Trends in psychotropic and other select central nervous system drug overdose deaths

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Combating opioid overdoses has become a key focus in population health over the past couple of decades as overdose rates have increased, but other drugs used to treat common diseases can also be dangerous if misused or not prescribed and managed safely.

Much of the focus concerning overdoses is on opioids, however, there are other categories of medications where reviewing overdose trends and associated factors may provide additional awareness about the extensive nature of medication misuse and abuse. Previous research indicates that certain demographics, like middle-aged men, or people with various psychiatric diagnoses such as anxiety and depression, are at a higher risk of overdose.[1] We completed an analysis of healthcare claims data and found that accidental drug overdose deaths due to psychotropic and other select central nervous system (CNS) medications (antiepileptic, sedative-hypnotic, and antiparkinsonian drugs listed in the Methodology section below) are increasing in prevalence and that commercially insured individuals with prescriptions for more than one of these therapeutic classes were more likely to experience an overdose from any substance than people without such prescriptions.

Millions of Americans struggle with mental health. In 2019, 10.8% of American adults reported symptoms of anxiety or depression.[2] The COVID-19 pandemic exacerbated mental health issues for many Americans and brought this topic to the forefront of many public health discussions. Oftentimes, mental health discussions are centered around increasing access to mental health professionals and, as a byproduct, to prescriptions of psychiatric drugs. Notably, a peer-reviewed study published by the American Psychological Association reported a 64% increase in people using antidepressants between 1999 and 2010.[3] Additionally, a peer-reviewed study published in the New England Journal of Medicine estimated a two-thirds increase in benzodiazepine prescriptions in adults from 1996 to 2013.[4]

With the increase in psychotropic prescriptions, CNS medications are more commonly prescribed in combination with psychotropic medications. A 2017 peer-reviewed study published by the National Institute of Health found that polypharmacy visits, which they define as an outpatient visit where "3 or more of the following medications were initiated or continued: antipsychotics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonists, tricyclic antidepressants, selective serotonin reuptake inhibitors, and opioids," increased from 0.6% of office visits in 2004 to 1.4% of office visits in 2013 for Americans over the age of 65 years.[5]

While pharmaceutical drugs can be useful for treating depression and anxiety, clinical side effects of many antidepressants include increased suicidal thoughts, particularly for children and adolescents.[6] Furthermore, these drugs can be dangerous if misused, either by taking too much or using in combination with other agents. Many people who struggle with depression and anxiety may also struggle with substance use disorders. Mixing antianxiety agents or antidepressants with alcohol, for example, can cause an increase in anxiety and depression or worsen the side effects from the medication.[1] Overdose of some types of psychiatric medications (such as selective serotonin reuptake inhibitors) may have low mortality rates, but the risks associated with overdose vary considerably across different types of psychiatric medications, especially when considering the interactions with other medications being taken.[7] In severe cases, misuse or overdose can lead to respiratory distress, seizures, hallucinations, cardiac arrest, comas, or even death.[1]

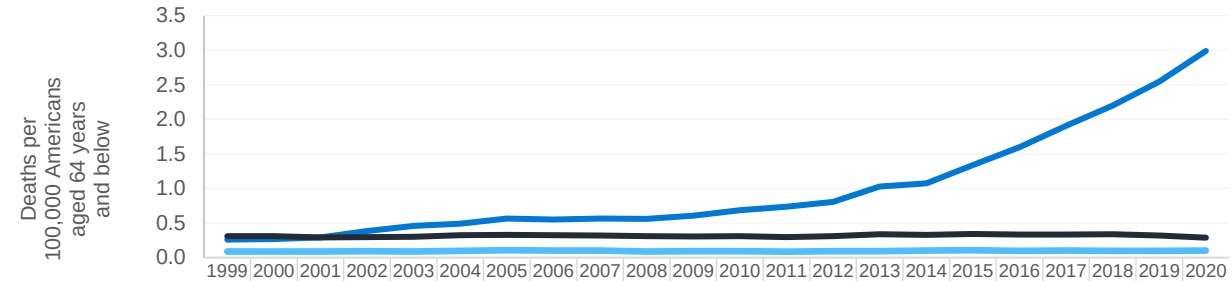
We used data from the Underlying Cause of Death database of the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) and Milliman's Consolidated Health Cost Guidelines™ Sources Database (CHSD) proprietary research claims database to analyze the prevalence and characteristics of psychotropic and select CNS drug overdoses.

Findings

Accidental overdose death rates due to psychotropic and select CNS medications are increasing in the United States

Based on CDC WONDER data, annual accidental psychotropic and select CNS drug overdose deaths per 100,000 Americans aged 64 years and younger have increased substantially over the past two decades of data collection (see Figure 1).

FIGURE 1: ANNUAL DRUG OVERDOSE DEATH RATE DUE TO PSYCHOTROPIC AND SELECT CENTRAL NERVOUS SYSTEM DRUGS, 1999 TO 2020



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Accidental	0.3	0.3	0.3	0.4	0.5	0.5	0.6	0.5	0.6	0.6	0.6	0.7	0.7	0.8	1.0	1.1	1.3	1.6	1.9	2.2	2.5	3.0
Intentional	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Unknown Intent	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Overdoses in the CDC WONDER Underlying Cause of Death database are classified by ICD-10-CM codes. A death is only classified under X41 (accidental), X61 (intentional), or Y11 (unknown intent) if overdose from psychotropic or select central nervous system drugs is the primary cause of death.

From 1999 to 2020, annual deaths where the primary cause of death was an accidental overdose—International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis code X41—due to one or more of these medications increased 1,048% (from 0.658 deaths per 100,000 in 1999 to 3.381 deaths per 100,000 in 2020). The annual rate of accidental overdose deaths due to these drugs has increased by around 17% each year on average over the past nine years in particular (see Figure 2).

FIGURE 2: CUMULATIVE (PLOTTED) AND ANNUAL (LABELED BELOW CHART) ACCIDENTAL OVERDOSE DEATH RATE PERCENTAGE INCREASE, 1999 TO 2020

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Psychotropic, Antiepileptic, Sedative-hypnotic, and Antiparkinsonian Related	4%	8%	32%	19%	7%	15%	-2%	3%	-1%	8%	13%	7%	10%	27%	5%	24%	19%	19%	15%	16%	17%
Other Substances	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%

Overdoses in the CDC WONDER Underlying Cause of Death database are classified by ICD-10-CM codes. A death is only classified under X41, X61, or Y11 if overdose from psychotropic or select central nervous system drugs is the primary cause of death, while any other code starting with X indicates "other" substance.

Drug overdose death rates due to psychotropic and select CNS medications increased almost two times faster than overdose deaths from other causes from 1999 to 2020 and accounted for 10.3% of drug overdose deaths in 2020 (up from 6.0% in 1999; see Figure 3).

FIGURE 3: COMPARISON BETWEEN CUMULATIVE ACCIDENTAL OVERDOSE DEATH RATE INCREASEBY SUBSTANCES, 1999 TO 2020

YEAR	PYSCHOTROPIC AND SELECT CENTRAL NERVOUS SYSTEM DRUG-RELATED OVERDOSE DEATHS	OTHER SUBSTANCE-RELATED OVERDOSE DEATHS
(a) 1999	0.260	4.087
(b) 2020	2.990	26.010
(c) Cumulative Rate Increase (b) / (a) – 1	1,048%	536%
Ratio of Cumulative Rate Increases (c1) / (c2)	1.95	

Overdoses in the CDC WONDER Underlying Cause of Death Database are classified by ICD-10-CM codes. A death is only classified under X41, X61, or Y11 if overdose from psychotropic or select central nervous system drugs is the primary cause of death, while any other code starting with X indicates “other” substance.

Drug overdoses related to psychotropic and select CNS medications affect Americans with commercial health insurance

In 2020, 35 per 100,000 commercially insured Americans aged 64 years and younger had a claim in an inpatient or emergency room setting with a recorded diagnosis for an overdose due to psychotropic or select CNS medications. 69% percent of the members that had a recorded overdose had an overdose-related inpatient stay and 40% of members with a recorded overdose had an overdose-related emergency room visit (see Figure 4). Additionally, slightly more than one-third of the members with a claim for an overdose did not fill a prescription for these drugs in 2020.

FIGURE 4: PYSCHOTROPIC AND SELECT CENTRAL NERVOUS SYSTEM-RELATED DRUG OVERDOSE RATES BY CLAIM TYPE AMONG COMMERCIALLY INSURED MEMBERS, 2020

SETTING	OVERDOSES PER 100,000 COMMERCIALLY INSURED AMERICANS AGED 64 YEARS	% OF OVERDOSES	% WITH PRESCRIPTION FILLS
Emergency Department	13.9	40%	66%
Inpatient	24.1	69%	59%
Both Emergency Department and Inpatient	3.1	9%	68%
Total	35.0	100%	61%

Overdoses in the CHSD were identified by at least one inpatient or emergency room claim with an ICD-10-CM diagnosis code of T42 or T43. The % of Overdose column does not add to 100% as certain members may have recorded inpatient and emergency room overdoses.

For members who filled a psychotropic or CNS medication prescription, 0.22% had a related drug overdose claim in 2020, a rate 15 times higher than members without a fill, who had a related overdose rate of 0.02% (see Figure 5). More than one in 25 members who filled prescriptions for neuroleptics in 2020 had claims with recorded diagnoses for a psychotropic and select CNS-related drug overdose in 2020.

FIGURE 5: OVERDOSE RATES BY PSYCHOTROPIC AND SELECT CENTRAL NERVOUS SYSTEM THERAPEUTIC CLASS AMONG COMMERCIALLY INSURED MEMBERS, 2020

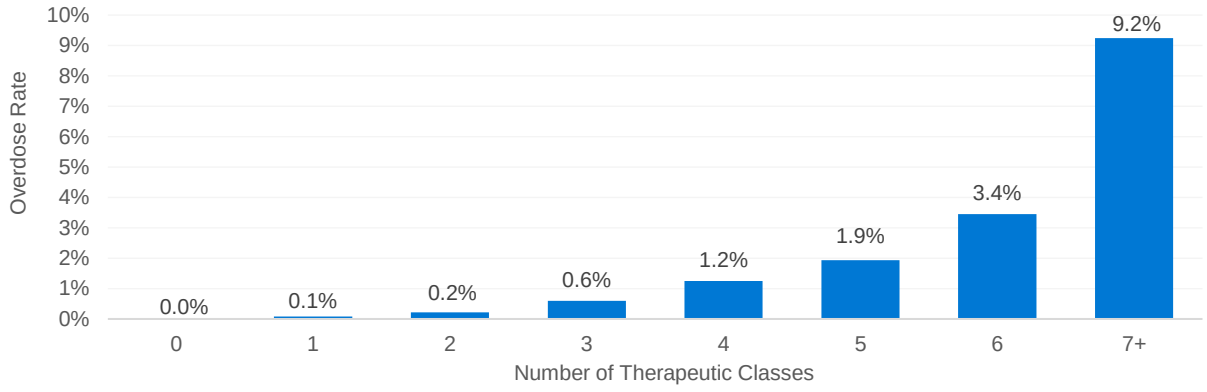
THERAPEUTIC CLASS	NUMBER OF MEMBERS WHO FILLED A PRESCRIPTION	RELATED DRUG OVERDOSE RATE
Antidepressants	851,462	0.29%
Antianxiety Agents	401,381	0.27%
Anticonvulsants	333,257	0.34%
Psychostimulants	142,993	0.35%
Tranquilizers	97,062	0.28%
Neuroleptics	94,207	1.31%
Other Classes	47,408	0.61%
Fills in at least one class	1,242,676	0.22%
No fills in these classes	11,576,625	0.02%

Overdoses in the CHSD were identified by at least one inpatient or emergency room claim with an ICD-10-CM diagnosis code of T42 or T43. Members who filled prescriptions for multiple classes are included in all classes.

The frequency of overdosing was also higher for members who filled prescriptions in multiple therapeutic classes included in the analysis (see Figure 6).

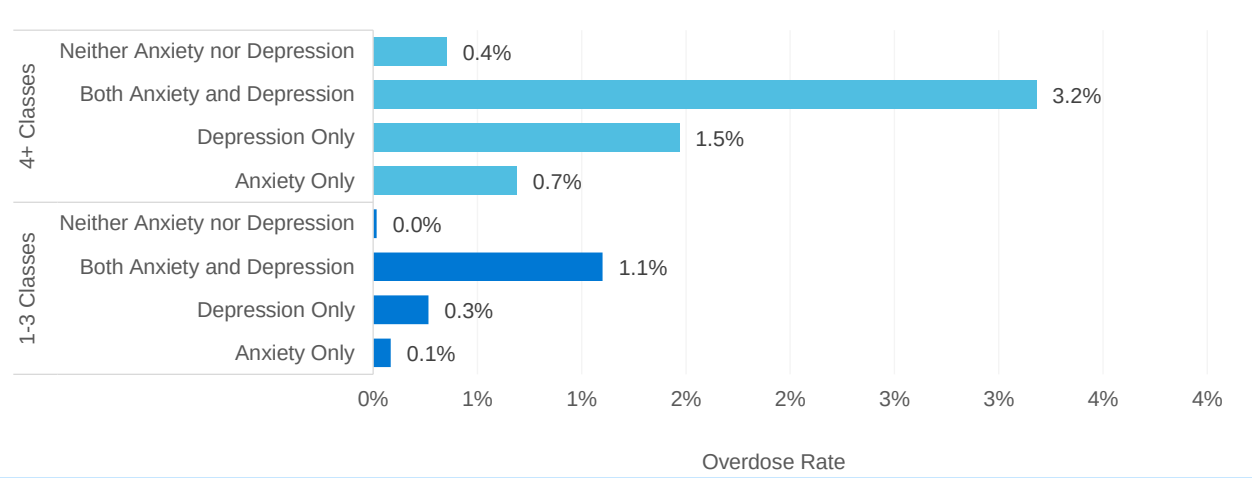
Members with recorded anxiety and depression diagnoses were more likely to overdose from psychotropic or select CNS drugs than members without this diagnosis, regardless of prescription fills. Members with recorded anxiety and depression diagnoses had an overdose frequency of 3.2% if they filled a prescription in four or more classes and a 1.1% overdose frequency if the member filled a prescription in one to three of the classes. Comparatively, members with recorded depression diagnoses who do not have recorded anxiety diagnoses had the second-highest overdose frequencies, 1.5% if they filled a prescription in four or more classes and 0.3% if the member filled a prescription in one to three classes (see Figure 7). Additionally, filling prescriptions in multiple therapeutic classes was associated with an increased frequency of overdose regardless of whether a member had a recorded diagnosis of anxiety or depression in 2020. Members without recorded diagnoses and had fills in four or more classes overdosed at a frequency of 0.4%, whereas members without recorded depression or anxiety diagnoses who filled prescriptions in one to three classes overdosed at a frequency of 0.02% (see Figure 7).

FIGURE 6: OVERDOSE RATES BY THE NUMBER OF THERAPEUTIC CLASSES AMONG COMMERCIALLY INSURED MEMBERS WITH PRESCRIPTION FILL(S), 2020



Overdoses in the CHSD were identified by at least one inpatient or emergency room claim with an ICD-10-CM diagnosis code of T42 or T43. Therapeutic classes include psychotropic, antiepileptic, sedative-hypnotic, and antiparkinsonian.

FIGURE 7: OVERDOSE RATES BY PSYCHIATRIC DIAGNOSIS AND NUMBER OF THERAPEUTIC CLASSES AMONG COMMERCIALLY INSURED MEMBERS WITH PRESCRIPTION FILL(S), 2020



Overdoses in the CHSD were identified by at least one inpatient or emergency room claim with an ICD-10-CM diagnosis code of T42 or T43. Number of therapeutic classes only includes those related to psychotropic, antiepileptic, sedative-hypnotic, and antiparkinsonian drugs.

Members with recorded anxiety or depression diagnoses were less likely to overdose if they only filled prescriptions for antianxiety agents or for antidepressants, but not both. However, members without an anxiety or depression diagnosis were more likely to overdose if they filled an antianxiety agent or antidepressant prescription than if they did not fill any prescription. Additionally, members who filled a prescription for both antianxiety agents and antidepressants were more likely to overdose than members who did not fill a prescription, regardless of anxiety or depression diagnoses (see Figure 8).

FIGURE 8: PERCENTAGE DIFFERENCE IN OVERDOSE RATE AMONG COMMERCIALLY INSURED MEMBERS WHO FILLED A PRESCRIPTION FOR ANTIANXIETY AGENTS OR ANTIDEPRESSANTS COMPARED TO MEMBERS WHO DID NOT FILL A PRESCRIPTION FOR THESE DRUGS, 2020

PRESCRIPTION FILL(S)	ANXIETY ONLY	DEPRESSION ONLY	BOTH ANXIETY AND DEPRESSION	NEITHER ANXIETY NOR DEPRESSION
Only antianxiety agents or only antidepressants	-12%	-19%	-3%	154%
Both antianxiety agents and antidepressants	109%	161%	78%	104%

Overdoses in the CHSD were identified by at least one inpatient or emergency room claim with an ICD-10-CM diagnosis code of T42 or T43. The percentage difference is calculated as the overdose rate for members with prescription fill(s) divided by the overdose rate for members without a prescription fill minus 1.

Discussion

Our research demonstrates that psychotropic and select CNS drug overdoses have been increasing recently and suggests it may represent an addressable burden for the healthcare system. It is difficult to discern from these data whether a potential association between overdose rates and these drug prescriptions is related to a riskier underlying population (e.g., members who are prescribed these drugs may be at an increased risk of alcohol or drug abuse due to their underlying mental health conditions) or prescription fill patterns, independent of other factors. Regardless, it may be important to clinically evaluate whether the use of these medications contributes to the likelihood that a member may unintentionally misuse other drugs as accidental overdoses continue to increase. Appropriate clinical supervision and prescription management may help mitigate the risks associated with psychotropics or select CNS medications.

We observed that members without a recorded anxiety or depression diagnosis experienced higher overdose rates when they filled prescriptions for psychotropic or select CNS medications. A 2011 Health Affairs peer-reviewed study noted that, in 2007, 72.7% of members who were prescribed antidepressants by nonpsychiatric providers had no recorded diagnoses, an increase from 59.5% in 1996.[8] Many of these antianxiety agents or antidepressants are multi-indicated (including for nonpsychiatric conditions in some cases), so there may be a reasonable clinical explanation why members without an anxiety or depression diagnosis are filling such prescriptions. At the same time, we found that, for members with anxiety or depression diagnoses, filling prescriptions for only antianxiety agents or only antidepressants might be associated with lower overdose rates. This could potentially indicate that, with proper clinical supervision, antidepressants and antianxiety agents may help to improve the member's mental health, leading to a reduced risk of overdose. Further research on these initial observations could provide additional insight.

We also observed that about a third of members who overdosed in 2020 did not have a prescription fill(s). Our research was not designed to evaluate a specific reason why a member would have an overdose inpatient, or emergency room, claim and no associated prescription fill for those drugs, but there are several possible explanations. Members may have filled a prescription before 2020 or filled a prescription in 2020 by paying out-of-pocket (thus not showing up in commercial claims data). It may also be the case that some of these overdoses reflect a diversion of prescription medications to individuals other than those for whom they were prescribed. We did not study the impact of access to nontraditional mental healthcare access, such as through digital health, on changes to prescription frequency during the time period of this study, which may also further complicate medication management, including the frequency of fills, use of insurance, and to whom the medication is accessible.

While we did not normalize our results for age, gender, and regional differences, we did assess the age, gender, and regional mix in the population studied. We found that the breakdown of these demographics was somewhat consistent across members with recorded depression or anxiety diagnoses, varying fill patterns, and recorded overdoses, but that members with recorded overdoses were slightly younger than the general population, and that women made up a disproportionate number of members with recorded diagnoses, overdoses, or prescription fills (see Figure 9).

FIGURE 9: DEMOGRAPHIC BREAKDOWN OF COMMERCIALLY INSURED MEMBERS BASED ON RECORDED PYSCHOTROPIC AND SELECT CENTRAL NERVOUS SYSTEM-RELATED DRUG OVERDOSE, RECORDED DIAGNOSIS, AND PRESCRIPTION FILLS, 2020, CHSD

MEMBER CATEGORY	AVERAGE AGE (YEARS)	GENDER	REGION			
		FEMALE	NORTHEAST	MIDWEST	WEST	SOUTH
Overdose	29	66%	19%	39%	18%	24%
4+ therapeutic class prescription fills	43	72%	21%	37%	18%	23%
1 to 3 therapeutic class prescription fills	44	67%	26%	39%	15%	20%
Diagnosis (anxiety, depression, or both)	41	71%	24%	37%	16%	22%
All	35	51%	20%	33%	20%	26%

Number of therapeutic classes only includes those related to psychotropic, antiepileptic, sedative-hypnotic, and antiparkinsonian drugs.

As overdoses due to psychotropic and select CNS medications increase steadily at a high rate, it is important to note the increase in antianxiety agent[8] and antidepressant prescribing rates.[3] A higher prescription rate could indicate a reduced stigma to treat mental health conditions and more people seeking care, an increased rate of anxiety and depression, or both; however, it could also indicate a greater focus on using prescription medication to treat anxiety and depression. As antianxiety agents and antidepressants become more accessible and the avenues to obtain a prescription expand (e.g., the recent increase in use of telehealth associated with the COVID-19 pandemic), it may be more difficult for providers to coordinate mental healthcare and determine whether psychiatric medications are the best course of treatment. It also may be difficult for insurance companies to regulate medication usage as members find they can purchase these drugs without involving their insurance.

Further research

Further research could be conducted to understand why overdoses due to psychotropic and select CNS medications are becoming more common and which members are at an increased risk. One next step could be to analyze the number of pharmacies where members fill prescriptions to see whether at-risk members exhibit pharmacy shopping patterns. Additionally, it may be interesting to evaluate prescribing patterns as well as diagnoses over time to evaluate whether members are more likely to be diagnosed with related conditions than in the past. Then, of those diagnosed, one could test whether they are more likely to be prescribed a drug than previously. Additionally, researching the frequency of other types of overdoses in members filling prescriptions in these therapeutic classes could provide useful insight into the interactions these drug classes have with other substances.

It may also be interesting to analyze the length of time that people have been taking certain medications with regard to the overdose rate or the likelihood of overdosing based on the number of unique providers that the member sees. There may be meaningful differences in overdose rates based on more granular anxiety and depression diagnoses.

An additional next step could be to evaluate the clinical diagnoses of members without related diagnoses who were prescribed these drugs and to investigate whether members had different diagnoses recorded that might explain why they were prescribed the medication. Further research could also be conducted to track whether the percentage of overdose claims from members without prescription fills changes over time as the ways in which members access mental healthcare continue to evolve.

Lastly, analyzing electronic health records of members with overdose claims in tandem with claims data could provide more holistic views of these patients and the circumstances that may have contributed to overdoses. This could also shed light on particular clinical risk factors or prescribing practices that are associated with greater overdose risk.

Limitations

To analyze overdose deaths, we studied CDC WONDER data, which included all Americans under the age of 65 years, regardless of insurance coverage, and includes the uninsured population. To analyze inpatient and emergency room overdoses and their potential association with psychiatric medications and diagnoses, we used a different population comprised only of commercially insured Americans, also under the age of 65 years. Commercially insured members differ from members with other insurance coverages in terms of demographics and acuity.

Because of the difference in our definition of overdose as recorded in the CDC WONDER data as opposed to claims data (death versus inpatient stays and emergency room visits) along with the difference in underlying population (general population versus commercial population under the age of 65 years), the CDC WONDER's overdose rates differ from overdose rates developed from Milliman's CHSD. We do not have claims for members who purchased drugs without processing them through their insurance coverage even if we have other claims from the member in the data. Thus, some members may be incorrectly labeled as "nonusers." Obtaining drugs without using insurance may enable certain members to elude the guardrails in place to limit prescription quantity, but we have no obvious means of testing this hypothesis.

The sensitivity and specificity of the diagnosis codes we used to identify the presence of a psychotropic and select CNS drug-related overdose and/or death is currently not known. However, published findings from a medical record review of emergency room records found that, while ICD-10-CM diagnosis codes for intentional self-harm were generally accurate for research purposes, the codes were less capable at delineating suicidal from non-suicidal intentional self-harm.[9] Though this study represents a different subset of diagnosis codes, and a few select states of the United States, it provides insight into the accuracy of ICD-10-CM coding used to determine cause of death in the CDC WONDER database and overdoses recorded in claims data as defined in our analysis. Our analysis was not designed to determine the intent (suicidality or not) of self-harm.

Additionally, there is limited data underlying certain combinations of diagnoses and prescription fill patterns in Milliman's CHSD.

Methodology and data sources

Data sources

This study utilized two main data sources. The first, CDC WONDER's Underlying Cause of Death database, includes cause of death from the years of 1999 through 2020 for all Americans. The underlying cause of death is defined by the World Health Organization (WHO) as "the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury." A single underlying cause of death is selected from the conditions entered by the physician on the cause of death section of the death certificate. When more than one cause or condition is entered by the physician, the underlying cause is determined by the sequence of conditions on the certificate, provisions of the ICD, and associated selection rules and modifications. Drug-induced causes exclude accidents, homicides, and other causes indirectly related to drug use." This database can be accessed here: https://wonder.cdc.gov/ucd-icd10.html.

Additionally, we analyzed claims data from Milliman's CHSD for commercially insured members in all 50 states, representing 75 million covered lives. These data were utilized to identify members with recorded diagnoses for psychotropic and select CNS drug-related overdoses on inpatient or emergency room claims, members who filled prescriptions for psychotropic and select CNS medications, and members with recorded diagnoses for depression or anxiety.

Methodology

To identify psychotropic and select CNS drug-related overdose deaths in the CDC WONDER Underlying Cause of Death database, we included data for all Americans age 64 and younger between the years of 1999 and 2020 with an ICD-10-CM code of X41 (Accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonian, and psychotropic drugs, not elsewhere classified), X61 (Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonian, and psychotropic drugs, not elsewhere classified), or Y11 (Poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonian, and psychotropic drugs, not elsewhere classified, undetermined intent).

Any other ICD-10-CM diagnosis code starting with X indicated an overdose death for another substance.

We included data for commercially insured members in the CHSD continuously enrolled from January 2020 through December 2020 age 64 and younger and used the following system to identify those with overdoses, related prescriptions, and depression and anxiety diagnoses:

We classified members as having an overdose if they had at least one inpatient or emergency room claim with an ICD-10-CM diagnosis code of T42 (Poisoning by, adverse effect of, and underdosing of antiepileptic, sedative-hypnotic, and antiparkinsonian drugs) and/or T43 (Poisoning by, adverse effect of, and underdosing of tricyclic and tetracyclic antidepressants), excluding codes for underdosing, adverse events, and assault, regardless of whether they filled prescriptions for a drug in a therapeutic class related to these overdose codes.

We identified members who filled a prescription for a drug in the following therapeutic classes using Medi-span Generic Product Identifiers (GPIs):

- Antianxiety agents
- Anticonvulsants
- Antidepressants
- Antiparkinsonians
- Barbiturates
- Hydantoin derivatives
- Iminostilbenes
- Neuroleptics
- Psychostimulants
- Succinimides
- Tranquilizers

We identified members with anxiety and depression diagnoses with at least one inpatient, outpatient, or professional claim with ICD-10-CM diagnosis codes F41, and F32 through F34, respectively.

The overdose rates we report indicate the frequency for which members experienced overdoses at least once in 2020 as opposed to the frequency of overdose claims in 2020.

Results were not normalized for age, sex, and regional differences, and the statistical significance of our findings was not evaluated.

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