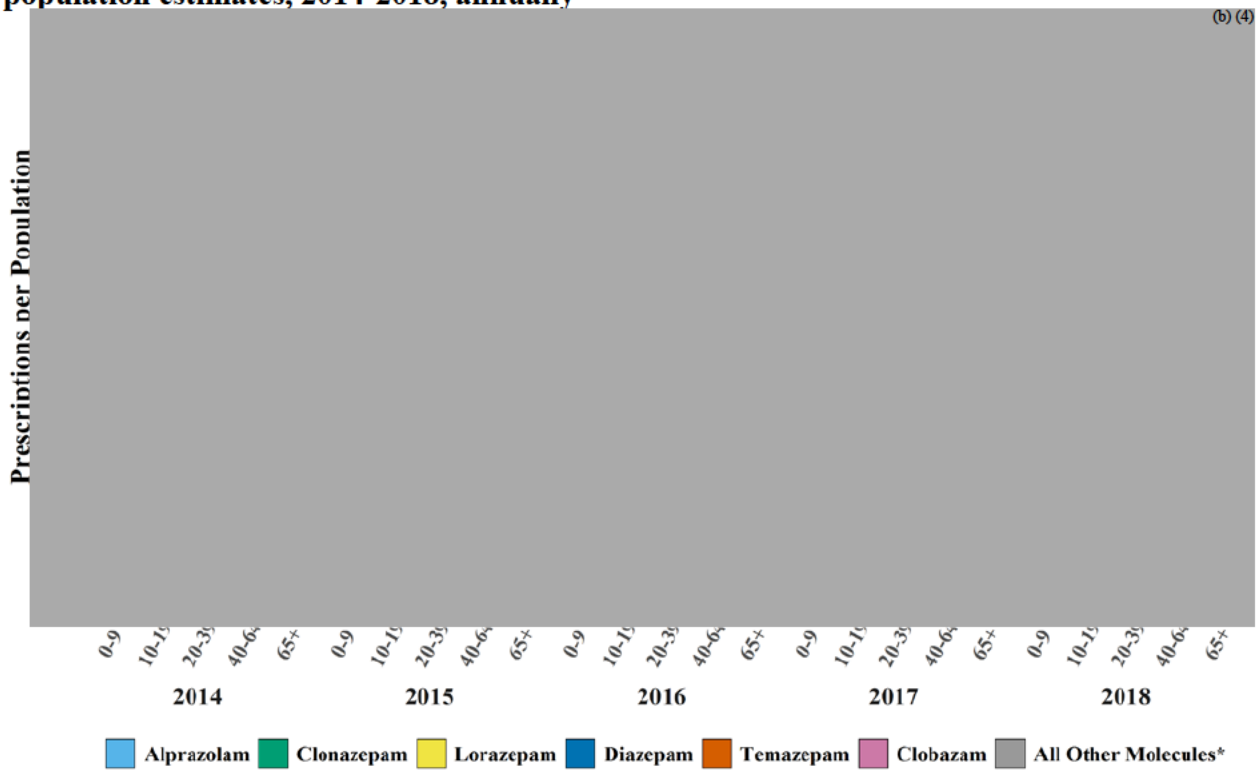

**Source: IQVIA, National Prescription Audit™ New To Brand (NPA NTB). January 2018 - December 2018. Data Extracted January 2019.**
**File: 2019-800 Benzo PI TRx 1-27-2019.csv**
***All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam**

**Table A.4 in Appendix A.1** provides the estimated number of benzodiazepine prescriptions dispensed from U.S. outpatient pharmacies, stratified by molecule and gender in 2018. Of note, approximately (b) (4) of the prescriptions dispensed to adult patients aged ≥ 20 were female.

**Figures 3.4 and 3.5 and Table A.5 in Appendix A.1** provide estimates of the number of prescriptions dispensed from U.S retail and mail order pharmacies stratified by molecule and age and standardized by U.S. Census population estimates from 2014 through 2018 annually. Of note, the number of prescriptions dispensed per individual in the pediatric population was at least an order of magnitude lower than in the adult population consistently over the examined time period.

**Figure 3.4**

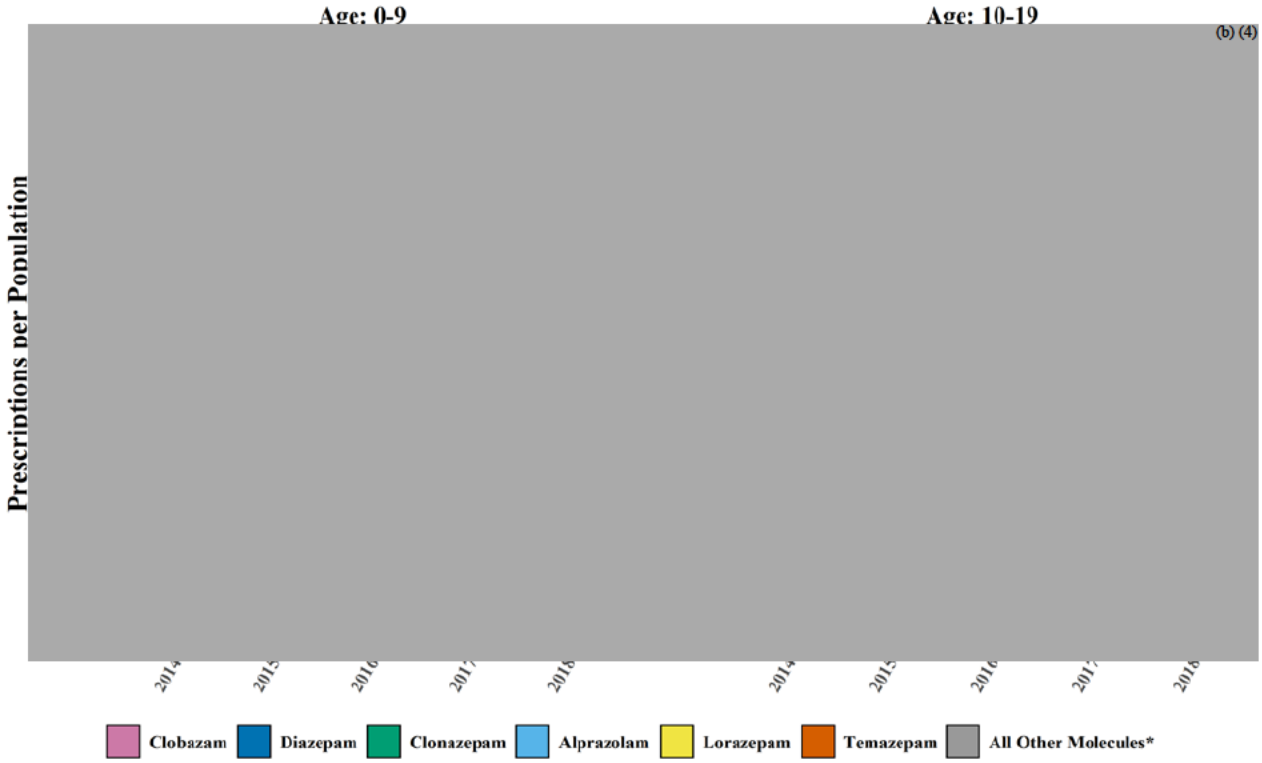
**Estimated number of benzodiazepine prescriptions dispensed from outpatient retail/mail order pharmacies, stratified by molecule and age group, and standardized by U.S. Census population estimates, 2014-2018, annually**




**Source: IQVIA, National Prescription Audit™ New To Brand (NPA NTB). January 2014 - December 2018. Data Extracted December 2019.File: 2019-800 Benzo PI TRx 1-27-2019.csv. NVSS Census Files. (2019). U.S. Census Populations With Bridged Race Categories. Retrieved from https://www.cdc.gov/nchs/nvss/bridged_race.htm. *All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam**

**Figure 3.5**

**Estimated number of benzodiazepine prescriptions dispensed from outpatient retail and mail order pharmacies, stratified by molecule and standardized by U.S. Census population estimates, 2014-2018 annually, pediatric age groups (0-9, 10-19)**

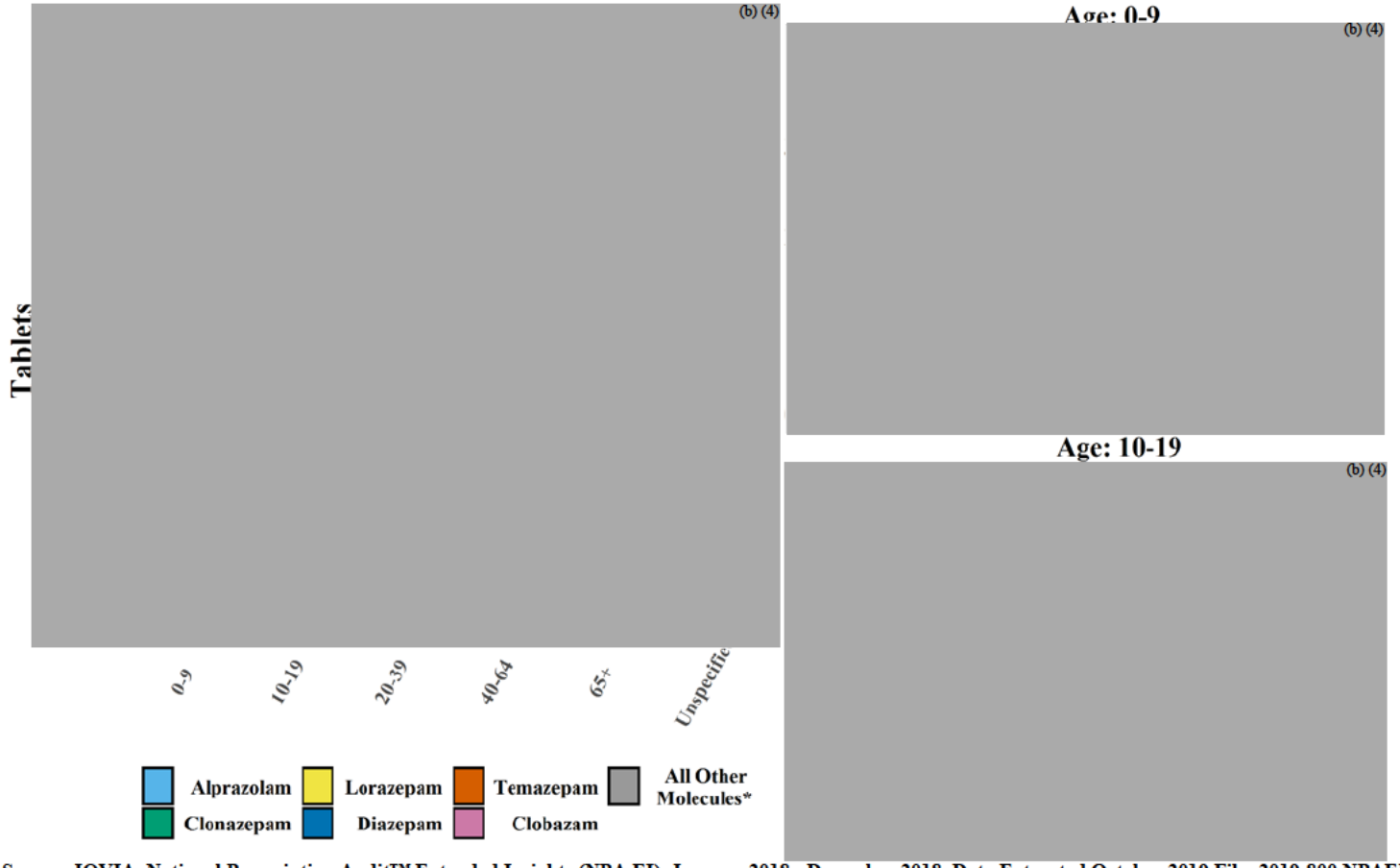



**Source: IQVIA, New To Brand (NTB). January 2014 - December 2018. Data Extracted December 2019.Files: 2019-800 Benzo PI TRx 1-27-2019.csv. NVSS Census Files. (2019). U.S. Census Populations With Bridged Race Categories. Retrieved from https://www.cdc.gov/nchs/nvss/bridged_race htm. *All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam**

**Figure 3.6 below and Table A.6 in Appendix A.1** provide the estimated number of benzodiazepine oral tablets dispensed from U.S. outpatient pharmacies in 2018, stratified by age. Of all dispensed benzodiazepine tablets, alprazolam was the most frequently dispensed benzodiazepine in adult age groups, and clonazepam was the most frequently dispensed in patients 0-19 years old.

**Figure 3.6**

**Estimated number of oral benzodiazepine *tablets* dispensed from outpatient pharmacies, stratified by molecule and age, 2018**




**Source: IQVIA, National Prescription Audit™ Extended Insights (NPA EI). January 2018 - December 2018. Data Extracted October 2019.File: 2019-800 NPAEI Benzo 1-30-2019.csv**
***All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam**

**Table A.7 in Appendix A.1** provides estimates of prescriptions dispensed stratified by molecule, age and formulation between 2014 and 2018 annually. Of note, the total number of oral liquid clobazam prescriptions in patients aged 0-9 years was substantially higher than in the adult population.

**Table A.8 in Appendix A.1** provides the estimated number of unique patients dispensed one of the top 6 oral benzodiazepine prescription from outpatient retail pharmacies, stratified by molecule and age from 2014 through 2018, annually. Of note, the pediatric population (ages ≤17 year old) comprised less than (b) (4)% of patients dispensed benzodiazepines each year over the examined time period.

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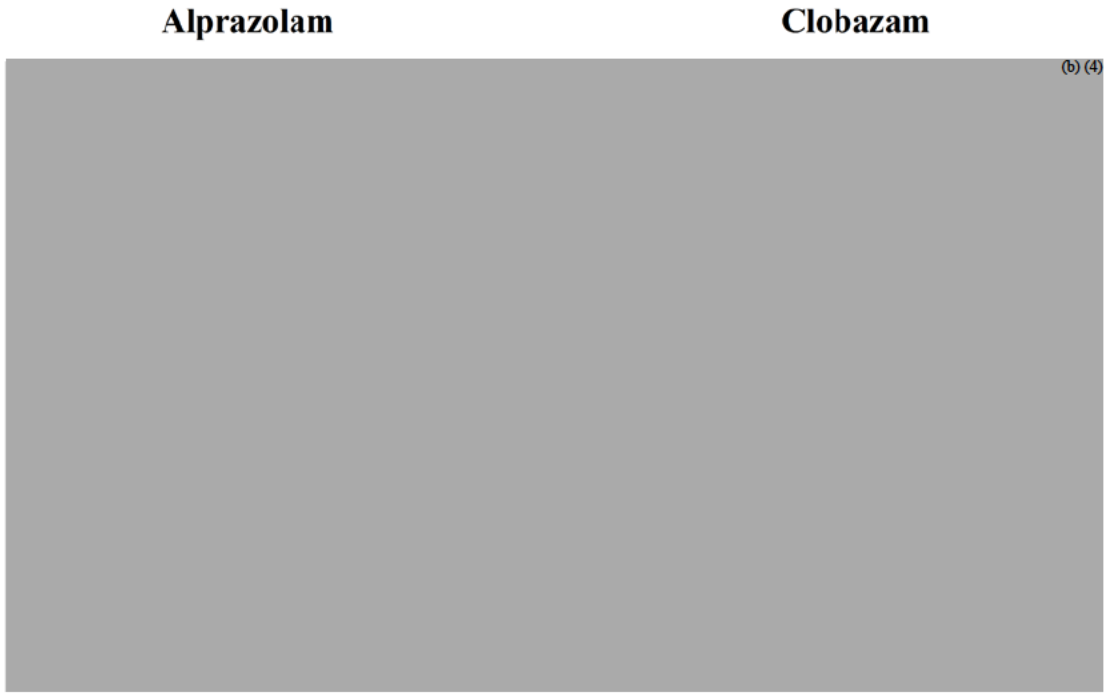
**Figure 3.7 below and Table A.9 in Appendix A1** provide the estimated number of benzodiazepine prescriptions dispensed from U.S. outpatient pharmacies in 2018, stratified by prescriber specialty**. As shown in fig 3.7 the prescriber specialty varied based on specific benzodiazepine. General practitioners prescribed the majority of alprazolam prescriptions in 2018 while neurologists prescribed the majority of clobazam prescriptions.

**Figure 3.7**

Estimated number of alprazolam and clobazam prescriptions dispensed from outpatient pharmacies, stratified by molecule and specialty, 2018.




**Source: IQVIA, National Prescription Audit™ Extended Insights (NPA EI). January 2018 - December 2018. Data Extracted January 2020.File: 2019-800 NPAEI Benzo 1-30-2019.csv**
***General Practitioner = Family Practice, Internal Medicine, Osteopathic Medicine, General Practice; Mid Level = Nurse Practitioner, Physician Assistant; Mental Health = Psychiatry, Psychology, Addiction Medicine**

**Table 3.1 below** provides the estimated number of patients, by duration of use and patient age, from U.S. outpatient retail pharmacies from January 2015 through December 2018, annually. Overall for all ages, each year, (b) (4) % of patients used benzodiazepines for more than 2 months. The median duration of use increased with increasing age. Median duration of use appeared to decrease over time for patients 65 years or older but remained relatively constant for other age groups. In the adult population (patients 18 years or older) (b) (4) % of patients were prescribed a benzodiazepine for more than 3 months.

**Table 3.1**

**National estimates of patients by duration of benzodiazepine* therapy based on prescriptions dispensed from U.S. outpatient retail pharmacies, stratified by age, January 2015 through December 2018, annually**

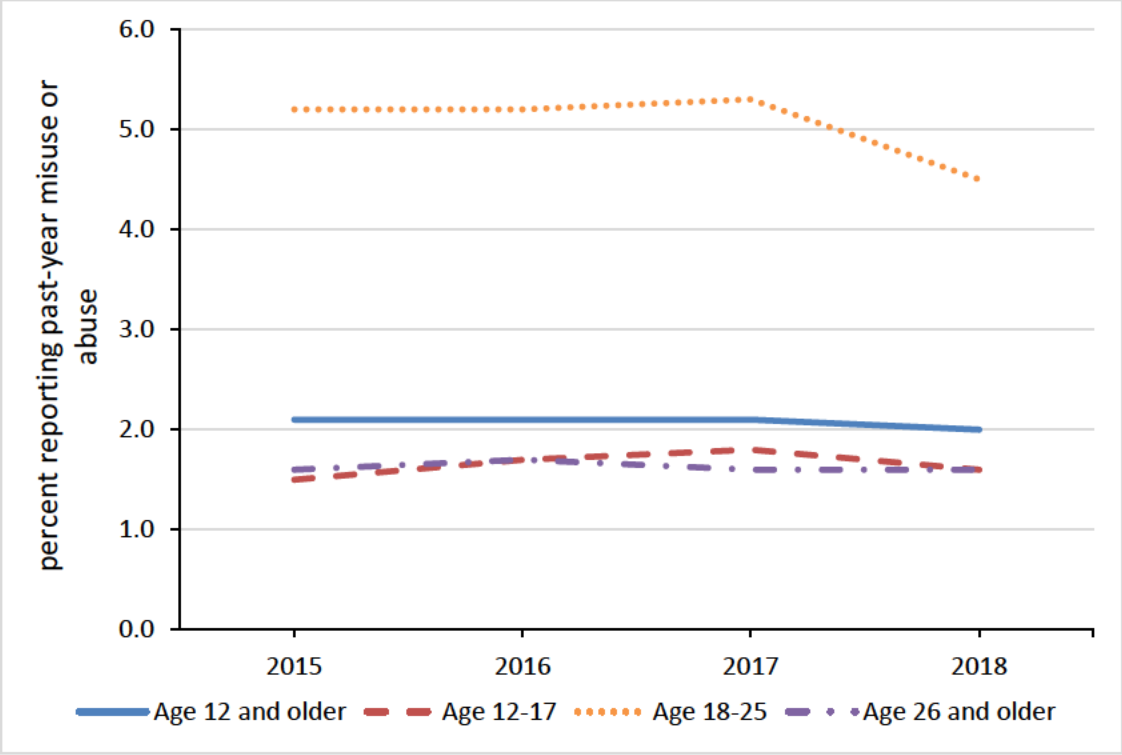
| | 2015 | | | 2016 | | | 2017 | | | 2018 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients | 50% of Patients | 25% of Patients | Patients | 50% of Patients | 25% of Patients | Patients | 50% of Patients | 25% of Patients | Patients | 50% of Patients | 25% of Patients |
| Total | (b) (4) | | | | | | | | | | | |
| 0-11 | | | | | | | | | | | | |
| 12-17 | | | | | | | | | | | | |
| 18-25 | | | | | | | | | | | | |
| 26-39 | | | | | | | | | | | | |
| 40-64 | | | | | | | | | | | | |
| 65+ | | | | | | | | | | | | |

**Source: Symphony Health, Integrated Dataverse™. January 2015 – December 2018. Data Extracted December 2019. Files: CPA Study (Benzodiazepine Market - Topline Results 2019_12_20.xls; FDA CPA Study (Benzodiazepine Market) - Deciles and Quartiles v 2019_12_20.xlsx.**
***Estimates of unique patients for stratifications may not sum exactly to annual totals due to rounding and estimation methodology utilized.**

## 3.2 THE NATIONAL SURVEY ON DRUG USE AND HEALTH

Among U.S. individuals age 12 and older in 2018, an estimated 5.4 million (2.0%) reported past-year misuse or abuse of benzodiazepines, similar to the 2.1% estimated each year from 2015 to 2017 (**Figure 3.7**). Stratified by age category, individuals 18 – 25 years old had the highest prevalence of benzodiazepine misuse or abuse each year. People who had misused or abused benzodiazepines in the past year represented 17.7% of people who had used benzodiazepines for any reason in the past year (**Table 3.2**). For context, past-year misuse or abuse of prescription pain relievers was reported by 3.6% of the population and 11.5% of past-year any users, and past-year misuse or abuse of prescription stimulants was reported by 1.9% of the population and 28.4% of past-year any-users (**Table 3.2**).

**Figure 3.7. Percent of People 12 Years and Older Reporting Past-Year Misuse or Abuse of Benzodiazepines, Overall and by Age Category: National Survey on Drug Use and Health, U.S., 2015-2018**




**Source:** NSDUH 2018 Detailed Tables: Tables 1.18b, 7.2b, 7.5b, 7.11b, 7.14b.

**Table 3.2. Any Use and Misuse or Abuse of Benzodiazepines, Opioid Analgesics, or Prescription Stimulants in the Past Year: National Survey on Drug Use and Health, U.S., 2018**

| Category of Age in years | Any Use, N (Thousands) | Misuse or Abuse, N (Thousands) | Misuse or Abuse, Percent of Population | Misuse or Abuse, Percent of Any Users |
|---|---|---|---|---|
| ***Benzodiazepines*** | | | | |
| 12 and older | 30,755 | 5,438 | 2.0 | 17.7 |
| 12-17 | 769 | 399 | 1.6 | 51.9 |
| 18-25 | 3,230 | 1,526 | 4.5 | 47.2 |
| 26-49 | 11,265 | 2,466 | 2.4 | 21.9 |
| 50 and older | 15,491 | 1,047 | 0.9 | 6.8 |
| ***Opioid Analgesics*** | | | | |
| 12 and older | 86,548 | 9,948 | 3.6 | 11.5 |
| ***Prescription Stimulants*** | | | | |
| 12 and older | 18,008 | 5,109 | 1.9 | 28.4 |

**Source:** NSDUH 2018 Detailed Tables: Tables 1.13a, 1.13b, 1.14a, 1.14b, 1.18a and 1.18b.

In a published analysis of NSDUH 2015-2016 data, the most commonly reported reason for the most recent episode of benzodiazepine misuse or abuse was to *"relax or relieve tension"* (46.3%) in NSDUH 2015 and 2016 [9]. Other frequently reported reasons were: "*help with sleep"* (22.4%), *"get high or* [respondent] *was hooked"* (11.8%), *"help with emotions"* (10.5%), and *"experiment or to see what the drug is like"* (5.7%) [9]. Common sources of the benzodiazepine they misused or abused most recently were: *"free from friend or relative"* (53.0%), *"from one doctor"* (19.7%) and *"bought from friend or relative"* (12.2%). Among the 53% who obtained it for free from a friend or relative, 80.4% of the friend or relatives obtained it from a doctor and 13% obtained it from another friend or relative [9]. In this study, an estimated 5.2 million adults annually reported past-year misuse or abuse of benzodiazepines and 0.50 (95% CI: 0.38–0.52) million also did not report misuse or abuse of other sedatives, hypnotics, or anxiolytics and met the criteria for Sedative, Hypnotic, or Anxiolytic Use Disorder, per DSM-IV: 0.30 [95% CI: 0.23–0.33] million for benzodiazepine dependence and 0.20 [95% CI: 0.13–0.21] million for benzodiazepine abuse [9].

## 3.3 MONITORING THE FUTURE

From 2007 through 2018, Xanax (Alprazolam) was the most commonly misused or abused benzodiazepine reported by 12th graders (**Table 3.3**). The percentage of 12th graders using Xanax among all 12th graders responding on the survey increased slightly from 3.3% in 2007 to 3.7% in 2010 and then decreased to 2.2% in 2018. Valium (Diazepam) and Klonopin (clonazepam) were the second and third most frequently misused or abused benzodiazepines reported by 12th graders. The percent of 12th graders misusing or abusing Valium decreased from 2.4% in 2007 to 0.3% in 2018. The pattern of Klonopin misuse or abuse was similar to Xanax, with a slight increase in 2010, followed by a decrease to 2018. We are unable to report an overall percentage of

benzodiazepine misuse or abuse since respondents are able to report more than one benzodiazepine. Additionally, these drugs fall into different categories in the survey.

**Table 3.3 Trends in annual prevalence of nonmedical use of selected benzodiazepines[a] for all 12th graders, Monitoring the Future, 2007-2018**

| | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ativan (lorezepam) | 0.2 | 0.4 | 0.4 | 0.4 | 0.5 | 0.3 | 0.2 | 0.2 | 0.2 | 0.0 | 0.2 | 0.0 |
| Dalmane (flurazepam) | -- | -- | -- | -- | -- | -- | 0.1 | 0.0 | * | 0.2 | * | 0.0 |
| Halcion (triazolam) | -- | -- | -- | -- | -- | -- | 0.1 | 0.0 | 0.1 | 0.3 | 0.5 | 0.1 |
| Librium (chlordiazepoxide) | 0.2 | 0.2 | 0.1 | 0.5 | 0.2 | * | 0.2 | * | 0.1 | 0.0 | 0.2 | 0.1 |
| Klonopin (clonazepam) | 1.2 | 1.3 | 1.5 | 1.7 | 0.8 | 1.3 | 1.0 | 0.4 | 0.4 | 0.2 | 0.1 | 0.5 |
| Restoril (temazepam) | -- | -- | -- | -- | -- | -- | 0.1 | * | 0.2 | 0.3 | * | 0.0 |
| Serax (oxazepam) | 0.1 | * | * | 0.4 | 0.1 | 0.2 | 0.2 | 0.1 | 0.0 | 0.0 | 0.2 | 0.1 |
| Valium (diazepam) | 2.4 | 1.9 | 1.9 | 1.9 | 1.6 | 1.1 | 1.4 | 1.0 | 0.9 | 0.6 | 0.6 | 0.3 |
| Xanax (alprazolam) | 3.3 | 3.3 | 3.6 | 3.7 | 2.8 | 3.1 | 2.6 | 3.4 | 2.5 | 2.8 | 2.4 | 2.2 |

[a] Selected benzodiazepines identified as either sedatives or tranquilizers in the Monitoring the Future Survey and referred to in the survey by brand name

Source: Monitoring the Future, 2018 Volume 1. Appendix tables C-3 and C-5 [12]

Note: case counts may be low for years when annual prevalence is particularly low; '—' indicates data not available. '*' indicates less than 0.05% but greater than 0%.

## 3.4 American Association of Poison Control Centers, National Poison Data System

**Benzodiazepine exposure call trends and characteristics, by year**

Over nine years (2009-2017), the annual number of exposure calls involving a benzodiazepine increased from 80,548 calls in 2009 to 82,278 in 2011, then declined to 69,632 in 2017 (**Table 3.4**). Similarly, calls involving abuse or misuse of benzodiazepines peaked in in 2011 (n=10,738) then declined through 2017.The net decrease for benzodiazepine exposure calls was reflected in both unintentional and intentional exposures; however, the decline was driven primarily by decreases in calls with minor clinical effects, whereas the number of benzodiazepine exposure calls with moderate or severe effects or death actually increased across the study period. This was true for both single- and multi-substance benzodiazepine exposure calls. At least 60% of affected individuals were female. Of note, the annual number of single-substance exposure calls involving benzodiazepine withdrawal increased from 158 in 2009 to 253 in 2017.

**Table 3.4 Exposure calls involving benzodiazepines: National Poison Data System, U.S., 2009-2017**

| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|---|
| **Total Exposure (n)** | 80,548 | 81,641 | 82,278 | 80,206 | 75,077 | 74,308 | 74,879 | 74,150 | 69,632 |
| **Gender, n (%)** | | | | | | | | | |
| **Female** | 48,133 (59.8%) | 49,014 (60.0%) | 49,601 (60.3%) | 48,635 (60.6%) | 45,946 (61.2%) | 46,104 (62.0%) | 46,133 (61.6%) | 45,425 (61.3%) | 42,847 (61.5%) |
| **Male** | 32,036 (39.8%) | 32,276 (39.5%) | 32,337 (39.3%) | 31,228 (39.3%) | 28,862 (38.4%) | 27,965 (37.6%) | 28,473 (38.0%) | 28,511 (38.5%) | 26,573 (38.2%) |
| **Unknown** | 379 (0.5%) | 351 (0.4%) | 340 (0.4%) | 343 (0.4%) | 269 (0.4%) | 239 (0.3%) | 273 (0.4%) | 214 (0.3%) | 212 (0.3%) |
| **Reason for Exposure** | | | | | | | | | |
| **Intentional, n (%)** | 58,982 (73.2%) | 60,279 (73.8%) | 61,417 (74.7%) | 60,198 (75.1%) | 56,359 (75.1%) | 56,679 (76.3%) | 57,590 (76.9%) | 57,374 (77.4%) | 53,763 (77.2%) |
| *Intentional Abuse, n (%)* | 6,070 (10.3%) | 6,365 (10.6%) | 6,607 (10.8%) | 6,107 (10.1%) | 5,100 (9.1%) | 5,000 (8.8%) | 5,452 (9.5%) | 5,834 (10.2%) | 5,471 (10.2%) |
| *Intentional Misuse, n (%)* | 4,086 (6.9%) | 4,131 (6.9%) | 4,131 (6.7%) | 4,122 (6.9%) | 3,665 (6.5%) | 3,675 (6.5%) | 3,807 (6.6%) | 3,789 (6.6%) | 3,290 (6.1%) |
| *Suspected Suicides, n (%)* | 45,887 (77.8%) | 46,476 (77.1%) | 47,057 (76.6%) | 46,451 (77.2%) | 44,488 (78.9%) | 45,007 (79.4%) | 45,192 (78.5%) | 44,721 (80.0%) | 42,255 (78.6%) |
| *Intentional Unknown, n (%)* | 2,939 (5.0%) | 3,307 (5.5%) | 3,622 (5.9%) | 3,518 (5.8%) | 3,106 (5.3%) | 2,997 (5.3%) | 3,139 (5.5%) | 3,030 (5.3%) | 2,747 (5.1%) |
| **Unintentional, *n*** | 18,245 | 18,069 | 17,479 | 16,741 | 15,687 | 14,703 | 14,290 | 13,633 | 12,840 |
| **Adverse Reaction** | 1,481 | 1,350 | 1,455 | 1,329 | 1,176 | 1,112 | 1,132 | 1,177 | 1,093 |
| **Withdrawal , *n*** | | | | | | | | | |
| *Withdrawal, single-substance* | 158 | 170 | 190 | 173 | 168 | 191 | 220 | 221 | 253 |
| *Withdrawal, multi-substance* | 105 | 124 | 121 | 122 | 125 | 91 | 124 | 152 | 119 |
| **Unknown Reason , *n*** | 1,358 | 1,390 | 1,395 | 1,478 | 1,364 | 1,383 | 1,379 | 1,426 | 1,438 |
| **Other** | 219 | 259 | 221 | 165 | 198 | 149 | 144 | 167 | 126 |
| **Related Medical Outcomes**** | | | | | | | | | |
| **Single substance, n (%)** | | | | | | | | | |
| Minor effect | 9,070 (73.8%) | 9,474 (72.8%) | 9,462 (72.0%) | 9,040 (71.2%) | 8,372 (70.0%) | 8,441 (69.6%) | 8,788 (70.0%) | 9,339 (71.5%) | 8,551 (69.0%) |
| Moderate effect | 2,935 (23.9%) | 3,194 (24.6%) | 3,368 (25.6%) | 3,353 (26.4%) | 3,282 (27.4%) | 3,313 (27.3%) | 3,406 (27.1%) | 3,363 (25.7%) | 3,419 (27.6%) |
| Major Effect | 281 (2.3%) | 329 (2.5%) | 296 (2.3%) | 299 (2.4%) | 295 (2.5%) | 365 (3.0%) | 351 (2.8%) | 356 (2.7%) | 412 (3.3%) |
| Death | 7 (0.1%) | 10 (0.1%) | 9 (0.1%) | 11 (0.1%) | 18 (0.2%) | 16 (0.1%) | 14 (0.1%) | 12 (0.1%) | 12 (0.1%) |
| **Multiple substances, n (%)** | | | | | | | | | |
| Minor effect | 15,845 (48.1%) | 16,331 (47.6%) | 16,139 (45.5%) | 15,896 (45.4%) | 14,551 (43.7%) | 14,758 (44.2%) | 15,012 (43.9%) | 15,051 (43.9%) | 13,559 (42.1%) |
| Moderate effect | 13,457 (40.8%) | 14,098 (41.1%) | 15,135 (42.7%) | 14,876 (42.5%) | 14,896 (44.7%) | 14,680 (44.0%) | 15,261 (44.7%) | 15,297 (44.6%) | 14,530 (45.2%) |
| Major Effect | 3,431 (10.4%) | 3,523 (10.3%) | 3,597 (10.1%) | 3,634 (104%) | 3,433 (10.3%) | 3,675 (11.0%) | 3,646 (10.7%) | 3,677 (10.7%) | 3,589 (11.2%) |
| Death | 235 (0.7%) | 337 (1.0%) | 605 (1.7%) | 601 (1.7%) | 424 (1.3%) | 257 (0.8%) | 250 (0.7%) | 267 (0.8%) | 492 (1.5%) |

*Other defined as other contamination tampering and other malicious.
**Medical outcomes among individuals with a related clinical effect.

**Reason for exposure, by age group**

During the nine-year period, the intentional exposure call rate was highest in the 20-39 year-old age group, with a rate of 293 exposures per 1,000,000 population. Among abuse and misuse calls specifically, people ages 13-19 years had the highest rate of exposure calls (64.7 exposures per 1,000,000). Among calls involving suspected suicide, the top two affected age groups were ages 20-39 years (227.6 exposures per 1,000,000) and 40-64 years (180.8 exposures per 1,000,000). **(Table 3.5; Appendix B Table B4)**

**Table 3.5 Reason for exposure by age group, counts and rates per 1,000,000 population, 2009-2017**

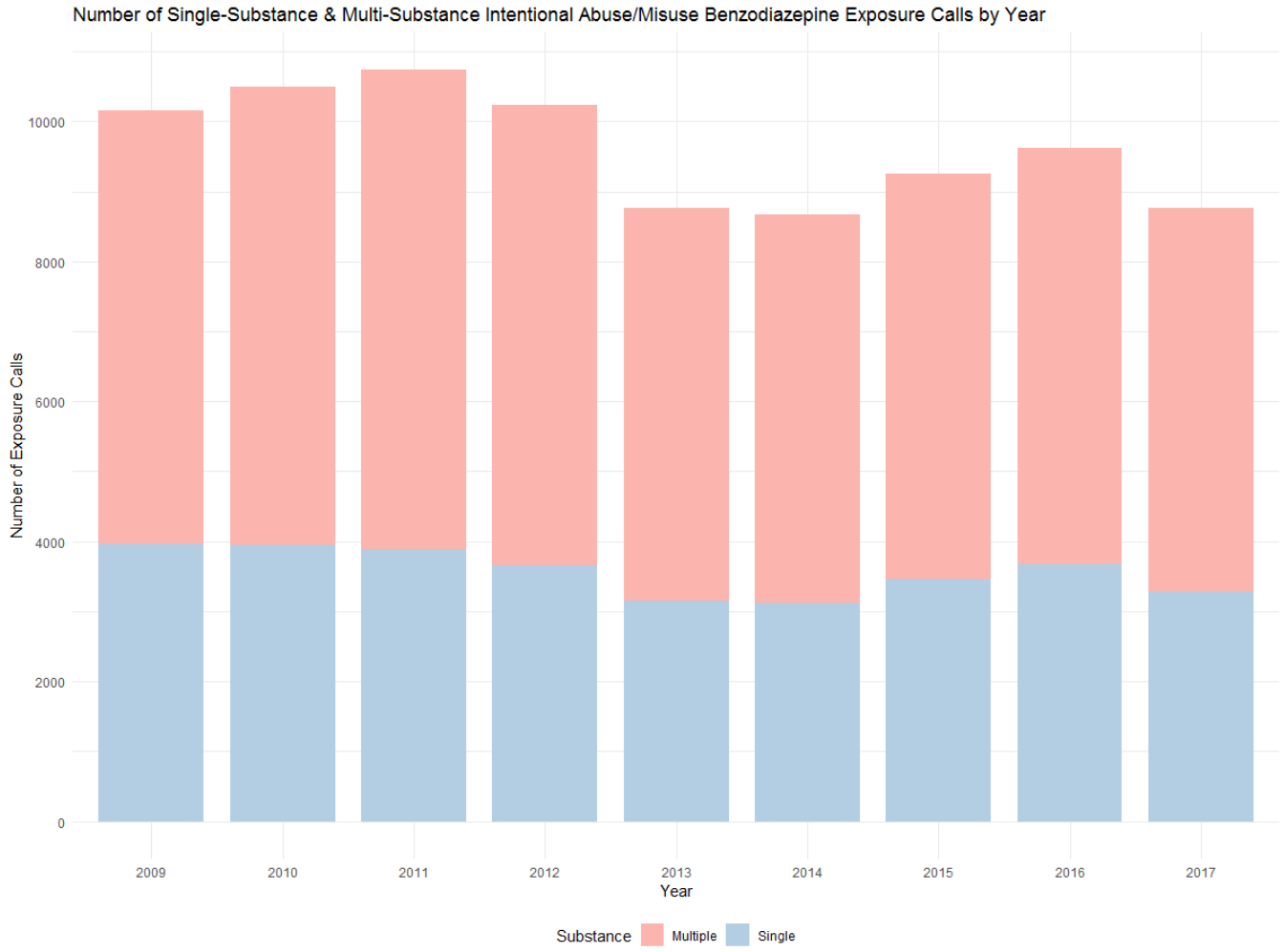
| Reason for Exposures by Age Group (year) | | 0-5 | 6-12 | 13-19 | 20-39 | 40-64 | 65 and older |
|---|---|---|---|---|---|---|---|
| **Total Exposures** | n | 62,474 | 8,936 | 63,561 | 254,797 | 236,180 | 36,658 |
| | Rate per 1,000,000 | 288.5 | 34.6 | 237.7 | 331.6 | 253.7 | 90.9 |
| **Intentional** | n | 113 | 1,758 | 56,713 | 225,368 | 200,249 | 18,660 |
| | Rate per 1,000,000 | 0.5 | 6.8 | 212.1 | 293.3 | 215.1 | 46.3 |
| ***Intentional Misuse/Abuse*** | n | 49 | 664 | 17313 | 38900 | 22231 | 2424 |
| | Rate per 1,000,000 | 0.2 | 2.6 | 64.7 | 50.6 | 23.9 | 6.0 |
| *Intentional Abuse* | n | 20 | 315 | 13,773 | 23,913 | 10,792 | 609 |
| | Rate per 1,000,000 | 0.1 | 1.2 | 51.5 | 31.1 | 11.6 | 1.5 |
| *Intentional Misuse* | n | 29 | 349 | 3,540 | 14,987 | 11,439 | 1,815 |
| | Rate per 1,000,000 | 0.1 | 1.4 | 13.2 | 19.5 | 12.3 | 4.5 |
| *Suspected Suicides* | n | 52 | 832 | 36,165 | 174,873 | 168,328 | 15,183 |
| | Rate per 1,000,000 | 0.2 | 3.2 | 135.2 | 227.6 | 180.8 | 37.6 |
| *Intentional Unknown* | n | 12 | 262 | 3,235 | 11,595 | 9,690 | 1,053 |
| | Rate per 1,000,000 | 0.1 | 1.0 | 12.1 | 15.1 | 10.4 | 2.6 |
| **Unintentional** | n | 61,881 | 6,658 | 4,805 | 19,976 | 26,553 | 15,248 |
| | Rate per 1,000,000 | 285.8 | 25.8 | 18.0 | 26.0 | 28.5 | 37.8 |

Note: exposures with unknown age are not included in this table. See Appendix B Table B4 for more information
Denominator populations 2009-2017: ages 0-5 years: n=216,520,037; ages 6-12 years: n=258,457,650; ages 13-19 years: n=267,410,680; ages 20-39 years n=768,500,867; ages 40-64 years: n=930,982,940; ages 65 and older: n=403,084,951; from: NCHS Bridged Race Files (https://wonder.cdc.gov/Bridged-Race-v2018.HTML)

**Single- versus multiple-substance abuse/misuse calls, by year**

In 2017, approximately 37% of abuse/misuse exposure calls for benzodiazepines involved benzodiazepines as a single drug substance (**Figure 3.8).**

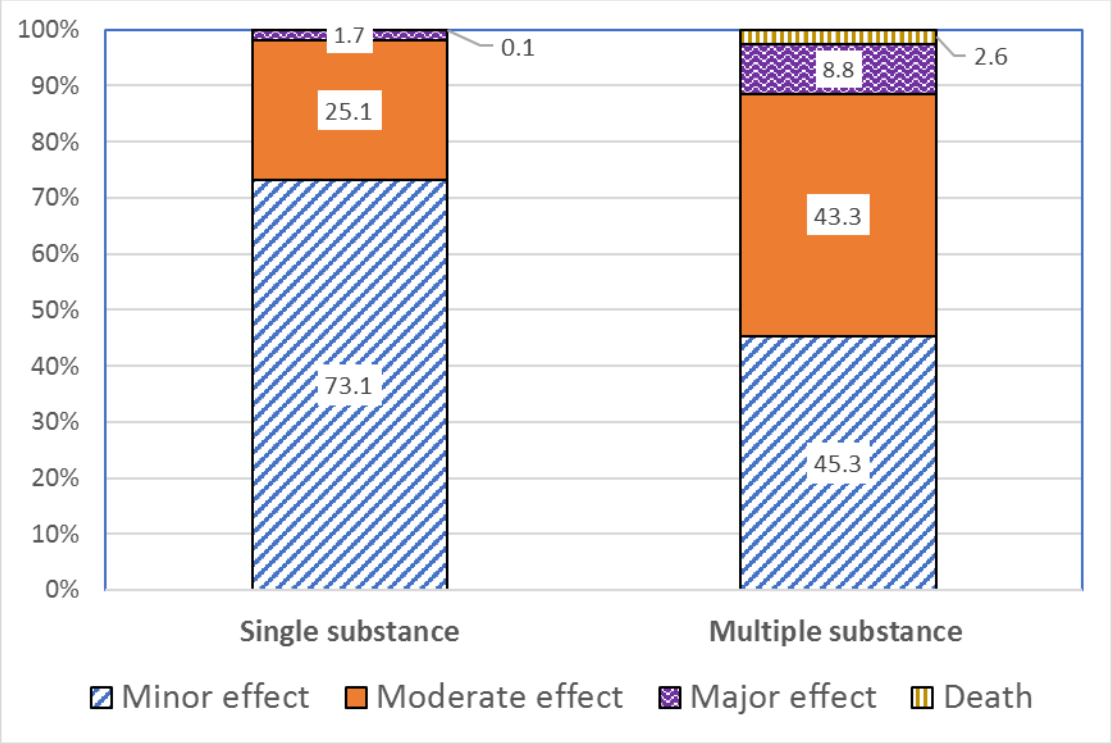
**Figure 3.8. Abuse/misuse exposure calls involving benzodiazepines, single and multiple-substances, by year**




## Severity of medical outcomes for cases with related clinical effects

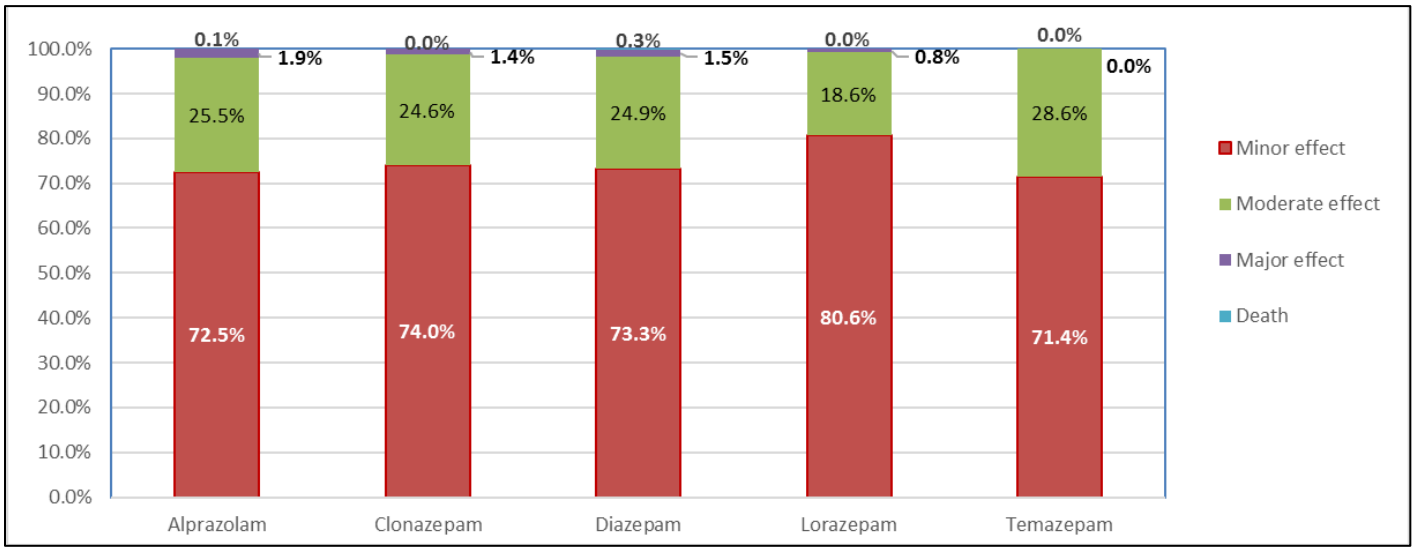
As shown in **Figure 3.9**, medical outcomes were generally more severe in benzodiazepine abuse/misuse calls involving multiple substances than in those involving just the benzodiazepine. Among single-substance benzodiazepine misuse/abuse exposure calls , minor effect (i.e., symptoms that are minimally bothersome to patients and usually resolved rapidly) was the most common category of related medical outcomes (73.1%), followed by moderate effect (i.e., symptoms that are prolonged and involved some treatments; 25.1%). In multiple-substance exposure calls involving abuse/misuse, the proportion of calls with a moderate effect (43.3%) was similar to the proportion with a minor effect (45.3%) **(Figure 3.9; Appendix B Table B5).** More information on medical outcome definition is provided in **Appendix B Table B3**.

**Figure 3.9 Severity of medical outcomes for abuse/misuse exposure calls with related clinical effects, by single and multiple-substance, 2013-2017**




The distribution of medical outcome severity in single-substance misuse/abuse calls was similar across the five most commonly prescribed benzodiazepines. **A**cross all five drugs, minor effect was the most common medical outcome, ranging between 71.4%-80.6%. Moderate effect was the second most common medical outcome, accounting for approximately one fifth of exposure calls involving abuse/misuse **(Figure 3.10).**

**Figure 3.10. Medical severity by active pharmaceutical ingredient among single Substance calls involving abuse or misuse: National Poison Data System, U.S., 2013-2017**




**Frequency of related clinical effects in exposures with moderate-to-severe medical outcomes**

As shown in **Table 3.6**, 15% (n=2,394) of 15,779 single-substance benzodiazepine exposure calls reported to poison centers specifically involving abuse between 2009-2017 reported moderate-to-severe medical outcomes in patients with clinical effects related to the exposure.

**Table 3.6. Single-substance benzodiazepine abuse exposure calls, 2009-2017**

| | N | % |
|---|---|---|
| **Total Single-Substance Abuse Exposure Calls** | 15,779 | 100% |
| **People with Related Clinical Effects with Moderate-to-Severe Medical Outcomes** | 2,394 | 100% |
| *Moderate* | 2,223 | 92.9% |
| *Major* | 162 | 6.8% |
| *Death* | 4 | 0.2% |
| *Death, indirect report* | 5 | 0.2% |

**Table 3.7** displays the top 25 most frequently reported clinical effect deemed by poison center specialists to be related to the single-substance benzodiazepine exposures described above with moderate-to-severe medical outcomes. The most commonly reported related clinical effects and corresponding frequency in these exposures included drowsiness/lethargy (76%), slurred speech (24%), confusion (14.1%), tachycardia (13.3%), hypotension (13.3%), and ataxia (13.1%). A full frequency table of all reported

related clinical effects for these exposures (N=2,394) may be found in **Appendix B Table B6.**

**Table 3.7 Related clinical effects for moderate-to-severe medical outcomes* involving single-substance intentional abuse benzodiazepine exposure calls, National Poison Data System 2009-2017 (Top 25)**

| Related Clinical Effect | Number (N) | Percentage (%) |
|---|---|---|
| **Drowsiness/lethargy** | 1,820 | 76.02% |
| **Slurred speech** | 573 | 23.93% |
| **Confusion** | 339 | 14.16% |
| **Tachycardia** | 319 | 13.32% |
| **Hypotension** | 318 | 13.28% |
| **Ataxia** | 315 | 13.16% |
| **Respiratory depression** | 218 | 9.11% |
| **Agitation** | 205 | 8.56% |
| **Bradycardia** | 197 | 8.23% |
| **Coma** | 173 | 7.23% |
| **Other - Miscellaneous** | 139 | 5.81% |
| **Mydriasis** | 82 | 3.43% |
| **Hypertension** | 75 | 3.13% |
| **Dizziness/vertigo** | 66 | 2.76% |
| **Hallucinations/delusions** | 62 | 2.59% |
| **Vomiting** | 56 | 2.34% |
| **Miosis** | 47 | 1.96% |
| **Syncope** | 47 | 1.96% |
| **Tremor** | 44 | 1.84% |
| **Nausea** | 38 | 1.59% |
| **Electrolyte abnormality** | 37 | 1.55% |
| **CPK elevated** | 34 | 1.42% |
| **Seizure (single)** | 28 | 1.17% |
| **Acidosis** | 27 | 1.13% |
| **Conduction disturbance** | 27 | 1.13% |

*** Includes clinical effects deemed by poison center specialists to be related to exposure for cases (N=2,394) with moderate to severe medical outcomes (moderate, major, death/death, indirect report)**

## Route of abuse/misuse

Among single-substance exposure calls for benzodiazepine abuse/misuse, almost all calls (97%) involved oral route of exposure (**Table 3.6**). Multiple-substance exposure calls for

benzodiazepine abuse/misuse had higher proportions of calls involving inhalation and injection, but it is unknown in these cases which of the involved substances were used via those routes.

**Table 3.8. Percent of abuse/misuse exposure calls reporting specific exposure routes**

| | Misuse/Abuse | |
|---|---|---|
| **Characteristics** | **Single substance exposures** N (% of column)* | **Multi-substance exposures** N (% of column)* |
| **Route of Use** (n)** | 32,137 | 54,565 |
| Oral*** | 31,412 (97.7%) | 52,512 (96.2%) |
| Nasal/inhalation | 578 (1.8%) | 5,443 (10.0%) |
| Injection | 234 (0.7%) | 2,491 (4.6%) |
| Other**** | 62 (0.2%) | 369 (0.7%) |
| Unknown | 96 (0.3%) | 1,984 (3.6%) |

*The counts of each route are not mutually exclusive.
**Route cannot be mapped to specific drug in multi-substance exposure
***Oral included aspiration with ingestion.
****Other included exposure routes: bite/sting, dermal, ocular, otic, vaginal, rectal, and/or other

By concomitant substance exposures

Among multiple-substance exposure calls involving abuse/misuse of benzodiazepines, the most common of the five categories of co-exposure we examined was prescription opioids (37.7%), followed by alcohol (24.8%), and stimulants (11.8%) **(Table 3.7).**

**Table 3.9. Calls involving abuse or misuse of benzodiazepines, multi-substance exposures, by co-exposures: National Poison Data System, U.S., 2009-2017**

| | Misuse/Abuse |
|---|---|
| **Characteristics** | **Multi-substance exposures** N (% of column) |
| **Total abuse/misuse (n)** | 54,565 |
| **Co-Exposures*** | |
| Prescription opioids | 18,937 (34.7) |
| Alcohol | 15,494 (28.4) |
| Stimulants (prescription and illicit) | 6,444 (11.8) |
| Marijuana | 3,731 (6.8) |
| Heroin, illicit fentanyl, analogues | 3,614 (6.6) |

*The counts of each co-exposure are not mutually exclusive.

## 3.5 National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance

There were an estimated 212,770 ED visits annually during 2016-2017 for AEs involving benzodiazepines. [20] Of these, 119,008 (55.9%) involved nonmedical use (i.e., abuse, therapeutic misuse, or overdose of unknown intent) of benzodiazepines **(Table 3.10).** In ED visits involving nonmedical use of benzodiazepines, 82.7% also involved at least one other class of substances, such as illicit drugs, alcohol, or prescription opioids **(Table**

**3.10).** Of these, 12,217 (10.3%) of ED visits involving nonmedical use of benzodiazepines involved prescription opioids as the only other substance. [20] Patients 15-34 years old made up over half of the visits involving nonmedical use of benzodiazepines and had the highest population rate (7.4 per 10,000 persons). [20] (**Appendix C Table C1**).

**Table 3.10. Emergency Department Visits Due to Adverse Events Involving Non-medical Use of Benzodiazepines, by Concurrent Substance, 2016-2017[a]**

| Concurrent Substance | Nonmedical Use of Benzodiazepines | | |
|---|---|---|---|
| | Annual Estimate | | |
| | No. | % | 95% CI |
| **Benzodiazepines only[b]** | **20,523** | **17.2** | **(14.6-19.9)** |
| **Benzodiazepines & one other class of substance** | **56,839** | **47.7** | **(45.3-50.3)** |
| Illicit drugs only[c] | 24,078 | 20.2 | (17.3-23.1) |
| Alcohol only | 14,096 | 11.8 | (9.2-14.4) |
| Prescription opioids only | 12,217 | 10.3 | (7.6-13.0) |
| Non-opioid medications only | 6,448 | 5.4 | (4.1-6.7) |
| **Benzodiazepines & multiple classes of substances** | **41,646** | **35.0** | **(31.2-38.8)** |
| Non-opioid medication(s) & (illicit drugs or alcohol) | 17,295 | 14.5 | (12.3-16.8) |
| Prescription opioid(s) & (illicit drugs or alcohol) | 9,358 | 7.9 | (5.6-10.1) |
| Prescription opioid(s) & Non-opioid medication(s)&/or (illicit drugs or alcohol) | 8,027 | 6.7 | (5.3-8.2) |
| Illicit drugs & alcohol | 6,966 | 5.9 | (4.6-7.2) |
| **Total** | **119,008** | **100.0** | **--** |

[a]Data are from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, CDC. Estimates based on <20 cases or total estimates <1,200 are considered statistically unstable and are not shown (--).
[b]Without documentation of involvement of other substances. Two different benzodiazepines were involved in 8 cases involving therapeutic use, 16 cases involving self-harm, and 24 cases involving nonmedical use.
[c]Includes unspecified opioids and unspecified amphetamines. Does not include prescription opioids, alcohol, or non-opioid medications.

**Source:** Moro RN, Geller AI, Weidle NJ, et al. Emergency Department Visits Involving Benzodiazepines, United States, 2016-2017 *(In Press).*

The adverse clinical outcomes that were most frequently documented in ED visits involving nonmedical use of benzodiazepines were altered mental status (44.3%) and cardiorespiratory arrest / unresponsiveness (24.2%) **(Appendix C Table C2).** [20] However, the frequency of cardiorespiratory arrest / unresponsiveness depended on whether benzodiazepines were co-implicated with other substances: it was noted in 18.5% (95% CI:8.5%-28.5%) of ED visits involving benzodiazepines alone, 29.2% (95% CI:22.2%-36.3%) of ED visits involving benzodiazepines and prescription opioids alone, and 38.0% (95% CI:28.4%-47.5%) of ED visits involving benzodiazepines and illicit drugs alone. [18]

To put the benzodiazepine ED visit data into context, in 2016, an estimated 167,845 ED visits involved nonmedical use of benzodiazepines, compared to an estimated 129,863

visits that involved nonmedical use of prescription opioids and substantially fewer visits involving nonmedical use of other psychoactive prescription drugs (**Table 3.11**). However, there were fewer ED visits involving nonmedical use of benzodiazepines alone compared to ED visits involving nonmedical use of prescription opioids alone (respective estimates, 23,335 and 40,499; **Table 3.11**). Also, among observed cases of ED visits involving nonmedical use of benzodiazepines, 26.4% (95% CI:19.7%-33.1%) were identified by laboratory test results only. Also, in 7.4% (95% CI: 4.1%, 10.7%) of visits involving opioids, the prescription opioid was identified by laboratory testing only.

**TABLE 3.11. Emergency Department visits due to non-medical use of pharmaceuticals, by category[a]: NEISS-CADES, U.S., 2016**

| | Implicated alone or with other substances,[b] annual national estimate[d] | | Implicated alone without other substances,[c] annual national estimate[e] | | |
|---|---|---|---|---|---|
| | N | % total visits (95% CI) | N | % total visits (95% CI) | % category (95% CI) |
| Benzodiazepine | 167,845 | 46.9 (42.5-51.2) | 23,335 | 6.5 (5.1-7.9) | 13.9 (10.9-16.9) |
| Prescription opioids | 129,863 | 36.2 (30.8-41.7) | 40,499 | 11.3 (8.6-14.0) | 31.2 (26.2-36.1) |
| Hypnotics (non-benzodiazepine) | 16,899 | 4.7 (3.8-5.7) | 2,374 | 0.7 (0.4-1.0) | 14.1 (7.8-20.3) |
| Antipsychotics | 15,874 | 4.4 (3.4-5.5) | 4,995 | 1.4 (1.0-1.8) | 31.5 (25.6-37.3) |
| Muscle relaxants | 14,731 | 4.1 (3.2-5.0) | 3,114 | 0.9 (0.5-1.2) | 21.1 (13.4-28.9) |
| Stimulants | 10,999 | 3.1 (1.8-4.4) | 3,677[f] | 1.0 (0.4-1.7) | 33.4 (22.1-44.8) |

[a]Estimates are from the National Electronic Injury Surveillance System−Cooperative Adverse Drug Event Surveillance project, Centers for Disease Control and Prevention.

[b]Implicated alone or in combination with other pharmaceuticals, alcohol, unspecified drugs, or illicit substances.

[c]Implicated alone, without other categories of pharmaceuticals, and without alcohol, unspecified drugs, or illicit substances.

[d]Annual estimates and percentages total more than 100% because a single visit may involve multiple pharmaceuticals from different categories.

[e]Annual estimates and percentages total less than 100% because additional visits involve pharmaceuticals from different categories and additional visits involve alcohol or illicit substances.

[f]Coefficient of variation >30%.

Source: Geller AL, Dowell D, Lovegrove MC, et al. U.S. Emergency Department Visits Resulting From Nonmedical Use of Pharmaceuticals, 2016. Am J Prev Med. 2019 May;56(5):639-647

## 3.6 TREATMENT EPISODE DATA SET-ADMISSIONS

TEDS included data on the primary, secondary, and tertiary drugs of abuse, as reported in 830,822, 440,134, and 185,082 admissions to publicly-funded substance use disorder treatment programs, respectively. Benzodiazepines represented 1.2% of all primary drugs reported, 7.3% of secondary drugs, and 9.8% of tertiary drugs (**Table 3.12**). Alprazolam was, by far, the most commonly reported benzodiazepine abused. For context, opioid analgesics were 3.1% of all primary drugs, 2.9% of secondary drugs, and 2.4% of tertiary drugs. Non-pharmaceutical substances—including alcohol, heroin, marijuana/hashish,

methamphetamine/speed, and cocaine—were reported as primary drugs of abuse in the large majority of admissions.

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**Table 3.12. Benzodiazepines and other drugs endorsed as the primary, secondary, and tertiary drug of abuse at substance use treatment admissions: TEDS, U.S., 2017**

| | Primary Drug of Abuse (N=830,822) | | Secondary Drug of Abuse (N=440,134) | | Tertiary Drug of Abuse (N=185,082) | |
|---|---|---|---|---|---|---|
| *Drug Reported* | N | *Percent of Admissions with Primary Drug Reported* | *N* | *Percent of Admissions with Secondary Drug Reported* | *N* | *Percent of Admissions with Tertiary Drug Reported* |
| **Benzodiazepines total** | **10,316** | **1.2** | **32,415** | **7.3** | **18,166** | **9.8** |
| Alprazolam | 6,152 | 0.7 | 18,990 | 4.3 | 10,093 | 5.5 |
| Clonazepam | 248 | * | 860 | 0.2 | 444 | 0.2 |
| Diazepam | 575 | 0.1 | 2,362 | 0.5 | 1,348 | 0.7 |
| Lorazepam | 69 | * | 196 | * | 112 | 0.1 |
| Other benzodiazepines | 3,272 | 0.4 | 10,007 | 2.3 | 6,169 | 3.3 |
| **Opioid analgesics total**** | **26,297** | **3.1** | **12,653** | **2.9** | **4,429** | **2.4** |
| *Drugs most frequently reported as primary drug of abuse* | | | | | | |
| Alcohol | 274,321 | 33.0 | 75,436 | 17.1 | 32,221 | 17.4 |
| Heroin | 255,762 | 30.8 | 30,266 | 6.9 | 8,241 | 4.5 |
| Marijuana/hashish | 97,421 | 11.7 | 106,169 | 24.1 | 50,830 | 27.5 |
| Methamphetamine/speed | 51,952 | 6.3 | 25,463 | 5.8 | 8,628 | 4.7 |
| Cocaine | 48,043 | 5.8 | 109,497 | 24.9 | 35,358 | 19.1 |

* Less than 0.05 percent
** TEDS collected data on the following opioid analgesics: codeine, hydrocodone, hydromorphone, meperidine, oxycodone, pentazocine, propoxyphene, and tramadol. This total did not include opioids for treating addiction, e.g., buprenorphine and methadone.
**Source:** Treatment Episode Data Set (TEDS) 2017, Table 2.18. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.

## 3.7 NATIONAL VITAL STATISTICS SYSTEM-MORTALITY

For the period from 2013 to 2017, the most recent five years of available data from the NVSS-M, there were 45,930 benzodiazepine-involved drug poisoning (overdose) deaths (**Table 3.13**). Among these deaths, 55.3% (n=25,421) involved prescription opioids with or without other drug substances, and 8.4% (n=3,837) involved psychostimulants with abuse potential with or without other drug substances. Among the deaths involving both benzodiazepine and prescription opioids, only 17.5% (n=4,454) had no documentation of another involved drug substance (drug substance: T36.0 to T50.9; does not include alcohol (T51.0)).

Among all benzodiazepine-involved poisoning deaths, only 3.2% (n=1,448) involved benzodiazepines with no indication of involvement of another drug (drugs identified by T36.0 to T50.9; these codes do not include alcohol (T51.0)), and 2.0% (n=928) were due

to benzodiazepines alone, with no code indicating another drug or alcohol (**Table 3.13**). Almost 20% (19.82%; n=287) of these single-drug deaths were intentional, nearly double the percentage of intentional deaths among all benzodiazepine-involved deaths (11.5%; n=5297). Also, among these single-drug benzodiazepine deaths, approximately 35.9% (n=520) involved alcohol, approximately three times the percent of deaths involving alcohol among all benzodiazepine-involved deaths (12.3%; n=5648).

**Table 3.13. Number (%) of deaths involving benzodiazepines, by decedent characteristics and other drug substances involved, U.S. Residents, 2013-2017, where underlying cause of death is drug poisoning[a], NVSS-M**

| | **Benzodiazepine** | **Benzodiazepine as single drug substance [b]** | **Benzodiazepine and prescription opioids** | **Benzodiazepine and prescription opioids only** | **Benzodiazepine and psychostimulants of abuse potential** |
|---|---|---|---|---|---|
| | N (% of row) | N (% of row) | N (% of row) | N (% of row) | N (% of row) |
| **Total** | 45930 (100.00) | 1448 (3.15) | 25421 (55.35) | 4454 (9.70) | 3837 (8.35) |
| **Sex** | | | | | |
| | N (% of column) | N (% of column) | N (% of column) | N (% of column) | N (% of column) |
| **Female** | 19423 (42.29) | 556 (38.40) | 11535 (45.38) | 1669 (37.47) | 1467 (38.23) |
| **Male** | 26507 (57.71) | 892 (61.60) | 13886 (54.62) | 2785 (62.53) | 2370 (61.77) |
| **Age Group (years)** | | | | | |
| **<10** | 16 (0.03) | 1 (0.07) | 8 (0.03) | 3 (0.07) | 1 (0.03) |
| **10-19** | 720 (1.57) | 18 (1.24) | 344 (1.35) | 96 (2.16) | 57 (1.49) |
| **20-39** | 19091 (41.57) | 423 (29.21) | 9347 (36.77) | 1721 (38.64) | 2177 (56.74) |
| **40-59** | 21282 (46.34) | 718 (49.59) | 12869 (50.62) | 2172 (48.77) | 1417 (36.93) |
| **60-64** | 2798 (6.09) | 128 (8.84) | 1734 (6.82) | 276 (6.20) | 136 (3.54) |
| **65+** | 2020 (4.40) | 159 (10.98) | 1118 (4.40) | 185 (4.15) | 49 (1.28) |
| **Missing** | 3 (0.01) | 1 (0.07) | 1 (0.00) | 1 (0.02) | -- |
| **Unintentional** | | | | | |
| **Yes** | 38545 (83.92) | 1048 (72.38) | 21693 (85.33) | 3925 (88.12) | 3441 (89.68) |
| **No** | 7385 (16.08) | 400 (27.62) | 3728 (14.67) | 529 (11.88) | 396 (10.32) |
| **Intentional** | | | | | |
| **Yes** | 5297 (11.53) | 287 (19.82) | 2509 (9.87) | 291 (6.53) | 239 (6.23) |
| **No** | 40633 (88.47) | 1161 (80.18) | 22912 (90.13) | 4163 (93.47) | 3598 (93.77) |
| **Assault/ Homicide** | | | | | |
| **Yes** | 43 (0.09) | 4 (0.28) | 17 (0.07) | 4 (0.09) | 10 (0.26) |
| **No** | 45887 (99.91) | 1444 (99.72) | 25404 (99.93) | 4450 (99.91) | 3827 (99.74) |

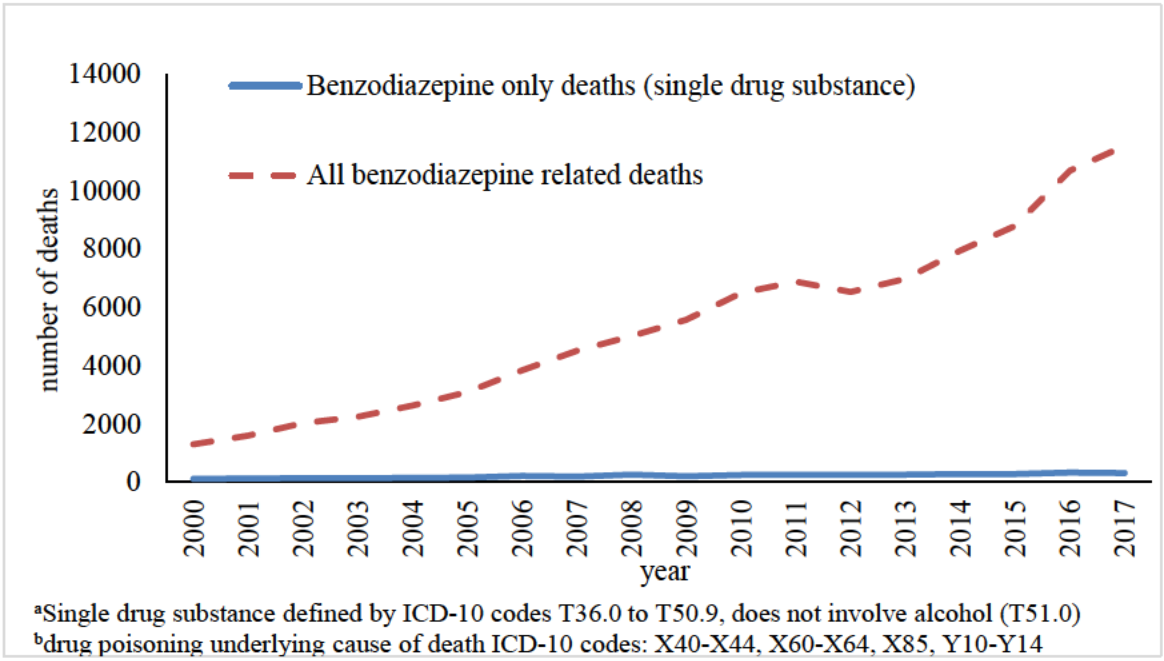
| Table 3.13. Number (%) of deaths involving benzodiazepines, by decedent characteristics and other drug substances involved, U.S. Residents, 2013-2017, where underlying cause of death is drug poisoning[a], NVSS-M | | | | | |
|---|---|---|---|---|---|
| **Undetermined Intent** | | | | | |
| **Yes** | 2045 (4.45) | 109 (7.53) | 1202 (4.73) | 234 (5.25) | 147 (3.83) |
| **No** | 43885 (95.55) | 1339 (92.47) | 24219 (95.27) | 4220 (94.75) | 3690 (96.17) |
| **Alcohol Involved** | | | | | |
| **Yes** | 5648 (12.29) | 520 (35.91) | 2254 (8.87) | 428 (9.61) | 319 (8.31) |
| **No** | 40282 (87.7) | 928 (64.09) | 23167 (91.13) | 4026 (90.36) | 3518 (91.69) |

[a] drug poisoning underlying cause of death ICD-10 codes: X40-X44, X60-X64, X85, Y10-Y14

[b] Single drug substance defined by ICD-10 codes T36.0 to T50.9, does not involve alcohol (T51.0)

From 2000 to 2017, benzodiazepine-involved poisoning deaths increased steadily from 1,298 in 2010 to 11,537 in 2017 (**Figure 3.11; Appendix D Table D1**). The frequency of deaths involving benzodiazepines as a single drug also increased, but the absolute number (n=112 in 2000 to n=308 in 2017) represented a small proportion of total benzodiazepine poisoning deaths. And the rate of increase was slower (i.e., nearly a 9-fold increase for all benzodiazepine-involved deaths compared to a 2.75-fold increase for deaths involving benzodiazepine as a single drug). The proportion of deaths due to benzodiazepines alone (single drug) out of all benzodiazepine-involved deaths decreased over this period, from 8.6% in 2000 to 2.7% in 2017.

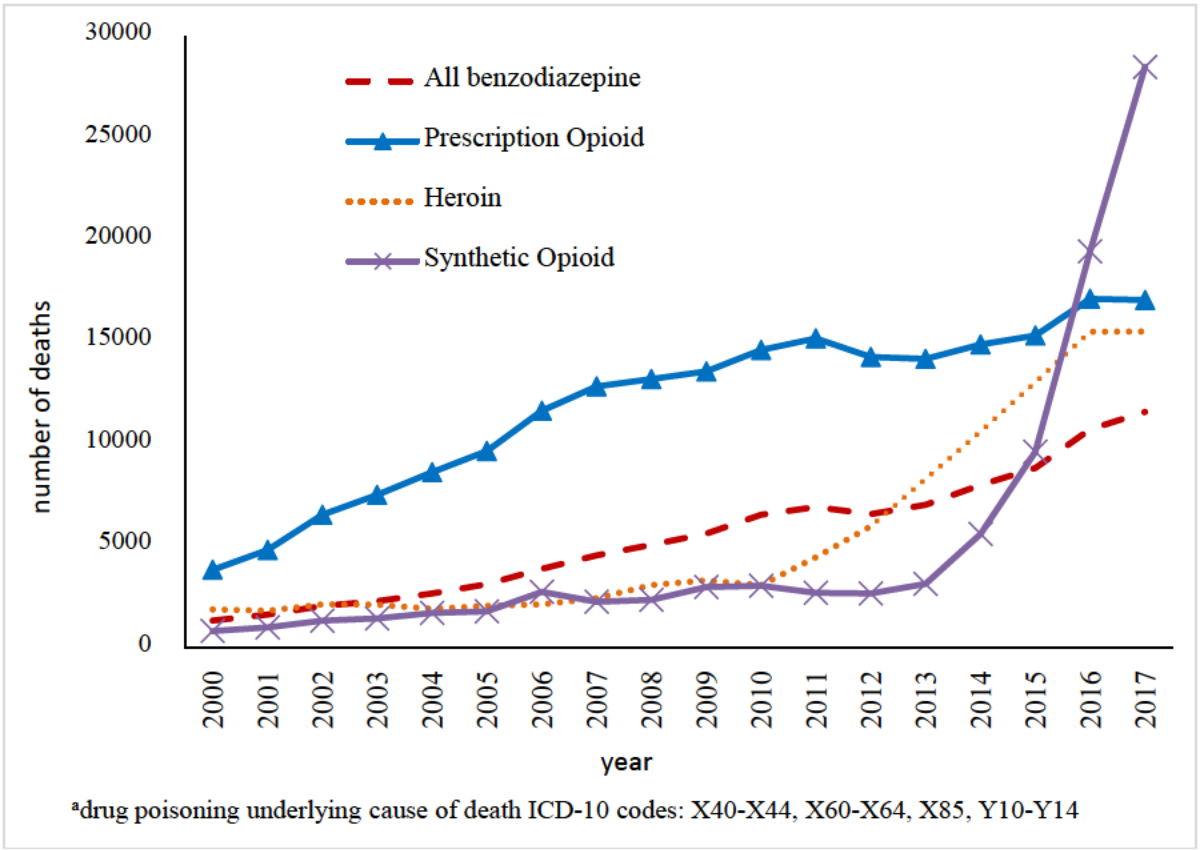
**Figure 3.11. Trends in number of all benzodiazepine-involved deaths and single drug substance benzodiazepine deaths[a], where underlying cause of death is drug poisoning[b], 2000-2017, NVSS-M**




[a]Single drug substance defined by ICD-10 codes T36.0 to T50.9, does not involve alcohol (T51.0)
[b]drug poisoning underlying cause of death ICD-10 codes: X40-X44, X60-X64, X85, Y10-Y14

The annual number of benzodiazepine-involved deaths and prescription opioid-related deaths both increased from 2000 to 2017 (**Figure 3.12; Appendix D Table D2**). Prescription opioid-involved deaths remained consistently higher than benzodiazepine-involved deaths from 2000 to 2017. However, benzodiazepine-involved deaths increased nearly 9-fold (8.8) and prescription opioid-involved deaths increased 4.5-fold during this period, both with a fairly steady rate of increase. In contrast, the annual number of synthetic opioid-involved deaths increased dramatically starting in 2013, and the annual number of heroin-involved deaths increased dramatically from 2010 to 2016. The annual number of heroin-involved deaths surpassed the annual number of benzodiazepine-related deaths in 2012. The annual number of synthetic opioid-involved deaths surpassed the annual number of benzodiazepine-involved deaths in 2015.

**Figure 3.12. Trends in number of all benzodiazepine-, prescription opioid-, heroin- or synthetic opioid-involved deaths, where underlying cause of death is drug poisoning[a], 2000-2017, NVSS-M**

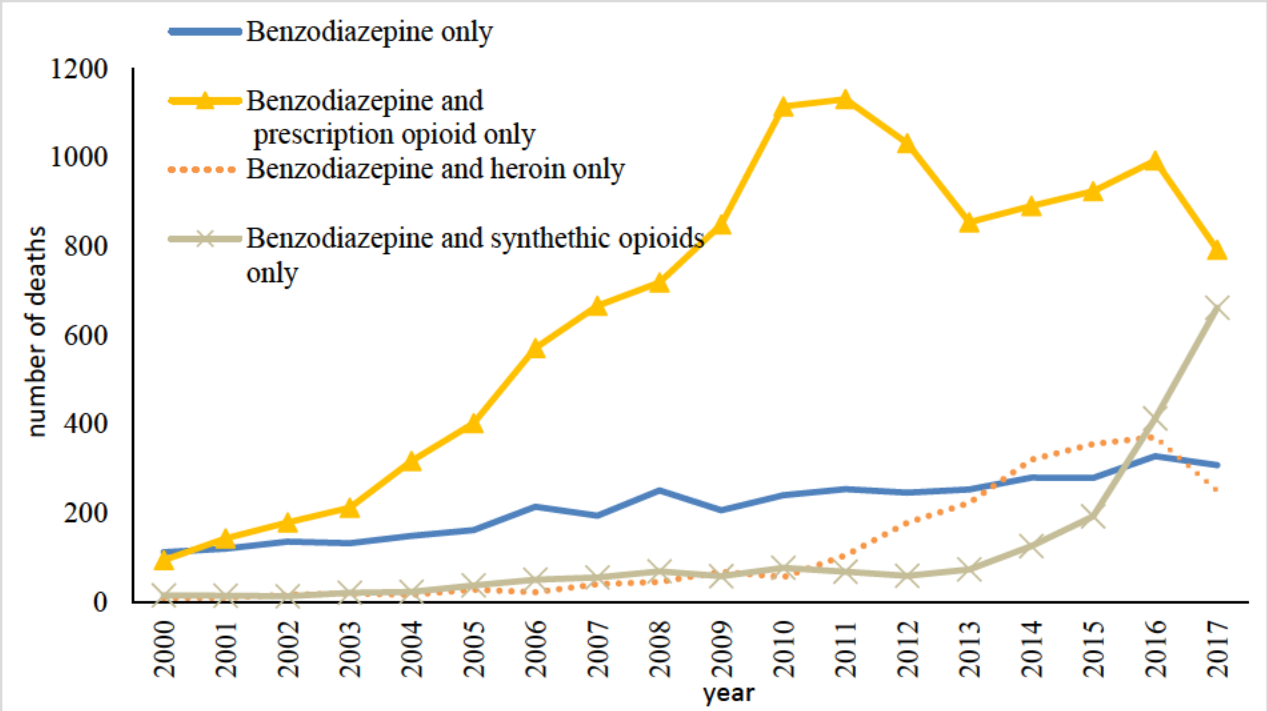



[a]drug poisoning underlying cause of death ICD-10 codes: X40-X44, X60-X64, X85, Y10-Y14

Considering benzodiazepine single-drug deaths and deaths involving a benzodiazepine in combination with only one other drug (prescription opioids, heroin, or synthetic opioids) (**Figure 3.13; Appendix D Table D3**), the number of deaths involving benzodiazepines and prescription opioids surpassed deaths from benzodiazepine as a single drug and also deaths involving both benzodiazepine and heroin or benzodiazepine and synthetic

opioids. However, the increase in deaths involving both benzodiazepine and prescription opioids was not smooth over this time period; there appeared to be a decrease in the annual number of deaths from 2011 to 2013 and from 2016 to 2017. Around 2011, deaths involving benzodiazepines and heroin began to increase, followed by deaths involving benzodiazepines and synthetic opioids. From 2000 through 2017, deaths involving only benzodiazepines steadily but slowly increased.

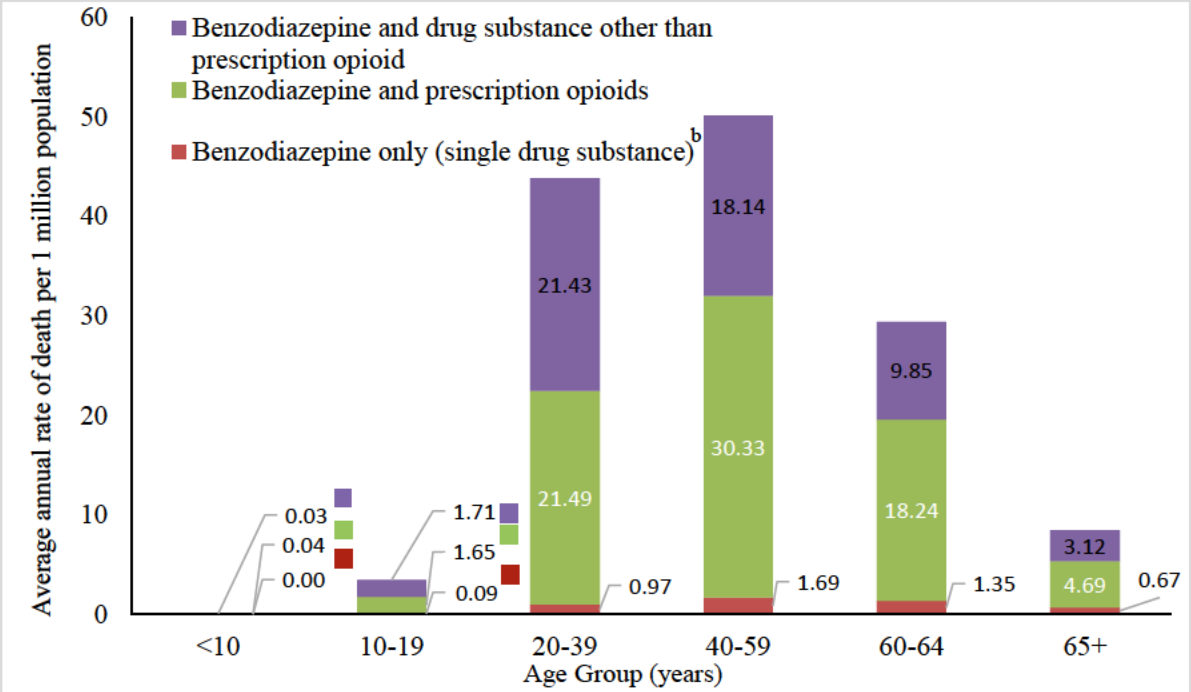
**Figure 3.13. Trends in number of single drug[a], benzodiazepine-involved deaths and benzodiazepine with only prescription opioid-, heroin- or synthetic opioid-involved deaths, where underlying cause of death is drug poisoning[b], 2000-2017, NVSS-M**




[a]Single drug defined by ICD-10 codes T36.0 to T50.9, does not involve alcohol (T51.0)
[b]Drug poisoning underlying cause of death ICD-10 codes: X40-X44, X60-X64, X85, Y10-Y14

The average annual rate of deaths involving benzodiazepines was highest among persons aged 40 to 59 years. This was true for all benzodiazepine-involved deaths (total of stacked bars), single drug benzodiazepine deaths, and deaths involving benzodiazepines and prescription opioids (**Figure 3.14; Appendix D Table D4**). For deaths involving benzodiazepines without prescription opioids, the average annual rate of death was highest among those aged 20 to 39 years, the only age group in whom benzodiazepine-related deaths more often involved another substance other than prescription opioids.

**Figure 3.14. Average annual rate of deaths involving benzodiazepines where the underlying cause of deaths is due to drug poisoning[a], per 1 million population, by age group, U.S. residents, 2013-2017, NVSS-M**




[a]Drug poisoning underlying cause of death ICD-10 codes: X40-X44, X60-X64, X85, Y10-Y14
[b]Single drug substance defined by ICD-10 codes T36.0 to T50.9, does not involve alcohol (T51.0)

## 3.8 LITERATURE REVIEW

### 3.8.1 Risks (dependence, misuse, abuse, addiction) associated with long-term benzodiazepine use

We did not identify any longitudinal studies describing the incidence of abuse, misuse or addiction associated with long-term benzodiazepine use. Expanded inclusion criteria yielded six articles, most describing characteristics of patients with chronic, high-dose or long-term benzodiazepine use or examining factors associated with chronic, high-dose, long-term use or dependence. Only one of these studies was conducted in the U.S., and this among veterans with PTSD, a select population [30]. Additionally, some studies were conducted among select populations such as patients with mental health conditions or other comorbidities [30] [31], patients with health insurance [32], or specific age groups, such the elderly [33], or younger age groups excluding the elderly [31].

Two studies, both using data from longitudinal cohorts, found that increasing age was associated with chronic (>12 weeks) or long-term (≥ 180 days) use of benzodiazepines [32] [33]. Depressive symptoms and female sex were also associated with long-term use and chronic use [33]. However, these associations with chronic use were only significant when the analysis included people who had no benzodiazepine dispensing over the study period and were weaker and not significant when the analysis was restricted to people with at least one benzodiazepine prescription [33]. In addition, one study found that 17.7% of participants filled at least one prescription for benzodiazepine became chronic

users [33]. One study found that persons living as single, separated, divorced or widowed had a higher likelihood of long-term benzodiazepine use [32], and the second study identified living alone as a protective factor [33] for chronic benzodiazepine use. Although similar concepts, these studies likely assessed different constructs of living alone, such as marital status versus independent living. These studies differed in that one study excluded patients with chronic benzodiazepine use at baseline [33] and the other did not, eliminating its ability to assess temporality [32]. Further, their definitions of long-term or chronic use were different.

A longitudinal study of U.S. veterans with posttraumatic stress disorder (PTSD) examined risk factors for receiving high dose benzodiazepines, defined as dosage in the top 10% of average daily doses, among patients with at least three prescription fills within a 120-day period [30]. This study included patients with new prescriptions for any of four anxiolytic benzodiazepines (alprazolam, clonazepam, diazepam, and lorazepam), and used longitudinal data from pharmacy and administrative claims databases to follow patients over a 6-year observation period. The study found that having a drug abuse diagnosis increased the risk of subsequent high-dose benzodiazepine use among those with long-term use. Using multivariable logistic regression, the study found that among PTSD patients with an alcoholism diagnosis, multiple factors resulted in increased odds of being prescribed a high dose of benzodiazepines. These factors were: younger age, having a drug abuse diagnosis, multiple concurrent benzodiazepine prescriptions, and concurrent acetaminophen/oxycodone prescriptions [30].

Two cross-sectional studies found that benzodiazepine dose and duration were positively associated with benzodiazepine dependence, but the study designs precluded a determination of the extent to which dose and duration contributed to benzodiazepine dependence [34] [31]. One study, which enrolled 1,048 consecutive patients who had taken benzodiazepines daily for at least one month and who were attending primary healthcare centers in Spain, found that benzodiazepine dependence, as measured by a self-report questionnaire (severity of dependence scale), was more common among women, and middle aged persons, and 47% of patients using benzodiazepines for more than 1 month reported dependence [34]. The second study described patients (n=401) who were currently using benzodiazepines and enrolled into a study of depression and anxiety from general practice and mental health care institutions in the Netherlands. The study assessed the cross-sectional association between patient score on a questionnaire to measure benzodiazepine dependence, the Bendep-SRQ, and various socio-demographic, psychological, physical, substance-use, and benzodiazepine-use related factors [31]. In multivariable-adjusted models, insomnia, antidepressant use, and alcohol dependence were associated with higher scores for benzodiazepine dependence. Similarly, both studies found benzodiazepine dependence was positively associated with antidepressant use (in one study this was true only before multivariable adjustment), but it was impossible to determine temporality, or to distinguish antidepressant use from depressive mood.

Finally, one study reported on characteristics of general practice patients with current or former long-term benzodiazepine use in the Netherlands and factors associated with benzodiazepine cravings [35]. Patients (n=193) completed questionnaires assessing benzodiazepine cravings, dependence severity, mood state, personality and lifestyle

characteristics. Craving was reported by 22.5% of the patients who had discontinued their use vs 40.7% of those who had not. Benzodiazepine dependence, psychopathology, negative mood state, and personality were associated with the patient reporting cravings. However, several limitations should be noted, including a low response rate (67%); and the potential for recall bias, especially considering the patients with former long-term benzodiazepine use [35].

In summary, studies found that female sex was positively associated with long-term/chronic use and dependence [32] [34] [33]. Other demographic factors associated with dependence, long-term, or high-dose benzodiazepine use included low education and low income [34] [32]. Multiple studies found older age to be associated with long-term/chronic use or high-dose benzodiazepine use [32] [30] [33]. Depression and concomitant antidepressant use were found to be associated with dependence, cravings and chronic/ long-term use [32] [31] [35] [33]. Other comorbid conditions associated with dependence or long-term benzodiazepine use included alcohol dependence and mental health conditions generally [31] [30].

### 3.8.2 Social factors influencing misuse and abuse of benzodiazepine drugs

At an inpatient drug treatment program in Texas in 2004, researchers interviewed 46 patients from ages 12 to 21 years old who reported they currently used alprazolam [36]. Current use was defined as at least once in the past 30 days. Participants were asked ten open-ended questions, including "why do you think Xanax is so popular?" Euphoric effect, price, self-medication and peer pressure were reported as answers to this question. High social approval was also mentioned as a reason that participants felt teenagers use Xanax, and the themes of high social approval and peer pressure were common throughout the interviews. This study provided insight into perceptions about alprazolam misuse and abuse; however, the study did not inquire about preference for alprazolam over other benzodiazepines.

The second study interviewed 13 young adults, ages 18 to 21 years, who abused benzodiazepines currently or in the past and who were receiving substance use services in Cork, Ireland from 2012-2013. [37]. Interview questions and study results did not differentiate between different benzodiazepines and instead reported on benzodiazepines generally, reporting motivations for and consequences of benzodiazepine abuse. Motivations included, to feel stoned or other similar terms to suggest relaxation, and to avoid daily stressors. The responses in this study focused more on the effects of benzodiazepine misuse, such as effects on family life, negatives of benzodiazepine misuse, and effects on social functioning. A minority of the responses were focused on the perceived benefits of benzodiazepine misuse, including being stoned, increased self-confidence and dissociation. There was little focus on peer pressure or social influence on a desire to misuse benzodiazepine. However, interviews were semi-structured, and common themes and responses elicited may have been influenced by the interviewer's adaptation of the interview guide.

Both studies were conducted among young adults and reported similar findings of the participants' desire to get high and escape daily problems. However, only the study from Texas [36] reported on external, social influences for the use of a specific benzodiazepine, perhaps due to the questions asked of the participants. Neither article

provided insight into potential preference for a specific benzodiazepine product over another.

## 3.9 FAERS

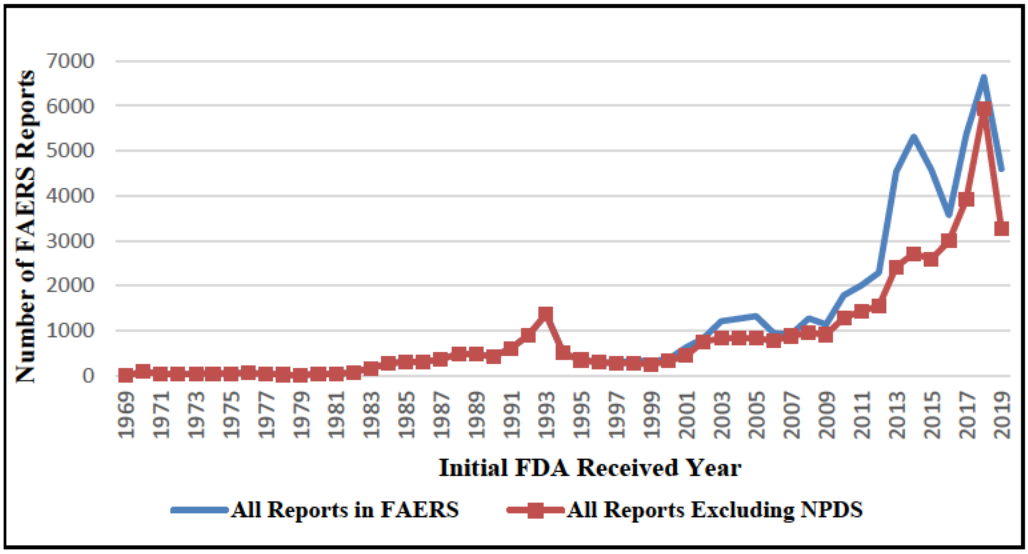
### 3.9.1 High-Level Overview of FAERS Reports

**Please note that these results may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.); causality and the role of the product in the coded event of drug abuse, dependence, and withdrawal have not been determined for the reports in this section.**

We used the FAERS search strategy described in **Table 2.7** and retrieved 58,921 reports, of which 15,038 reports are also accounted for in NPDS.

**Figure 3.15** shows all reports distributed by initial FDA received year with two trendlines; one showing all reports and the second showing all reports *excluding* those also reported to NPDS. There are two noticeable spikes in the all reports in FAERS trendline, one in 2014 and another in 2018. It should be noted that benzodiazepines have received increased media attention over the past several years, which may have influenced reporting of AEs to FAERS involving benzodiazepines. In addition, the number of total FAERS reports received by the FDA has steadily increased in recent years, with a large increase from 1,815,346 reports in 2017 to 2,155,067 reports in 2018. [38] The date range for our FAERS search ended midway through 2019, creating the appearance of a spike in reporting in 2018. The increase in overall reporting to FAERS combined with the partial 2019 data shown in **Figure 3.16** may explain the appearance of an increase in reports in 2018.

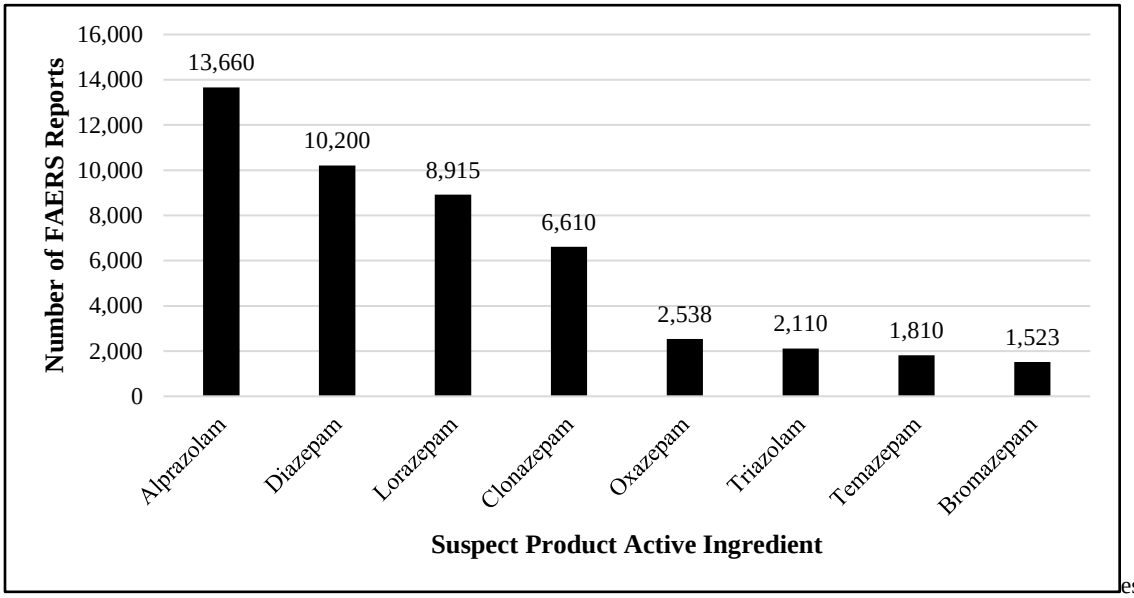
**Figure 3.15. All FAERS Reports of Benzodiazepines and *Drug abuse dependence and withdrawal* (SMQ) Broad Search through June 30, 2019 (N=58,921*) and All FAERS Reports Excluding NPDS (N=43,883*)**




*May include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.); we have not assessed the causality and the role of benzodiazepines in the coded event(s).
FAERS = FDA Adverse Event Reporting System; NPDS = National Poison Data System; SMQ = Standardised MedDRA Query

**Figure 3.16** displays the total report counts by suspect product active ingredient for the top eight most frequently reported benzodiazepines in FAERS with respect to the *Drug abuse dependence and withdrawal* (SMQ) Broad search. The four most frequently reported benzodiazepines were alprazolam, diazepam, lorazepam, and clonazepam, listed in decreasing order of frequency.

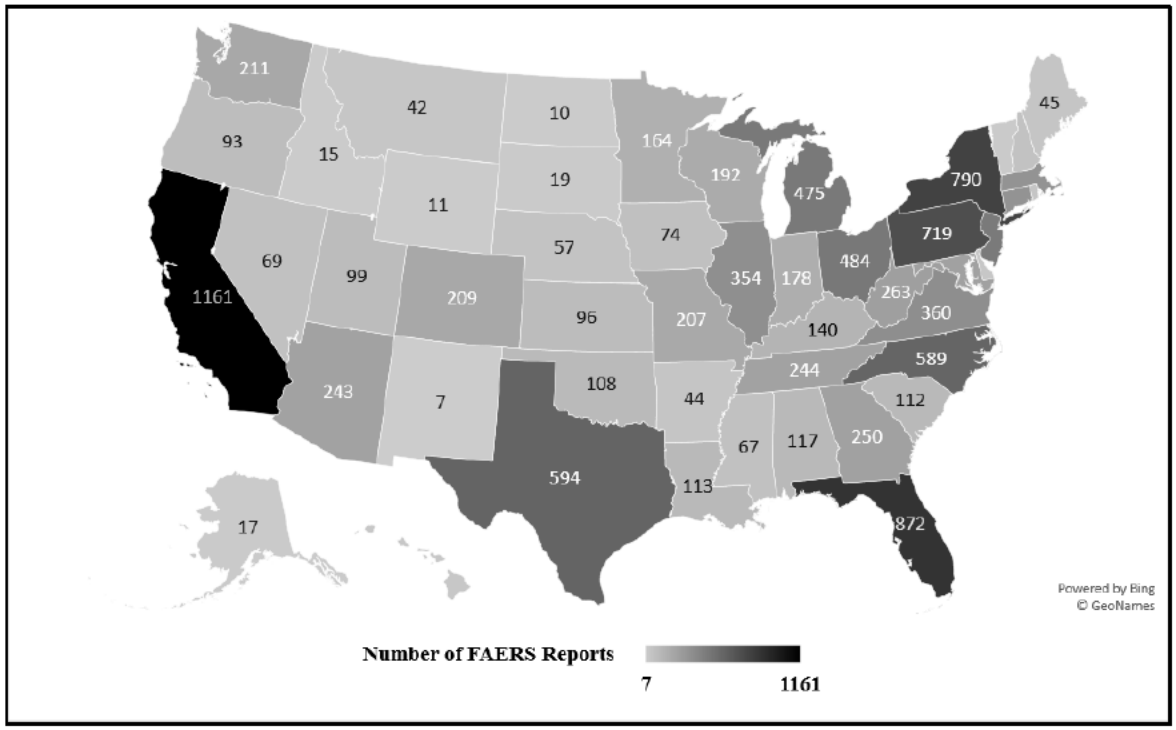
**Figure 3.16. FAERS Reports by Suspect Product Active Ingredient through June 30, 2019 for the Most Frequently Reported Benzodiazepines and *Drug abuse dependence and withdrawal* (SMQ) Broad Search, Excluding NPDS (N=43,883*)**




*May include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.); we have not assessed the causality and the role of benzodiazepines in the coded event(s).
FAERS = FDA Adverse Event Reporting System; NPDS = National Poison Data System; SMQ = Standardised MedDRA Query

**Figure 3.17** below displays the distribution of benzodiazepine and abuse, dependence, and withdrawal reports by geographic location, namely the state of the reporter, with California, Florida, and New York having the highest frequency of reporting, as expected based on their large populations.

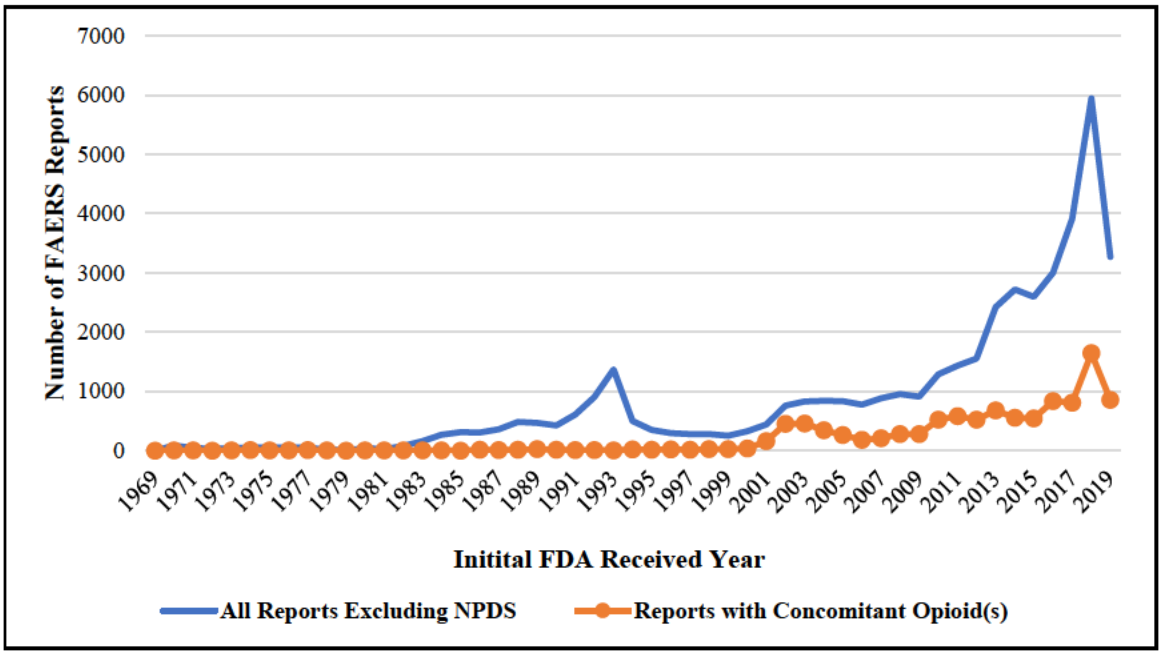
**Figure 3.17. FAERS Reports* by State of Reporter through June 30, 2019 for Benzodiazepines and *Drug abuse dependence and withdrawal* (SMQ) Broad Search, Excluding NPDS**




*May include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.); we have not assessed the causality and the role of benzodiazepines in the coded event(s).
FAERS = FDA Adverse Event Reporting System; NPDS = National Poison Data System; SMQ = Standardised MedDRA Query

**Figure 3.18** displays number of all reports of benzodiazepines and abuse, dependence, or withdrawal in FAERS excluding NPDS, and reports of benzodiazepines with a concomitant suspect opioid. **Table 3.14** contains descriptive characteristics for each of these data sets for comparison.

**Figure 3.18. *Drug abuse dependence and withdrawal* (SMQ) Broad Search in FAERS through June 30, 2019 Excluding NPDS for All Reports of Benzodiazepines (N=43,883*) and All Reports with Concomitant Opioid(s) (N=10,426*)**




*May include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.); we have not assessed the causality and the role of benzodiazepines in the coded event(s).
FAERS = FDA Adverse Event Reporting System; NPDS = National Poison Data System; SMQ = Standardised MedDRA Query

**Table 3.14. Descriptive Characteristics of FAERS Reports of Benzodiazepines and *Drug abuse dependence and withdrawal* (SMQ) Broad Search, and FAERS Reports With Concomitant Opioid(s)*, Excluding NPDS, Received by FDA through June 30, 2019**

| | | All Reports N=43,883† | With Concomitant Opioid(s)† N=10,426 |
|---|---|---|---|
| **Age, years** | | **N=33,204‡** | **N=8,561‡** |
| | Median | 42 | 42 |
| | Mean | 42 | 42 |
| | Range | 0 to 102 | 0 to 99 |
| **Sex** | | **N=39,964** | **N=9,509** |
| | Female | 22,144 | 3,870 |
| | Male | 17,820 | 5,639 |

**Table 3.14. Descriptive Characteristics of FAERS Reports of Benzodiazepines and *Drug abuse dependence and withdrawal* (SMQ) Broad Search, and FAERS Reports With Concomitant Opioid(s)[*], Excluding NPDS, Received by FDA through June 30, 2019**

| | | All Reports N=43,883[†] | With Concomitant Opioid(s)[†] N=10,426 |
|---|---|---|---|
| **Type of Report** | Expedited (15-day) | 35,119 | 8,674 |
| | Non-expedited | 7,126 | 1,622 |
| | Direct | 1638 | 130 |
| **Initial FDA Received Year** | 1968 – 1975 | 304 | 10 |
| | 1976 – 1985 | 1,012 | 25 |
| | 1986 – 1995 | 5,771 | 124 |
| | 1996 – 2005 | 5,137 | 1,782 |
| | 2006 – 2015 | 15,533 | 4,342 |
| | 2016 – 2019 | 16,126 | 4,143 |
| **Country Derived** | United States | 17,590 | 5,364 |
| | Italy | 6,577 | 226 |
| | France | 4,545 | 1,056 |
| | Great Britain | 4,146 | 1,142 |
| | Germany | 1,915 | 321 |
| | Austria | 1,192 | 641 |
| | Canada | 1,148 | 613 |
| | Japan | 1,141 | 31 |
| | Sweden | 749 | 231 |
| | Brazil | 648 | 2 |
| | Other | 4,232 | 799 |
| **Outcome[§]** | Death | 10,448 | 6,302 |
| | Life-threatening | 3,634 | 722 |
| | Hospitalization | 19,123 | 2,497 |
| | Disability | 2,056 | 91 |
| | Other serious | 19,938 | 4,201 |
| | Non-serious | 2,819 | 145 |

[*]The following product active ingredients and product names were considered opioids for the purpose of this review and used to filter for reports with concomitant opioid(s): "buprenorphine," "carfentanil," "codeine," "fentanyl," "hydrocodone," "hydromorphone," "methadone," "morphine," "oxycodone," "oxymorphone," "Demerol," "Dilaudid," "Duragesic," "Kadian," "Opana," "Oxycontin," "Percocet," "Roxicodone," "Subutex," and "Vicodin"

[†]May include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.); we have not assessed the causality and the role of benzodiazepines in the coded event(s).

[‡]Ages expressed as negative numbers in FAERS reports (*in utero* exposures) were not included in the age calculations

[§]For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A case may have more than one serious outcome.

FAERS = FDA Adverse Event Reporting System, NPDS = National Poison Data System, SMQ = Standardised MedDRA Query

Approximately 24% of all FAERS reports of benzodiazepines and abuse, dependence, or withdrawal also reported concomitant opioid(s). The distribution of age, type of report, and year received by the FDA were similar across the two groups.

**Table 3.15** below contains a list of the Top 25 most frequently reported PTs in FAERS for all reports of benzodiazepines and abuse, dependence or withdrawal, excluding those also reported to NPDS, with a breakdown of this PT distribution by product active ingredient.

**It is important to note that causality has not been assessed for this high-level overview, therefore conclusions cannot be drawn regarding the relatedness of these AEs to benzodiazepines. Because of the spontaneous nature of the reports, incidence of a given AE cannot be calculated using FAERS data and comparisons between drugs are not accurate.**

**Table 3.15. Top 25 Most Frequently Reported PTs* in FAERS for Benzodiazepines and *Drug abuse dependence and withdrawal* (SMQ) Broad through June 30, 2019, Excluding NPDS**

| PT<br>Number of Reports (Frequency, %) | | | | |
|---|---|---|---|---|
| **All Benzodiazepines (N=43,883†)** | **Alprazolam (N=13,660†)** | **Diazepam (N=10,200†)** | **Lorazepam (N=8,916†)** | **Clonazepam (N=6,610†)** |
| *Toxicity to various agents*<br>9,446 (21.5) | *Drug withdrawal syndrome*<br>1,897 (23.7) | *Toxicity to various agents*<br>1,264 (34.4) | *Drug dependence*<br>1,634 (31.1) | *Withdrawal syndrome*<br>565 (18.9) |
| *Overdose*<br>8,634 (19.7) | *Drug dependence*<br>1,544 (19.3) | *Overdose*<br>803 (21.8) | *Drug withdrawal syndrome*<br>1,487 (28.3) | *Drug withdrawal syndrome*<br>560 (18.8) |
| *Drug abuse*<br>7,013 (16.0) | *Drug abuse*<br>1,356 (16.9) | *Drug abuse*<br>546 (14.9) | *Drug abuse*<br>863 (16.4) | *Overdose*<br>480 (16.1) |
| *Intentional overdose*<br>6,991 (15.9) | *Overdose*<br>1,188 (14.8) | *Intentional overdose*<br>486 (13.2) | *Intentional overdose*<br>721 (13.7) | *Drug abuse*<br>327 (11) |
| *Drug withdrawal syndrome*<br>5,748 (13.1) | *Toxicity to various agents*<br>1,135 (14.2) | *Drug dependence*<br>374 (10.2) | *Anxiety*<br>673 (12.8) | *Toxicity to various agents*<br>324 (10.9) |
| *Drug dependence*<br>5,720 (13.0) | *Intentional overdose*<br>848 (10.6) | *Drug withdrawal syndrome*<br>310 (8.4) | *Suicide attempt*<br>647 (12.3) | *Insomnia*<br>323 (10.8) |
| *Suicide attempt*<br>4,540 (10.3) | *Suicide attempt*<br>621 (7.8) | *Coma*<br>238 (6.5) | *Overdose*<br>600 (11.4) | *Anxiety*<br>321 (10.8) |
| *Sopor*<br>2,908 (6.6) | *Sopor*<br>542 (6.8) | *Intentional product misuse*<br>237 (6.4) | *Sopor*<br>593 (11.3) | *Drug dependence*<br>321 (10.8) |
| *Somnolence*<br>2,886 (6.6) | *Anxiety*<br>525 (6.6) | *Suicide attempt*<br>235 (6.4) | *Depression*<br>456 (8.7) | *Intentional overdose*<br>286 (9.6) |

**Table 3.15. Top 25 Most Frequently Reported PTs* in FAERS for Benzodiazepines and *Drug abuse dependence and withdrawal* (SMQ) Broad through June 30, 2019, Excluding NPDS**

| PT<br>Number of Reports (Frequency, %) | | | | |
|---|---|---|---|---|
| **All Benzodiazepines (N=43,883†)** | **Alprazolam (N=13,660†)** | **Diazepam (N=10,200†)** | **Lorazepam (N=8,916†)** | **Clonazepam (N=6,610†)** |
| *Coma*<br>2,858 (6.5) | *Withdrawal syndrome*<br>491 (6.1) | *Drug interaction*<br>223 (6.1) | *Insomnia*<br>388 (7.4) | *Suicide attempt*<br>271 (9.1) |
| *Anxiety*<br>2,416 (5.5) | *Insomnia*<br>406 (5.1) | *Somnolence*<br>175 (4.8) | *Nervousness*<br>369 (7) | *Drug ineffective*<br>233 (7.8) |
| *Accidental overdose*<br>2,360 (5.4) | *Seizure*<br>404 (5) | *Withdrawal syndrome*<br>160 (4.4) | *Somnolence*<br>363 (6.9) | *Tremor*<br>219 (7.3) |
| *Intentional self-injury*<br>2,121 (4.8) | *Intentional product misuse*<br>395 (4.9) | *Sopor*<br>154 (4.2) | *Amnesia*<br>345 (6.6) | *Depression*<br>214 (7.2) |
| *Withdrawal syndrome*<br>2,116 (4.8) | *Tremor*<br>369 (4.6) | *Accidental overdose*<br>131 (3.6) | *Toxicity to various agents*<br>341 (6.5) | *Somnolence*<br>203 (6.8) |
| *Intentional product misuse*<br>2,034 (4.6) | *Coma*<br>367 (4.6) | *Respiratory depression*<br>121 (3.3) | *Palpitations*<br>340 (6.5) | *Dizziness*<br>179 (6) |
| *Drug interaction*<br>1,974 (4.5) | *Somnolence*<br>366 (4.6) | *Loss of consciousness*<br>111 (3) | *Tachycardia*<br>283 (5.4) | *Suicidal ideation*<br>173 (5.8) |
| *Insomnia*<br>1,904 (4.3) | *Drug ineffective*<br>343 (4.2) | *Anxiety*<br>110 (3) | *Confusional state*<br>252 (4.8) | *Headache*<br>168 (5.6) |
| *Depression*<br>1,849 (4.2) | *Accidental overdose*<br>*335 (4.2)* | *Hypotension*<br>105 (2.9) | *Agitation*<br>244 (4.6) | *Feeling abnormal*<br>154 (5.2) |
| *Confusional state*<br>1,678 (3.8) | *Depression*<br>319 (4) | *Agitation*<br>102 (2.8) | *Intentional self-injury*<br>235 (4.5) | *Sopor*<br>151 (5.1) |
| *Hypotension*<br>1,664 (3.8) | *Intentional self-injury*<br>285 (3.6) | *Intentional self-injury*<br>102 (2.8) | *Tremor*<br>227 (4.3) | *Nausea*<br>146 (4.9) |
| *Loss of consciousness*<br>1,621 (3.7) | *Headache*<br>257 (3.2) | *Depressed level of consciousness*<br>99 (2.7) | *Withdrawal syndrome*<br>221 (4.2) | *Confusional state*<br>139 (4.7) |
| *Tremor*<br>1,470 (3.3) | *Confusional state*<br>255 (3.2) | *Completed suicide*<br>97 (2.6) | *Major depression*<br>211 (4) | *Seizure*<br>136 (4.6) |
| *Agitation*<br>1,465 (3.3) | *Agitation*<br>252 (3.1) | *Sedation*<br>91 (2.5) | *Vomiting*<br>205 (3.9) | *Fatigue*<br>133 (4.5) |
| *Seizure*<br>1,430 (3.3) | *Loss of consciousness*<br>234 (2.9) | *Death*<br>90 (2.4) | *Emotional disorder*<br>199 (3.8) | *Malaise*<br>123 (4.1) |

**Table 3.15. Top 25 Most Frequently Reported PTs* in FAERS for Benzodiazepines and *Drug abuse dependence and withdrawal* (SMQ) Broad through June 30, 2019, Excluding NPDS**

| PT<br>Number of Reports (Frequency, %) | | | | |
|---|---|---|---|---|
| **All Benzodiazepines (N=43,883†)** | **Alprazolam (N=13,660†)** | **Diazepam (N=10,200†)** | **Lorazepam (N=8,916†)** | **Clonazepam (N=6,610†)** |
| *Vomiting*<br>1,385 (3.2) | *Dizziness*<br>225 (2.8) | *Confusional state*<br>84 (2.3) | *Neurosis*<br>199 (3.8) | *Memory impairment*<br>123 (4.1) |

*A report may have more than one coded PT. We have not assessed the causality and the role of benzodiazepines in the coded event(s).
†May include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.).
FAERS = FDA Adverse Event Reporting System; NPDS = Nation Poison Data System; PT = Preferred Term

The 25 most frequently reported PTs listed in **Table 3.15** above reflect expected AEs associated with benzodiazepines as a pharmacologic class. Although the distribution of most frequently reported PTs slightly varies with each benzodiazepine, we found no major differences or unexpected PTs in this high-level overview of alprazolam, diazepam, lorazepam or clonazepam.

**Table 3.16** below shows the report counts by reported serious outcome for benzodiazepines and *Drug abuse dependence and withdrawal* (SMQ) Broad through June 30, 2019, excluding those reported to NPDS.

**Table 3.16. FAERS Report Counts by Reported Serious Outcomes* for Benzodiazepines and *Drug abuse dependence and withdrawal* (SMQ) Broad Search through June 30, 2019, Excluding NPDS**

| Reported Outcome | All BZD N=43,883† (%) | Alprazolam N=13,660† (%) | Diazepam N=10,201† (%) | Lorazepam N=8,916† (%) | Clonazepam N=6,611† (%) |
|---|---|---|---|---|---|
| **Death** | 10,448 (23.8) | 3,333 (24.4) | 4,390 (43) | 909 (10.2) | 1,133 (17.1) |
| **Life Threatening** | 3,634 (8.3) | 914 (6.7) | 812 (8) | 710 (8) | 701 (10.6) |
| **Hospitalization** | 19,123 (43.6) | 5,294 (38.8) | 3,551 (34.8) | 5,090 (57) | 2,915 (44) |
| **Disability** | 2,056 (4.7) | 282 (2.1) | 191 (1.9) | 1,196 (13.4) | 350 (5.3) |
| **Other Serious** | 19,938 (45.4) | 6,197 (45.4) | 4,192 (41) | 4,452 (50) | 3,217 (48.7) |

*A report may have more than one reported outcome. We have not assessed the causality and the role of benzodiazepines in the coded outcomes.
†May include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.).
BZD = benzodiazepine; FAERS = FDA Adverse Event Reporting System; NPDS = Nation Poison Data System; SMQ = Standardised MedDRA Query

### *3.9.1.1 Analysis of Fatal Reports Identified in FAERS High-Level Overview*

Notably, 60% of fatal reports of benzodiazepines and abuse, dependence, or withdrawal, reported concomitant opioid(s). Approximately 3% (n=343) of the 10,448 fatal reports of abuse, dependence, or withdrawal involved only a benzodiazepine (i.e., single drug substance, without coded concomitant substances or illicit substances mentioned in the narrative). We did not conduct a report-level review of these reports; therefore, there may be reports that involve other unknown substances not coded in the report or captured in our narrative text search. **It is important to note that causality has not been assessed for this high-level overview; therefore, conclusions cannot be drawn regarding the role of benzodiazepines and their contribution to the fatal outcome.**

**Table 3.17** provides the product active ingredients reported in the 343 benzodiazepine single drug substance fatal reports.

**Table 3.17. Frequency of Product Active Ingredients Reported in Fatal* FAERS Reports of Abuse, Dependence, or Withdrawal with a Benzodiazepine as a Single Drug Substance† through June 30, 2019, Excluding NPDS (N=343)**

| Product Active Ingredients‡ | Number of Reports§ (%) |
|---|---|
| Triazolam | 141 (41.1) |
| Alprazolam | 69 (20.1) |
| Diazepam | 56 (16.3) |
| Clonazepam | 35 (10.2) |
| Temazepam | 15 (4.4) |
| Lorazepam | 14 (4.1) |
| Midazolam hydrochloride | 8 (2.3) |
| Estazolam | 3 (0.9) |
| Oxazepam | 2 (0.6) |

*__Causality has not been assessed for this high-level overview; therefore, conclusions cannot be drawn regarding the relatedness of these adverse events to benzodiazepines or the role of benzodiazepines and their contribution to the fatal outcome.__

†We removed those reports that had any concomitant medications coded. We then used a narrative text search for the following terms to further identify and remove cases of multiple drug exposures and those with illicit substances mentioned in the narrative only: "multiple drug overdose," "THC," "marijuana," "cocaine," "opiate," "alcohol," "heroin." We did not conduct a report-level review of these reports; therefore, there may be reports that involve other unknown substances not coded in the report or captured in our narrative text search.

‡ A report may have more than one product active ingredient.

§May include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.).

FAERS = FDA Adverse Event Reporting System; NPDS = National Poison Data System

Upon screening the 141 triazolam fatal reports, only 44% (n=62) actually reported triazolam as a single drug substance. Of those 62 reports, approximately 50% were death by suicide or possible overdose, and 25% were accidental deaths (e.g., house fire after ingestion of triazolam), homicides, or deaths of an unconfirmed cause. The remaining 25% were unrelated to triazolam or lacked information necessary to fully evaluate causality (e.g., time of ingestion of drug relative to AE, dose, concomitant medications, medical history of the patient).

**Table 3.18** provides a breakdown of PTs in the 343 benzodiazepine single drug substance fatal reports.

**Table 3.18. Frequency of Top 15 PTs Reported in Fatal* FAERS Reports of Abuse, Dependence, or Withdrawal with a Benzodiazepine as a Single Drug Agent† through June 30, 2019, Excluding NPDS (N=343)**

| PTs* | Number of Reports‡ (%) |
|---|---|
| *Overdose* | 180 (52.5) |
| *Intentional overdose* | 69 (20.1) |
| *Death* | 57 (16.6) |
| *Suicide attempt* | 28 (8.2) |
| *Completed suicide* | 26 (7.6) |
| *Drug dependence* | 22 (6.4) |
| *Drug withdrawal syndrome* | 17 (5) |
| *Coma* | 16 (4.7) |
| *Accidental overdose* | 13 (3.8) |
| *Cardiac arrest* | 12 (3.5) |
| *Drug level above therapeutic* | 12 (3.5) |
| *Intentional product misuse* | 10 (2.9) |
| *Withdrawal syndrome* | 9 (2.6) |
| *Drug abuse* | 8 (2.3) |
| *Seizure* | 8 (2.3) |

*__Causality has not been assessed for this high-level overview; therefore, conclusions cannot be drawn regarding the relatedness of these adverse events to benzodiazepines or the role of benzodiazepines and their contribution to the fatal outcome.__ A report may have more than one coded PT.

†We removed those reports that had any concomitant medications coded. We then used a narrative text search for the following terms to further identify and remove cases of multiple drug exposures and those with illicit substances mentioned in the narrative only: "multiple drug overdose," "THC," "marijuana," "cocaine," "opiate," "alcohol," "heroin." We did not conduct a report-level review of these reports; therefore, there may be reports that involve other unknown substances not coded in the report or captured in our narrative text search.

‡May include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.)

FAERS = FDA Adverse Event Reporting System; NPDS = National Poison Data System; SMQ = Standardised MedDRA Query; PT = Preferred Term

**Tables 3.19 and 3.20** describe the remaining 3,803 fatal reports of benzodiazepines with concomitant drugs other than opioids. **Table 3.19** includes the product active ingredients *other than benzodiazepines* that were coded in these reports, but their relative contribution to the fatal outcome has not been assessed at the report level. **Table 3.20** provides a breakdown of PTs reported in these reports.

**Table 3.19. Frequency of All Product Active Ingredients Reported with Benzodiazepines in Fatal* FAERS Reports of Abuse, Dependence, or Withdrawal through June 30, 2019, Excluding Concomitant Opioid(s) and NPDS (N=3,803†)**

| Product Active Ingredients† | Number of Reports‡ (%) |
|---|---|
| Alcohol | 404 (10.6) |
| Citalopram hydrobromide | 276 (7.3) |
| Acetaminophen | 259 (6.8) |
| Fluoxetine hydrochloride | 243 (6.4) |
| Zolpidem tartrate | 214 (5.6) |
| Quetiapine | 207 (5.4) |
| Olanzapine | 201 (5.3) |
| Venlafaxine | 177 (4.7) |
| Mirtazapine | 164 (4.3) |
| Pregabalin | 164 (4.3) |
| Tramadol | 156 (4.1) |
| Sertraline | 154 (4) |

***Causality has not been assessed for this high-level overview; therefore, conclusions cannot be drawn regarding the relatedness of these adverse events to benzodiazepines or concomitant drugs or the role of benzodiazepines or concomitant drugs and their contribution to the fatal outcome.**

†A report may have more than one product active ingredient

‡May include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.)

FAERS = FDA Adverse Event Reporting System; NPDS = National Poison Data System

**Table 3.20. Frequency of Top 15 PTs Involved in Fatal* FAERS Reports of Abuse, Dependence, or Withdrawal with Benzodiazepines through June 30, 2019, Excluding Cases with Concomitant Opioid(s) and NPDS (N=3,803)**

| PTs | Number of Reports† (%) |
|---|---|
| *Toxicity to various agents* | 1,662 (43.7) |
| *Overdose* | 1,118 (29.4) |
| *Intentional overdose* | 732 (19.2) |
| *Completed suicide* | 714 (18.8) |
| *Accidental overdose* | 333 (8.8) |
| *Drug interaction* | 314 (8.3) |
| *Drug abuse* | 249 (6.5) |
| *Suicide attempt* | 235 (6.2) |
| *Coma* | 234 (6.2) |
| *Cardiac arrest* | 221 (5.8) |
| *Death* | 212 (5.6) |
| *Pulmonary oedema* | 172 (4.5) |
| *Hypotension* | 153 (4) |
| *Respiratory depression* | 141 (3.7) |
| *Depressed level of consciousness* | 140 (3.7) |

*__Causality has not been assessed for this high-level overview; therefore, conclusions cannot be drawn regarding the relatedness of these adverse events to benzodiazepines or the role of benzodiazepines and their contribution to the fatal outcome.__ A report may have more than one coded PT.

† May include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.)

FAERS = FDA Adverse Event Reporting System; NPDS = Nation Poison Data System; PT = Preferred Term

### 3.9.2 FAERS Case Selection for Report-Level Review

We used the FAERS search described in **Table 2.7** and retrieved 346 reports. After applying the case definition in **Section 2.10.3** and accounting for duplicate reports, we included 104 cases in our case series of abuse, dependence, or withdrawal reported with benzodiazepine as a single drug substance (i.e., monotherapy) (see **Figure 3.19**).

**Figure 3.19. FAERS Case Selection**

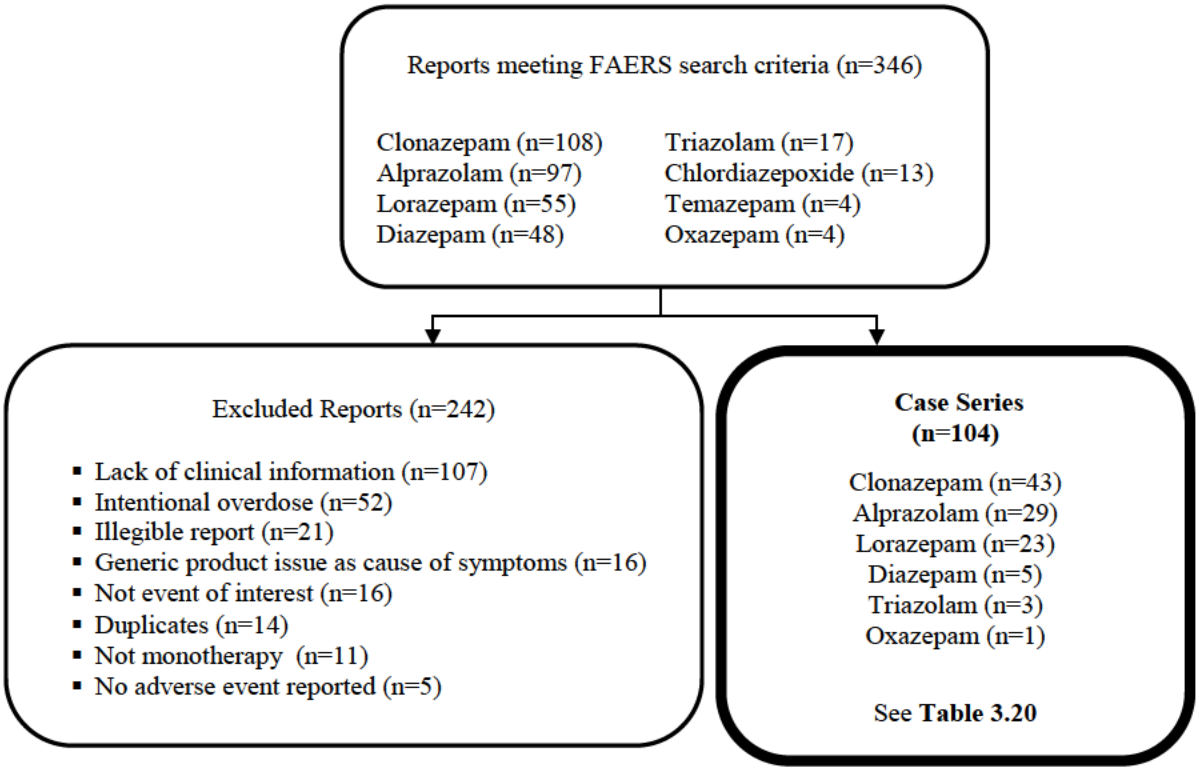



**Table 3.21** summarizes the 104 FAERS cases of abuse, dependence, or withdrawal reported with benzodiazepine as a single drug substance by consumers and healthcare professionals directly to the FDA for this case series.

**Appendix G3** contains a line listing of the 104 cases in this case series.

| **Table 3.21. Descriptive Characteristics of Abuse, Dependence, or Withdrawal with Benzodiazepine as a Single Drug Substance Direct Reports to FDA, Received by FDA through June 30, 2019 (N=104)** | | |
|---|---|---|
| **Age, years**<br>**N=91** | Median<br>Mean<br>Range | 45<br>44<br>17 to 77 |
| **Sex**<br>**N=101** | Female<br>Male | 67<br>34 |
| **Drug of Interest** | Clonazepam<br>Alprazolam<br>Lorazepam<br>Diazepam<br>Triazolam<br>Oxazepam | 43<br>29<br>23<br>5<br>3<br>1 |

| **Table 3.21. Descriptive Characteristics of Abuse, Dependence, or Withdrawal with Benzodiazepine as a Single Drug Substance Direct Reports to FDA, Received by FDA through June 30, 2019 (N=104)** | | |
|---|---|---|
| **Reporter** | Patient | 82 |
| | Prescriber | 13 |
| | Pharmacist | 5 |
| | Patient's relative | 4 |
| **Reason for Use, n=102*** | Anxiety† | 59 |
| | Depression | 6 |
| | Insomnia | 22 |
| | Panic attack or panic disorder | 17 |
| | Post-traumatic stress disorder | 4 |
| | Other‡ | 8 |
| **Original Source of Drug§** | Prescription | 102 |
| | Unknown | 2 |
| **Initial FDA Received Year** | 1968 – 1975 | 3 |
| | 1976 – 1985 | 3 |
| | 1986 – 1995 | 13 |
| | 1996 – 2005 | 32 |
| | 2006 – 2015 | 39 |
| | 2016 – 2019 | 14 |
| **Type of Event*‖** | Abuse | 4 |
| | Dependence | 90 |
| | Withdrawal | 94 |
| **Outcome¶** | Life Threatening | 21 |
| | Hospitalization | 29 |
| | Disability | 33 |
| | Other serious | 53 |
| | Required intervention | 17 |
| | Non-serious | 12 |

*A case may report more than one.

†Anxiety includes any of the following reasons for use: acute anxiety, anxiety, nerves, pre-procedure anxiety, social anxiety disorder, situational anxiety

‡Other reasons for use included: alcoholism (n=1), Bipolar, mixed (n=1), cerebellar syndrome (n=1), chronic nausea (n=1), drug abuse (n=1), neuromuscular pain (n=1), obsessive compulsive disorder (n=1), vertigo (n=1).

§Zero cases reported obtaining the benzodiazepine by illegal means.

‖Abuse, dependence and withdrawal determination made by using definitions **in Tables 2.5** and **2.6** in **Section 2.10.1** after report-level review of the case narrative, rather than using MedDRA coded events.

¶For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A case may have more than one serious outcome.

FAERS = FDA Adverse Event Reporting System; MedDRA = Medical Dictionary for Regulatory Activities

All but two cases in this case series described AEs that developed with prescription use of benzodiazepines. There were no cases that either described obtaining benzodiazepines by illegal means or that described patients who started out with a valid prescription for a benzodiazepine and then switched to obtaining the drug by illegal means. Four of the 104 cases included in this case series described a case of benzodiazepine abuse. It is important to note that there may be a bias against identifying cases of abuse or illicit use because we limited our search to direct reports only. We assume that patients generally do not self-report abuse or illicit use of substances to the FDA, and most cases in this case series (n=82, 79%) were submitted by the patients themselves.

**Table 3.22** below displays the median and range of the following data points from this case series: time to onset of symptoms of dependence or tolerance, duration of benzodiazepine use, and duration of withdrawal symptoms. **Because of the spontaneous nature of the reports, incidence of a given AE cannot be calculated using FAERS data and comparisons between drugs are not accurate.**

**Table 3.22. Time to Onset of Dependence, Duration of Use, and Duration of Withdrawal Symptoms* in Direct Reports to FDA of Abuse, Dependence, or Withdrawal for Benzodiazepines as a Single Drug Substance, Received by FDA through June 30, 2019**

| | Median (Range) Time to Onset of Dependence or Tolerance, days | Median (Range) Duration of Use, months | Median (Range) Duration of Withdrawal Symptoms, months |
|---|---|---|---|
| **All Reported Benzodiazepines** | 14<br>(1 day to 4 years)<br>N=45 | 19.5<br>(6 days to 25 years)<br>N=96 | 9.5<br>(2 weeks to 8 years)<br>N=44 |
| **Alprazolam** | 3<br>(1 day to 1 year)<br>N=13 | 18<br>(6 days to 10 years)<br>N=27 | 21<br>(12 weeks to 5 years)<br>N=8 |
| **Clonazepam** | 20.5<br>(1 day to 3 years)<br>N=18 | 30<br>(1 month to 25 years)<br>N=41 | 13<br>(2 weeks to 5 years)<br>N=25 |
| **Diazepam** | 3<br>N=1 | 12<br>(3 months to 2.5 years)<br>N=3 | 26<br>N=1 |
| **Lorazepam** | 21 (1 day to 4 years)<br>N=12 | 10<br>(21 days to 18 years)<br>N=21 | 3.5<br>(2 weeks to 8 years)<br>N=9 |
| **Triazolam** | 21<br>N=1 | 10 (2 months to 3 years)<br>N=3 | 2 weeks<br>N=1 |
| **Oxazepam** | --- | 24<br>N=1 | --- |

*Incidence of a given adverse event cannot be calculated using FAERS data and comparisons between drugs are not accurate.
FAERS = FDA Adverse Event Reporting System

Notably, 18 of the 44 cases that provided duration of withdrawal information also stated that withdrawal symptoms were still ongoing at the time of the report. The breakdown by product for the cases describing ongoing withdrawal is as follows: lorazepam (n=6), alprazolam (n=5), clonazepam (n=5), diazepam (n=1), triazolam (n=1).

Approximately 80% (83/104) of the cases in this case series described specific symptoms of withdrawal. **Table 3.23** on the following page provides a summary of the top 20 verbatim (not coded MedDRA term) symptoms of withdrawal reported in this case series. We included the number and percentage of cases in which each symptom was reported for all benzodiazepines, and the number of cases for each of the top four reported benzodiazepines (alprazolam, diazepam, lorazepam, and clonazepam).

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| **Table 3.23. Symptoms of Withdrawal Described in >5% of Direct Reports to FDA of Abuse, Dependence or Withdrawal with Benzodiazepine as a Single Drug Substance, Received by FDA through June 30, 2019 (N=83)** | | | | | |
|---|---|---|---|---|---|
| **Verbatim terms*** | **All Reported Benzodiazepines N=83[†](%)** | **Alprazolam N=23** | **Clonazepam N=35** | **Diazepam N=3** | **Lorazepam N=19** |
| Insomnia | 32 (38.6) | 11 | 13 | 1 | 6 |
| Anxiety or panic | 27 (32.5) | 6 | 11 | 0 | 9 |
| Heart palpitations; Tachycardia or bradycardia; Non-specific arrhythmias | 24 (28.9) | 8 | 8 | 1 | 6 |
| Gastrointestinal (GI) upset (includes nausea, diarrhea, or other non-specific GI symptoms) | 23 (27.7) | 6 | 12 | 0 | 3 |
| Headache or migraine (includes head pressure, head pain) | 18 (21.7) | 2 | 12 | 0 | 4 |
| Dizziness, lightheadedness, or vertigo | 18 (21.7) | 6 | 7 | 0 | 4 |
| Memory impairment, confusion, disorientation, cognitive decline, cognition issues, or dementia | 17 (20.5) | 2 | 10 | 0 | 4 |
| Pain | 16 (19.2) | 4 | 8 | 0 | 3 |
| Depression | 13 (15.7) | 4 | 6 | 1 | 2 |
| Tremor(s) or trembling | 13 (15.7) | 3 | 7 | 0 | 2 |
| Sweating or diaphoresis | 13 (15.7) | 4 | 4 | 0 | 4 |
| Suicidal ideation or suicide attempt | 12 (14.5) | 1 | 9 | 0 | 2 |
| Hypertension | 9 (10.8) | 4 | 2 | 1 | 2 |
| Derealization or depersonalization | 9 (10.8) | 2 | 3 | 0 | 4 |
| Convulsions, myoclonus, shakes or twitching | 9 (10.8) | 1 | 4 | 2 | 2 |

**Table 3.23. Symptoms of Withdrawal Described in >5% of Direct Reports to FDA of Abuse, Dependence or Withdrawal with Benzodiazepine as a Single Drug Substance, Received by FDA through June 30, 2019 (N=83)**

| Verbatim terms* | All Reported Benzodiazepines N=83[†](%) | Alprazolam N=23 | Clonazepam N=35 | Diazepam N=3 | Lorazepam N=19 |
|---|---|---|---|---|---|
| Muscle spasms, cramps, or "locked muscles" (includes involuntary muscle contractions) | 8 (9.6) | 1 | 7 | 0 | 0 |
| Fatigue | 7 (8.4) | 3 | 1 | 0 | 3 |
| Weight loss or weight increase | 6 (7.2) | 0 | 2 | 0 | 3 |
| Withdrawal seizure | 5 (6) | 4 | 0 | 1 | 0 |
| Hallucinations (auditory or visual); delirium | 5 (6) | 3 | 2 | 0 | 0 |
| Vivid dreams (including nightmares) | 5 (6) | 1 | 4 | 0 | 0 |
| Brain zaps, head jolts, electric shocks | 5 (6) | 1 | 4 | 0 | 0 |
| Loss of appetite | 5 (6) | 1 | 2 | 0 | 2 |
| Rage, agitation | 5 (6) | 1 | 2 | 0 | 1 |
| Agoraphobia, fear | 5 (6) | 0 | 2 | 0 | 3 |

*These verbatim terms were extracted directly from the case narratives. We grouped similar terms together and manually tallied the results. Most cases reported more than one symptom of withdrawal. Verbatim terms that were described less than 5% of cases, listed in descending order, include: akathisia (including restlessness); tinnitus or hearing disturbance; paraesthesias or extremity numbness; photosensitivity or visual disturbances; breathing or non-specific respiratory problems; paranoia; difficult concentrating; flu-like symptoms; mood swings or mood lability; dilated pupils; slurred speech. **Incidence of a given adverse event cannot be calculated using FAERS data and comparisons between drugs are not accurate.**

[†] Two cases with oxazepam and one case with triazolam described specific symptoms

FAERS = FDA Adverse Event Reporting System

Thirteen out of 104 cases described the need for additional or more prominent warnings on benzodiazepines or increased prescriber education about the potential for dependence and subsequent withdrawal. Several cases specifically mentioned the need for a Boxed Warning, an example of which is summarized below in **Section 3.8.2.1.**

### 3.9.2.1 Example Cases from the FAERS Case Series of Direct Reports of Drug Abuse, Dependence and Withdrawal with Benzodiazepine as a Single Drug Substance

**Case 1**
**FAERS# 6167935, Version 1, Initially received by FDA October 2006**
**Drug of Interest:** Clonazepam
**Outcomes:** Life threatening, Other serious

A 41-year-old male patient was prescribed clonazepam 0.5 mg every 12 hours as needed for anxiety. He reports that he never received any re-evaluation or follow up after receiving this initial prescription and because he was taking less than the amount prescribed, he thought "he would never have a problem with becoming physically dependent on the drug." He reports that the withdrawal he experienced was much worse than the anxiety symptoms he had to begin with. After approximately six months, the patient began to have dizziness that his doctors did not attribute to clonazepam, but instead to the patient's worsening anxiety. He continued with clonazepam for three more months at which point he decreased his dose by half and began to experience the following symptoms: "dizzy, nausea, floor moving sensations, head feeling pressurized, vibrating in skull." A psychiatrist recommended that the patient stop the drug "cold turkey" because the patient was on a "low dose." The patient stopped clonazepam and experienced "complete loss of appetite, weight loss, nausea, dizziness, insomnia." These symptoms reportedly lasted approximately three months and at the time of the report the patient felt "99% better" and remained off clonazepam. The patient further states that the reason he wrote his MedWatch report was "in the hopes of getting a Black Box Warning on Benzodiazepines. There is nothing in the information sent out with the drug regarding the symptoms of dependency and the signs of interdose withdrawal, tolerance, the speed of dependency …or the fact that people can get dependent on a low dose as needed benzo."

*Reviewer's comment: This case describes a patient who was prescribed a "low dose" clonazepam on an as needed basis and experienced symptoms of dependency after six months of use followed by three months of withdrawal symptoms after stopping the drug. Notably, he described the withdrawal symptoms as much worse than the anxiety symptoms that the clonazepam was prescribed to manage. The initial dose for panic disorder in the clonazepam product labeling is 0.25 mg twice daily, making his prescribed dose twice that of the recommended dose. Additionally, he may have experienced less severe withdrawal symptoms or no symptoms had he been instructed to taper as the product labeling recommends: "Treatment should be discontinued gradually, with a decrease of 0.125 mg twice daily every 3 days, until the drug is completely withdrawn." Furthermore, the product labeling also includes recommendations that "… the physician who elects to use Klonopin for extended periods*

*should periodically reevaluate the long-term usefulness of the drug for the individual patient." This patient reported that he was not re-evaluated after receiving the initial prescription, with which he continued for six months. He feels strongly that additional warnings are warranted on benzodiazepines. He may not have experienced the AEs if the existing product labeling recommendations were followed for dosing, monitoring, and tapering schedule.*

*The following is an excerpt from the DRUG ABUSE AND DEPENDENCE section of the current product labeling for clonazepam which contains the same language as the version from August 2006:*

> "The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed (see DOSAGE AND ADMINISTRATION). Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving clonazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence." [39] [40]

*This reviewer concurs that, while there are adequate warnings regarding the potential for dependence and withdrawal in the clonazepam product labeling, information is lacking regarding the potential for dependence and withdrawal at low or as needed dosing in patients without a history of substance use disorder or dependence. This reviewer also believes that there is a need for re-educating healthcare professionals regarding the appropriate use of benzodiazepines, and reinforce that the instructions on dosing, monitoring, and tapering schedule are included in the product labeling for reference.*

**Case 2**

**FAERS# 5923616, Version 1, Initially received by FDA November 2005**
**Drug of Interest:** Clonazepam
**Outcomes:** Hospitalization, Life threatening, Other serious
A 34-year old female patient was prescribed clonazepam for insomnia (early morning waking) that began after starting sertraline. The initial prescribed dose was 0.5 mg once daily. While taking clonazepam, her "body became addicted" and she began to "experience withdrawals" while on the drug. The prescribing physician increased the dose so that "she could feel normal again." By eight weeks, her clonazepam dose had been increased to 2 mg daily. At this point, the patient realized that she was "completely addicted" and began to wean her dose by ¼ tablet every one to three months. She began to experience more withdrawal symptoms with each dose reduction including "rebound anxiety, insomnia, vertigo affecting driving, vomiting, chills, profound muscle cramping, shakes, nightmares…twitches, memory loss, agitation to extreme, limbs going numb." When she went to her physician about these symptoms, he told her "symptoms could not be from withdrawal…tons of practitioners were trying to figure it out." The patient was referred to a neurologist who tested her for Parkinson's disease, multiple sclerosis, and a

brain tumor, and "all tests were normal." It took the patient one year to wean off of 2 mg because of the withdrawal symptoms. The patient said, "I have experienced this drug to be horrendously addictive at low, normal prescribed dosages and it was extremely dangerous to my well-being."

**Case 3**

**FAERS# 5923616, Version 1, Initially received by FDA April 2005**

**Drug of Interest:** Alprazolam

**Outcomes:** Life threatening, Other serious

An adult female patient of unknown age was prescribed alprazolam 0.25 mg three times daily for anxiety after an ED visit for chest pain. Within days of starting alprazolam, the patient began experiencing what she described as "tolerance withdrawal" and began suffering from "severe head pressure, dizziness, panic attacks and eventually a total nervous breakdown." The patient presented several times to her family doctor with these symptoms and he never attributed them to alprazolam, but instead told her that she needed to "double up" her dose. The patient ended up having multiple tests done including an MRI to rule out a brain tumor and multiple sclerosis, and an echocardiogram to work-up her dizziness. The patient "finally figured out it was the Xanax" and discontinued it abruptly after six weeks. Since the patient was on a low dose for a relatively short period of time, the physician reportedly never mentioned tapering the patient's dose. After discontinuing alprazolam, the patient experienced "terrible insomnia, tremors, night terrors, derealization, depersonalization, panic, anxiety, spots in vision, dizziness and heart palpitations." At the time of the report, the patient had been completely off alprazolam for two years and stated that the symptoms had diminished, but she still had spots in her vision, increased anxiety and insomnia.

**Case 4**

**FAERS# 6203360, Version 1, Initially received by FDA December 2006**

**Drug of Interest:** Lorazepam

**Outcomes:** Life threatening, Other serious

A 36-year-old female patient was prescribed lorazepam 0.25 mg twice daily as needed as a sleep aid and to help with occasional anxiety. She was given three refills with the first prescription and no instructions to follow-up. Four months later, the patient was taking 0.25 mg twice daily and felt that her anxiety had improved so stopped taking the morning dose. She began to feel such severe withdrawals that she restarted the morning dose. After speaking with a pharmacist, the patient went back to the prescribing physician to explain that she was having side effects from decreasing the dose and she was told that "the problem was her and that the correct way to taper Ativan was to cut the total daily dose in half and she should've been fine." The patient reportedly experienced the following withdrawal symptoms: severe anxiety, panic attacks, heart palpitations, excessive sweating, psychotic thinking, depersonalization, derealization, headaches, tremors, vision disturbances, hearing problem, loss of appetite and weight loss. The patient went to a new physician who is helping her slowly discontinue lorazepam. The patient reported that these symptoms have greatly diminished now that the patient is "on a proper taper."

*Reviewer's comment: Cases 2-4 describe situations where a benzodiazepine was prescribed for either insomnia or anxiety at low doses. In all three cases, the patients took the benzodiazepine as directed (or less frequently) and developed symptoms of dependence. When the patients then expressed concerns to their prescribers, the prescribers believed that the problem must not be the benzodiazepine use because the doses were low. In all three cases, the patients experienced symptoms consistent with benzodiazepine withdrawal and required a slow tapering schedule in order to successfully discontinue their respective medications.*

*In Case 3, similar to Case 1, the patient was not instructed to taper the benzodiazepine. She may have experienced less severe withdrawal symptoms or no symptoms had she been instructed to discontinue alprazolam as recommended in the Dosage and Administration section for Dose Reduction in the alprazolam product labeling:*

> "Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided (see WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE).
>
> In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction.
>
> In any case, reduction of dose must be undertaken under close supervision and must be gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be reinstituted and, only after stabilization, should a less rapid schedule of discontinuation be attempted. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every 3 days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens." [7]

*In Case 4, she was given three refills with her first prescription for lorazepam and no instructions for follow-up. Her adverse experiences with lorazepam may have been avoided if she was seen two to four weeks after receiving the initial prescription to evaluate the need for further treatment with lorazepam. The Warning section for Physical and Psychological Dependence in the lorazepam product labeling states:*

> "In general, benzodiazepines should be prescribed for short periods only (e.g., 2 to 4 weeks). Extension of the treatment period should not take place without reevaluation of the need for continued therapy. Continuous long-term use of product is not recommended. Withdrawal symptoms (e.g., rebound insomnia) can appear following cessation of recommended doses after as little as one week of

therapy. Abrupt discontinuation of product should be avoided and a gradual dosage-tapering schedule followed after extended therapy." [41]

**Case 5**
**FAERS# 13710638, Version 1, Initially received by FDA July 2017**
**Drug of Interest:** Alprazolam
**Outcomes:** Life threatening, Disability
A 49-year-old male patient was prescribed alprazolam 0.25 mg to help with insomnia. Over the next two years, he experienced non-specific "interdose withdrawal" symptoms and his prescribed dose was increased from 0.5 mg to 3 mg per day. Two years after initially starting alprazolam, he was advised to "quit the medication cold turkey" and he has been experiencing rebound insomnia ever since (for the last four years). No concomitant medication or medical history was provided in the case.

**Case 6**
**FAERS# 15731646, Version 1, Initially received by FDA December 2018**
**Drug of Interest:** Lorazepam
**Outcomes:** Hospitalization, Disability
A 25-year-old male patient with a medical history significant for obsessive compulsive disorder and schizophrenia was prescribed lorazepam 1 mg daily during a psychiatric hospital admission. At an unspecified time after discharge from the hospital, the patient ran out of his lorazepam. He reportedly experienced severe withdrawal effects including: "dry, burning pain all over his body, intrusive thoughts, intolerance to certain foods, intense fears (ranging from dissociation of actions from self to suicidal thoughts), months of low-functionality, and many more bizarre symptoms that would be too numerous to list and hard to believe." According to the patient, these symptoms recurred each time he attempted to discontinue the lorazepam. The case did not provide any additional information regarding instructions from the prescriber.

*Reviewer's comment: Cases 5 and 6 describe scenarios where a patient was given incorrect instructions ("to quit cold turkey") or very little instruction regarding the continued use of their benzodiazepine prescription when experiencing symptoms of dependence and withdrawal. These cases were received by the FDA in 2017 and 2018, respectively, indicating that this incorrect guidance, or lack thereof, is a current issue.*

# 4 DISCUSSION

## 4.1 USE, MISUSE, AND ABUSE OF BENZODIAZEPINES AND ASSOCIATED MORBIDITY AND MORTALITY

Drug Utilization Data

The estimated number of benzodiazepine prescriptions and tablets dispensed from U.S. outpatient retail and mail-order pharmacies has decreased in recent years; however, benzodiazepines remain a widely prescribed class of drugs in the U.S., with approximately (b) (4) tablets dispensed in 2018 alone. The estimated number of benzodiazepine prescriptions dispensed increased from approximately (b) (4) prescriptions in 2006 to (b) (4) prescriptions in 2013, and then decreased to (b) (4)

(b) (4) prescriptions in 2018[5]. Solid oral formulations of benzodiazepines were predominantly dispensed to adult female patients. (b) (4) of patients aged 18 years or older are estimated to have received a benzodiazepine prescription for three months or longer. From 2014 through 2018, alprazolam, diazepam, lorazepam, and clonazepam were the most-frequently dispensed benzodiazepines.

Epidemiologic data

Our examination of available data suggest that benzodiazepine misuse, abuse and associated morbidity and mortality are substantial but primarily occur in the context of polysubstance use.

- Annually from 2015 to 2018, approximately 5.4 million (2.0%) U.S. individuals aged 12 and older are estimated to have misused or abused benzodiazepines. The highest prevalence was in the 18-25 year-old age group, in which almost half of past-year benzodiazepine users reported misusing or abusing the drugs. The most commonly reported reasons for benzodiazepine misuse or abuse were to "relax or relieve tension" (46.3%), "help with sleep" (22.4%), "get high or [respondent] was hooked" (11.8%), "help with emotions" (10.5%), and "experiment or to see what the drug is like" (5.7%).
- Among 12th graders, estimated nonmedical use of several commonly used benzodiazepines has declined over the past decade, paralleling downward trends in use of multiple other prescription and illicit drugs in this group.
- In 2016, the nationally estimated number of ED visits due to nonmedical use of benzodiazepines (n=167,845), was higher than the corresponding estimate for prescription opioids (n=129,863), although a relatively small proportion of visits involved benzodiazepines alone—13.9% (n=23,335) compared to 31.2% (n=40,499) for visits due to prescription opioid nonmedical use.
- There was a high frequency of exposure calls to U.S. poison centers involving benzodiazepine misuse or abuse, and trends were generally consistent with prescribing trends. The annual number of exposure calls involving a benzodiazepine misuse or abuse increased from 10,156 in 2009 to 10,738 in 2011, then decreased to 8,761 in 2017. However, the observed declines in benzodiazepine exposure calls were driven by calls with minor clinical effects, whereas benzodiazepines exposure calls with more severe medical outcomes increased across the study period. Approximately 63% of benzodiazepine misuse/abuse calls in 2017 involved multiple substances—most commonly prescription opioids, alcohol, or stimulants—and medical outcomes in these cases are more severe than in cases involving benzodiazepines alone. The distribution of medical outcome severity in single-substance misuse/abuse calls was similar across the five most commonly prescribed benzodiazepines.

[5] Estimates of dispensed prescriptions were affected by a methodology change in the underlying data source to account for prescription voids and reversals, resulting in a trend break between estimates prior to 2017. Estimates for 2017 and 2018 were (b) (4) approximately (b) (4) due to the change in methodology.

- Upon analysis of 15,779 single-substance benzodiazepine exposure calls reported to U.S. poison centers specifically involving abuse between 2009-2017, 15% (n=2,394) reported moderate-to-severe medical outcomes in patients with clinical effects related to the exposure. The most commonly reported related clinical effects and corresponding frequency in these exposures included drowsiness/lethargy (76%), slurred speech (24%), confusion (14.1%), tachycardia (13.3%), hypotension (13.3%), and ataxia (13.1%).

- Benzodiazepine-involved poisoning deaths increased from 1,298 in 2010 to 11,537 in 2017. The proportion of deaths due to benzodiazepines alone was small and decreased over this period, from 8.6% in 2000 to 2.7% in 2017. From 2013-2017, 55.4% of benzodiazepine-involved fatal poisonings also involved prescription opioids, but only 9.7% involved benzodiazepines and prescriptions opioids without mention of any additional substances.

- We identified no high-quality longitudinal studies assessing the risk of addiction associated with benzodiazepine use. However, in 2017, 1.2% of admissions (n=10,316) to publicly-funded substance use disorder treatment programs indicated that benzodiazepines were the primary drug of abuse, compared to 3.1% for opioid analgesics. An additional 7.3% and 9.8% of admissions indicated benzodiazepines as the secondary and tertiary drug of abuse, respectively. In one published analysis of NSDUH data from 2015-2016, an estimated 0.5 million people ages 18 and older annually reported misuse or abuse of benzodiazepines, did not report misuse or abuse of other sedatives, hypnotics, or anxiolytics, and met the criteria for Sedative, Hypnotic, or Anxiolytic Use Disorder, per the Diagnostic and Statistical Manual of Mental Disorders, 4$^{th}$ Edition (DSM-IV). Although these data cannot be used to estimate the risk of benzodiazepine addiction associated with use of these medications, they indicate that both primary benzodiazepine use disorders and polysubstance addiction involving benzodiazepines do occur.

FAERS Data: High-level Overview

The high-level overview of FAERS reports revealed that, after exclusion of those reports also included in NPDS to avoid duplicate counts with DEPI's NPDS analysis, almost 44,000 reports related to benzodiazepine abuse, dependence, or withdrawal were reported to FDA from the time of approval through June 30, 2019, of which approximately 24% involved a concomitant opioid. The most frequently reported PTs across the top four most frequently reported benzodiazepines (in descending order: alprazolam, diazepam, lorazepam, clonazepam) were similar and mostly related to overdose, abuse, dependence, or withdrawal. There were slight differences in distribution of PTs across the four drugs, but no major differences were noted. Sixty percent of all fatal reports involving a benzodiazepine also involved a concomitant opioid, with approximately 3% of fatal reports involving a benzodiazepine as a single drug substance. The remaining fatal reports involved a benzodiazepine along with one or more of the following, listed in decreasing order of frequency: alcohol, various antidepressants, acetaminophen, zolpidem and various antipsychotics (See **Section 3.8.1** and **Table 3.16** for additional

details). The FAERS findings were congruent with the epidemiologic data, which demonstrated high levels of benzodiazepine abuse and increased severity of clinical effects when benzodiazepines abuse involved other drugs.

## 4.2 DEPENDENCE AND WITHDRAWAL

Epidemiologic Data

From 2009 to 2017, the number of calls to U.S. poison centers for benzodiazepine withdrawal increased from 263 to 372. A small number of published longitudinal studies described risk factors for long-term or high-dose benzodiazepine use or dependence. These included female sex, older age, mental health conditions, and concomitant use of certain medications (e.g., antidepressants). However, most of these studies were conducted in non-U.S. populations and had other limitations.

FAERS Data: Report-level Review

The report-level review of 104 FAERS cases of benzodiazepine as single drug substance submitted directly to FDA from patients and healthcare providers (i.e., direct reports) mostly consisted of reports of dependence or withdrawal occurring with use of a benzodiazepine as prescribed, rather than abuse. Because we limited our search to direct reports only, there is likely a bias against identifying cases of abuse or illicit use, especially because most cases in this case series (n=82, 79%) were submitted by the patients themselves.

We identified dependence and subsequent withdrawal, in some cases with high morbidity, that developed during therapeutic use of benzodiazepines (clonazepam, alprazolam, lorazepam, diazepam, triazolam, or oxazepam). Approximately 80% of the cases in this case series described symptoms associated with withdrawal from benzodiazepines that included mainly central nervous system effects (e.g., insomnia, increased anxiety or panic attacks, memory impairment, depression), cardiovascular effects (e.g., heart rate or rhythm fluctuations), and gastrointestinal effects (e.g., abdominal pain, nausea, diarrhea). The median time to onset of dependence or tolerance was within two weeks of initiating use, ranging from one day to four years. The majority of cases reported a duration of use ranging from months to years, rather than the short-term use of no more than several weeks currently recommended in some benzodiazepine product labeling. The median duration of withdrawal symptoms for all benzodiazepines was approximately 9.5 months and ranged from two weeks to eight years. An important limitation in the assessment of these cases was the difficulty in differentiating withdrawal symptoms from potential re-emergence or continuation of symptoms for which the benzodiazepine was being used. The Drug Abuse and Dependence Section of the current Xanax product labeling also acknowledges the difficulty of distinguishing withdrawal and recurrence, especially in patients undergoing dose reduction.

Our analysis of the FAERS dependence and withdrawal cases, coupled with the findings of prevalent longer-term use and increasing numbers of poison center calls for

benzodiazepine withdrawal, suggest a need for enhanced communication about these risks and the appropriate management of patients treated with benzodiazepines. Although benzodiazepine product labeling includes varying recommendations for dosing, duration of use, and tapering schedules, we noted FAERS cases from patients and prescribers who described the need for increased prescriber education about the risk of dependence and withdrawal even when the drugs are used at therapeutic doses for short periods of time, including the lowest available dosages. In addition, the series includes cases from patients and prescribers who specifically requested additional or more prominent warnings in benzodiazepine product labeling with respect to the potential for dependence and subsequent withdrawal, suggesting that additional emphasis on these serious AEs in the product labeling may be warranted. Based on the cases described in **Section 3.8.2.1**, it is possible that if the patients had been managed by the providers according to recommendations in the product labeling, the serious symptoms of dependence and subsequent withdrawal may have been lessened or avoided altogether.

### 4.3 CONSIDERATIONS FOR REGULATORY ACTIONS

Findings from this review suggest that benzodiazepines confer substantial risks and public health burden, although some measures suggest a modest decline in recent years as dispensing has decreased. Some harms could potentially be mitigated by enhanced communication of risks and recommended prescribing practices. FDA has a number of regulatory and non-regulatory options worth considering to achieve this goal and optimize the benefit-risk balance for this drug class. These include changes in product labeling, public communications (e.g., drug safety communications), (b) (5)

The FDA Guidance for labeling states that a Boxed Warning may be used when there is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation [1]. A Boxed Warning to alert prescribers to the risk of abuse, misuse, addiction, dependence and withdrawal could increase awareness of risks, improve the safety of use, and improve the benefit-risk balance of benzodiazepines. The epidemiologic data reviewed in this document provide evidence of substantial morbidity and mortality associated with benzodiazepine misuse and abuse, predominantly in the setting of polysubstance use that includes, but is not limited to, opioids. The FAERS data reviewed provide some evidence that there is a lack of awareness or misconceptions among prescribers about appropriate management of patients taking benzodiazepines, including the requirement for careful patient selection and close monitoring to identify a pre-existing or emergent substance use disorder; the risks of developing dependence and subsequent withdrawal with benzodiazepine use, even at therapeutic doses for relatively short periods of time; and the need for dose tapering to prevent or lessen serious withdrawal symptoms. We identified cases where serious dependence and withdrawal symptoms may have been lessened or avoided altogether had the prescriber followed prescribing and dose reduction recommendations in the product labeling.

The review team also identified inconsistencies in current benzodiazepine product labeling. For example, some benzodiazepines are lacking language related to risk of withdrawal, while others have entire sections devoted to this risk. These inconsistencies may give the perception of a differential risk of abuse, dependence and withdrawal among the different benzodiazepines. Therefore, there is an additional need to harmonize language in all sections of the product labeling related to abuse, dependence, and withdrawal across the benzodiazepine class.

These (b) (5) tools to enhance risk communication should be considered, (b) (5)
These could include a drug safety communication (DSC) in conjunction with labeling changes, (b) (5)

(b) (5)

(b) (5)
For example, a boxed warning could cause some prescribers to substitute other, less safe medications (e.g., barbiturates) or to suddenly discontinue benzodiazepines, resulting in serious withdrawal symptoms and possibly patients turning to illicit sources of benzodiazepines, some of which may be counterfeit or adulterated with lethal synthetic opioids. (b) (5)

## 4.4 DATA AND METHODS CONSIDERATIONS

### 4.4.1 Drug Utilization

Findings from this review should be interpreted in the context of the known limitations of the databases used. Drug utilization data is provided for the benzodiazepine products sold and dispensed in the U.S. The data are meant to provide contextual information on general utilization trends over a 5-year period. The drug utilization data provides

estimates from where the majority of benzodiazepines are dispensed, outpatient retail and mail-order pharmacies. The data captures dispensed prescriptions across all payment methods and can be trended across time.

The IQVIA NPA and TPT databases are proprietary dynamic data sources; changes to the underlying source data and projection methodologies have been implemented by the data vendor over time. [6]

Of note, the data obtained from the proprietary databases are estimated prescription and/or patient counts based on projections of sample prescription claims data and therefore have some degree of inherent uncertainty. These estimates are not intended to be representations of exact enumerations and should be interpreted with caution particularly if they are based on a small sample size. Summarization of projected prescription estimates may lead to differences in prescription counts due to rounding attributable to the projection methodology utilized. No statistical tests were performed on these data.

We focused our analyses primarily on the outpatient retail and mail order pharmacy settings. Consequently, these national estimates may not be generalized to other settings of care in which these products are used (i.e. clinics, non-federal hospitals, etc.).

### 4.4.2 Epidemiologic Data on Benzodiazepine Abuse, Dependence, and Related Outcomes

#### 4.4.2.1 NPDS

Strengths:
A strength of the NPDS dataset is its ability to record detailed drug exposure information from self-reported information from callers, by using standard procedures for data collection and management.

Limitations:
NPDS does not contain all cases of misuse/abuse that warrant medical attention, because not every case generates a call to a PCC. Also, we speculate that people would not call PCC for withdrawal symptoms, so it is not ideal for surveillance of benzodiazepine dependence and withdrawal. It is uncertain what fraction of events result in a PCC call, and to what extent this fraction varies over time. The most severe events, resulting in out-of-hospital overdose death, may be unlikely to generate a call to a PCC. Therefore, NPDS may disproportionately fail to capture cases involving drugs with the highest risk of such fatal overdoses. Calls related to misuse/abuse of benzodiazepines may be affected by the overall decline in calls to U.S. PCCs in recent years and by changes in the awareness of the risks and effects of these drugs by medical personnel and the public. Finally, follow-up and medical outcomes are not available for all calls.

[6] Source: IQVIA, National Prescription Audit (NPA). January 2016 - December 2018. Data Extracted April 2019.Files: VRAF USC Product Combined Guidance Nov 2016 - Dec 20418 FINAL xlsx.;

#### 4.4.2.2 NEISS-CADES

Strengths:
NEISS-CADES has the notable strengths of national representativeness, narrative details of AE circumstances, and high data quality, due to the rigorous standards for ED medical chart abstraction.

Limitations:
NEISS-CADES data can be used to calculate national estimates of ED visits for AEs attributed to medication use, with the limitation that NEISS-CADES excludes cases that do not result in an ED visit, cases that result in death before or during ED evaluation, and cases of people presenting to the ED due to inadequate therapy or drug withdrawal. The quality of these surveillance data depends on the completeness and accuracy of medical record documentation by the healthcare provider and, to be included in NEISS-CADES, cases require documentation by the healthcare provider that a drug or drug class (e.g., "benzodiazepine") was implicated in the ED visit.

#### 4.4.2.3 TEDS

Strengths:
To our knowledge, TEDS is the largest source of nationwide data on the primary, secondary, and tertiary substances abused at SUD treatment admission. Data collection is systematic to comply with mandatory state reporting. These features enable the most feasible, approximate estimate of the burden of SUD associated with benzodiazepines abuse.

Limitations:
TEDS does not draw from a nationally-representative sample of SUD treatment admissions. So, it cannot estimate the national burden of SUD treatment associated with benzodiazepines, or the frequency of benzodiazepine abuse. For the same reason, caution should be used in comparing TED's estimate of the burden of SUD treatment associated with benzodiazepines with that of other drugs or substances. TEDS contains data from all SUD admissions that are funded by Federal Block Grant funds, state alcohol/drug agencies, or both; also, some data are from privately-funded admissions to treatment sites that receive state funding. TEDS lacks data from centers operated by federal agencies.

#### 4.4.2.4 NVSS-M

Strengths:
National Vital Statistics System Mortality data provide a comprehensive description of deaths in the U.S. population. Information on the death certificate is coded by a professional who is legally responsible for the registration of the death, and the death certificate allows the opportunity for specifying a single underlying cause of death and up to twenty contributing causes. The death certificate also includes demographic information, providing valuable information for epidemiologic analyses.

Limitations:

One important limitation to consider for the use of death certificate data is that variation exists in the death investigation, including conducting autopsy, interpreting toxicology results, and determination of which drugs to include on the death certificate [42]. This variation could result in bias for certain populations, such as underreporting for populations less likely to be suspected of drug overdose and improvements in reporting could affect trends overtime [42].

#### 4.4.2.5 NSDUH

Strengths:
NSDUH is designed to estimate the annual prevalence of misuse and abuse of benzodiazepines and other drugs and substances among the U.S. civilian, non-institutionalized population, age 12 and older.

Limitations:
Individuals with advanced substance use disorders may be underrepresented, particularly if they become homeless, incarcerated, or enter a residential treatment facility. Also, these survey results are subject to the inherent limitations of self-reported data, such as non-response bias, misclassification, and recall bias. In addition, their construct of misuse and abuse encompasses a broad range of behaviors, including misuse for therapeutic purposes as well as use of the drug to gain a high or euphoric effect. Finally, the survey does not collect data on route of administration.

### 4.4.3 FAERS

Strengths:
This is the first postmarketing review completed that includes a broad search of FAERS for benzodiazepines and drug abuse, dependence, and withdrawal. Using FAERS, we have the ability to detect rare, but serious, AEs, especially those that occur soon after drug exposure. It includes all marketed products, uses, and patient populations for a given drug or therapeutic biologic product.

Limitations:
Because abuse, dependence, and withdrawal with benzodiazepines is a common and a well-known AE, there is a high volume of reports included in this review. Therefore, a report-level analysis of all reports was not feasible. It is important to note that causality has not been assessed for the high-level overview portion of this review, so conclusions cannot be drawn regarding the relatedness of these AEs to benzodiazepines.

FAERS is a database containing spontaneous AE reports; therefore, reporting rates are affected by the following: media attention, litigation (class action lawsuits), nature of the AE, type of drug product and new indications, length of time on market, extent and quality of manufacturer's surveillance system, and changes in reporting regulations, among others. Because of the spontaneous nature of the reports, incidence of a given AE cannot be calculated using FAERS data and comparisons between drugs are not accurate. Additionally, there is no certainty that the reported event was actually due to the product. FAERS reports do not always contain enough detail to properly evaluate an event. Therefore, the conclusions that can be made from FAERS reports are highly dependent

on the quality of reports. Specifically, for this review, there was difficulty in differentiating withdrawal symptoms from potential re-emergence or continuation of symptoms for which the benzodiazepine was being used. See **Appendix G1** for a full description of the FAERS database, including additional limitations.

### 4.4.4 Epidemiology Literature Review

Strengths:
We reviewed multiple databases and included a wide range of years to identify articles for both of the epidemiologic literature reviews.

Limitations:
Although the review of the epidemiologic literature was conducted by two reviewers, each article was only screened by one reviewer due to time constraints. Additionally, there were many articles that were pulled from the databases. As with any literature review, and especially considering the large number of articles, it is possible that relevant articles were missed during the screening process. Additionally, for the first literature search, many of the studies identified potentially confounding factors such as mental health conditions as potentially associated with long-term use or dependence and there was variation in the confounding factors that each study adjusted for. Finally, one major limitation for many of these studies was that the analysis was not adequately designed to assess temporality and the risk of the outcome from the exposure and instead reported on associations between factors.

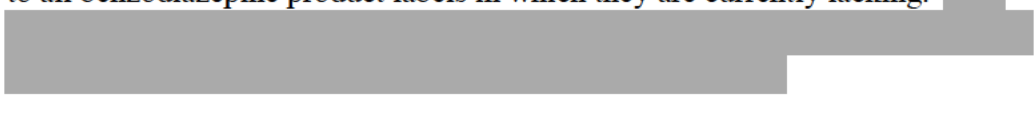
## 5 CONCLUSIONS

In this review, we describe substantial morbidity and mortality associated with benzodiazepine use, misuse, and abuse, most often in the context of polysubstance use that includes but is not limited to prescription opioids. We also describe potentially preventable harms from benzodiazepine dependence and withdrawal. Below, we provide considerations and recommendations for addressing these risks to improve the benefit-risk balance of this class of drugs.

## 6 RECOMMENDATIONS


Foremost, we recommend consideration of the following actions:

1. Harmonize the benzodiazepine class labeling by making the following additions to all benzodiazepine product labels in which they are currently lacking. (b) (5)



(b) (4), (b) (5)

2. Consider a Boxed Warning for all benzodiazepines describing the risks of misuse and abuse, dependence, withdrawal, addiction, and overdose, and the need for gradual dose tapering. Suggested language is included as an example below, (b) (5)

(b) (4), (b) (5)

3. Issue a DSC to accompany any labeling changes

4. (b) (5)

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# 8 APPENDICES

## 8.1 APPENDIX A. DRUG UTILIZATION

### Appendix A1. Drug Utilization Data Tables

**TABLE A.1**

**Estimated number of prescriptions for oral benzodiazepines dispensed from U.S. outpatient retail/mail order pharmacies, 2014 – 2018****

| | 2006 | | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | | 2012 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TRx (N) | Share (%) | TRx (N) | Share (%) | TRx (N) | Share (%) | TRx (N) | Share (%) | TRx (N) | Share (%) | TRx (N) | Share (%) | TRx (N) | Share (%) |
| Total | | | | | | | | | | | | | | (b) (4) |
| Alprazolam | | | | | | | | | | | | | | |
| Clonazepam | | | | | | | | | | | | | | |
| Lorazepam | | | | | | | | | | | | | | |
| Diazepam | | | | | | | | | | | | | | |
| Temazepam | | | | | | | | | | | | | | |
| Clobazam | | | | | | | | | | | | | | |
| All Other Molecules* | | | | | | | | | | | | | | |

| | 2013 | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TRx (N) | Share (%) | TRx (N) | Share (%) | TRx (N) | Share (%) | TRx (N) | Share (%) | TRx (N) | Share (%) | TRx (N) | Share (%) |
| Total | | | | | | | | | | | | (b) (4) |
| Alprazolam | | | | | | | | | | | | |
| Clonazepam | | | | | | | | | | | | |
| Lorazepam | | | | | | | | | | | | |
| Diazepam | | | | | | | | | | | | |
| Temazepam | | | | | | | | | | | | |
| Clobazam | | | | | | | | | | | | |
| All Other Molecules* | | | | | | | | | | | | |

Source: IQVIA, National Prescription Audit™ (NPA). January 2014 - December 2018. Data Extracted October 2019.Files: 2019-800 NPA benzo current.csv. TRx=prescriptions.
*All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam
**There was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided and/or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017, data prior to January 2017 have not been adjusted to the new methodology, therefore, the dotted line represents a trend break and any changes over time must be interpreted in the context of the changes in methodology. Overall, estimates using this new methodology were approximately (b) (4) compared with estimates using legacy estimation methodology. Changes in the projection methodology do not affect prescription volumes dispensed from the mail-order/specialty pharmacies.

## TABLE A.2

**Estimated number of units (tablets) for oral benzodiazepines dispensed from U.S. outpatient retail/mail order pharmacies, 2014 – 2018****

| Year | 2006 | | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | | 2012 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Units (N) | Share (%) | Units (N) | Share (%) | Units (N) | Share (%) | Units (N) | Share (%) | Units (N) | Share (%) | Units (N) | Share (%) | Units (N) | Share (%) |
| Total | | | | | | | | | | | | | | (b) (4) |
| Alprazolam | | | | | | | | | | | | | | |
| Clonazepam | | | | | | | | | | | | | | |
| Lorazepam | | | | | | | | | | | | | | |
| Diazepam | | | | | | | | | | | | | | |
| Temazepam | | | | | | | | | | | | | | |
| Clobazam | | | | | | | | | | | | | | |
| All Other Molecules* | | | | | | | | | | | | | | |

| Year | 2013 | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Units (N) | Share (%) | Units (N) | Share (%) | Units (N) | Share (%) | Units (N) | Share (%) | Units (N) | Share (%) | Units (N) | Share (%) |
| Total | | | | | | | | | | | | (b) (4) |
| Alprazolam | | | | | | | | | | | | |
| Clonazepam | | | | | | | | | | | | |
| Lorazepam | | | | | | | | | | | | |
| Diazepam | | | | | | | | | | | | |
| Temazepam | | | | | | | | | | | | |
| Clobazam | | | | | | | | | | | | |
| All Other Molecules* | | | | | | | | | | | | |

Source: IQVIA, National Prescription Audit™ (NPA). January 2006 – December 2018. Data Extracted October 2019.Files: 2019-800 NPA benzo current.csv; 2019-800 benzo static 2006-2011.csv; 2019-800 benzo static 2012-2015.csv

*All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam

****There was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided and/or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017, data prior to January 2017 have not been adjusted to the new methodology, therefore, the dotted line represents a trend break and any changes over time must be interpreted in the context of the changes in methodology. Overall, estimates using this new methodology were approximately (b) (4) compared with estimates using legacy estimation methodology. Changes in the projection methodology do not affect prescription volumes dispensed from the mail-order/specialty pharmacies.**

**TABLE A.3**

**Estimated number of oral benzodiazepine prescriptions dispensed from U.S. outpatient retail/mail order pharmacies, stratified by molecule and age, 2018**

| | | Alprazolam | | Clonazepam | | Lorazepam | | Diazepam | | Temazepam | | Clobazam | | All Other Molecules* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Formulation | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) |
| 0-9 | Total | (b) (4) | | | | | | | | | | | | | |
| | Oral Solid | | | | | | | | | | | | | | |
| | Oral Liquid | | | | | | | | | | | | | | |
| 10-19 | Total | | | | | | | | | | | | | | |
| | Oral Solid | | | | | | | | | | | | | | |
| | Oral Liquid | | | | | | | | | | | | | | |
| 20-39 | Total | | | | | | | | | | | | | | |
| | Oral Solid | | | | | | | | | | | | | | |
| | Oral Liquid | | | | | | | | | | | | | | |
| 40-64 | Total | | | | | | | | | | | | | | |
| | Oral Solid | | | | | | | | | | | | | | |
| | Oral Liquid | | | | | | | | | | | | | | |
| 65+ | Total | | | | | | | | | | | | | | |
| | Oral Solid | | | | | | | | | | | | | | |
| | Oral Liquid | | | | | | | | | | | | | | |
| Unspecified | Total | | | | | | | | | | | | | | |
| | Oral Solid | | | | | | | | | | | | | | |
| | Oral Liquid | | | | | | | | | | | | | | |

**Source: IQVIA, National Prescription Audit™ New To Brand (NPA NTB). January 2018 - December 2018. Data Extracted January 2020.Files: 2019-800 Benzo PI TRx 1-27-2019.csv.**

***All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam.** TRx = total number of prescriptions

**TABLE A.4**

**Estimated number of oral benzodiazepine prescriptions dispensed from U.S outpatient retail and mail order pharmacies, stratified by molecule, age and gender, 2018**

| | | Alprazolam | | Clonazepam | | Lorazepam | | Diazepam | | Temazepam | | Clobazam | | All Other Molecules* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Gender | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) |
| 0-9 | Total | | | | | | | | | | | | | | (b) (4) |
| | Female | | | | | | | | | | | | | | |
| | Male | | | | | | | | | | | | | | |
| | Unspecified | | | | | | | | | | | | | | |
| 10-19 | Total | | | | | | | | | | | | | | |
| | Female | | | | | | | | | | | | | | |
| | Male | | | | | | | | | | | | | | |
| | Unspecified | | | | | | | | | | | | | | |
| 20-39 | Total | | | | | | | | | | | | | | |
| | Female | | | | | | | | | | | | | | |
| | Male | | | | | | | | | | | | | | |
| | Unspecified | | | | | | | | | | | | | | |
| 40-64 | Total | | | | | | | | | | | | | | |
| | Female | | | | | | | | | | | | | | |
| | Male | | | | | | | | | | | | | | |
| | Unspecified | | | | | | | | | | | | | | |
| 65+ | Total | | | | | | | | | | | | | | |
| | Female | | | | | | | | | | | | | | |
| | Male | | | | | | | | | | | | | | |
| | Unspecified | | | | | | | | | | | | | | |
| Unspecified | Total | | | | | | | | | | | | | | |
| | Female | | | | | | | | | | | | | | |
| | Male | | | | | | | | | | | | | | |
| | Unspecified | | | | | | | | | | | | | | |

**Source: IQVIA, National Prescription Audit™ New To Brand (NPA NTB). January 2018 - December 2018. Data Extracted January 2020.Files: 2019-800 Benzo PI TRx 1-27-2019.csv.**

***All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam.** TRx = total number of prescriptions

**Table A.5**

**Estimated number of oral benzodiazepine prescriptions dispensed from U.S. outpatient retail/mail order pharmacies stratified by age and molecule and standardized by U.S. Census population estimates, 2014-2018 annually.**

| | | 2014 | | | 2015 | | | 2016 | | | 2017 | | | 2018 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Molecule | TRx | Population | TRx per 10K population | TRx | Population | TRx per 10K population | TRx | Population | TRx per 10K population | TRx | Population | TRx per 10K population | TRx | Population | TRx per 10K population |
| 0-9 | Total | | | | | | | | | | | | | | | (b) (4) |
| | Alprazolam | | | | | | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | | | | | | |
| | Diazepam | | | | | | | | | | | | | | | |
| | Temazepam | | | | | | | | | | | | | | | |
| | Clobazam | | | | | | | | | | | | | | | |
| | All Other Molecules^ | | | | | | | | | | | | | | | |
| 10-19 | Total | | | | | | | | | | | | | | | |
| | Alprazolam | | | | | | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | | | | | | |
| | Diazepam | | | | | | | | | | | | | | | |
| | Temazepam | | | | | | | | | | | | | | | |
| | Clobazam | | | | | | | | | | | | | | | |
| | All Other Molecules^ | | | | | | | | | | | | | | | |
| 20-39 | Total | | | | | | | | | | | | | | | |
| | Alprazolam | | | | | | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | | | | | | |
| | Diazepam | | | | | | | | | | | | | | | |
| | Temazepam | | | | | | | | | | | | | | | |
| | Clobazam | | | | | | | | | | | | | | | |
| | All Other Molecules^ | | | | | | | | | | | | | | | |
| 40-64 | Total | | | | | | | | | | | | | | | |
| | Alprazolam | | | | | | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | | | | | | |
| | Diazepam | | | | | | | | | | | | | | | |
| | Temazepam | | | | | | | | | | | | | | | |
| | Clobazam | | | | | | | | | | | | | | | |
| | All Other Molecules* | | | | | | | | | | | | | | | |
| 65+ | Total | | | | | | | | | | | | | | | |
| | Alprazolam | | | | | | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | | | | | | |
| | Diazepam | | | | | | | | | | | | | | | |
| | Temazepam | | | | | | | | | | | | | | | |
| | Clobazam | | | | | | | | | | | | | | | |
| | All Other Molecules^ | | | | | | | | | | | | | | | |

**Source: IQVIA, National Prescription Audit™ New To Brand (NPA NTB). January 2014 - December 2018. Data Extracted January 2020.Files: 2019-800 Benzo PI TRx 1-27-2019.csv. NVSS Census Files. (2019). U.S. Census Populations With Bridged Race Categories. Retrieved from https://www.cdc.gov/nchs/nvss/bridged_race.htm *All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam.** TRx = total number of prescriptions.

**Table A.6**

**Estimated number of oral benzodiazepine tablets dispensed from U.S. outpatient retail/mail order pharmacies, stratified by molecule and age, 2018**

| | Alprazolam | | Clonazepam | | Lorazepam | | Diazepam | | Temazepam | | Clobazam | | All Other Molecules* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Tablets | Share | Tablets | Share | Tablets | Share | Tablets | Share | Tablets | Share | Tablets | Share | Tablets | Share |
| Total | (b) (4) | | | | | | | | | | | | | |
| 0-9 | | | | | | | | | | | | | | |
| 10-19 | | | | | | | | | | | | | | |
| 20-39 | | | | | | | | | | | | | | |
| 40-64 | | | | | | | | | | | | | | |
| 65+ | | | | | | | | | | | | | | |
| Unspecified | | | | | | | | | | | | | | |

**Source: IQVIA, National Prescription Audit™ Extended Insights (NPA EI). January 2018 - December 2018. Data Extracted October 2019.Files: 2019-800 NPAEI Benzo 1-30-2019.csv.**

***All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam**

**Table A.7 Estimated number of oral benzodiazepine prescriptions dispensed from U.S. outpatient retail/mail order pharmacies stratified by molecule, age, and formulation, 2014-2018 annually**.**

| | | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Molecule | Formulation | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) |
| Total | Total | Total | | | | | | | | | | |
| 0-9 | Total | Total | | | | | | | | | | |
| | Alprazolam | Total | | | | | | | | | | |
| | Alprazolam | Oral Solid | | | | | | | | | | |
| | Alprazolam | Oral Liquid | | | | | | | | | | |
| | Clonazepam | Total | | | | | | | | | | |
| | Clonazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Total | | | | | | | | | | |
| | Lorazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Oral Liquid | | | | | | | | | | |
| | Diazepam | Total | | | | | | | | | | |
| | Diazepam | Oral Solid | | | | | | | | | | |
| | Diazepam | Oral Liquid | | | | | | | | | | |
| | Temazepam | Total | | | | | | | | | | |
| | Temazepam | Oral Solid | | | | | | | | | | |
| | Clobazam | Total | | | | | | | | | | |
| | Clobazam | Oral Solid | | | | | | | | | | |
| | Clobazam | Oral Liquid | | | | | | | | | | |
| | All Other Molecules* | Total | | | | | | | | | | |
| | All Other Molecules* | Oral Solid | | | | | | | | | | |
| | All Other Molecules* | Oral Liquid | | | | | | | | | | |
| 10-19 | Total | Total | | | | | | | | | | |
| | Alprazolam | Total | | | | | | | | | | |
| | Alprazolam | Oral Solid | | | | | | | | | | |
| | Alprazolam | Oral Liquid | | | | | | | | | | |
| | Clonazepam | Total | | | | | | | | | | |
| | Clonazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Total | | | | | | | | | | |
| | Lorazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Oral Liquid | | | | | | | | | | |
| | Diazepam | Total | | | | | | | | | | |
| | Diazepam | Oral Solid | | | | | | | | | | |
| | Diazepam | Oral Liquid | | | | | | | | | | |
| | Temazepam | Total | | | | | | | | | | |
| | Temazepam | Oral Solid | | | | | | | | | | |
| | Clobazam | Total | | | | | | | | | | |
| | Clobazam | Oral Solid | | | | | | | | | | |
| | Clobazam | Oral Liquid | | | | | | | | | | |
| | All Other Molecules* | Total | | | | | | | | | | |
| | All Other Molecules* | Oral Solid | | | | | | | | | | |
| | All Other Molecules* | Oral Liquid | | | | | | | | | | |

(b) (4)

**Table continued below**

# Table A.7 continued

| | | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Molecule | Formulation | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) |
| 20-39 | Total | Total | (b) (4) | | | | | | | | | |
| | Alprazolam | Total | | | | | | | | | | |
| | Alprazolam | Oral Solid | | | | | | | | | | |
| | Alprazolam | Oral Liquid | | | | | | | | | | |
| | Clonazepam | Total | | | | | | | | | | |
| | Clonazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Total | | | | | | | | | | |
| | Lorazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Oral Liquid | | | | | | | | | | |
| | Diazepam | Total | | | | | | | | | | |
| | Diazepam | Oral Solid | | | | | | | | | | |
| | Diazepam | Oral Liquid | | | | | | | | | | |
| | Temazepam | Total | | | | | | | | | | |
| | Temazepam | Oral Solid | | | | | | | | | | |
| | Clobazam | Total | | | | | | | | | | |
| | Clobazam | Oral Solid | | | | | | | | | | |
| | Clobazam | Oral Liquid | | | | | | | | | | |
| | All Other Molecules* | Total | | | | | | | | | | |
| | All Other Molecules* | Oral Solid | | | | | | | | | | |
| | All Other Molecules* | Oral Liquid | | | | | | | | | | |
| 40-64 | Total | Total | | | | | | | | | | |
| | Alprazolam | Total | | | | | | | | | | |
| | Alprazolam | Oral Solid | | | | | | | | | | |
| | Alprazolam | Oral Liquid | | | | | | | | | | |
| | Clonazepam | Total | | | | | | | | | | |
| | Clonazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Total | | | | | | | | | | |
| | Lorazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Oral Liquid | | | | | | | | | | |
| | Diazepam | Total | | | | | | | | | | |
| | Diazepam | Oral Solid | | | | | | | | | | |
| | Diazepam | Oral Liquid | | | | | | | | | | |
| | Temazepam | Total | | | | | | | | | | |
| | Temazepam | Oral Solid | | | | | | | | | | |
| | Clobazam | Total | | | | | | | | | | |
| | Clobazam | Oral Solid | | | | | | | | | | |
| | Clobazam | Oral Liquid | | | | | | | | | | |
| | All Other Molecules* | Total | | | | | | | | | | |
| | All Other Molecules* | Oral Solid | | | | | | | | | | |
| | All Other Molecules* | Oral Liquid | | | | | | | | | | |

Table continued below

# Table A.7 continued

| | | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Molecule | Formulation | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) | TRx | Share (%) |
| 65+ | Total | Total | (b) (4) | | | | | | | | | |
| | Alprazolam | Total | | | | | | | | | | |
| | Alprazolam | Oral Solid | | | | | | | | | | |
| | Alprazolam | Oral Liquid | | | | | | | | | | |
| | Clonazepam | Total | | | | | | | | | | |
| | Clonazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Total | | | | | | | | | | |
| | Lorazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Oral Liquid | | | | | | | | | | |
| | Diazepam | Total | | | | | | | | | | |
| | Diazepam | Oral Solid | | | | | | | | | | |
| | Diazepam | Oral Liquid | | | | | | | | | | |
| | Temazepam | Total | | | | | | | | | | |
| | Temazepam | Oral Solid | | | | | | | | | | |
| | Clobazam | Total | | | | | | | | | | |
| | Clobazam | Oral Solid | | | | | | | | | | |
| | Clobazam | Oral Liquid | | | | | | | | | | |
| | All Other Molecules* | Total | | | | | | | | | | |
| | All Other Molecules* | Oral Solid | | | | | | | | | | |
| | All Other Molecules* | Oral Liquid | | | | | | | | | | |
| Unspecified | Total | Total | | | | | | | | | | |
| | Alprazolam | Total | | | | | | | | | | |
| | Alprazolam | Oral Solid | | | | | | | | | | |
| | Alprazolam | Oral Liquid | | | | | | | | | | |
| | Clonazepam | Total | | | | | | | | | | |
| | Clonazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Total | | | | | | | | | | |
| | Lorazepam | Oral Solid | | | | | | | | | | |
| | Lorazepam | Oral Liquid | | | | | | | | | | |
| | Diazepam | Total | | | | | | | | | | |
| | Diazepam | Oral Solid | | | | | | | | | | |
| | Diazepam | Oral Liquid | | | | | | | | | | |
| | Temazepam | Total | | | | | | | | | | |
| | Temazepam | Oral Solid | | | | | | | | | | |
| | Clobazam | Total | | | | | | | | | | |
| | Clobazam | Oral Solid | | | | | | | | | | |
| | Clobazam | Oral Liquid | | | | | | | | | | |
| | All Other Molecules* | Total | | | | | | | | | | |
| | All Other Molecules* | Oral Solid | | | | | | | | | | |
| | All Other Molecules* | Oral Liquid | | | | | | | | | | |

**Source: IQVIA, National Prescription Audit™ New To Brand (NPA NTB). January 2014 - December 2018. Data Extracted January 2020.Files:** 2019-800 Benzo PI TRx 1-27-2019.csv

***All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam**

**There was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided and/or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017, data prior to January 2017 have not been adjusted to the new methodology, therefore, the dotted line represents a trend break and any changes over time must be interpreted in the context of the changes in methodology. Overall, estimates using this new methodology were approximately (b) (4) compared with estimates using legacy estimation methodology. Changes in the projection methodology do not affect prescription volumes dispensed from the mail-order/specialty pharmacies.

## TABLE A.8

**Estimated number of unique patients dispensed one of the top 6 benzodiazepines* from outpatient retail pharmacies, stratified by molecule and age, 2014-2018****

| | | 2014 | | 2015 | | 2016 | | 2017 | | 2018 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Molecule | Patients (N) | Share | Patients (N) | Share | Patients (N) | Share | Patients (N) | Share | Patients (N) | Share |
| | Age Group Total | | | | | | | | | | (b) (4) |
| 0 - 11 | Alprazolam | | | | | | | | | | |
| | Clobazam | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | |
| | Diazepam | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | |
| | Temazepam | | | | | | | | | | |
| 12 - 17 | Age Group Total | | | | | | | | | | |
| | Alprazolam | | | | | | | | | | |
| | Clobazam | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | |
| | Diazepam | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | |
| | Temazepam | | | | | | | | | | |
| 18 - 25 | Age Group Total | | | | | | | | | | |
| | Alprazolam | | | | | | | | | | |
| | Clobazam | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | |
| | Diazepam | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | |
| | Temazepam | | | | | | | | | | |
| 26 - 39 | Age Group Total | | | | | | | | | | |
| | Alprazolam | | | | | | | | | | |
| | Clobazam | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | |
| | Diazepam | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | |
| | Temazepam | | | | | | | | | | |
| 40 - 64 | Age Group Total | | | | | | | | | | |
| | Alprazolam | | | | | | | | | | |
| | Clobazam | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | |
| | Diazepam | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | |
| | Temazepam | | | | | | | | | | |
| 65+ | Age Group Total | | | | | | | | | | |
| | Alprazolam | | | | | | | | | | |
| | Clobazam | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | |
| | Diazepam | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | |
| | Temazepam | | | | | | | | | | |
| Unknown Age | Age Group Total | | | | | | | | | | |
| | Alprazolam | | | | | | | | | | |
| | Clobazam | | | | | | | | | | |
| | Clonazepam | | | | | | | | | | |
| | Diazepam | | | | | | | | | | |
| | Lorazepam | | | | | | | | | | |
| | Temazepam | | | | | | | | | | |

**Source: IQVIA, Total Patient Tracker™ (TPT) January 2014 - December 2018. Data Extracted October 2019.Files:** 2019-800 TPT Benzo Age molecule 11-21-2019.xlsx. ***Top benzodiazepines included alprazolam, clobazam, clonazepam, diazepam, lorazepam, or temazepam.**

**** Due to methodology changes, there was a data break between 2016 and 2017 data. Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.**

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## Table A.9

**Estimated number of oral benzodiazepine prescriptions dispensed from U.S outpatient retail/mail order pharmacies, stratified by molecule and specialty, 2018**

| Molecule | Specialty | Prescriptions | Share (%) |
|---|---|---|---|
| Alprazolam | Total | | (b) (4) |
| | General Practitioner | | |
| | Mid Level | | |
| | Mental Health | | |
| | Neurology | | |
| | Ob/Gyn | | |
| | Cardiology | | |
| | All Other Specialties* | | |
| Clonazepam | Total | | |
| | General Practitioner | | |
| | Mid Level | | |
| | Mental Health | | |
| | Neurology | | |
| | Pediatrics | | |
| | Specialty Unspecified | | |
| | All Other Specialties* | | |
| Lorazepam | Total | | |
| | General Practitioner | | |
| | Mid Level | | |
| | Mental Health | | |
| | Neurology | | |
| | Emergency Medicine | | |
| | Oncology | | |
| | All Other Specialties* | | |
| Diazepam | Total | | |
| | General Practitioner | | |
| | Mid Level | | |
| | Mental Health | | |
| | Neurology | | |
| | Dentistry | | |
| | Emergency Medicine | | |
| | All Other Specialties* | | |
| Temazepam | Total | | |
| | General Practitioner | | |
| | Mid Level | | |
| | Mental Health | | |
| | Neurology | | |
| | Oncology | | |
| | Cardiology | | |
| | All Other Specialties* | | |
| Clobazam | Total | | |
| | General Practitioner | | |
| | Mid Level | | |
| | Neurology | | |
| | Pediatrics | | |
| | Specialty Unspecified | | |
| | Sleep Medicine | | |
| | All Other Specialties* | | |
| All Other Molecules* | Total | | |
| | General Practitioner | | |
| | Mid Level | | |
| | Mental Health | | |
| | Neurology | | |
| | Dentistry | | |
| | Emergency Medicine | | |
| | All Other Specialties* | | |

Source: IQVIA, National Prescription Audit™ Extended Insights (NPA EI). January 2018 - December 2018. Data Extracted January 2020 File: 2019-800 NPAEI Benzo 1-30-2020.csv

*All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam ** General Practitioner = Family Practice, Internal Medicine, Osteopathic Medicine, General Practice; Mid Level = Nurse Practitioner, Physician Assistant; Mental Health = Psychiatry, Psychology, Addiction Medicine

## Appendix A.2: Drug Utilization Database Descriptions

### IQVIA National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### IQVIA National Prescription Audit™

The IQVIA National Prescription Audit™ (NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, and long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is sold to the patient. Data for the NPA audit is a national level estimate of the drug activity from these three channels. NPA receives over 3.8 billion retail prescription claims per year, captured from a sample of the universe of approximately 58,900 retail pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent ~92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available in IQVIA's business intelligence tool SMART for 72-rolling months. Each month, NPA is updated to include the most recent data month and made available between the 12-18 days after the end of the month.

Due to the changing pharmaceutical marketplace, IQVIA has implemented changes to its prescription database to manage prescription voids, reversals, and abandonments that span multiple weeks. Beginning in January 2019, IQVIA has projected published prescription volumes dispensed from the retail pharmacies based on sold date, instead of date of adjudication (i.e., fill date). Projected estimates have been adjusted and restated in the database back to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and 2017 prescription volumes dispensed from the retail pharmacies, any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

Dispensed prescription estimates are nationally projected based on a sample of prescriptions claims. Summarization of projected prescription estimates may lead to differences in prescription count due to rounding attributable to the projection methodology utilized. No statistical tests were performed on these estimates to determine statistically significant changes over time. Therefore, all changes over time should be considered approximate, and may be due to random error.

NPA New to Brand (NPA NTB) provides enhanced visibility to the volume of a patient's true, first-time use of a brand by using IQVIA's patented patient de-identification algorithm to determine if a patient has filled a prescription for that brand or another brand within the market within a predetermined look back period (typically 12 months, shorter for acute markets).

### Symphony Health Integrated Dataverse IDV®

IDV (Integrated Dataverse) from Symphony Health contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescriptions claims linked to over 280 million unique prescription patients of with an average of 5 years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9/10 diagnosis history of which nearly 180 million prescription drug patients are linked to a diagnosis. The overall sample

represents over 65,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

**IQVIA Total Patient Tracker™ (TPT)**

IQVIA Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 92% coverage and a sample of ~58,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. TPT is projected to the known universe of retail pharmacies.

Due to the changing pharmaceutical marketplace, IQVIA has implemented changes to its prescription database, National Prescription Audit™ (NPA), to manage prescription voids, reversals, and abandonments that span multiple weeks. Beginning in January 2019, IQVIA has projected published prescription volumes dispensed from the retail pharmacies based on sold date, instead of date of adjudication (i.e., fill date). Because TPT patient data are derived from NPA prescription data, projected patient estimates have been adjusted and restated in the database back to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and 2017 patient estimates who received prescriptions dispensed from the retail pharmacies; any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

Patient estimates are nationally projected based on a sample of prescriptions claims. Summarization of projected patient estimates across age groups or time periods may lead to differences in patient count due to rounding attributable to the projection methodology utilized.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

Of note, the estimated prescription and/or patient counts provided are based on projections of sample prescription claims data and therefore have some degree of inherent sampling error. These estimates are not intended to be representations of exact enumerations and should be interpreted with caution particularly if they are based on a small sample size. In addition, the data cannot be validated due to lack of access to medical records in the data sources.

## 8.2 APPENDIX B. AMERICAN ASSOCIATION OF POISON CONTROL CENTERS

**Table B1. AAPCC/NPDS generic codes product codes**

**Generic codes**

| Generic code | Description |
|---|---|
| (b) (4) | Benzodiazepines |

**Table B2. Product codes**

| Drug | Product code<br>Note: These product codes must be redacted for public release |
|---|---|
| Alprazolam | (b) (4) |

| Drug | Product code<br>Note: These product codes must be redacted for public release |
|---|---|
| | (b) (4) |
| **Clonazepam** | (b) (4) |

| Drug | Product code<br>Note: These product codes must be redacted for public release |
|---|---|
| Diazepam | (b) (4) |

| Drug | Product code<br>Note: These product codes must be redacted for public release |
|---|---|
| | (b) (4) |
| **Lorazepam** | (b) (4) |

| Drug | Product code<br>Note: These product codes must be redacted for public release |
|---|---|
| | (b) (4) |
| **Temazepam** | (b) (4) |

| Drug | Product code<br>Note: These product codes must be redacted for public release |
|---|---|
| | (b) (4) |

**Table B3. AAPCC NPDS Definitions of Exposure Reasons**

**REASON:**

*Unintentional*: An unintentional exposure results from an unforeseen or unplanned event. For example, a child gaining access to a toxic substance, when it is obvious the child did not realize the danger of the action, is an unintentional exposure. The following eight coding options are available for unintentional exposures. (Includes sub-categories: *General*; *Environmental*; *Occupational*; *Therapeutic Error*; *Misuse*; *Bite/Sting*, *Food Poisoning*; *Unknown*)

*Intentional*: A purposeful action results in an exposure. The following four categories relate to intentional exposures. (Includes sub-categories: *Suspected Suicidal*; *Misuse*; *Abuse***;** *Unknown*)

| **Intentional exposure reasons** | **Definition** |
|---|---|
| Suspected Suicides | "An exposure resulting in the inappropriate use of a substance for self-harm or self-destruction or manipulative reasons" |
| Abuse | "An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect", including recreational use of a substance for any effect |
| Misuse | "An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect" |
| Unknown | Exposures that are deemed to be intentional although the specific motive is undetermined |
| Source: American Association of Poison Control Centers. National Poison Data System (NPDS) Data Dictionary. Version 2016.07.11. July 11, 2016 | |

*Adverse Reaction*: This category is used to monitor adverse reactions (experiences) to a variety of products, including drugs, foods, cosmetics and industrial or household chemicals. (Includes sub- categories: *Drug*; *Food*; *Other*)

*Other/Unknown*: This category is used when the reason for the exposure cannot be determined or if no other category is appropriate. (Includes sub-categories: *Contaminant/Tampering*; *Malicious*; *Withdrawal*; *Unknown*)

*Other/Unknown*: This category is used when the reason for the exposure cannot be determined or if no other category is appropriate. (Includes sub-categories: *Contaminant/Tampering*; *Malicious*; *Withdrawal*; *Unknown*)

**MEDICAL OUTCOME:**

*No Effect*: The patient developed no symptoms (clinical effects) as a result of the exposure. Follow-up is required to make this determination unless the initial poison center call occurs

sufficiently long enough after the exposure that the poison center is reasonably certain no effects will occur.

*Minor Effect*: The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not worsen. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.

*Moderate Effect*: The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening, and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.

*Major Effect*: The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the symptoms are anticipated to be long-term or permanent.

*Death*: The patient died as a result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not preceded the complication. Only include those deaths which are probably or undoubtedly related to the exposure. A fatality verification is required. Also include deaths in which the exposure was a contributing factor in the death. For deaths determined to be unrelated to the exposure (those in which the most clinically significant clinical effects are coded as unrelated) the outcome is coded as "Unrelated effect" (the exposure was probably not responsible for the effect[s]).

*Other* – Includes sub-categories:
*Case not followed to a known outcome*: In some circumstances it is not appropriate or possible to follow a patient to a reasonably certain medical outcome. In these instances, choose one of the following:

*Not followed, judged as nontoxic exposure*: The patient was not followed, per clinical judgment the exposure was likely to be nontoxic because the agent involved was nontoxic. The amount implicated in the exposure was insignificant (nontoxic), and/or the route of exposure was unlikely to result in a clinical effect. If this response is selected, there must be reasonable certainty that the patient will not experience

any clinical effect from the exposure. Cases that refused follow-up if the exposure was judged as nontoxic may also be included.

*Not followed, minimal clinical effects possible*: The patient was not followed because, per clinical judgment, the exposure was likely to result in only minimal toxicity of a trivial nature. If this response is selected, the poison center must be reasonably certainty, in a worst case scenario, that the patient will experience no more than a minor effect. Cases that refused follow-up if the exposure would possibly result in minimal clinical effects and would cause no more than a minor effect may also be included.

*Unable to follow, judged as a potentially toxic exposure*: The patient was lost to follow-up (or the poison center neglected to provide follow-up) and per clinical judgment the exposure was significant and may have resulted in toxic manifestations with A MODERATE, MAJOR OR DEATH OUTCOME.

*Exposure not responsible for the effect*: This category is provided for those patients who exhibit clinical effects, which in the final analysis are determined unrelated to a toxic problem.

*Unrelated Effect*: Based upon all the information available, the exposure was probably not responsible for the effect(s). If this response is selected, all coded clinical effects must be coded as "unrelated".

**Table B4. Reason for exposure by age group, 2009-2017**

| Reason for Exposures by Age Group (year) | 0-5 | 6-12 | 13-19 | 20-39 | 40-64 | 65 and older | Unknown |
|---|---|---|---|---|---|---|---|
| **Total Exposures** | 62,474 | 8,936 | 63,561 | 254,797 | 236,180 | 36,658 | 30,113 |
| **Intentional, n** | 113 | 1,758 | 56,713 | 225,368 | 200,249 | 18,660 | 19,780 |
| ***Intentional Misuse/Abuse*** | 49 | 664 | 17313 | 38900 | 22231 | 2424 | 5121 |
| ***Intentional Abuse*** | 20 | 315 | 13,773 | 23,913 | 10,792 | 609 | 2,584 |
| ***Intentional Misuse*** | 29 | 349 | 3,540 | 14,987 | 11,439 | 1,815 | 2,537 |
| ***Suspected Suicides*** | 52 | 832 | 36,165 | 174,873 | 168,328 | 15,183 | 12,101 |
| ***Intentional Unknown*** | 12 | 262 | 3,235 | 11,595 | 9,690 | 1,053 | 2,558 |
| **Unintentional** | 61,881 | 6,658 | 4,805 | 19,976 | 26,553 | 15,248 | 6,566 |
| **Adverse Reaction** | 192 | 260 | 572 | 3,428 | 3,454 | 1,599 | 1,800 |
| **Withdrawal** | | | | | | | |
| ***Withdrawal, single-substance*** | 8 | 0 | 103 | 720 | 532 | 104 | 277 |
| ***Withdrawal, multi-substance*** | 9 | 2 | 50 | 480 | 389 | 46 | 107 |
| **Unknown Reason** | 180 | 198 | 1,107 | 4,101 | 4,754 | 976 | 1,295 |
| **Other*** | 91 | 64 | 211 | 724 | 249 | 21 | 288 |
| ***Other defined as other contamination tampering and other malicious.** | | | | | | | |

**Table B5. Severity of medical outcomes for abuse/misuse exposure calls with related clinical effects, by single and multiple-substance, 2013-2017**

| Medical Outcomes | Single substance exposures N (% of column) | Multiple-substance exposures N (% of column) |
|---|---|---|
| Total | 8,031 | 19,277 |
| Minor effect | 5,871 (73.1%) | 8,732 (45.3%) |
| Moderate effect | 2,017 (25.1%) | 8346 (43.3%) |
| Major Effect | 136 (1.7%) | 1,698 (8.8%) |
| Death | 7 (0.1%) | 501 (2.6%) |
| *Related clinical effect cannot be mapped to specific drug in multi-substance exposure | | |

**Table B6. Related Clinical Effects for Moderate-to-Severe Medical Outcomes* Involving Single-Substance Intentional Abuse Benzodiazepine Exposure Calls, National Poison Data System 2009-2017 (all reported)**

| Related Clinical Effect | Number (N) | Percentage (%) |
|---|---|---|
| Drowsiness/lethargy | 1820 | 76.02% |
| Slurred speech | 573 | 23.93% |
| Confusion | 339 | 14.16% |
| Tachycardia | 319 | 13.32% |
| Hypotension | 318 | 13.28% |
| Ataxia | 315 | 13.16% |
| Respiratory depression | 218 | 9.11% |
| Agitation | 205 | 8.56% |
| Bradycardia | 197 | 8.23% |
| Coma | 173 | 7.23% |
| Other - Miscellaneous | 139 | 5.81% |
| Mydriasis | 82 | 3.43% |
| Hypertension | 75 | 3.13% |
| Dizziness/vertigo | 66 | 2.76% |
| Hallucinations/delusions | 62 | 2.59% |
| Vomiting | 56 | 2.34% |
| Miosis | 47 | 1.96% |
| Syncope | 47 | 1.96% |

| Related Clinical Effect | Number (N) | Percentage (%) |
|---|---|---|
| **Tremor** | 44 | 1.84% |
| **Nausea** | 38 | 1.59% |
| **Electrolyte abnormality** | 37 | 1.55% |
| **CPK elevated** | 34 | 1.42% |
| **Seizure (single)** | 28 | 1.17% |
| **Acidosis** | 27 | 1.13% |
| **Conduction disturbance** | 27 | 1.13% |
| **Diaphoresis** | 26 | 1.09% |
| **Hyperventilation/tachypnea** | 21 | 0.88% |
| **Dyspnea** | 20 | 0.84% |
| **Fever/hyperthermia** | 17 | 0.71% |
| **Creatinine increased** | 16 | 0.67% |
| **Hypothermia** | 16 | 0.67% |
| **X-ray findings(+)** | 16 | 0.67% |
| **Respiratory arrest** | 15 | 0.63% |
| **Cyanosis** | 14 | 0.58% |
| **Muscle weakness** | 12 | 0.50% |
| **ECG change (other/N.O.S.)** | 11 | 0.46% |
| **EPS - dystonia** | 11 | 0.46% |
| **Nystagmus** | 11 | 0.46% |
| **Urinary incontinence** | 11 | 0.46% |
| **Anion gap increased** | 10 | 0.42% |
| **Seizures (multi/discrete)** | 10 | 0.42% |
| **Headache** | 9 | 0.38% |
| **Pneumonitis** | 9 | 0.38% |
| **Rhabdomyolysis** | 9 | 0.38% |
| **ADR to treatment** | 8 | 0.33% |
| **AST, ALT>100<=1,000** | 8 | 0.33% |
| **Chest pain (incl. noncardiac)** | 8 | 0.33% |
| **Abdominal Pain** | 6 | 0.25% |
| **Erythema/flushed** | 6 | 0.25% |

| Related Clinical Effect | Number (N) | Percentage (%) |
|---|---|---|
| **Pallor** | 6 | 0.25% |
| **Puncture wound/sting** | 6 | 0.25% |
| **Pupil(s) nonreactive** | 6 | 0.25% |
| **Asystole** | 5 | 0.21% |
| **Blurred vision** | 5 | 0.21% |
| **Cardiac arrest** | 5 | 0.21% |
| **Dermal - Irritation/pain** | 5 | 0.21% |
| **Edema** | 5 | 0.21% |
| **Pain (not dermal, GI, ocular)** | 5 | 0.21% |
| **Red eye/conjunctivitis** | 4 | 0.17% |
| **Urine color change** | 4 | 0.17% |
| **Diarrhea** | 3 | 0.13% |
| **Dysrhythmia (other/N.O.S.)** | 3 | 0.13% |
| **Hypoglycemia** | 3 | 0.13% |
| **Muscle rigidity** | 3 | 0.13% |
| **Alkalosis** | 2 | 0.08% |
| **Anorexia** | 2 | 0.08% |
| **Bronchospasm** | 2 | 0.08% |
| **Cough/choke** | 2 | 0.08% |
| **Dehydration** | 2 | 0.08% |
| **Dysphagia** | 2 | 0.08% |
| **Ecchymosis** | 2 | 0.08% |
| **Excess secretions** | 2 | 0.08% |
| **Hyperglycemia** | 2 | 0.08% |
| **Oliguria/anuria** | 2 | 0.08% |
| **Pulmonary edema** | 2 | 0.08% |
| **Renal failure** | 2 | 0.08% |
| **Urinary retention** | 2 | 0.08% |
| **Visual defect** | 2 | 0.08% |
| **AST, ALT>1,000** | 1 | 0.04% |
| **Blisters - Bullae** | 1 | 0.04% |

| Related Clinical Effect | Number (N) | Percentage (%) |
|---|---|---|
| **Deafness** | 1 | 0.04% |
| **Fecal incontinence** | 1 | 0.04% |
| **Hematemesis** | 1 | 0.04% |
| **Hematuria** | 1 | 0.04% |
| **Hemo/myoglobinuria** | 1 | 0.04% |
| **Ileus/no bowel sounds** | 1 | 0.04% |
| **LFT abnormality - other** | 1 | 0.04% |
| **Necrosis** | 1 | 0.04% |
| **Numbness** | 1 | 0.04% |
| **Oropharyngeal edema** | 1 | 0.04% |
| **Osmolal gap increased** | 1 | 0.04% |
| **Peripheral neuropathy** | 1 | 0.04% |
| **Seizures (status)** | 1 | 0.04% |
| **Throat irritation** | 1 | 0.04% |
| **V. tachycardia/V. fibrillation** | 1 | 0.04% |

* Includes clinical effects deemed by evaluators to be related to exposure for cases (N=2,394) with moderate to severe medical outcomes (moderate, major, death/death, indirect report)

## 8.3 APPENDIX C. NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM–COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE

**Table C1. Emergency Department Visits due to Adverse Events Involving Benzodiazepines, by Patient Characteristics, 2016-2017[a]**

| Patient Characteristics | Nonmedical Use of Benzodiazepines[b] | | | |
|---|---|---|---|---|
| | Cases | Annual Estimate | | |
| | No. | No. | % | 95% CI |
| **Patient age (years)[c]** | | | | |
| <5 | 0 | -- | -- | -- |
| 5-14 | 50 | 1,215[d] | 1.0[d] | (0.3-1.7) |
| 15-24 | 902 | 30,929 | 26 | (20.6-31.4) |
| 25-34 | 1,004 | 34,239 | 28.8 | (24.8-32.8) |
| 35-44 | 562 | 18,076 | 15.2 | (12.8-17.5) |
| 45-54 | 512 | 17,278 | 14.5 | (12.5-16.5) |
| 55-64 | 381 | 12,740 | 10.7 | (8.7-12.7) |
| 65-74 | 104 | 3,640 | 3.1 | (2.0-4.1) |
| ≥75 | 22 | 838[f] | 0.7 | (0.3-1.1) |

[a]Data are from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, CDC. Estimates based on <20 cases or total estimates <1,200 are considered statistically unstable and are not shown (--).
[b]Includes abuse, therapeutic misuse, and overdoses without documentation of therapeutic intent, self-harm, abuse, or misuse.
[c]Missing age for 2 cases of nonmedical use.
[d]Coefficient of variation >30%.

**Source:** Moro RN, Geller AI, Weidle NJ, et al. Emergency Department Visits Involving Benzodiazepines, United States, 2016-2017 *(In Press).*

**Table C2. Emergency Department Visits due to Adverse Events Involving Benzodiazepines, by Clinical Manifestations**

| Manifestations | Nonmedical use of Benzodiazepines | | |
|---|---|---|---|
| | Annual Estimate | | |
| | No. | % | 95% CI |
| Cardiorespiratory arrest / unresponsiveness | 28,741 | 24.2 | (17.7-30.6) |
| Altered mental status | 52,750 | 44.3 | (39.0-49.6) |
| Presyncope / syncope / dyspnea / fall | 6,054 | 5.1 | (3.7-6.5) |
| Psychiatric or other central nervous system effect | 4,346 | 3.7 | (2.7-4.6) |
| Cardiovascular effect | 1,220 | 1.0 | (0.6-1.5) |
| Other manifestations | 2,742 | 2.3 | (1.6-3.0) |
| No documented clinical manifestations | 23,157 | 19.5 | (14.3-24.6) |

[a]Data are from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, CDC. Estimates based on <20 cases or total estimates <1,200 are considered statistically unstable and are not shown (--).Clinical manifestations were categorized in a mutually exclusive and hierarchical manner based on severity (e.g., a case involving confusion and blurred vision would be classified as altered mental status based on documentation of confusion).
[b]Coefficient of variation >30%.

**Source:** Moro RN, Geller AI, Weidle NJ, et al. Emergency Department Visits Involving Benzodiazepines, United States, 2016-2017 *(In Press).*

## 8.4 APPENDIX D. NATIONAL VITAL STATISTICS SYSTEM-MORTALITY

**Table D1. Number of all benzodiazepine-related deaths and single drug substance benzodiazepine deaths, where underlying cause of death is drug poisoning [a], 2000-2017, NVSS-M**

| Year | All benzodiazepine-related deaths | Benzodiazepine only deaths (single drug) |
|---|---|---|
| 2000 | 1298 | 112 |
| 2001 | 1594 | 120 |
| 2002 | 2022 | 136 |
| 2003 | 2248 | 132 |
| 2004 | 2627 | 149 |
| 2005 | 3084 | 162 |
| 2006 | 3835 | 214 |
| 2007 | 4500 | 194 |
| 2008 | 5010 | 251 |
| 2009 | 5567 | 206 |
| 2010 | 6497 | 240 |
| 2011 | 6872 | 254 |
| 2012 | 6524 | 246 |
| 2013 | 6973 | 253 |
| 2014 | 7945 | 280 |
| 2015 | 8791 | 279 |
| 2016 | 10684 | 328 |
| 2017 | 11537 | 308 |
| **TOTAL** | **97608** | **3864** |

[a] where underlying cause of death is drug poisoning (X40-X44, X60-X64, X85, Y10-Y14)

**Table D2. Number of all benzodiazepine-, prescription opioid-, heroin- or synthetic opioid-related deaths, where underlying cause of death is drug poisoning [a], 2000-2017, NVSS-M**

| Year | All benzodiazepine-related deaths | All prescription opioid-related deaths | All heroin-related deaths | All synthetic opioid-related deaths |
|---|---|---|---|---|
| 2000 | 1298 | 3785 | 1842 | 782 |
| 2001 | 1594 | 4770 | 1779 | 957 |
| 2002 | 2022 | 6483 | 2089 | 1295 |
| 2003 | 2248 | 7461 | 2080 | 1400 |
| 2004 | 2627 | 8577 | 1878 | 1664 |
| 2005 | 3084 | 9612 | 2009 | 1742 |
| 2006 | 3835 | 11589 | 2088 | 2707 |
| 2007 | 4500 | 12796 | 2399 | 2213 |
| 2008 | 5010 | 13149 | 3041 | 2306 |
| 2009 | 5567 | 13523 | 3278 | 2946 |
| 2010 | 6497 | 14583 | 3036 | 3007 |
| 2011 | 6872 | 15140 | 4397 | 2666 |
| 2012 | 6524 | 14240 | 5925 | 2628 |
| 2013 | 6973 | 14145 | 8257 | 3105 |
| 2014 | 7945 | 14838 | 10574 | 5544 |
| 2015 | 8791 | 15281 | 12989 | 9580 |
| 2016 | 10684 | 17087 | 15469 | 19413 |
| 2017 | 11537 | 17029 | 15482 | 28466 |
| **TOTAL** | **97608** | **214088** | **98612** | **92421** |

[a]where underlying cause of death is drug poisoning (X40-X44, X60-X64, X85, Y10-Y14)

**Table D3. Number of single drug substance [a] benzodiazepine-related deaths and benzodiazepine with prescription opioid-, heroin- or synthetic opioid-related deaths, where underlying cause of death is drug poisoning [b], 2000-2017, NVSS-M**

| Years | Benzodiazepine only | Benzodiazepine and prescription opioid only | Benzodiazepine and heroin only | Benzodiazepine and synthetic opioid only |
|---|---|---|---|---|
| 2000 | 112 | 94 | 9 | 15 |
| 2001 | 120 | 143 | 10 | 14 |
| 2002 | 136 | 179 | 16 | 13 |
| 2003 | 132 | 212 | 19 | 21 |
| 2004 | 149 | 317 | 16 | 23 |
| 2005 | 162 | 402 | 28 | 37 |
| 2006 | 214 | 571 | 22 | 50 |
| 2007 | 194 | 666 | 40 | 55 |
| 2008 | 251 | 719 | 45 | 69 |
| 2009 | 206 | 849 | 68 | 58 |
| 2010 | 240 | 1115 | 56 | 77 |
| 2011 | 254 | 1131 | 105 | 68 |
| 2012 | 246 | 1032 | 178 | 59 |
| 2013 | 253 | 854 | 223 | 73 |
| 2014 | 280 | 891 | 320 | 126 |
| 2015 | 279 | 924 | 355 | 193 |
| 2016 | 328 | 993 | 371 | 413 |
| 2017 | 308 | 792 | 250 | 662 |
| **TOTAL** | **3864** | **11884** | **2131** | **2026** |

[a]Drug substances: T36.0 to T50.9; does not include alcohol (T51.0)

[b]where underlying cause of death is drug poisoning (X40-X44, X60-X64, X85, Y10-Y14)

**Table D4. Average annual rate of deaths involving benzodiazepines among deaths with underlying cause of death due to drug poisoning[a], per 1,000,000 persons [b], by age group, US Residents, 2013-2017**

| Age Group | Benzodiazepine | Benzodiazepine as single drug substance [c] | Benzodiazepine and prescription opioids | Benzodiazepines and drug substance other than prescription opioids |
|---|---|---|---|---|
| **Rates per 1,000,000 population** | | | | |
| **<10** | 0.079 | 0.005 | 0.040 | 0.035 |
| **10-19** | 3.447 | 0.086 | 1.647 | 1.714 |
| **20-39** | 43.892 | 0.973 | 21.490 | 21.430 |
| **40-59** | 50.160 | 1.692 | 30.331 | 18.137 |
| **60-64** | 29.433 | 1.346 | 18.241 | 9.846 |
| **65+** | 8.470 | 0.667 | 4.688 | 3.115 |

[a] drug poisoning underlying cause of death ICD-10 codes: X40-X44, X60-X64, X85, Y10-Y14
[b] Denominator populations: age <10: n=201,750,486; age 10-19: n=208,864,296; age 20-39: n=434,955,026; age 40-59: n=424,278,541; age 60-64: n=95,063,029; age 65+: n=238,493,906; from: https://wonder.cdc.gov/Bridged-Race-v2018.HTML
[c] Single drug substance defined by ICD-10 codes T36.0 to T50.9, does not involve alcohol (T51.0)

## 8.5 APPENDIX E. LITERATURE REVIEW

### Epidemiologic Literature Search

| Table E1. Epidemiologic Literature Search #1. Search strings and additional parameters |
|---|
| **Pubmed** |
| **Date of search: July 25, 2019**<br>**Returned 486 results** |
| (("benzodiazepine" [Ti] OR "benzodiazepines" [Ti] OR "alprazolam"[Ti] OR "xanax"[Ti] OR "chlordiazepoxide"[Ti] OR "librium"[Ti] OR "librax"[Ti] OR "clobazam"[Ti] OR "onfi"[Ti] OR "clonazepam"[Ti] OR "klonopin"[Ti] OR "clorazepate"[Ti] OR "tranxene"[Ti] OR "T-tab"[Ti] OR "Gen-Xene"[Ti] OR "diazepam"[Ti] OR "diastat"[Ti] OR "AcuDial"[Ti] OR "valium"[Ti] OR "estazolam"[Ti] OR "prosom"[Ti] OR "flurazepam"[Ti] OR "dalmane"[Ti] OR "dalmadon"[Ti] OR "lorazepam"[Ti] OR "ativan"[Ti] OR "oxazepam"[Ti] OR "serax"[Ti] OR "quazepam"[Ti] OR "doral"[Ti] OR "temazepam"[Ti] OR "restoril"[Ti] OR "triazolam"[Ti] OR "halcion"[Ti] OR "midazolam"[Ti] OR "versed"[Ti] OR "bromazepam"[Ti] OR "flunitrazepam"[Ti] OR "rohypnol")<br><br>AND (("substance-related disorders"[MeSH Terms] OR ("substance-related"[tiab] AND "disorders"[ tiab]) OR "substance-related disorders"[tiab])<br><br>OR misuse [tiab] OR "nonmedical use" [tiab] OR "non-medical use" [tiab] OR "NMU" [tiab] OR "nonmedical abuse" [tiab] OR "recreational use" [tiab] OR abuse[tiab]<br><br>OR ("behavior, addictive"[MeSH Terms] OR ("behavior"[tiab] AND "addictive"[tiab]) OR "addictive behavior"[tiab] OR "addiction"[tiab]) OR (dependence [tiab] OR "biological dependence" [tiab])<br><br>OR ("drug overdose"[MeSH Terms] OR (drug[tiab] AND overdose[tiab]) OR "drug overdose"[tiab] OR "overdose"[tiab]) OR (death[MeSH Terms] OR death[tiab] OR mortality [tiab]))<br><br>AND ("systematic review"[tw] OR cohort[tw] OR "matched-cohort"[tw] OR "matched cohort"[tw] OR "case-control"[tw] OR "cross sectional"[tw] OR "cross-sectional"[tw] OR survey[tw] OR observational[tw] OR "prevalence study"[tw] OR "longitudinal study"[tw] OR "before-after study"[tw] OR "pre-intervention"[tw] OR "post-intervention"[tw] OR "pre-post"[tw]-OR "real world"[tw] OR "real-world"[tw] OR "interrupted time-series"[tw] OR "interrupted time series"[tw] OR "population-based"[tw] OR retrospective[tw] OR prospective[tw] OR |

"pooled analysis"[tw] OR crossover[tw] OR “meta-analysis”[tw] OR “meta analysis”[tw] OR incidence[tw] OR prevalence[tw] OR risk[tw] OR incidence[tw] OR longitudinal[tw] OR prospective[tw] OR “risk factors”[tw] OR “risk factor”[tw] OR “natural history”[tw])

NOT (“randomized control trial”[tw] OR “randomized-control trial”[tw] OR “randomized control trials”[tw] OR “randomized-control trials”[tw] OR “randomized controlled trial”[tw] OR “randomized controlled trials”[tw] OR “randomized-controlled trial”[tw] OR “randomized-controlled trials”[tw] OR “randomised control trial”[tw] OR “randomised-control trial”[tw] OR “randomised control trials”[tw] OR “randomised-control trials”[tw] OR “randomised controlled trial”[tw] OR “randomised controlled trials”[tw] OR “randomised-controlled trial”[tw] OR “randomised-controlled trials”[tw] OR RCT[tw] OR “randomized trial”[tw] OR “randomised trial”[tw] OR “randomized control”[tw] OR “randomised control”[tw] OR “cluster-randomized trial”[tw] OR “cluster-randomised trial”[tw] OR “randomized double-blind”[tw] OR “clinical trial”[tw] OR “clinical trials”[tw] OR “clinical study”[tw] OR “clinical studies”[tw] OR “clinical conference”[tw] OR “clinical conferences”[tw] OR “open label”[tw] OR “open-label”[tw] OR “phase I”[tw] OR “phase 1”[tw] OR “phase II”[tw] OR “phase 2”[tw] OR “phase III”[tw] OR “phase 3”[tw] OR autobiography[tw] OR biography[tw] OR “patient education handout”[tw] OR webcast[tw])

NOT (cell[tw] OR "cell line"[tw] OR cellular[tw] OR tissue[tw] OR "in vitro"[tw] OR “in vivo”[tw] OR spectroscopic[tw] OR spectrometer[tw] OR spectrophotometry[tw] OR "transformation products"[tw] OR "gene variants"[tw] OR plant[tw] OR pharmacokinetic[tw] OR pharmacodynamic[tw] OR microscopy[tw] OR chromatography[tw] OR “mass spectrometry”[tw] OR “gene expression”[tw])

NOT (animals[tiab] OR animal[tiab] OR "Pogona vitticeps"[tiab] OR mice[tiab] OR mus[tiab] OR mouse[tiab] OR murine[tiab] OR woodmouse[tiab] OR rats[tiab] OR rat[tiab] OR murinae[tiab] OR muridae[tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[tiab] OR rodent[tiab] OR rodents[tiab] OR pigs[tiab] OR pig[tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR "sus scrofa"[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat[tiab] OR polecats[tiab] OR "mustela putorius"[tiab] OR "guinea pigs"[tiab] OR "guinea pig"[tiab] OR cavia[tiab] OR callithrix[tiab] OR marmoset[tiab] OR marmosets[tiab] OR cebuella[tiab] OR hapale[tiab] OR octodon[tiab] OR chinchilla[tiab] OR chinchillas[tiab] OR gerbillinae[tiab] OR gerbil[tiab] OR gerbils[tiab] OR jird[tiab] OR jirds[tiab] OR merione[tiab] OR meriones[tiab] OR rabbits[tiab] OR rabbit[tiab] OR hares[tiab] OR hare[tiab] OR diptera[tiab] OR flies[tiab] OR fly[tiab] OR dipteral[tiab] OR drosphila[tiab] OR drosophilidae[tiab] OR cats[tiab] OR cat[tiab] OR carus[tiab] OR felis[tiab] OR nematoda[tiab] OR nematode[tiab] OR nematoda[tiab] OR nematode[tiab] OR nematodes[tiab] OR sipunculida[tiab] OR dogs[tiab] OR dog[tiab] OR canine[tiab] OR canines[tiab] OR canis[tiab] OR sheep[tiab] OR sheeps[tiab] OR mouflon[tiab] OR mouflons[tiab] OR ovis[tiab] OR goats[tiab] OR goat[tiab] OR capra[tiab] OR capras[tiab] OR rupicapra[tiab] OR chamois[tiab] OR haplorhini[tiab] OR monkey[tiab] OR monkeys[tiab] OR anthropoidea[tiab] OR anthropoids[tiab] OR saguinus[tiab] OR tamarin[tiab] OR tamarins[tiab] OR leontopithecus[tiab] OR hominidae[tiab] OR ape[tiab] OR apes[tiab] OR pan[tiab] OR paniscus[tiab] OR "pan paniscus"[tiab] OR bonobo[tiab] OR bonobos[tiab] OR troglodytes[tiab] OR "pan troglodytes"[tiab] OR gibbon[tiab] OR gibbons[tiab] OR siamang[tiab] OR siamangs[tiab] OR nomascus[tiab] OR symphalangus[tiab] OR chimpanzee[tiab] OR chimpanzees[tiab] OR prosimians[tiab] OR "bush baby"[tiab] OR prosimian[tiab] OR "bush babies"[tiab] OR galagos[tiab] OR galago[tiab] OR pongidae[tiab] OR gorilla[tiab] OR gorillas[tiab] OR

pongo[tiab] OR pygmaeus[tiab] OR "pongo pygmaeus"[tiab] OR orangutans[tiab] OR pygmaeus[tiab] OR lemur[tiab] OR lemurs[tiab] OR lemuridae[tiab] OR horse[tiab] OR horses[tiab] OR pongo[tiab] OR equus[tiab] OR cow[tiab] OR calf[tiab] OR bull[tiab] OR chicken[tiab] OR chickens[tiab] OR gallus[tiab] OR quail[tiab] OR bird[tiab] OR birds[tiab] OR quails[tiab] OR poultry[tiab] OR poultries[tiab] OR fowl[tiab] OR fowls[tiab] OR reptile[tiab] OR reptilia[tiab] OR reptiles[tiab] OR snakes[tiab] OR snake[tiab] OR lizard[tiab] OR lizards[tiab] OR alligator[tiab] OR alligators[tiab] OR crocodile[tiab] OR crocodiles[tiab] OR turtle[tiab] OR turtles[tiab] OR amphibian[tiab] OR amphibians[tiab] OR amphibia[tiab] OR frog[tiab] OR frogs[tiab] OR bombina[tiab] OR salientia[tiab] OR toad[tiab] OR toads[tiab] OR "epidalea calamita"[tiab] OR salamander[tiab] OR salamanders[tiab] OR eel[tiab] OR eels[tiab] OR fish[tiab] OR fishes[tiab] OR pisces[tiab] OR catfish[tiab] OR catfishes[tiab] OR siluriformes[tiab] OR arius[tiab] OR heteropneustes[tiab] OR sheatfish[tiab] OR perch[tiab] OR perches[tiab] OR percidae[tiab] OR perca[tiab] OR trout[tiab] OR trouts[tiab] OR char[tiab] OR chars[tiab] OR salvelinus[tiab] OR "fathead minnow"[tiab] OR minnow[tiab] OR cyprinidae[tiab] OR carps[tiab] OR carp[tiab] OR zebrafish[tiab] OR zebrafishes[tiab] OR goldfish[tiab] OR goldfishes[tiab] OR guppy[tiab] OR guppies[tiab] OR chub[tiab] OR chubs[tiab] OR tinca[tiab] OR barbels[tiab] OR barbus[tiab] OR pimephales[tiab] OR promelas[tiab] OR "poecilia reticulata"[tiab] OR mullet[tiab] OR mullets[tiab] OR seahorse[tiab] OR seahorses[tiab] OR mugil curema[tiab] OR "atlantic cod"[tiab] OR shark[tiab] OR sharks[tiab] OR catshark[tiab] OR anguilla[tiab] OR salmonid[tiab] OR salmonids[tiab] OR whitefish[tiab] OR whitefishes[tiab] OR salmon[tiab] OR salmons[tiab] OR sole[tiab] OR solea[tiab] OR "sea lamprey"[tiab] OR lamprey[tiab] OR lampreys[tiab] OR pumpkinseed[tiab] OR sunfish[tiab] OR sunfishes[tiab] OR tilapia[tiab] OR tilapias[tiab] OR turbot[tiab] OR turbots[tiab] OR flatfish[tiab] OR flatfishes[tiab] OR sciuridae[tiab] OR squirrel[tiab] OR squirrels[tiab] OR chipmunk[tiab] OR chipmunks[tiab] OR suslik[tiab] OR susliks[tiab] OR vole[tiab] OR voles[tiab] OR lemming[tiab] OR lemmings[tiab] OR muskrat[tiab] OR muskrats[tiab] OR lemmus[tiab] OR otter[tiab] OR otters[tiab] OR marten[tiab] OR martens[tiab] OR martes[tiab] OR weasel[tiab] OR badger[tiab] OR badgers[tiab] OR ermine[tiab] OR mink[tiab] OR minks[tiab] OR sable[tiab] OR sables[tiab] OR gulo[tiab] OR gulos[tiab] OR wolverine[tiab] OR wolverines[tiab] OR minks[tiab] OR mustela[tiab] OR llama[tiab] OR llamas[tiab] OR alpaca[tiab] OR alpacas[tiab] OR camelid[tiab] OR camelids[tiab] OR guanaco[tiab] OR guanacos[tiab] OR chiroptera[tiab] OR chiropteras[tiab] OR bat[tiab] OR bats[tiab] OR fox[tiab] OR foxes[tiab] OR iguana[tiab] OR iguanas[tiab] OR "xenopus laevis"[tiab] OR parakeet[tiab] OR parakeets[tiab] OR parrot[tiab] OR parrots[tiab] OR donkey[tiab] OR donkeys[tiab] OR mule[tiab] OR mules[tiab] OR zebra[tiab] OR zebras[tiab] OR shrew[tiab] OR shrews[tiab] OR bison[tiab] OR bisons[tiab] OR buffalo[tiab] OR buffaloes[tiab] OR deer[tiab] OR deers[tiab] OR bear[tiab] OR bears[tiab] OR panda[tiab] OR pandas[tiab] OR "wild hog"[tiab] OR "wild boar"[tiab] OR fitchew[tiab] OR fitch[tiab] OR beaver[tiab] OR beavers[tiab] OR jerboa[tiab] OR jerboas[tiab] OR capybara[tiab] OR capybaras[tiab])

AND English [la]

AND (("2000/01/01"[Date - Entrez] : "2019/07/25"[Date - Entrez]))

**Embase**

**Search date: July 26, 2019**

| **Returned 1,012 results** |
| --- |
| ('benzodiazepine':ti OR 'benzodiazepines':ti OR 'alprazolam':ti OR 'xanax':ti OR 'chlordiazepoxide':ti OR 'librium':ti OR 'librax':ti OR 'clobazam':ti OR 'onfi':ti OR 'clonazepam':ti OR 'klonopin':ti OR 'clorazepate':ti OR 'tranxene':ti OR 'T-tab':ti OR 'gen-xene':ti OR 'diazepam':ti OR 'diastat':ti OR 'acudial':ti OR 'valium':ti OR 'estazolam':ti OR 'prosom':ti OR 'flurazepam':ti OR 'dalmane':ti OR 'dalmadon':ti OR 'lorazepam':ti OR 'ativan':ti OR 'oxazepam':ti OR 'serax':ti OR 'quazepam':ti OR 'doral':ti OR 'temazepam':ti OR 'restoril':ti OR 'triazolam':ti OR 'halcion':ti OR 'midazolam':ti OR 'versed':ti OR 'bromazepam':ti OR 'flunitrazepam':ti OR 'rohypnol'/exp OR 'rohypnol') AND ('substance-related disorders'/exp OR 'substance-related disorders' OR ('substance-related':ti,ab AND 'disorders':ti,ab) OR 'substance-related disorders':ti,ab OR misuse:ti,ab OR 'nonmedical use':ti,ab OR 'non-medical use':ti,ab OR 'nmu':ti,ab OR 'nonmedical abuse':ti,ab OR 'recreational use':ti,ab OR abuse:ti,ab OR 'behavior, addictive'/exp OR 'behavior, addictive' OR ('behavior':ti,ab AND 'addictive':ti,ab) OR 'addictive behavior':ti,ab OR 'addiction':ti,ab OR dependence:ti,ab OR 'biological dependence':ti,ab OR 'drug overdose'/exp OR 'drug overdose' OR (drug:ti,ab AND overdose:ti,ab) OR 'drug overdose':ti,ab OR 'overdose':ti,ab OR 'death'/exp OR death OR death:ti,ab OR mortality:ti,ab) AND ('systematic review':ti,ab OR cohort:ti,ab OR 'matched-cohort':ti,ab OR 'matched cohort':ti,ab OR 'case-control':ti,ab OR 'cross sectional':ti,ab OR 'cross-sectional':ti,ab OR survey:ti,ab OR observational:ti,ab OR 'prevalence study':ti,ab OR 'longitudinal study':ti,ab OR 'before-after study':ti,ab OR 'pre-intervention':ti,ab OR 'post-intervention':ti,ab OR 'pre-post':ti,ab OR 'real world':ti,ab OR 'real-world':ti,ab OR 'interrupted time-series':ti,ab OR 'interrupted time series':ti,ab OR 'population-based':ti,ab OR retrospective:ti,ab OR 'pooled analysis':ti,ab OR crossover:ti,ab OR 'meta-analysis':ti,ab OR 'meta analysis':ti,ab OR prevalence:ti,ab OR risk:ti,ab OR incidence:ti,ab OR longitudinal:ti,ab OR prospective:ti,ab OR 'risk factors':ti,ab OR 'risk factor':ti,ab OR 'natural history':ti,ab) NOT ('randomized control trial':ti,ab OR 'randomized-control trial':ti,ab OR 'randomized control trials':ti,ab OR 'randomized-control trials':ti,ab OR 'randomized controlled trial':ti,ab OR 'randomized controlled trials':ti,ab OR 'randomized-controlled trial':ti,ab OR 'randomized-controlled trials':ti,ab OR 'randomised control trial':ti,ab OR 'randomised-control trial':ti,ab OR 'randomised control trials':ti,ab OR 'randomised-control trials':ti,ab OR 'randomised controlled trial':ti,ab OR 'randomised controlled trials':ti,ab OR 'randomised-controlled trial':ti,ab OR 'randomised-controlled trials':ti,ab OR rct:ti,ab OR 'randomized trial':ti,ab OR 'randomised trial':ti,ab OR 'randomized control':ti,ab OR 'randomised control':ti,ab OR 'cluster-randomized trial':ti,ab OR 'cluster-randomised trial':ti,ab OR 'randomized double-blind':ti,ab OR 'clinical trial':ti,ab OR 'clinical trials':ti,ab OR 'clinical study':ti,ab OR 'clinical studies':ti,ab OR 'clinical conference':ti,ab OR 'clinical conferences':ti,ab OR 'open label':ti,ab OR 'open-label':ti,ab OR 'phase i':ti,ab OR 'phase 1':ti,ab OR 'phase ii':ti,ab OR 'phase 2':ti,ab OR 'phase iii':ti,ab OR 'phase 3':ti,ab OR autobiography:ti,ab OR biography:ti,ab OR 'patient education handout':ti,ab OR webcast:ti,ab) NOT (cell:ti,ab OR 'cell line':ti,ab OR cellular:ti,ab OR tissue:ti,ab OR 'in vitro':ti,ab OR 'in vivo':ti,ab OR spectroscopic:ti,ab OR spectrometer:ti,ab OR spectrophotometry:ti,ab OR 'transformation products':ti,ab OR 'gene variants':ti,ab OR plant:ti,ab OR pharmacokinetic:ti,ab OR pharmacodynamic:ti,ab OR microscopy:ti,ab OR chromatography:ti,ab OR 'mass spectrometry':ti,ab OR 'gene expression':ti,ab) NOT ((animals:ti,ab OR animal:ti,ab OR 'pogona vitticeps':ti,ab OR mice:ti,ab OR mus:ti,ab OR mouse:ti,ab OR murine:ti,ab OR woodmouse:ti,ab OR rats:ti,ab OR rat:ti,ab OR murinae:ti,ab OR muridae:ti,ab OR cottonrat:ti,ab OR cottonrats:ti,ab OR hamster:ti,ab OR hamsters:ti,ab OR cricetinae:ti,ab OR rodentia:ti,ab OR rodent:ti,ab OR rodents:ti,ab OR pigs:ti,ab OR |

pig:ti,ab OR swine:ti,ab OR swines:ti,ab OR piglets:ti,ab OR piglet:ti,ab OR boar:ti,ab OR boars:ti,ab OR 'sus scrofa':ti,ab OR ferrets:ti,ab OR ferret:ti,ab OR polecat:ti,ab OR polecats:ti,ab OR 'mustela putorius':ti,ab OR 'guinea pigs':ti,ab OR 'guinea pig':ti,ab OR cavia:ti,ab OR callithrix:ti,ab OR marmoset:ti,ab OR marmosets:ti,ab OR cebuella:ti,ab OR hapale:ti,ab OR octodon:ti,ab OR chinchilla:ti,ab OR chinchillas:ti,ab OR gerbillinae:ti,ab OR gerbil:ti,ab OR gerbils:ti,ab OR jird:ti,ab OR jirds:ti,ab OR merione:ti,ab OR meriones:ti,ab OR rabbits:ti,ab OR rabbit:ti,ab OR hares:ti,ab OR hare:ti,ab OR diptera:ti,ab OR flies:ti,ab OR fly:ti,ab OR dipteral:ti,ab OR drosphila:ti,ab OR drosophilidae:ti,ab OR cats:ti,ab OR cat:ti,ab OR carus:ti,ab OR felis:ti,ab OR nematoda:ti,ab OR nematode:ti,ab OR nematodes:ti,ab OR sipunculida:ti,ab OR dogs:ti,ab OR dog:ti,ab OR canine:ti,ab OR canines:ti,ab OR canis:ti,ab OR sheep:ti,ab OR sheeps:ti,ab OR mouflon:ti,ab OR mouflons:ti,ab OR ovis:ti,ab OR goats:ti,ab OR goat:ti,ab OR capra:ti,ab OR capras:ti,ab OR rupicapra:ti,ab OR chamois:ti,ab OR haplorhini:ti,ab OR monkey:ti,ab OR monkeys:ti,ab OR anthropoidea:ti,ab OR anthropoids:ti,ab OR saguinus:ti,ab OR tamarin:ti,ab OR tamarins:ti,ab OR leontopithecus:ti,ab OR hominidae:ti,ab OR ape:ti,ab OR apes:ti,ab OR pan:ti,ab OR paniscus:ti,ab OR 'pan paniscus':ti,ab OR bonobo:ti,ab OR bonobos:ti,ab OR troglodytes:ti,ab OR 'pan troglodytes':ti,ab OR gibbon:ti,ab OR gibbons:ti,ab OR siamang:ti,ab OR siamangs:ti,ab OR nomascus:ti,ab OR symphalangus:ti,ab OR chimpanzee:ti,ab OR chimpanzees:ti,ab OR prosimians:ti,ab OR 'bush baby':ti,ab OR prosimian:ti,ab OR 'bush babies':ti,ab OR galagos:ti,ab OR galago:ti,ab OR pongidae:ti,ab OR gorilla:ti,ab OR gorillas:ti,ab OR 'pongo pygmaeus':ti,ab OR orangutans:ti,ab OR pygmaeus:ti,ab OR lemur:ti,ab OR lemurs:ti,ab OR lemuridae:ti,ab OR horse:ti,ab OR horses:ti,ab OR pongo:ti,ab OR equus:ti,ab OR cow:ti,ab OR calf:ti,ab OR bull:ti,ab OR chicken:ti,ab OR chickens:ti,ab OR gallus:ti,ab OR quail:ti,ab OR bird:ti,ab OR birds:ti,ab OR quails:ti,ab OR poultry:ti,ab OR poultries:ti,ab OR fowl:ti,ab OR fowls:ti,ab OR reptile:ti,ab OR reptilia:ti,ab OR reptiles:ti,ab OR snakes:ti,ab OR snake:ti,ab OR lizard:ti,ab OR lizards:ti,ab OR alligator:ti,ab OR alligators:ti,ab OR crocodile:ti,ab OR crocodiles:ti,ab OR turtle:ti,ab OR turtles:ti,ab OR amphibian:ti,ab OR amphibians:ti,ab OR amphibia:ti,ab OR frog:ti,ab OR frogs:ti,ab OR bombina:ti,ab OR salientia:ti,ab OR toad:ti,ab OR toads:ti,ab OR 'epidalea calamita':ti,ab OR salamander:ti,ab OR salamanders:ti,ab OR eel:ti,ab OR eels:ti,ab OR fish:ti,ab OR fishes:ti,ab OR pisces:ti,ab OR catfish:ti,ab OR catfishes:ti,ab OR siluriformes:ti,ab OR arius:ti,ab OR heteropneustes:ti,ab OR sheatfish:ti,ab OR perch:ti,ab OR perches:ti,ab OR percidae:ti,ab OR perca:ti,ab OR trout:ti,ab OR trouts:ti,ab OR char:ti,ab OR chars:ti,ab OR salvelinus:ti,ab OR 'fathead minnow':ti,ab OR minnow:ti,ab OR cyprinidae:ti,ab OR carps:ti,ab OR carp:ti,ab OR zebrafish:ti,ab OR zebrafishes:ti,ab OR goldfish:ti,ab OR goldfishes:ti,ab OR guppy:ti,ab OR guppies:ti,ab OR chub:ti,ab OR chubs:ti,ab OR tinca:ti,ab OR barbels:ti,ab OR barbus:ti,ab OR pimephales:ti,ab OR promelas:ti,ab OR 'poecilia reticulata':ti,ab OR mullet:ti,ab OR mullets:ti,ab OR seahorse:ti,ab OR seahorses:ti,ab OR 'mugil'/exp OR mugil) AND curema:ti,ab OR 'atlantic cod':ti,ab OR shark:ti,ab OR sharks:ti,ab OR catshark:ti,ab OR anguilla:ti,ab OR salmonid:ti,ab OR salmonids:ti,ab OR whitefish:ti,ab OR whitefishes:ti,ab OR salmon:ti,ab OR salmons:ti,ab OR sole:ti,ab OR solea:ti,ab OR 'sea lamprey':ti,ab OR lamprey:ti,ab OR lampreys:ti,ab OR pumpkinseed:ti,ab OR sunfish:ti,ab OR sunfishes:ti,ab OR tilapia:ti,ab OR tilapias:ti,ab OR turbot:ti,ab OR turbots:ti,ab OR flatfish:ti,ab OR flatfishes:ti,ab OR sciuridae:ti,ab OR squirrel:ti,ab OR squirrels:ti,ab OR chipmunk:ti,ab OR chipmunks:ti,ab OR suslik:ti,ab OR susliks:ti,ab OR vole:ti,ab OR voles:ti,ab OR lemming:ti,ab OR lemmings:ti,ab OR muskrat:ti,ab OR muskrats:ti,ab OR lemmus:ti,ab OR otter:ti,ab OR otters:ti,ab OR marten:ti,ab OR martens:ti,ab OR martes:ti,ab OR weasel:ti,ab OR badger:ti,ab OR badgers:ti,ab OR ermine:ti,ab OR mink:ti,ab OR sable:ti,ab OR sables:ti,ab OR gulo:ti,ab OR gulos:ti,ab OR wolverine:ti,ab OR wolverines:ti,ab OR minks:ti,ab OR mustela:ti,ab OR llama:ti,ab OR llamas:ti,ab OR

alpaca:ti,ab OR alpacas:ti,ab OR camelid:ti,ab OR camelids:ti,ab OR guanaco:ti,ab OR guanacos:ti,ab OR chiroptera:ti,ab OR chiropteras:ti,ab OR bat:ti,ab OR bats:ti,ab OR fox:ti,ab OR foxes:ti,ab OR iguana:ti,ab OR iguanas:ti,ab OR 'xenopus laevis':ti,ab OR parakeet:ti,ab OR parakeets:ti,ab OR parrot:ti,ab OR parrots:ti,ab OR donkey:ti,ab OR donkeys:ti,ab OR mule:ti,ab OR mules:ti,ab OR zebra:ti,ab OR zebras:ti,ab OR shrew:ti,ab OR shrews:ti,ab OR bison:ti,ab OR bisons:ti,ab OR buffalo:ti,ab OR buffaloes:ti,ab OR deer:ti,ab OR deers:ti,ab OR bear:ti,ab OR bears:ti,ab OR panda:ti,ab OR pandas:ti,ab OR 'wild hog':ti,ab OR 'wild boar':ti,ab OR fitchew:ti,ab OR fitch:ti,ab OR beaver:ti,ab OR beavers:ti,ab OR jerboa:ti,ab OR jerboas:ti,ab OR capybara:ti,ab OR capybaras:ti,ab) AND [english]/lim AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim) AND [2000-2019]/py

**Web of Science**

**Search date: July 30, 2019**
**Returned 190 results**
**English language, years: 2000 to 2019, Web of Science Core Collection**

((TI=(“benzodiazepine” OR “benzodiazepines” OR "alprazolam" OR "xanax" OR "chlordiazepoxide" OR "librium" OR "librax" OR "clobazam" OR "onfi" OR "clonazepam" OR "klonopin" OR "clorazepate" OR "tranxene" OR "T-tab" OR "Gen-Xene" OR "diazepam" OR "diastat" OR "AcuDial" OR "valium" OR "estazolam" OR "prosom" OR "flurazepam" OR "dalmane" OR "dalmadon" OR "lorazepam" OR "ativan" OR "oxazepam" OR "serax" OR "quazepam" OR "doral" OR "temazepam" OR "restoril" OR "triazolam" OR "halcion" OR "midazolam" OR "versed" OR "bromazepam" OR "flunitrazepam" OR “rohypnol”)) AND (ALL=("substance-related disorders" OR "substance-related disorders" OR misuse OR “nonmedical use” OR “non-medical use” OR “NMU” OR “nonmedical abuse” OR “recreational use” OR abuse OR "addictive behavior" OR "addiction" OR dependence OR “biological dependence” OR "drug overdose" OR "overdose" OR death OR mortality)) AND (TI=(“systematic review” OR cohort OR "matched-cohort" OR “matched cohort” OR "case-control" OR "cross sectional" OR "cross-sectional" OR survey OR observational OR "prevalence study" OR "longitudinal study" OR "before-after study" OR “pre-intervention” OR “post-intervention” OR “pre-post” OR “real world” OR “real-world” OR “interrupted time-series” OR “interrupted time series” OR "population-based" OR retrospective OR prospective OR "pooled analysis" OR crossover OR “meta-analysis” OR “meta analysis” OR incidence OR prevalence OR risk OR incidence OR longitudinal OR prospective OR “risk factors” OR “risk factor” OR “natural history”)) NOT (TS=(“randomized control trial” OR “randomized-control trial” OR “randomized control trials” OR “randomized-control trials” OR “randomized controlled trial” OR “randomized controlled trials” OR “randomized-controlled trial” OR “randomized-controlled trials” OR “randomised control trial” OR “randomised-control trial” OR “randomised control trials” OR “randomised-control trials” OR “randomised controlled trial” OR “randomised controlled trials” OR “randomised-controlled trial” OR “randomised-controlled trials” OR

RCT OR “randomized trial” OR “randomised trial” OR “randomized control” OR “randomised control” OR “cluster-randomized trial” OR “cluster-randomised trial” OR “randomized double-blind” OR “clinical trial” OR “clinical trials” OR “clinical study” OR “clinical studies” OR “clinical conference” OR “clinical conferences” OR “open label” OR “open-label” OR “phase I” OR “phase 1” OR “phase II” OR “phase 2” OR “phase III” OR “phase 3” OR autobiography OR biography OR “patient education handout” OR webcast cell OR "cell line" OR cellular OR tissue OR "in vitro" OR “in vivo” OR spectroscopic OR spectrometer OR spectrophotometry OR "transformation products" OR "gene variants" OR plant OR pharmacokinetic OR pharmacodynamic OR microscopy OR chromatography OR “mass spectrometry” OR “gene expression” animals OR animal OR "Pogona vitticeps" OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR "bush babies" OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR mugil curema OR "atlantic cod" OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR "xenopus laevis" OR parakeet OR parakeets OR parrot OR parrots

OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras)))

**Table E2. Epidemiologic Literature Search #2. Search strings and additional parameters**

| Pubmed |
| --- |
| **Date of search: November 13, 2019**<br>**Returned 61 results** |
| ((“benzodiazepine”[Ti] OR “benzodiazepines”[Ti] OR "alprazolam"[Ti] OR "xanax"[Ti] OR "chlordiazepoxide"[Ti] OR "librium"[Ti] OR "librax"[Ti] OR "clobazam"[Ti] OR "onfi"[Ti] OR "clonazepam"[Ti] OR "klonopin"[Ti] OR "clorazepate"[Ti] OR "tranxene"[Ti] OR "T-tab"[Ti] OR "Gen-Xene"[Ti] OR "diazepam"[Ti] OR "diastat"[Ti] OR "AcuDial"[Ti] OR "valium"[Ti] OR "estazolam"[Ti] OR "prosom"[Ti] OR "flurazepam"[Ti] OR "dalmane"[Ti] OR "dalmadon"[Ti] OR "lorazepam"[Ti] OR "ativan"[Ti] OR "oxazepam"[Ti] OR "serax"[Ti] OR "quazepam"[Ti] OR "doral"[Ti] OR "temazepam"[Ti] OR "restoril"[Ti] OR "triazolam"[Ti] OR "halcion"[Ti] OR "midazolam"[Ti] OR "versed"[Ti] OR "bromazepam"[Ti] OR "flunitrazepam"[Ti] OR “rohypnol”[Ti])<br>AND (("substance-related disorders"[MeSH Terms] OR ("substance-related"[tiab] AND "disorders"[ tiab]) OR "substance-related disorders"[tiab])<br>OR misuse [tiab] OR “nonmedical use”[tiab] OR “non-medical use”[tiab] OR “NMU”[tiab] OR “nonmedical abuse”[tiab] OR “recreational use”[tiab] OR abuse[tiab]<br>OR ("behavior, addictive"[MeSH Terms] OR ("behavior"[tiab] AND "addictive"[tiab]) OR "addictive behavior"[tiab] OR "addiction"[tiab]) OR (dependence [tiab] OR “biological dependence”[tiab])<br>OR ("drug overdose"[MeSH Terms] OR (drug [tiab] AND overdose [tiab]) OR "drug overdose"[tiab] OR "overdose"[tiab]) OR (death [MeSH Terms] OR death [tiab] OR mortality [tiab]))<br><br>AND (“systematic review”[tw] OR cohort[tw] OR "matched-cohort"[tw] OR “matched cohort”[tw] OR "case-control"[tw] OR "cross sectional"[tw] OR "cross-sectional"[tw] OR survey[tw] OR observational[tw] OR "prevalence study"[tw] OR "longitudinal study"[tw] OR "before-after study"[tw] OR “pre-intervention”[tw] OR “post-intervention”[tw] OR “pre-post”[tw]-OR “real world”[tw] OR “real-world”[tw] OR “interrupted time-series”[tw] OR “interrupted time series”[tw] OR "population-based"[tw] OR retrospective[tw] OR prospective[tw] OR "pooled analysis"[tw] OR crossover[tw] OR “meta-analysis”[tw] OR “meta analysis”[tw] OR incidence[tw] OR prevalence[tw] OR risk[tw] OR incidence[tw] OR longitudinal[tw] OR prospective[tw] OR “risk factors”[tw] OR “risk factor”[tw] OR “natural history”[tw] OR “qualitative”[tw] OR “focus group”[tw] OR “survey”[tw] OR “questionnaire”[tw] OR “web scrapping”[tw] OR “cryptomarket”[tw] OR “darknet”[tw] OR “digital trace”[tw] OR “AlphaBay”[tw] OR “Valhalla”[tw] OR “Tor Network”[tw] OR “market data”[tw] OR “social media”[tw] OR “social environment”[tw]) |

AND (“social factors”[tw] OR “Social influencing”[tw] OR “social influence”[tw] OR “motivation”[tw] OR “perception”[tw] OR “belief”[tw] OR “social norms”[tw] OR “preference”[tw] OR “social media”[tw] OR “attitude”[tw] OR “behavior”[tw] )

NOT (“randomized control trial”[tw] OR “randomized-control trial”[tw] OR “randomized control trials”[tw] OR “randomized-control trials”[tw] OR “randomized controlled trial”[tw] OR “randomized controlled trials”[tw] OR “randomized-controlled trial”[tw] OR “randomized-controlled trials”[tw] OR “randomised control trial”[tw] OR “randomised-control trial”[tw] OR “randomised control trials”[tw] OR “randomised-control trials”[tw] OR “randomised controlled trial”[tw] OR “randomised controlled trials”[tw] OR “randomised-controlled trial”[tw] OR “randomised-controlled trials”[tw] OR RCT[tw] OR “randomized trial”[tw] OR “randomised trial”[tw] OR “randomized control”[tw] OR “randomised control”[tw] OR “cluster-randomized trial”[tw] OR “cluster-randomised trial”[tw] OR “randomized double-blind”[tw] OR “clinical trial”[tw] OR “clinical trials”[tw] OR “clinical study”[tw] OR “clinical studies”[tw] OR “clinical conference”[tw] OR “clinical conferences”[tw] OR “open label”[tw] OR “open-label”[tw] OR “phase I”[tw] OR “phase 1”[tw] OR “phase II”[tw] OR “phase 2”[tw] OR “phase III”[tw] OR “phase 3”[tw] OR autobiography[tw] OR biography[tw] OR “patient education handout”[tw] OR webcast[tw])

NOT (cell[tw] OR "cell line"[tw] OR cellular[tw] OR tissue[tw] OR "in vitro"[tw] OR “in vivo”[tw] OR spectroscopic[tw] OR spectrometer[tw] OR spectrophotometry[tw] OR "transformation products"[tw] OR "gene variants"[tw] OR plant[tw] OR pharmacokinetic[tw] OR pharmacodynamic[tw] OR microscopy[tw] OR chromatography[tw] OR “mass spectrometry”[tw] OR “gene expression”[tw])

NOT (animals[tiab] OR animal[tiab] OR "Pogona vitticeps"[tiab] OR mice[tiab] OR mus[tiab] OR mouse[tiab] OR murine[tiab] OR woodmouse[tiab] OR rats[tiab] OR rat[tiab] OR murinae[tiab] OR muridae[tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[tiab] OR rodent[tiab] OR rodents[tiab] OR pigs[tiab] OR pig[tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR "sus scrofa"[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat[tiab] OR polecats[tiab] OR "mustela putorius"[tiab] OR "guinea pigs"[tiab] OR "guinea pig"[tiab] OR cavia[tiab] OR callithrix[tiab] OR marmoset[tiab] OR marmosets[tiab] OR cebuella[tiab] OR hapale[tiab] OR octodon[tiab] OR chinchilla[tiab] OR chinchillas[tiab] OR gerbillinae[tiab] OR gerbil[tiab] OR gerbils[tiab] OR jird[tiab] OR jirds[tiab] OR merione[tiab] OR meriones[tiab] OR rabbits[tiab] OR rabbit[tiab] OR hares[tiab] OR hare[tiab] OR diptera[tiab] OR flies[tiab] OR fly[tiab] OR dipteral[tiab] OR drosphila[tiab] OR drosophilidae[tiab] OR cats[tiab] OR cat[tiab] OR carus[tiab] OR felis[tiab] OR nematoda[tiab] OR nematode[tiab] OR nematoda[tiab] OR nematode[tiab] OR nematodes[tiab] OR sipunculida[tiab] OR dogs[tiab] OR dog[tiab] OR canine[tiab] OR canines[tiab] OR canis[tiab] OR sheep[tiab] OR sheeps[tiab] OR mouflon[tiab] OR

mouflons[tiab] OR ovis[tiab] OR goats[tiab] OR goat[tiab] OR capra[tiab] OR capras[tiab] OR rupicapra[tiab] OR chamois[tiab] OR haplorhini[tiab] OR monkey[tiab] OR monkeys[tiab] OR anthropoidea[tiab] OR anthropoids[tiab] OR saguinus[tiab] OR tamarin[tiab] OR tamarins[tiab] OR leontopithecus[tiab] OR hominidae[tiab] OR ape[tiab] OR apes[tiab] OR pan[tiab] OR paniscus[tiab] OR "pan paniscus"[tiab] OR bonobo[tiab] OR bonobos[tiab] OR troglodytes[tiab] OR "pan troglodytes"[tiab] OR gibbon[tiab] OR gibbons[tiab] OR siamang[tiab] OR siamangs[tiab] OR nomascus[tiab] OR symphalangus[tiab] OR chimpanzee[tiab] OR chimpanzees[tiab] OR prosimians[tiab] OR "bush baby"[tiab] OR prosimian[tiab] OR "bush babies"[tiab] OR galagos[tiab] OR galago[tiab] OR pongidae[tiab] OR gorilla[tiab] OR gorillas[tiab] OR pongo[tiab] OR pygmaeus[tiab] OR "pongo pygmaeus"[tiab] OR orangutans[tiab] OR pygmaeus[tiab] OR lemur[tiab] OR lemurs[tiab] OR lemuridae[tiab] OR horse[tiab] OR horses[tiab] OR pongo[tiab] OR equus[tiab] OR cow[tiab] OR calf[tiab] OR bull[tiab] OR chicken[tiab] OR chickens[tiab] OR gallus[tiab] OR quail[tiab] OR bird[tiab] OR birds[tiab] OR quails[tiab] OR poultry[tiab] OR poultries[tiab] OR fowl[tiab] OR fowls[tiab] OR reptile[tiab] OR reptilia[tiab] OR reptiles[tiab] OR snakes[tiab] OR snake[tiab] OR lizard[tiab] OR lizards[tiab] OR alligator[tiab] OR alligators[tiab] OR crocodile[tiab] OR crocodiles[tiab] OR turtle[tiab] OR turtles[tiab] OR amphibian[tiab] OR amphibians[tiab] OR amphibia[tiab] OR frog[tiab] OR frogs[tiab] OR bombina[tiab] OR salientia[tiab] OR toad[tiab] OR toads[tiab] OR "epidalea calamita"[tiab] OR salamander[tiab] OR salamanders[tiab] OR eel[tiab] OR eels[tiab] OR fish[tiab] OR fishes[tiab] OR pisces[tiab] OR catfish[tiab] OR catfishes[tiab] OR siluriformes[tiab] OR arius[tiab] OR heteropneustes[tiab] OR sheatfish[tiab] OR perch[tiab] OR perches[tiab] OR percidae[tiab] OR perca[tiab] OR trout[tiab] OR trouts[tiab] OR char[tiab] OR chars[tiab] OR salvelinus[tiab] OR "fathead minnow"[tiab] OR minnow[tiab] OR cyprinidae[tiab] OR carps[tiab] OR carp[tiab] OR zebrafish[tiab] OR zebrafishes[tiab] OR goldfish[tiab] OR goldfishes[tiab] OR guppy[tiab] OR guppies[tiab] OR chub[tiab] OR chubs[tiab] OR tinca[tiab] OR barbels[tiab] OR barbus[tiab] OR pimephales[tiab] OR promelas[tiab] OR "poecilia reticulata"[tiab] OR mullet[tiab] OR mullets[tiab] OR seahorse[tiab] OR seahorses[tiab] OR mugil curema[tiab] OR "atlantic cod"[tiab] OR shark[tiab] OR sharks[tiab] OR catshark[tiab] OR anguilla[tiab] OR salmonid[tiab] OR salmonids[tiab] OR whitefish[tiab] OR whitefishes[tiab] OR salmon[tiab] OR salmons[tiab] OR sole[tiab] OR solea[tiab] OR "sea lamprey"[tiab] OR lamprey[tiab] OR lampreys[tiab] OR pumpkinseed[tiab] OR sunfish[tiab] OR sunfishes[tiab] OR tilapia[tiab] OR tilapias[tiab] OR turbot[tiab] OR turbots[tiab] OR flatfish[tiab] OR flatfishes[tiab] OR sciuridae[tiab] OR squirrel[tiab] OR squirrels[tiab] OR chipmunk[tiab] OR chipmunks[tiab] OR suslik[tiab] OR susliks[tiab] OR vole[tiab] OR voles[tiab] OR lemming[tiab] OR lemmings[tiab] OR muskrat[tiab] OR muskrats[tiab] OR lemmus[tiab] OR otter[tiab] OR otters[tiab] OR marten[tiab] OR martens[tiab] OR martes[tiab] OR weasel[tiab] OR badger[tiab] OR badgers[tiab] OR ermine[tiab] OR mink[tiab] OR minks[tiab] OR sable[tiab] OR sables[tiab] OR gulo[tiab] OR gulos[tiab] OR wolverine[tiab] OR wolverines[tiab] OR minks[tiab] OR mustela[tiab] OR llama[tiab] OR llamas[tiab] OR alpaca[tiab] OR alpacas[tiab] OR camelid[tiab] OR camelids[tiab] OR guanaco[tiab] OR guanacos[tiab] OR chiroptera[tiab] OR chiropteras[tiab] OR bat[tiab] OR bats[tiab]

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| OR fox[tiab] OR foxes[tiab] OR iguana[tiab] OR iguanas[tiab] OR "xenopus laevis"[tiab] OR parakeet[tiab] OR parakeets[tiab] OR parrot[tiab] OR parrots[tiab] OR donkey[tiab] OR donkeys[tiab] OR mule[tiab] OR mules[tiab] OR zebra[tiab] OR zebras[tiab] OR shrew[tiab] OR shrews[tiab] OR bison[tiab] OR bisons[tiab] OR buffalo[tiab] OR buffaloes[tiab] OR deer[tiab] OR deers[tiab] OR bear[tiab] OR bears[tiab] OR panda[tiab] OR pandas[tiab] OR "wild hog"[tiab] OR "wild boar"[tiab] OR fitchew[tiab] OR fitch[tiab] OR beaver[tiab] OR beavers[tiab] OR jerboa[tiab] OR jerboas[tiab] OR capybara[tiab] OR capybaras[tiab])<br><br>AND English [la]<br><br>AND (("2000/01/01"[Date - Entrez] : "2019/11/13"[Date - Entrez])) |
| **Embase** |
| **Search date: November 13, 2019**<br>**Returned 68 results** |
| ('benzodiazepine':ti OR 'benzodiazepines':ti OR 'alprazolam':ti OR 'xanax':ti OR 'chlordiazepoxide':ti OR 'librium':ti OR 'librax':ti OR 'clobazam':ti OR 'onfi':ti OR 'clonazepam':ti OR 'klonopin':ti OR 'clorazepate':ti OR 'tranxene':ti OR 'T-tab':ti OR 'gen-xene':ti OR 'diazepam':ti OR 'diastat':ti OR 'acudial':ti OR 'valium':ti OR 'estazolam':ti OR 'prosom':ti OR 'flurazepam':ti OR 'dalmane':ti OR 'dalmadon':ti OR 'lorazepam':ti OR 'ativan':ti OR 'oxazepam':ti OR 'serax':ti OR 'quazepam':ti OR 'doral':ti OR 'temazepam':ti OR 'restoril':ti OR 'triazolam':ti OR 'halcion':ti OR 'midazolam':ti OR 'versed':ti OR 'bromazepam':ti OR 'flunitrazepam':ti OR 'rohypnol'/exp OR 'rohypnol') AND ('substance-related disorders'/exp OR 'substance-related disorders' OR ('substance-related':ti,ab AND 'disorders':ti,ab) OR 'substance-related disorders':ti,ab OR misuse:ti,ab OR 'nonmedical use':ti,ab OR 'non-medical use':ti,ab OR 'nmu':ti,ab OR 'nonmedical abuse':ti,ab OR 'recreational use':ti,ab OR abuse:ti,ab OR 'behavior, addictive'/exp OR 'behavior, addictive' OR ('behavior':ti,ab AND 'addictive':ti,ab) OR 'addictive behavior':ti,ab OR 'addiction':ti,ab OR dependence:ti,ab OR 'biological dependence':ti,ab OR 'drug overdose'/exp OR 'drug overdose' OR (drug:ti,ab AND overdose:ti,ab) OR 'drug overdose':ti,ab OR 'overdose':ti,ab OR 'death'/exp OR death OR death:ti,ab OR mortality:ti,ab) AND ('systematic review':ti,ab OR cohort:ti,ab OR 'matched-cohort':ti,ab OR 'matched cohort':ti,ab OR 'case-control':ti,ab OR 'cross sectional':ti,ab OR 'cross-sectional':ti,ab OR survey:ti,ab OR observational:ti,ab OR 'prevalence study':ti,ab OR 'longitudinal study':ti,ab OR 'before-after study':ti,ab OR 'pre-intervention':ti,ab OR 'post-intervention':ti,ab OR 'pre-post':ti,ab OR 'real world':ti,ab OR 'real-world':ti,ab OR 'interrupted time-series':ti,ab OR 'interrupted time series':ti,ab OR 'population-based':ti,ab OR retrospective:ti,ab OR 'pooled analysis':ti,ab OR crossover:ti,ab OR 'meta-analysis':ti,ab OR 'meta analysis':ti,ab OR prevalence:ti,ab OR risk:ti,ab OR incidence:ti,ab OR longitudinal:ti,ab OR prospective:ti,ab OR 'risk factors':ti,ab OR 'risk factor':ti,ab OR 'natural history':ti,ab OR ‘qualitative’:ti,ab OR ‘focus group’:ti,ab OR |

‘survey’:ti,ab OR ‘questionnaire’:ti,ab OR ‘web scrapping’:ti,ab OR ‘cryptomarket’:ti,ab OR ‘darknet’:ti,ab OR ‘digital trace’:ti,ab OR ‘AlphaBay’:ti,ab OR ‘Valhalla’:ti,ab OR ‘Tor Network’:ti,ab OR ‘market data’:ti,ab OR ‘social media’:ti,ab OR ‘social environment’:ti,ab) AND (‘social factors’:ti,ab OR ‘Social influencing’:ti,ab OR ‘social influence’:ti,ab OR ‘motivation’:ti,ab OR ‘perception’:ti,ab OR ‘belief’:ti,ab OR ‘social norms’:ti,ab OR ‘preference’:ti,ab OR ‘social media’:ti,ab OR ‘attitude’:ti,ab OR ‘behavior’:ti,ab)

NOT ('randomized control trial':ti,ab OR 'randomized-control trial':ti,ab OR 'randomized control trials':ti,ab OR 'randomized-control trials':ti,ab OR 'randomized controlled trial':ti,ab OR 'randomized controlled trials':ti,ab OR 'randomized-controlled trial':ti,ab OR 'randomized-controlled trials':ti,ab OR 'randomised control trial':ti,ab OR 'randomised-control trial':ti,ab OR 'randomised control trials':ti,ab OR 'randomised-control trials':ti,ab OR 'randomised controlled trial':ti,ab OR 'randomised controlled trials':ti,ab OR 'randomised-controlled trial':ti,ab OR 'randomised-controlled trials':ti,ab OR rct:ti,ab OR 'randomized trial':ti,ab OR 'randomised trial':ti,ab OR 'randomized control':ti,ab OR 'randomised control':ti,ab OR 'cluster-randomized trial':ti,ab OR 'cluster-randomised trial':ti,ab OR 'randomized double-blind':ti,ab OR 'clinical trial':ti,ab OR 'clinical trials':ti,ab OR 'clinical study':ti,ab OR 'clinical studies':ti,ab OR 'clinical conference':ti,ab OR 'clinical conferences':ti,ab OR 'open label':ti,ab OR 'open-label':ti,ab OR 'phase i':ti,ab OR 'phase 1':ti,ab OR 'phase ii':ti,ab OR 'phase 2':ti,ab OR 'phase iii':ti,ab OR 'phase 3':ti,ab OR autobiography:ti,ab OR biography:ti,ab OR 'patient education handout':ti,ab OR webcast:ti,ab) NOT (cell:ti,ab OR 'cell line':ti,ab OR cellular:ti,ab OR tissue:ti,ab OR 'in vitro':ti,ab OR 'in vivo':ti,ab OR spectroscopic:ti,ab OR spectrometer:ti,ab OR spectrophotometry:ti,ab OR 'transformation products':ti,ab OR 'gene variants':ti,ab OR plant:ti,ab OR pharmacokinetic:ti,ab OR pharmacodynamic:ti,ab OR microscopy:ti,ab OR chromatography:ti,ab OR 'mass spectrometry':ti,ab OR 'gene expression':ti,ab) NOT ((animals:ti,ab OR animal:ti,ab OR 'pogona vitticeps':ti,ab OR mice:ti,ab OR mus:ti,ab OR mouse:ti,ab OR murine:ti,ab OR woodmouse:ti,ab OR rats:ti,ab OR rat:ti,ab OR murinae:ti,ab OR muridae:ti,ab OR cottonrat:ti,ab OR cottonrats:ti,ab OR hamster:ti,ab OR hamsters:ti,ab OR cricetinae:ti,ab OR rodentia:ti,ab OR rodent:ti,ab OR rodents:ti,ab OR pigs:ti,ab OR pig:ti,ab OR swine:ti,ab OR swines:ti,ab OR piglets:ti,ab OR piglet:ti,ab OR boar:ti,ab OR boars:ti,ab OR 'sus scrofa':ti,ab OR ferrets:ti,ab OR ferret:ti,ab OR polecat:ti,ab OR polecats:ti,ab OR 'mustela putorius':ti,ab OR 'guinea pigs':ti,ab OR 'guinea pig':ti,ab OR cavia:ti,ab OR callithrix:ti,ab OR marmoset:ti,ab OR marmosets:ti,ab OR cebuella:ti,ab OR hapale:ti,ab OR octodon:ti,ab OR chinchilla:ti,ab OR chinchillas:ti,ab OR gerbillinae:ti,ab OR gerbil:ti,ab OR gerbils:ti,ab OR jird:ti,ab OR jirds:ti,ab OR merione:ti,ab OR meriones:ti,ab OR rabbits:ti,ab OR rabbit:ti,ab OR hares:ti,ab OR hare:ti,ab OR diptera:ti,ab OR flies:ti,ab OR fly:ti,ab OR dipteral:ti,ab OR drosphila:ti,ab OR drosophilidae:ti,ab OR cats:ti,ab OR cat:ti,ab OR carus:ti,ab OR felis:ti,ab OR nematoda:ti,ab OR nematode:ti,ab OR nematodes:ti,ab OR sipunculida:ti,ab OR dogs:ti,ab OR dog:ti,ab OR canine:ti,ab OR canines:ti,ab OR canis:ti,ab OR sheep:ti,ab OR sheeps:ti,ab OR mouflon:ti,ab OR mouflons:ti,ab OR ovis:ti,ab OR

goats:ti,ab OR goat:ti,ab OR capra:ti,ab OR capras:ti,ab OR rupicapra:ti,ab OR chamois:ti,ab OR haplorhini:ti,ab OR monkey:ti,ab OR monkeys:ti,ab OR anthropoidea:ti,ab OR anthropoids:ti,ab OR saguinus:ti,ab OR tamarin:ti,ab OR tamarins:ti,ab OR leontopithecus:ti,ab OR hominidae:ti,ab OR ape:ti,ab OR apes:ti,ab OR pan:ti,ab OR paniscus:ti,ab OR 'pan paniscus':ti,ab OR bonobo:ti,ab OR bonobos:ti,ab OR troglodytes:ti,ab OR 'pan troglodytes':ti,ab OR gibbon:ti,ab OR gibbons:ti,ab OR siamang:ti,ab OR siamangs:ti,ab OR nomascus:ti,ab OR symphalangus:ti,ab OR chimpanzee:ti,ab OR chimpanzees:ti,ab OR prosimians:ti,ab OR 'bush baby':ti,ab OR prosimian:ti,ab OR 'bush babies':ti,ab OR galagos:ti,ab OR galago:ti,ab OR pongidae:ti,ab OR gorilla:ti,ab OR gorillas:ti,ab OR 'pongo pygmaeus':ti,ab OR orangutans:ti,ab OR pygmaeus:ti,ab OR lemur:ti,ab OR lemurs:ti,ab OR lemuridae:ti,ab OR horse:ti,ab OR horses:ti,ab OR pongo:ti,ab OR equus:ti,ab OR cow:ti,ab OR calf:ti,ab OR bull:ti,ab OR chicken:ti,ab OR chickens:ti,ab OR gallus:ti,ab OR quail:ti,ab OR bird:ti,ab OR birds:ti,ab OR quails:ti,ab OR poultry:ti,ab OR poultries:ti,ab OR fowl:ti,ab OR fowls:ti,ab OR reptile:ti,ab OR reptilia:ti,ab OR reptiles:ti,ab OR snakes:ti,ab OR snake:ti,ab OR lizard:ti,ab OR lizards:ti,ab OR alligator:ti,ab OR alligators:ti,ab OR crocodile:ti,ab OR crocodiles:ti,ab OR turtle:ti,ab OR turtles:ti,ab OR amphibian:ti,ab OR amphibians:ti,ab OR amphibia:ti,ab OR frog:ti,ab OR frogs:ti,ab OR bombina:ti,ab OR salientia:ti,ab OR toad:ti,ab OR toads:ti,ab OR 'epidalea calamita':ti,ab OR salamander:ti,ab OR salamanders:ti,ab OR eel:ti,ab OR eels:ti,ab OR fish:ti,ab OR fishes:ti,ab OR pisces:ti,ab OR catfish:ti,ab OR catfishes:ti,ab OR siluriformes:ti,ab OR arius:ti,ab OR heteropneustes:ti,ab OR sheatfish:ti,ab OR perch:ti,ab OR perches:ti,ab OR percidae:ti,ab OR perca:ti,ab OR trout:ti,ab OR trouts:ti,ab OR char:ti,ab OR chars:ti,ab OR salvelinus:ti,ab OR 'fathead minnow':ti,ab OR minnow:ti,ab OR cyprinidae:ti,ab OR carps:ti,ab OR carp:ti,ab OR zebrafish:ti,ab OR zebrafishes:ti,ab OR goldfish:ti,ab OR goldfishes:ti,ab OR guppy:ti,ab OR guppies:ti,ab OR chub:ti,ab OR chubs:ti,ab OR tinca:ti,ab OR barbels:ti,ab OR barbus:ti,ab OR pimephales:ti,ab OR promelas:ti,ab OR 'poecilia reticulata':ti,ab OR mullet:ti,ab OR mullets:ti,ab OR seahorse:ti,ab OR seahorses:ti,ab OR 'mugil'/exp OR mugil) AND curema:ti,ab OR 'atlantic cod':ti,ab OR shark:ti,ab OR sharks:ti,ab OR catshark:ti,ab OR anguilla:ti,ab OR salmonid:ti,ab OR salmonids:ti,ab OR whitefish:ti,ab OR whitefishes:ti,ab OR salmon:ti,ab OR salmons:ti,ab OR sole:ti,ab OR solea:ti,ab OR 'sea lamprey':ti,ab OR lamprey:ti,ab OR lampreys:ti,ab OR pumpkinseed:ti,ab OR sunfish:ti,ab OR sunfishes:ti,ab OR tilapia:ti,ab OR tilapias:ti,ab OR turbot:ti,ab OR turbots:ti,ab OR flatfish:ti,ab OR flatfishes:ti,ab OR sciuridae:ti,ab OR squirrel:ti,ab OR squirrels:ti,ab OR chipmunk:ti,ab OR chipmunks:ti,ab OR suslik:ti,ab OR susliks:ti,ab OR vole:ti,ab OR voles:ti,ab OR lemming:ti,ab OR lemmings:ti,ab OR muskrat:ti,ab OR muskrats:ti,ab OR lemmus:ti,ab OR otter:ti,ab OR otters:ti,ab OR marten:ti,ab OR martens:ti,ab OR martes:ti,ab OR weasel:ti,ab OR badger:ti,ab OR badgers:ti,ab OR ermine:ti,ab OR mink:ti,ab OR sable:ti,ab OR sables:ti,ab OR gulo:ti,ab OR gulos:ti,ab OR wolverine:ti,ab OR wolverines:ti,ab OR minks:ti,ab OR mustela:ti,ab OR llama:ti,ab OR llamas:ti,ab OR alpaca:ti,ab OR alpacas:ti,ab OR camelid:ti,ab OR camelids:ti,ab OR guanaco:ti,ab OR guanacos:ti,ab OR chiroptera:ti,ab OR chiropteras:ti,ab OR bat:ti,ab OR bats:ti,ab OR fox:ti,ab OR foxes:ti,ab OR iguana:ti,ab OR iguanas:ti,ab OR 'xenopus laevis':ti,ab OR parakeet:ti,ab OR parakeets:ti,ab OR parrot:ti,ab OR

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| parrots:ti,ab OR donkey:ti,ab OR donkeys:ti,ab OR mule:ti,ab OR mules:ti,ab OR zebra:ti,ab OR zebras:ti,ab OR shrew:ti,ab OR shrews:ti,ab OR bison:ti,ab OR bisons:ti,ab OR buffalo:ti,ab OR buffaloes:ti,ab OR deer:ti,ab OR deers:ti,ab OR bear:ti,ab OR bears:ti,ab OR panda:ti,ab OR pandas:ti,ab OR 'wild hog':ti,ab OR 'wild boar':ti,ab OR fitchew:ti,ab OR fitch:ti,ab OR beaver:ti,ab OR beavers:ti,ab OR jerboa:ti,ab OR jerboas:ti,ab OR capybara:ti,ab OR capybaras:ti,ab) AND [english]/lim AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim) AND [2000-2019]/py |
| **Web of Science** |
| **Search date: November 13, 2019**<br>**Returned 0 results**<br>**English language, years: 2000 to 2019, Web of Science Core Collection** |
| ((TI=(“benzodiazepine” OR “benzodiazepines” OR "alprazolam" OR "xanax" OR "chlordiazepoxide" OR "librium" OR "librax" OR "clobazam" OR "onfi" OR "clonazepam" OR "klonopin" OR "clorazepate" OR "tranxene" OR "T-tab" OR "Gen-Xene" OR "diazepam" OR "diastat" OR "AcuDial" OR "valium" OR "estazolam" OR "prosom" OR "flurazepam" OR "dalmane" OR "dalmadon" OR "lorazepam" OR "ativan" OR "oxazepam" OR "serax" OR "quazepam" OR "doral" OR "temazepam" OR "restoril" OR "triazolam" OR "halcion" OR "midazolam" OR "versed" OR "bromazepam" OR "flunitrazepam" OR “rohypnol”)) AND (ALL=("substance-related disorders" OR "substance-related disorders" OR misuse OR “nonmedical use” OR “non-medical use” OR “NMU” OR “nonmedical abuse” OR “recreational use” OR abuse OR "addictive behavior" OR "addiction" OR dependence OR “biological dependence” OR "drug overdose" OR "overdose" OR death OR mortality)) AND (TI=(“systematic review” OR cohort OR "matched-cohort" OR “matched cohort” OR "case-control" OR "cross sectional" OR "cross-sectional" OR survey OR observational OR "prevalence study" OR "longitudinal study" OR "before-after study" OR “pre-intervention” OR “post-intervention” OR “pre-post” OR “real world” OR “real-world” OR “interrupted time-series” OR “interrupted time series” OR "population-based" OR retrospective OR prospective OR "pooled analysis" OR crossover OR “meta-analysis” OR “meta analysis” OR incidence OR prevalence OR risk OR incidence OR longitudinal OR prospective OR “risk factors” OR “risk factor” OR “natural history” OR “qualitative” OR “focus group” OR “survey” OR “questionnaire” OR “web scrapping” OR “cryptomarket” OR “darknet” OR “digital trace” OR “AlphaBay” OR “Valhalla” OR “Tor Network” OR “market data” OR “social media” OR “social environment”)) AND (TI=(“social factors” OR “Social influencing” OR “social influence” OR “motivation” OR “perception” OR “belief” OR “social norms” OR “preference” OR “social media” OR “attitude” OR “behavior”)) NOT (TS=(“randomized control trial” |

OR “randomized-control trial” OR “randomized control trials” OR “randomized-control trials” OR “randomized controlled trial” OR “randomized controlled trials” OR “randomized-controlled trial” OR “randomized-controlled trials” OR “randomised control trial” OR “randomised-control trial” OR “randomised control trials” OR “randomised-control trials” OR “randomised controlled trial” OR “randomised controlled trials” OR “randomised-controlled trial” OR “randomised-controlled trials” OR RCT OR “randomized trial” OR “randomised trial” OR “randomized control” OR “randomised control” OR “cluster-randomized trial” OR “cluster-randomised trial” OR “randomized double-blind” OR “clinical trial” OR “clinical trials” OR “clinical study” OR “clinical studies” OR “clinical conference” OR “clinical conferences” OR “open label” OR “open-label” OR “phase I” OR “phase 1” OR “phase II” OR “phase 2” OR “phase III” OR “phase 3” OR autobiography OR biography OR “patient education handout” OR webcast cell OR "cell line" OR cellular OR tissue OR "in vitro" OR “in vivo” OR spectroscopic OR spectrometer OR spectrophotometry OR "transformation products" OR "gene variants" OR plant OR pharmacokinetic OR pharmacodynamic OR microscopy OR chromatography OR “mass spectrometry” OR “gene expression” animals OR animal OR "Pogona vitticeps" OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR "bush babies" OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR

zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR mugil curema OR "atlantic cod" OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR "xenopus laevis" OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras)))

## 8.6 APPENDIX F. LITERATURE REVIEW ABSTRACTION

**Table F1. Articles included Literature Review: Risks (Dependence, Misuse, Abuse, Addiction) Associated with Long-term Benzodiazepine Use**

| First author, year | Data Source | Study Design (include years) | Population | Exposure | Outcomes | Notable findings | Comments |
|---|---|---|---|---|---|---|---|
| Airagnes, 2019 [a] | National prescription drug benefit administrative database (2009-2015), self-report questionnaire for social and demographic information | Population-based cross-sectional study (CONSTANCES cohort) | Random sample of French population (covered by general health insurance scheme), aged 18–69 years in 2015; 4,686 men and 4,849 women | Sociodemographic variables: age, gender, occupational status, occupational grade, household income, marital status, education level, depressive symptoms (depressive state was defined as a total score > 18 at the Center for Epidemiological Studies Depression Scale), at-risk alcohol use | Long-term benzodiazepine use: a continuous period of prescription benzodiazepine longer than 12 weeks (binary variable i.e., presence vs absence): 1) At least two refills in the 12 weeks following the first prescription and 2) at least one refill in week 13–14 or at least one refill in week 15–16 if the last refill observed during the first 12 weeks occurs on week 11–12. Assessed as cross-sectional data | Weighted analyses to provide representative results of the French general population. Weighted prevalence of benzodiazepine long-term use during 2009-2015: 2.8% (95% CI:2.3–3.4) for men and 3.8% (95% CI: 3.3–4.5) for women. Individual models for each factor stratified by sex. Factors positively associated with benzodiazepine long-term use, adjusted for sex: increased age, low education, not being at-work, low occupational grade, low income, not being in a couple and depressive symptoms. | Cross-sectional data precluded assessment of temporality, e.g., for the association with depressive symptoms. Cross-sectional associations were stratified by sex with no further adjustment. Although over 90% of the French population was eligible for the sample, people were not eligible if they were self-employed or agricultural workers. |

**Table F1. Articles included Literature Review: Risks (Dependence, Misuse, Abuse, Addiction) Associated with Long-term Benzodiazepine Use**

| First author, year | Data Source | Study Design (include years) | Population | Exposure | Outcomes | Notable findings | Comments |
|---|---|---|---|---|---|---|---|
| de las Cuevas, 2003 [b] | Severity Dependence Scale (SDS) and Health records | Cross-sectional study; Jan to April 2002 | Inclusion criteria: Consecutive patients (N=1,048) attending primary care health centers in the Canary Islands Health Service, currently on benzodiazepine treatment for 1 month or longer (mean 38.2+/-52 months, range 1–360 months). Age 18-80 years old and a stable maintenance dosage of their benzodiazepine at the time of the study entry in the range of 2.5–50 mg/day of diazepam or its equivalent. Exclusion criteria: current diagnosis of schizophrenia or organic brain syndrome, alcoholism or | Patient factors: gender, age, marital status, education, employment.<br>Characteristics of benzodiazepine use: dose, duration of use. | Benzodiazepine dependence, using the severity of dependence scale (SDS) which is a short is a 5-item, self-report questionnaire. cross-sectional measurement with exposures | 47% of patients using benzodiazepines for more than 1 month reported dependence. Benzodiazepine dependence was more prevalent among women, middle aged. In logistic regression model adjusting for dosage, duration and antidepressant use, the probability of developing benzodiazepine dependence was associated with the benzodiazepine dose used (1.04; 95% CI 1.03, 1.06), the duration of this use (1.01; 95% CI 1.009, 1.02)) and suggestively with the concomitant use of antidepressants (0.681; (95% CI: 0.45, 1.03). Concomitant use of antidepressants was positively associated with dependence before adjusting for dose and duration. | Strengths: relatively large sample size; wide range of age (18-80); included sociodemographic information;<br>Limitations:<br>-cross-sectional measurement of exposure and outcomes precluded assessment of causality;<br>-unclear why only three variables were included in the multivariable-adjusted model. |

**Table F1. Articles included Literature Review: Risks (Dependence, Misuse, Abuse, Addiction) Associated with Long-term Benzodiazepine Use**

| First author, year | Data Source | Study Design (include years) | Population | Exposure | Outcomes | Notable findings | Comments |
|---|---|---|---|---|---|---|---|
| | | | substance abuse (past 12 months). Acute or unstable medical or psychiatric condition, unable to complete questionnaire. | | | | |
| Hermos, 2007 [d] | Pharmacy and medical claims databases from the Veterans Administration, New England Veterans Integrated Service Network | Retrospective population-based study; 1997-2003 (six-year follow-up window) | Veteran patients in the eight distinct New England VA Medical Centers and affiliated clinics in New England Veterans Integrated Service Network; Inclusion criteria: patients with new prescriptions for alprazolam, clonazepam, diazepam, or lorazepam; treatment episodes defined as long-term use, i.e., three benzodiazepine | Clinical diagnoses coded prior to or concurrent with initial benzodiazepine prescription (using ICD-9 codes) of PTSD, alcohol dependence and abuse, alcoholism related medical and psychiatric diagnoses, psychoactive drug dependence, drug abuse and withdrawal syndromes. | High-dose (defined as patients whose average daily dose for their longest treatment episode was in the top 10% for each agent) anxiolytic benzodiazepine prescriptions | Using descriptive analyses, they found drug abuse diagnosis associated with *high-dose benzodiazepines.* Multivariable logistic regression (adjusted for sex, age, year treatment started, treatment duration, drug abuse and concurrent acetaminophen/ oxycodone prescription) among patients with PTSD and alcoholism diagnoses receiving long-term, found that risks for high-dose benzodiazepines were higher in younger ages (OR 2.98 95% CI 1.30-6.84), having 12-26 | Strengths: Longitudinal study design with long follow-up and large sample size (n=3,612 with new benzodiazepine prescription and PTSD diagnosis).<br>Limitations: VA data may have limited information on medical diagnoses; lack of generalizability: VA population with PTSD; Older data; unclear why logistic regression was used instead |

**Table F1. Articles included Literature Review: Risks (Dependence, Misuse, Abuse, Addiction) Associated with Long-term Benzodiazepine Use**

| First author, year | Data Source | Study Design (include years) | Population | Exposure | Outcomes | Notable findings | Comments |
|---|---|---|---|---|---|---|---|
| | | | prescriptions filled within 120-day period; and at least 2 diagnosis of posttraumatic stress disorder (PTSD) prior to or concurrent with new benzodiazepine prescription | | | months duration of treatment (OR 2.54 95% CI: 1.33-4.86), drug abuse diagnoses (OR 1.80 95% CI 1.06-3.08), concurrent benzodiazepine (OR 5.55 95% CI 2.31-13.33) and concurrent acetaminophen/oxycodone (OR 2.43 95% CI 1.22-4.83) | of cox proportional hazard models.<br>Also, unclear why multivariable analysis was conducted in a sub population of patients diagnosed with PTSD and alcoholism receiving long-term benzodiazepines. |
| Luijendijk, 2008 [e] | Interview (including instruments for depressive symptoms, anxiety, cognitive function, and self-rated health) and prescription drug dispensing data | Prospective cohort study<br>Baseline data collection: July 1993 to December 1995. Participants followed until event (chronic benzodiazepine use), death, loss-to-follow-up, or end of study (January 1, 2003) | Elderly (ages 55 and older at baseline) residents of Rotterdam, the Netherlands, n=5364<br>Exclusion criteria: Participants who had chronic benzodiazepine use (see outcome) in the 2 years before baseline | Three domains of potential predictors: social support, psychiatric and somatic health, participant's health perception and behavior | Chronic benzodiazepine use: at least 180 days of continuous or intermittent use during a consecutive period of 365 days<br>assessed among two populations: 1. general population (n=5364) and 2. subset that filled at least one benzodiazepine prescription (n=2490) | Average follow-up: 7.3 years<br>440 new chronic benzodiazepine users among 39,164 person-years.<br>2,490 participants filled at least one prescription for benzodiazepine and 17.7% became chronic users<br>Cox proportional hazard analyses, multivariable (HR (95% CI)):<br>Predictors for new-onset chronic benzodiazepine use in those who had filled at least one prescription: increasing | Strengths: longitudinal study design; assessed depressive symptoms and anxiety via in-person instrument<br>Limitations: Underlying physical and mental health status may have confounded the inverse association between living alone and chronic BZD use; anxiety information was limited (only information on |

**Table F1. Articles included Literature Review: Risks (Dependence, Misuse, Abuse, Addiction) Associated with Long-term Benzodiazepine Use**

| First author, year | Data Source | Study Design (include years) | Population | Exposure | Outcomes | Notable findings | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | | age (1.04 (1.03, 1.06)), public health insurance (1.24 (1.01, 1.51)) and pain related joint complaints predicted (1.32 (1.06, 1.64)); living alone was protective (0.73 (0.58, 0.93)). | subset of population); not clear how all variables were assessed in the interview |
| Manthey, 2012 [f] | self-report questionnaires, telephone and in-person interviews, medical examination | Cross-sectional study | Subjects (n=401) recruited from community as well as general practice and mental health care institutions; Were part of a larger sample designed to be representative of individuals ages 18-64 years with depressive and/or anxiety disorders in the Netherlands. Inclusion criteria: benzodiazepine use in the month prior to interview, completion of the Bendep-SRQ, screen positive for affective or anxiety disorders. | Domains for potential correlates of benzodiazepine dependence: (i) socio-demographic factors, (ii) psychological factors, (iii) physical factors, (iv) addiction-related factors and (v) factors related to the use of BZDs | Dependence measured on the Bendep-SRQ in three domains: (i) awareness of problematic use, (ii) preoccupation with the availability of benzodiazepines and (iii) lack of compliance with the therapeutic regimen | Analyses: descriptive and multivariable linear regression. Median duration of benzodiazepine use was 24 months (interquartile range: 5-96) and the average daily dose was 2.8-mg diazepam equivalents per day Factors that displayed cross-sectional correlation with domains of dependence score in multivariable linear regression are listed below. Coefficients are difficult to interpret and are therefore not reported here. Problematic use: more GP contacts in the past 6 months, severity of insomnia and antidepressant use. Consistent results among subset of participants with | Strengths: Assessed benzodiazepine dependence using a validated instrument to collect patient-reported information, rather than relying on prescription dispensing data. Limitations: Cross-sectional study design could examine factors correlated with BZD dependence; impossible to assess their respective contribution to dependence. Results were presented as beta coefficients only |

**Table F1. Articles included Literature Review: Risks (Dependence, Misuse, Abuse, Addiction) Associated with Long-term Benzodiazepine Use**

| First author, year | Data Source | Study Design (include years) | Population | Exposure | Outcomes | Notable findings | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | | frequent benzodiazepine use but antidepressant use was less associated.<br>Positively associated with preoccupation with availability of benzodiazepines (multivariable linear regression): higher scores on the Beck Anxiety Inventory, antidepressant use, alcohol dependence and a higher daily dosage of BZDs. Alcohol dependence and anxiety remained significant among subset of participants with frequent benzodiazepine use.<br>Associated with lack of compliance: older age, unemployment due to sickness or disability, more severe insomnia, antidepressant use and alcohol dependence.<br>Unemployment, insomnia and alcohol dependence, and antidepressant use remained stable among subset of participants with frequent benzodiazepine use.<br>Insomnia, antidepressant | with limited interpretation provided by authors |

**Table F1. Articles included Literature Review: Risks (Dependence, Misuse, Abuse, Addiction) Associated with Long-term Benzodiazepine Use**

| First author, year | Data Source | Study Design (include years) | Population | Exposure | Outcomes | Notable findings | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | | use and alcohol dependence may increase the risk of benzodiazepine dependence among individuals who use benzodiazepines. | |
| Mol, 2005 [g] | 32-item Benzodiazepine Craving Questionnaire (BCQ) and multiple self-report questionnaires: information on lifestyle, dependence characteristics, personality traits (Dutch shortened MMPI (NVM), short-term changeable mood-states (Dutch shortened Profile of Mood States (POMS), psychopathology | Cross-sectional and only included information from the Benzodiazepine Craving Questionnaire completed at baseline of larger study focusing long-term benzodiazepine use in general practice. Study years: August 1998 and December 2001. | Netherlands; General practice patients who recently discontinued their long-term benzodiazepine or failed to do so (n=113 long-term and 80 former long-term patients using benzodiazepines); long-term use defined as use for more than 3 months;<br>Exclusion criteria: current psychiatric | benzodiazepine craving from BCQ | Domains of potential predictors for benzodiazepine craving: benzodiazepine dependence severity, psychopathology, mood state, personality, and lifestyle | Statistical comparison between patients reporting benzodiazepine cravings and patients not reporting benzodiazepine cravings. Bivariate and multivariate logistic regression with craving (yes/no) as dependent variable. Craving was reported by 22.5% (18/80) of the patients who had discontinued their use vs 40.7% (46/113) of those who had not. Eight factors (anger, depression, mental health, role functioning, social functioning, somatization, negativism, score on GHQ-12) were associated | Patients reporting cravings differed from patients not reporting craving in the following domains: benzodiazepine dependence, psychopathology, negative mood state, and personality<br>Strengths: Directly assessed a patient-reported measure of benzodiazepine dependence and its cross-sectional correlation with measures of mood |

**Table F1. Articles included Literature Review: Risks (Dependence, Misuse, Abuse, Addiction) Associated with Long-term Benzodiazepine Use**

| First author, year | Data Source | Study Design (include years) | Population | Exposure | Outcomes | Notable findings | Comments |
|---|---|---|---|---|---|---|---|
| | (General Health Questionnaire 12-item), health related quality of life (Medical Outcome Study Short-Form 36-item) | | treatment, current treatment for drug or alcohol dependence, medical history of psychosis, epilepsy or terminal illness and inability to communicate in Dutch language. | | | with craving after adjusting for current use status (no other factors in model).<br>Results from multivariable-adjusted models: no factors other than depression and somatization, which were highly correlated, remained significant. | and psychopathology among patients with current or past long-term BZD use.<br>Limitations: Cross-sectional study. Adjusting for current use status in the regression model make the correlations difficult to interpret – would have been more straightforward to present results stratified by current use status. |

[a] Airagnes, G., Lemogne, C., Renuy, A., Goldberg, M., Hoertel, N., Roquelaure, Y., Zins, M. (2019). Prevalence of prescribed benzodiazepine long-term use in the French general population according to sociodemographic and clinical factors: findings from the CONSTANCES cohort. *Bmc Public Health*.

[b] de las Cuevas, C., San, E., & de la Fuente, J. (2003). Benzodiazepines: more "behavioural" addiction than dependence. *Psychopharmacology (Berl)*, 297-303.

[c] Fride Tvete, I., Bjørner, T., & Skomedal, T. (2015). Risk factors for excessive benzodiazepine use in a working age population: a nationwide 5-year survey in Norway. *Scandinavian journal of primary health care*, 252-259.

[d] Hermos, J. A., Young, M. M., Lawler, E. V., Rosenbloom, D., & Fiore, L. D. (2007). Long-term, high-dose benzodiazepine prescriptions in veteran patients with PTSD: influence of preexisting alcoholism and drug-abuse diagnoses. *J Trauma Stress*, 909-14.

[e] Luijendijk, H. J., Tiemeier, H., Hofman, A., Heeringa, J., & Stricker, B. H. (2008). Determinants of chronic benzodiazepine use in the elderly: a longitudinal study. *British Journal of Clinical Pharmacology*, *65*, 593-599.

**Table F1. Articles included Literature Review: Risks (Dependence, Misuse, Abuse, Addiction) Associated with Long-term Benzodiazepine Use**

| First author, year | Data Source | Study Design (include years) | Population | Exposure | Outcomes | Notable findings | Comments |
|---|---|---|---|---|---|---|---|

[f] Manthey, L., Lohbeck, M., Giltay, E. J., van Veena, T., Zitman, F. G., & Penninx, B. W. (2012). Correlates of benzodiazepine dependence in the Netherlands Study of Depression and Anxiety. *Addiction, 107*, 2173-2182.

[g] Mol, A. J., Gorgels, W. J., Oude Voshaar, R. C., Breteler, M. H., van Balkom, A. J., van de Lisdonk, E. H., Zitman, F. G. (2005). Associations of benzodiazepine craving with other clinical variables in a population of general practive patients. *Comprehensive Psychiatry, 46*, 353-360.

| Table F2. Articles Included in Literature Review: Social Influence on Misuse and Abuse of Benzodiazepine Drugs | | | | | | |
|---|---|---|---|---|---|---|
| **First Author, Year** | **Study Design and Sample Size** | **Time Period** | **Study Population and Inclusion Criteria** | **Topic Drug** | **Study Findings** | **Comments** |
| Peters, 2007 [a] | Qualitative interviews, (10 open-ended questions), N=46 | Spring 2004 | Youth attending inpatient drug treatment program in Texas, self-identifying as current alprazolam users<br>Inclusion criteria: ages 12 to 21 years, entered treatment facility less than 5 days prior, have used alprazolam at least once during the past 30 days. | Alprazolam/ Xanax | High social approval and peer pressure were common concepts among the 27 common themes identified by the researchers. | Inclusion criteria did not distinguish between use and misuse or abuse. Commonly identified themes may reflect questions asked rather than prominent beliefs of the participants. |
| Murphy, 2017 [b] | Qualitative semi-structured interviews, N=13 | June 2012 to April 2013 | Participants recruited from substance misuse treatment centers in Cork, Ireland. Inclusion criteria required participants to be currently using benzodiazepines and less than 21 years of age or have used benzodiazepines when they less than 21 years of age. All participants were between 18 and 21 years of age at the time of the interview. | Benzodiazepine | Reported motivations included: to feel stoned or relaxation, and to avoid daily stressors.<br>Responses focused on the effects of benzodiazepine misuse, such as effects on family life, negatives of benzodiazepine misuse, and effects on social functions. There was little focus on peer pressure or social influence on a desire to misuse benzodiazepine. | This study did not report a distinction of use from misuse or abuse for study inclusion. Participants attending drug treatment centers have history of regular, high-dose benzodiazepine use.<br>Interviews were semi-structured based on an interview guide and interviewer bias should be considered. Interview questions inquired about all benzodiazepines. |

[a] Peters RJ, Meshack AF, Kelder SH, Webb P, Smith D, Garner K. (2007) Alprazolam (Xanax) Use Among Southern Youth: Beliefs and Social Norms Concerning Dangerous Rides on “Handlebars.” J. Drug Education, 37:4. 417-428.

[b] Murphy KD, Lambert S, McCarthy S, Sahm LJ and Byrne S. (2018) “You Don’t Feel”: The Experience of Youth Benzodiazepine Misuse in Ireland, Journal of Psychoactive Drugs, 50:2, 121-128.

## 8.7 APPENDIX G. PHARMACOVIGILANCE DATA AND DESCRIPTIONS

### Appendix G1. FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

**Appendix G2. Drug Abuse Dependence and Withdrawal (SMQ) Preferred Terms Lists**

| ***Drug abuse dependence and withdrawal* (SMQ)** | **Preferred Terms** |
|---|---|
| Broad Search | *Dopamine dysregulation syndrome; Drug abuse; Drug abuser; Drug dependence; Drug dependence, antepartum; Drug dependence, postpartum; Drug use disorder; Drug use disorder, antepartum; Drug use disorder, postpartum; Intentional overdose; Intentional product misuse; Maternal use of illicit drugs; Neonatal complications of substance abuse; Substance abuse; Substance abuser; Substance dependence; Substance use disorder; Accidental overdose; Dependence; Disturbance in social behaviour; Drug detoxification; Drug diversion; Drug level above therapeutic; Drug level increased; Drug screen; Drug screen positive; Drug tolerance; Drug tolerance increased; Drug tolerance decreased; Intentional product use issue; Medication overuse headache; Narcotic bowel syndrome; Needle track marks; Overdose; Prescribed overdose; Prescription drug used without a prescription; Prescription form tampering; Reversal of opiate activity; Substance use; Substance-induced mood disorder; Substance-induced psychotic disorder; Toxicity to various agents; Drug withdrawal convulsions; Drug withdrawal headache; Drug withdrawal maintenance therapy; Drug withdrawal syndrome; Drug withdrawal syndrome neonatal; Drug rehabilitation; Rebound effect; Steroid withdrawal syndrome; Withdrawal arrhythmia; Withdrawal catatonia; Withdrawal syndrome* |
| Narrow Search | *Dopamine dysregulation syndrome; Drug abuse; Drug abuser; Drug dependence; Drug dependence, antepartum; Drug dependence, postpartum; Drug use disorder; Drug use disorder, antepartum; Drug use disorder, postpartum; Intentional overdose; Intentional product misuse; Maternal use of illicit drugs; Neonatal complications of substance abuse; Substance abuse; Substance abuser; Substance dependence; Substance use disorder; Drug withdrawal convulsions; Drug withdrawal headache; Drug withdrawal maintenance therapy; Drug withdrawal syndrome; Drug withdrawal syndrome neonatal* |

**Appendix G3. FAERS Line Listing of Direct Reports of Drug Abuse Dependence and Withdrawal with Benzodiazepine As a Single Drug Substance**

| | Initial FDA Received Date | FAERS Case #* | Age (years) | Sex | Drug of Interest | Country Derived | Serious Outcome(s)† |
|---|---|---|---|---|---|---|---|
| 1 | 7/8/1999 | 3304029 | 24 | Female | Clonazepam | USA | DS |
| 2 | 6/13/2001 | 3665677 | 51 | Female | Clonazepam | USA | RI, OT |
| 3 | 6/14/2001 | 3667051 | 32 | Female | Clonazepam | USA | HO, DS, RI, OT |
| 4 | 4/2/2002 | 3779197 | 35 | Male | Clonazepam | USA | HO, LT, DS, RI, OT |
| 5 | 11/26/2003 | 4036024 | 36 | Male | Clonazepam | USA | DS, RI |
| 6 | 7/9/2004 | 4171089 | 48 | Female | Clonazepam | USA | DS, OT |
| 7 | 7/21/1993 | 5016691 | 68 | Male | Clonazepam | USA | HO |
| 8 | 5/27/1994 | 5121032 | 39 | Female | Clonazepam | USA | HO |
| 9 | 4/22/2005 | 5790289 | 29 | Female | Clonazepam | USA | HO, OT |
| 10 | 8/10/2005 | 5859811 | 56 | Female | Clonazepam | USA | HO, LT, RI |
| 11 | 8/16/2005 | 5865214 | Unknown | Male | Clonazepam | USA | OT |
| 12 | 8/25/2005 | 5870254 | 48 | Female | Clonazepam | USA | DS, OT |
| 13 | 8/29/2005 | 5871662 | 45 | Female | Clonazepam | USA | HO, DS, OT |
| 14 | 10/3/2005 | 5892174 | 41 | Female | Clonazepam | USA | OT |
| 15 | 11/3/2005 | 5921930 | Unknown | Female | Clonazepam | USA | OT |
| 16 | 11/7/2005 | 5922148 | 45 | Male | Clonazepam | USA | RI |
| 17 | 11/9/2005 | 5923616 | 34 | Female | Clonazepam | USA | HO, LT, OT |
| 18 | 10/31/2006 | 6167935 | 41 | Male | Clonazepam | USA | OT |
| 19 | 11/7/2006 | 6171230 | 27 | Female | Clonazepam | USA | HO, OT |
| 20 | 5/4/2007 | 6310586 | 42 | Female | Clonazepam | USA | OT |
| 21 | 6/18/2007 | 6340907 | 76 | Male | Clonazepam | USA | HO |
| 22 | 7/27/2007 | 6375367 | 49 | Female | Clonazepam | USA | RI |
| 23 | 9/5/2007 | 6413391 | 37 | Female | Clonazepam | USA | |
| 24 | 11/12/2008 | 6816025 | 66 | Female | Clonazepam | USA | OT |
| 25 | 12/24/2008 | 6872127 | 36 | Female | Clonazepam | USA | LT, OT |

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|---|---|---|---|---|---|---|---|
| 26 | 10/16/2009 | 7155001 | 21 | Male | Clonazepam | USA | LT, RI, OT |
| 27 | 1/25/2010 | 7260690 | 47 | Female | Clonazepam | USA | RI, OT |
| 28 | 2/26/2010 | 7304445 | 45 | Female | Clonazepam | USA | OT |
| 29 | 10/7/2010 | 7642431 | 45 | Female | Clonazepam | USA | HO, LT, DS, RI, OT |
| 30 | 10/17/2013 | 9632018 | 30 | Male | Clonazepam | USA | HO, DS |
| 31 | 11/19/2013 | 9697422 | 53 | Female | Clonazepam | USA | DS, OT |
| 32 | 8/4/2014 | 10366014 | 54 | Female | Clonazepam | USA | OT |
| 33 | 10/9/2014 | 10510562 | 53 | Male | Clonazepam | USA | DS |
| 34 | 10/31/2014 | 10560296 | 46 | Male | Clonazepam | USA | DS |
| 35 | 6/6/2016 | 12442042 | 61 | Male | Clonazepam | USA | HO |
| 36 | 6/21/2017 | 13677252 | 38 | Female | Clonazepam | USA | HO, DS |
| 37 | 6/22/2017 | 13681454 | 56 | Male | Clonazepam | USA | HO, LT, DS, OT |
| 38 | 6/24/2017 | 13689186 | 48 | Female | Clonazepam | USA | OT |
| 39 | 6/26/2017 | 13693239 | 45 | Female | Clonazepam | USA | LT, DS |
| 40 | 7/1/2017 | 13711080 | 37 | Female | Clonazepam | USA | DS |
| 41 | 7/6/2017 | 13725699 | 41 | Female | Clonazepam | USA | HO, LT, DS |
| 42 | 7/11/2017 | 13744842 | 41 | Female | Clonazepam | USA | DS |
| 43 | 5/1/2019 | 16263948 | 54 | Male | Clonazepam | USA | LT, DS |
| 44 | 4/27/1998 | 3133694 | 41 | Male | Alprazolam | USA | OT |
| 45 | 7/3/2001 | 3676662 | 58 | Female | Alprazolam | USA | DS, RI, OT |
| 46 | 9/4/2001 | 3707064 | Unknown | Female | Alprazolam | USA | OT |
| 47 | 12/3/2002 | 3872341 | 45 | Male | Alprazolam | USA | LT |
| 48 | 1/14/2004 | 4072698 | Unknown | Male | Alprazolam | USA | DS |
| 49 | 3/24/2004 | 4115278 | 33 | Female | Alprazolam | USA | |
| 50 | 7/22/1983 | 4383855 | 56 | Female | Alprazolam | CAN | OT |
| 51 | 12/2/1988 | 4632864 | 64 | Female | Alprazolam | USA | HO |
| 52 | 3/14/1989 | 4644916 | 39 | Female | Alprazolam | USA | OT |
| 53 | 5/24/1989 | 4657064 | 39 | Female | Alprazolam | USA | OT |
| 54 | 10/6/1989 | 4675592 | Unknown | Not Reported | Alprazolam | USA | HO |
| 55 | 3/16/1990 | 4710419 | Unknown | Not Reported | Alprazolam | USA | |

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|---|---|---|---|---|---|---|---|
| 56 | 4/24/1992 | 4874072 | 41 | Male | Alprazolam | USA | HO, OT |
| 57 | 6/1/1993 | 5001135 | 35 | Female | Alprazolam | USA | OT |
| 58 | 8/14/1994 | 5147944 | 57 | Male | Alprazolam | USA | |
| 59 | 3/9/1995 | 5231816 | 41 | Female | Alprazolam | USA | OT |
| 60 | 2/17/2005 | 5749622 | 46 | Male | Alprazolam | USA | OT |
| 61 | 3/8/2005 | 5758741 | 38 | Female | Alprazolam | USA | LT |
| 62 | 4/8/2005 | 5778319 | Unknown | Female | Alprazolam | USA | LT, OT |
| 63 | 1/2/2007 | 6241218 | 56 | Female | Alprazolam | USA | RI |
| 64 | 3/26/2007 | 6281537 | 30 | Female | Alprazolam | USA | LT, OT |
| 65 | 9/5/2007 | 6411690 | 55 | Male | Alprazolam | USA | OT |
| 66 | 8/25/2008 | 6742205 | 28 | Female | Alprazolam | USA | HO, LT, RI, OT |
| 67 | 9/29/2008 | 6779524 | 62 | Female | Alprazolam | USA | HO, RI, OT |
| 68 | 7/30/2009 | 7081777 | 77 | Male | Alprazolam | USA | HO |
| 69 | 12/2/2009 | 7200346 | 58 | Female | Alprazolam | USA | OT |
| 70 | 1/25/2010 | 7260891 | 38 | Female | Alprazolam | USA | |
| 71 | 6/23/2017 | 13688768 | 29 | Male | Alprazolam | USA | HO, DS, OT |
| 72 | 7/2/2017 | 13710638 | 49 | Male | Alprazolam | USA | LT, DS |
| 73 | 5/14/2003 | 3948669 | 56 | Male | Diazepam | USA | |
| 74 | 9/1/1972 | 4269228 | Unknown | Male | Diazepam | USA | |
| 75 | 9/1/1972 | 4269244 | Unknown | Female | Diazepam | USA | |
| 76 | 9/1/1972 | 4269323 | Unknown | Female | Diazepam | USA | |
| 77 | 3/3/2009 | 6935505 | 31 | Male | Diazepam | USA | OT |
| 78 | 4/19/2000 | 3464536 | 49 | Male | Lorazepam | USA | HO, LT, DS, RI |
| 79 | 1/30/2001 | 3604333 | 57 | Female | Lorazepam | USA | OT |
| 80 | 5/21/2003 | 3951188 | 68 | Female | Lorazepam | USA | OT |
| 81 | 10/1/1981 | 4346370 | Unknown | Male | Lorazepam | USA | |
| 82 | 5/31/1991 | 4798299 | 67 | Male | Lorazepam | USA | HO |
| 83 | 8/25/2005 | 5870280 | Unknown | Female | Lorazepam | USA | DS, OT |
| 84 | 8/29/2005 | 5871146 | 71 | Female | Lorazepam | USA | OT |
| 85 | 12/7/2005 | 5939177 | 53 | Male | Lorazepam | USA | OT |

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|---|---|---|---|---|---|---|---|
| 86 | 2/27/2006 | 5999604 | 57 | Female | Lorazepam | USA | |
| 87 | 12/14/2006 | 6203360 | 36 | Female | Lorazepam | USA | OT |
| 88 | 10/18/2007 | 6455489 | 55 | Female | Lorazepam | USA | OT |
| 89 | 4/1/2009 | 6965911 | 50 | Female | Lorazepam | USA | HO |
| 90 | 9/23/2009 | 7136030 | 51 | Female | Lorazepam | USA | LT |
| 91 | 10/12/2011 | 8177082 | 31 | Female | Lorazepam | USA | OT |
| 92 | 2/6/2012 | 8391411 | 55 | Female | Lorazepam | USA | DS |
| 93 | 7/22/2014 | 10335062 | 34 | Male | Lorazepam | USA | DS |
| 94 | 9/11/2014 | 10449928 | 17 | Female | Lorazepam | USA | LT |
| 95 | 10/31/2014 | 10559460 | 43 | Female | Lorazepam | USA | DS |
| 96 | 10/31/2014 | 10560024 | 38 | Female | Lorazepam | USA | DS |
| 97 | 6/30/2015 | 11230472 | 46 | Female | Lorazepam | USA | DS |
| 98 | 6/23/2017 | 13688615 | 58 | Female | Lorazepam | USA | HO, LT, OT |
| 99 | 6/23/2017 | 13688791 | 55 | Male | Lorazepam | USA | DS |
| 100 | 12/17/2018 | 15731646 | 25 | Male | Lorazepam | USA | HO, DS |
| 101 | 5/10/2004 | 4140852 | 34 | Female | Triazolam | USA | RI, OT |
| 102 | 5/13/1983 | 4380179 | Unknown | Not Reported | Triazolam | USA | |
| 103 | 1/13/1989 | 4635619 | 36 | Female | Triazolam | USA | HO |
| 104 | 5/21/2009 | 7007367 | 49 | Female | Oxazepam | USA | LT, DS, RI, OT |

*All FAERS cases in this case series are direct reports and have only one version; therefore, manufacturer control numbers and version nu

†As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.

Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, RI=Required Intervention, OT=Other Medically Significant

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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AMY E SEITZ
09/24/2020 11:54:11 AM

SARANRAT WITTAYANUKORN
09/24/2020 11:55:37 AM

SHEKHAR H MEHTA
09/24/2020 01:55:50 PM

KELLY M HARBOURT
09/24/2020 01:59:08 PM

SARA KARAMI
09/24/2020 02:04:38 PM

CHRISTINA R GREENE
09/24/2020 02:06:08 PM

ROSE G RADIN
09/24/2020 02:34:48 PM

CORINNE M WOODS
09/24/2020 02:46:50 PM

VICKY C CHAN
09/24/2020 02:59:00 PM

JANA K MCANINCH
09/24/2020 03:07:01 PM

RAJDEEP K GILL
09/25/2020 05:59:20 PM
For Travis Ready

CINDY M KORTEPETER
09/25/2020 09:27:02 PM

JUDY A STAFFA
09/26/2020 05:56:19 AM

JUDY A STAFFA
09/26/2020 05:56:19 AM