Overdose deaths involving non-BZD hypnotic/sedatives in the USA: Trends analyses

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Summary

Background There is sparse knowledge on overdose deaths resulting from non-benzodiazepines and gabapentinoids usage. We examined overdose death rate across demographics categories and the overdose death trends over time.

Methods Using data from the National Center for Health Statistics (USA), we identified 21,167 persons that died with an overdose ICD code as the underlying cause of death and had a T42.6/T42.7 ICD code, which include gabapentinoids and z-drugs, among their multiple causes of death. The overdose death rate was calculated per 100,000 persons for every year between 2000 and 2018. We used joinpoint regression analyses to assess trends over time.

Results We identified a rise in the proportion of deaths with a T42.6/T42.7 ICD code between 2000 and 2006 (yearly change: +0.06) and between 2006 and 2015 (yearly change: +0.32). From 2000 to 2008, the proportion of deaths with any other T code rose significantly (yearly change: +3.56). Between 2008 and 2018, there was also a significant rise (yearly change: +1.31). From 2000 to 2015, the proportion of deaths with a T42.6/T42.7 ICD code with any other T code rose (yearly change: +2.58). From 2000 to 2015, the proportion of deaths with a T42.6/T42.7 ICD code with a concurrent benzodiazepine T code rose (yearly change: +1.98). From 2000 to 2005, the proportion of alcohol T codes rose non-significantly (yearly change: +0.35). Finally, the proportion of alcohol T codes fell significantly between 2008 and 2018 (yearly change: - 0.74).

Interpretation Deaths due to non-benzodiazepine hypnotics and gabapentinoids increased significantly over the last two decades. Clinicians should not assume that replacing benzodiazepines and opioids with these medications necessarily lowers risk to the patient.

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Introduction

Prescription opioids and benzodiazepines are the most common medication classes involved in drug-related emergency department visits[1] and drug overdose deaths in the United States.[2] When taken in excess, both benzodiazepines and prescription opioids promote respiratory depression.[3] Their concurrent use is especially threatening as these drugs can act synergically, promoting respiratory symptoms,[4] and increasing the risk of overdose deaths. In 2018, data from 25 US states showed that 32.5% of opioid-related deaths occurred with the simultaneous use of a benzodiazepine.[5] Clinicians have garnered awareness about the risks of opioids after the catastrophic consequences of their widespread use, and prescriptions have decreased notably since 2012.[6] Drug monitoring initiatives have already been implemented successfully to reduce prescribing of benzodiazepines as well,[7] even though illegal markets have been increasingly gaining importance as a source of benzodiazepines - often with uncertain potency.[8] As such, prescribers seek safer interventions, including other medications.

Gabapentinoids pregabalin and gabapentin, drugs approved for the treatment of some forms of epilepsy as

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Research in context

Evidence before this work

After the rise in opioid-related overdose deaths in the USA, often involving benzodiazepines, prescribers would seek for safer pharmacologic alternatives to treat pain and insomnia. As such, the prescription of gabapentinoids and z-drugs rose significantly over the last two decades. Potential harms and abuse potential of these medication classes are established in the medical literature, but little is known about their participation in overdose deaths. Moreover, there is scarce knowledge about their concurrent involvement with any other substances and, specifically, other central nervous system depressant substances, such as opioids, benzodiazepines, and alcohol, in fatal drug overdoses.

Added value of this work

We describe a joinpoint analysis of the proportion of overdose deaths involving a z-drug or gabapentinoid between 2000 and 2018 in the USA. This type of analysis allows to identify significant trends in temporal series. The involvement of z-drugs and gabapentinoids in fatal overdoses rose significantly in the USA between 2000 and 2015. Moreover, the concurrent involvement of those classes of medications in overdose deaths with opioids and benzodiazepines also increased significantly over the same period.

Implications of all the available evidence

Z-drugs and gabapentinoids are increasingly involved in overdose deaths in the USA over the past two decades. Furthermore, they are also increasingly present in opioid or benzodiazepine-related overdose deaths. This suggests those drugs can pose their own harms. Clinicians should be aware when prescribing, especially when trying to replace benzodiazepines or opioids, as z-drugs and gabapentinoids can be misused concurrently with the substances they intend to replace.

well as for pain disorders, are classified as having lower abuse potential compared to opioids.[9,10] Prescribers may use them for a myriad of off-label indications, including anxiety and insomnia.[11] The potential for addiction and higher risk of overdose among those simultaneously using opioids and benzodiazepines has been a cause of concern as gabapentinoid prescription rates rise steadily from 2002 to 2015.[12] Similarly, non-benzodiazepine sedative-hypnotics (also known as Z-drugs), approved for short-term treatment of insomnia, were touted as safe alternatives to the popular benzodiazepines when introduced to the market as less prone to abuse or dependence.[13,14] Yet, recent evidence suggests that this alternative may also be as harmful as the product it intended to replace partially; in addition, they are associated with similar side effects as benzodiazepines, such as drowsiness, dizziness, and bradypnea[12] and have considerable abuse potential for their euphoric effects in higher doses.[15]

Both gabapentinoids and Z-drug prescription rates have experienced a significant rise due to perception of safety compared to their more common and harmful alternatives of opioids and benzodiazepines. Despite research findings regarding the potentially harmful effects of Z-drugs, between 1993 and 2010, a decline in benzodiazepine prescribing coincided with an increase in Z-drug prescribing.[13] Conversely, a serial cross-sectional study found a two-fold increase in outpatient benzodiazepine prescriptions between 2003 and 2015.[16] The rise in z-drug prescription may be explained by clinicians and patients perceiving them as safer drugs despite a lack of evidence supporting improved efficacy of Z-drugs or fewer side effects.[14,17] This is in direct contrast with a study that supports the possibility of higher dependence of Z-drugs compared to benzodiazepine hypnotics, as well as common adverse effects affecting those on either drug equally.[14] Moreover, these trends do not prevent concurrent medical and non-medical use of Z-drugs and benzodiazepines, indicating that this replacement is difficult and erratic.[18] Gabapentinoids usage also rose steeply, more than tripling between 2002 and 2015.[12] Here too, some perception of safety may affect this increase. As described by Bonnet and Scherbaum, an "anti-adverse selection" process whereby gabapentinoids are regarded as safer drugs in comparison to opioid and multidrug for "risky" patients may, thus, be the cause for such a steep increase. Despite presenting an addictive risk, gabapentinoids should be preferred against more toxic substances. Extensive literature exists, for example, on the lethal effects and addictive power of gabapentinoids for patients with other current or past substance use disorders — especially among opioid dependents and multidrug users.[11]

Data on overdose deaths involving non-benzodiazepines and gabapentinoids are scarce in the literature. There is evidence of the increased harm of gabapentinoid overdoses used with other substances, especially psychoactive drugs.[11] Further, the top 1% of users consume more than 15% of the United States' national supply of gabapentin, at an average daily consumption of more than three times the maximum label dosage recommended.[19] As such, overdose deaths involving gabapentinoids are a genuine concern.[10] With Z-drugs, too, findings suggest an association regarding overdose deaths among those with opioid dependence as Z-drugs might add to respiratory depressant effects of opioids.[20] This effect is similar to that of alcohol and benzodiazepines, commonly involved in opioid-related overdose deaths.[21] This study aims to fill the gap in knowledge and report trends in the proportion of overdose deaths involving non-benzodiazepines and gabapentinoids in the USA using individual-level data.

Methods

Population & data

We utilized data from the National Center for Health Statistics multiple cause of death public-use files for the given period. The data is delivered by the CDC WONDER system.[22] We analyzed data where the ICD codes for unintentional (X40-X44), intentional (X60-64), and undetermined (Y10-14) overdose deaths and alcohol-related (X45, X65, and Y15) were underlying causes of deaths during the 2000–2018 period in the United States following other studies from the CDC,[21,23,24] except for the X85 code (Assault by drugs, medicaments, and biological substances).

The United States death certificate lists the underlying cause of death (the condition leading directly to the decease) and up to 20 multiple causes of death that potentially contributed to the event. We selected for this report a subset of individuals who had the ICD codes T42.6 (Poisoning by, adverse effect of and underdosing of other antiepileptic and sedative-hypnotic drugs) or T42.7 (Poisoning by, adverse effect of and underdosing of unspecified antiepileptic and sedative-hypnotic drugs) listed among their multiple causes of death. We chose these codes because we wanted to assess the involvement of gabapentinoid antiepileptics used to treat pain and non-benzodiazepine sleep inductors (also known as z-drugs) in recent overdose deaths. These drugs would fit into unspecified drug categories due to not having specific T ICD codes, as opposed to opioid painkillers (T40.0-T40.4) and benzodiazepine sedatives (T42.4). We used the STROBE guideline[25] for cross-sectional studies to ensure quality and transparency of the present research.

Outcomes

Analysis of unique deceased individuals was ensured by sorting deaths by factors that only appear once on the death record, such as age, race, sex, residence, and year of death.

We reported the proportion of deaths with a T42.6/T42.7 ICD code among all overdose deaths with a T-code from 2000 to 2018. We chose to use all deaths with a T code as the denominator rather than all deaths because there was a rising trend in the proportion of death certificates with a T-code between 2000 and 2018, due to improvement in reporting of death certificates.[26] As such, the rise in the specific T codes of interest in this study would be biased by the overall rise in the presence of T-codes in death certificates as the proportion of deaths with any T code has risen throughout the study timeframe. Also, for the same timeframe, we reported proportions of deaths with any other T code and specific T codes for opioids (T40.0-T40.4 & T40.6), benzodiazepines (T42.4), and alcohol (T51.0-T51.9) among the overdose deaths with a T42.6/T42.7 ICD code.

Analysis

The overdose death rate was calculated per 100,000 persons for every year between 2000 and 2018. The total population within this timeframe was described by sex, education status, race, marital status, autopsy status, and manner of death.

We used joinpoint regression analyses to assess the statistical significance of the T42.6/T42.7 overdose deaths trends over time.[27] Joinpoint analysis fits a trend curve into a regression model that describes the data as parsimoniously as possible. By doing so, this technique attributes joinpoints to the curve that separates different trend lines. The ideal number of joinpoints is calculated using a permutation test,[28] comparing models with zero to 3 joinpoints with at least two observations between every two joinpoints (default number recommended for 19 data points corresponding to years 2000–2018).[29] The point estimates for each trend line are the variations in proportions provided with *p*-values, following this equation for a linear model:

$$g(y) = Bo + B1 * X1 + B2 * k(x1 - T * k) + ei$$

Where g(y) is a function of the proportion of deaths in each of the models, T is time, B1 is the fixed effect of covariates X1, B2 is the change in slope of B1 by a *k* number of points in time (T), and ei is an error term assumed independent and normally distributed.

We specified the type of variable as "proportion" assuming homoscedasticity, following other studies using similar methods.[30,31] The Joinpoint Regression Program version 4.8.0.1[29] was used for data analysis.

Role of the funding source

Funders had no role in study design, data collection, data analysis, interpretation, writing of the report.

Results

Sociodemographics

Between 2000 and 2018, 788,135 persons died with an overdose ICD code as the underlying cause of death. Of those, 587,884 persons had any T code among their multiple causes of death. In turn, 21,167 among those had a T42.6/T42.7 ICD code, which include gabapentinoids and z-drugs, among their multiple causes of death.

In Table 1, we report sociodemographic characteristics of the overall and T42.6/T42.7-specific populations. Our population had a higher proportion of women (57.2%), higher education (41.8%), and whites (93.0%). Table 2 shows yearly and overall counts of deaths (total and by T code).

Joinpoint analyses

Two joinpoints were identified for the proportion of deaths with a T42.6/T42.7 ICD code among all

USA Overdoses of other Antiepileptic and Sedative-hypnotic Drugs 2000–2018 (*N* = 21,167)	
Age (SD[1])	47.2 (12.7)
Sex	
Female	12,109 (57.2%)
Male	9,058 (42.8%)
Education	
Incomplete High School or Less	3,108 (14.7%)
High School Graduate	8,553 (40.4%)
Some College or More	8,837 (41.8%)
Unknown	669 (3.16%)
Race	
White	19,677 (93.0%)
Non-White	1,490 (7.04%)
Marital Status	
Single	6,215 (29.4%)
Married	6,854 (32.4%)
Widowed or Divorced	7,794 (36.8%)
Unknown	304 (1.4%)
Autopsy	
Yes	16,428 (77.6%)
No	3,684 (17.4%)
Unknown	377 (1.78%)
Missing	678 (3.20%)
Manner of Death	
Accident	13,120 (62.0%)
Suicide	6,320 (29.9%)
Homicide	1 (0.00%)
Pending Investigation	50 (0.24%)
Could not determine	1,478 (6.98%)
Natural	127 (0.60%)
Missing	71 (0.34%)
Other Substance Use	
Any Other Substance	17,597 (83.1%)
Opioid	14,274 (67.4%)
Cocaine	1,350 (6.4%)
Cannabis	214 (1.01%)
LSD	2 (0.01%)
Other Psychodysleptics (hallucinogens)	2 (0.01%)
Other Psychostimulants	1,273 (6.01%)
Benzodiazepines	8,302 (39.2%)
Alcohol	3,456 (16.3%)

***Table 1*: Sociodemographic data of all individuals involved in an overdose death between 2000 and 2018 with codes T42.6 or T42.7 listed between their multiple causes of death.**

[1] SD: Standard deviation.

overdose deaths with a T code (2006 and 2015). As such, three linear segments were present in the model: 2000–2006, 2006–2015, and 2015–2018. We identified a rise in the proportion of deaths with a T42.6/T42.7 ICD code between 2000 and 2006, with a yearly change of +0.06 (p = 0.02). Likewise, the period between 2006 and 2015 also presented a rise in the proportion of deaths with a T42.6/T42.7 ICD code, with a yearly change of +0.32 ($p < 0.01$). The period between 2015 and 2018 had a non-significant yearly change of +0.05 (p = 0.49). The proportion of deaths with a T42.6/T42.7 ICD code among all overdose deaths with a T code was 1.46% in 2000 and 4.97% in 2018. See Figure 1.

We also report the percentage of other T codes among deaths with a T42.6/T42.7 ICD code. We assessed the proportion of any concurrent T code, an opioid T code, a benzodiazepine T code, and an alcohol T code among those with a T42.6/42.7 ICD code.

For any T code among all deaths with a T42.6/T42.7 code, one joinpoint was identified (2008). From 2000 to 2008, the proportion of deaths with any other T code rose significantly, with a yearly change of +3.56 ($p < 0.01$). Between 2008 and 2018, there was also a significant rise, with a yearly change of +1.31 ($p < 0.01$). See Figure 2.

For an opioid T code among all deaths with a T42.6/T42.7 code, one joinpoint was identified (2015). From 2000 to 2015, the proportion of deaths with a T42.6/T42.7 ICD code with any other T code significantly rose with a yearly change of +2.58 ($p < 0.01$). After that, there was a non-significant increase in the proportion of a concurrent opioid T code in the 2015–2018 period, with a yearly change of +0.21 (p = 0.88). See Figure 3.

For a benzodiazepine T code among all deaths with a T42.6/T42.7 code, one joinpoint was identified (2015). From 2000 to 2015, the proportion of deaths with a T42.6/T42.7 ICD code with a concurrent benzodiazepine T code rose with a yearly change of +1.98 ($p < 0.01$). Then, there was a non-significant decline in the proportion of a concurrent benzodiazepine T code in the following years (i.e., 2015–2018), with a yearly change of -1.83 (p = 0.21). See Figure 4.

For an alcohol T code among all deaths with a T42.6/T42.7 code, two joinpoints were identified (2005 and 2008). From 2000 to 2005, the proportion of alcohol T codes rose non-significantly with a yearly change of +0.35 (p = 0.24). Between 2005 and 2008, the proportion of alcohol T codes also rose non-significantly with a yearly change of +2.46% (p = 0.07). Finally, the proportion of alcohol T codes fell significantly between 2008 and 2018, with a yearly change of - 0.74 ($p < 0.01$). See Figure 5.

Discussion

This study examines trends in mortality data that include Z-drug and gabapentinoids in the US from 2000 to 2018 using data from the National Center for Health Statistics multiple causes of death public-use files. The proportion of overdose deaths involving a T42.6 or T42.7 ICD code increased more than threefold between 2000 and 2018, coinciding with exponential prescription increases since their introduction into the market.[12,13] Data from the last decade indicate a

Year	Z-Drugs & Gabapentinoids (T42.6, T42.7)	Opioids (T40.0-T40.4, T40.6)	Benzodiazepines (T42.4)	Alcohol (T51.0-T51.9)
2000	174	56	33	22
2001	206	75	42	25
2002	298	126	49	39
2003	300	130	64	37
2004	330	153	71	47
2005	388	203	101	56
2006	460	227	131	70
2007	587	317	171	116
2008	638	355	227	147
2009	802	475	267	163
2010	940	586	342	181
2011	1,069	681	406	181
2012	1,158	754	434	222
2013	1,357	889	579	244
2014	1,640	1,154	722	272
2015	2,202	1,668	1,037	329
2016	2,554	1,917	1,107	396
2017	2,997	2,219	1,288	469
2018	3,067	2,289	1,231	440
Total	**21,167**	**14,274**	**8,302**	**3,456**

***Table 2*: Counts of deceases involving each drug class included in our analyses between 2000 and 2018 in the USA.**

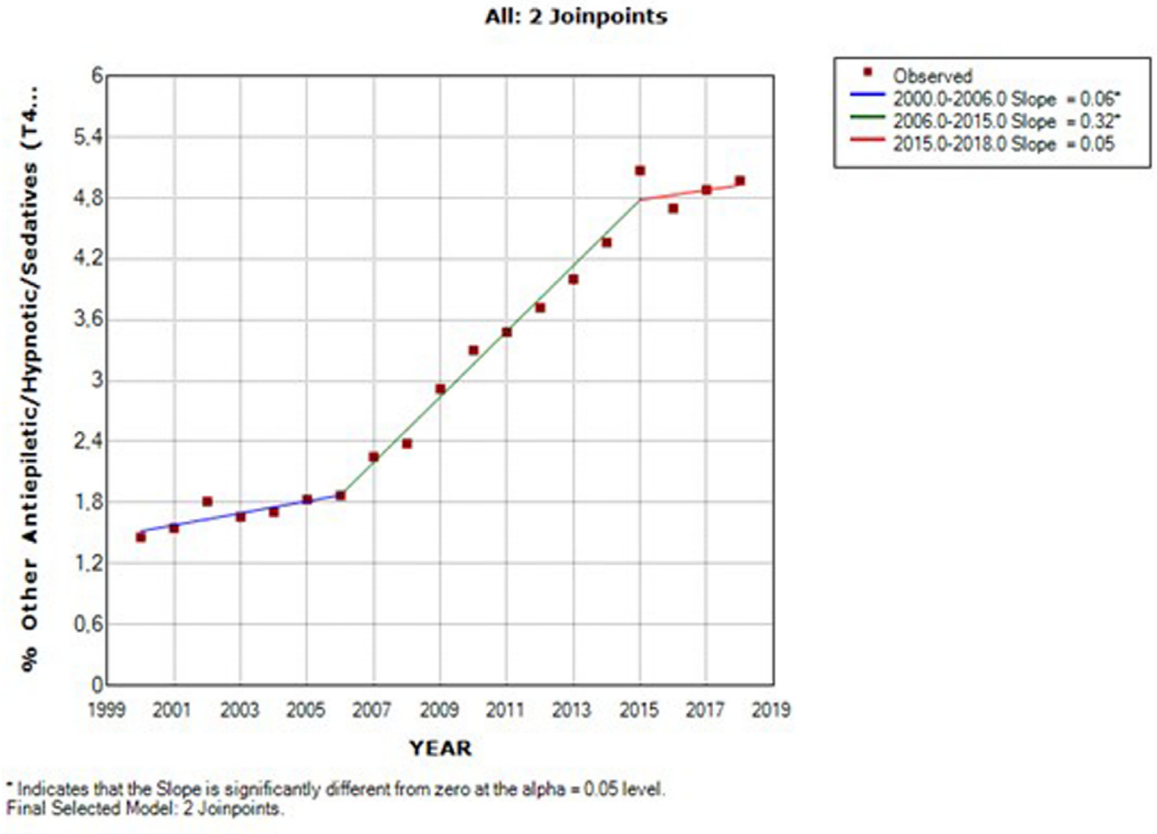

Figure 1. Joinpoint regression model with trends of the percentage of deaths involving a T42.6/T42.7 ICD code among all overdose deaths with a T code from 2000 to 2018 in the USA (Y-axis truncated for best visualization).

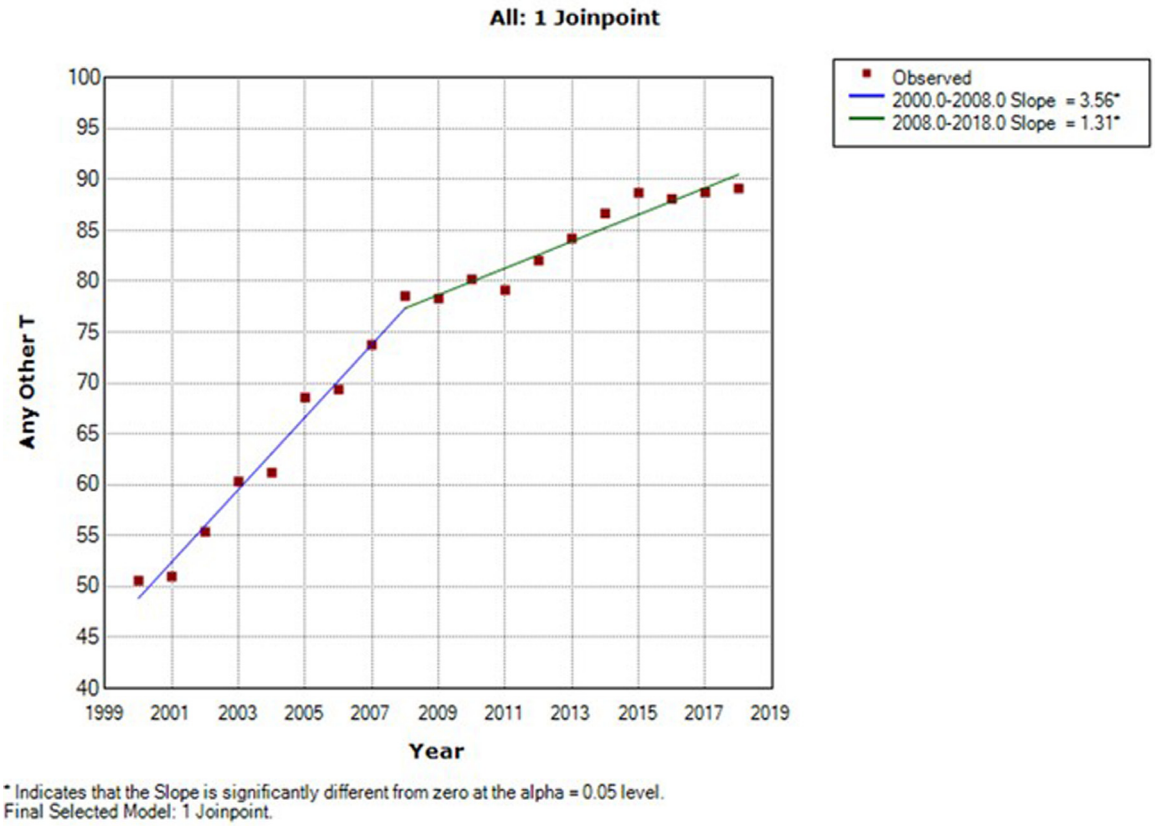

Figure 2. Joinpoint regression model with proportion of deaths involving any other concurrent T code among deaths involving a T42.6/T42.7 ICD code deaths from 2000 to 2018 in the USA(Y-axis truncated for best visualization).

slight decrease in zolpidem prescribing among a commercially insured population in the United States (an average reduction of 2.3% per year between 2011 and 2018),[32] following a nationwide population study that found a two to three-fold increase in non-benzodiazepine hypnotics during the decade before.[33] Conversely, gabapentin prescriptions doubled between 2009 and 2016 in another sample of commercially insured individuals.[34] The rise in gabapentin prescriptions roughly accompanies the involvement of z-drugs and gabapentinoids in overdose deaths, which suggests they can be playing a meaningful role in those deaths. These drug classes were introduced as less dangerous alternatives to opioids and benzodiazepines, creating perceptions among physicians and patients of their supposed increased safety, even without guidelines or formidable data to back up such perceptions and leading to such increases in prescribing.[14,17] In fact, a recent study has shown that the combination of a z-drug with a prescription opioid increases the risk of an overdose death as much as the combination of a benzodiazepine with an opioid.[35]

A rising trend in the proportion of deaths involving a T42.6/T42.7 ICD code is noticeable until 2015, after which this proportion has become stable. Nationwide data show that zolpidem prescriptions were going through a consistent slow decrease between 2011 and 2018, with no particular changes in trend around 2015.[32] Gabapentin prescriptions on the other hand rose steadily between 2012 and 2016,[36] also with no particular changes in trend around 2015. Therefore, the explanation for this spike on prescriptions followed by a plateau is probably unrelated to prescribing rates. A 2013 FDA warning, however, recommended lower starting doses for z-drugs,[37] which could have had an impact on its misuse one to two years later. Rather, the rise in the involvement of synthetic opioids, namely fentanyl, in overdose deaths in the USA is a gallopant phenomenom hitherto and started to increase disproportionally in 2015.[38] The extraordinary rise of this potent type of opioid drug can have masked the ascending trend in overdose deaths involving an T42.6/T42.7 ICD code, as drugs like fentanyl can be lethal even without concurrent synergistic drugs especially for non-tolerant individuals. Moreover, fentanyl does not have a specific T code as do other opioids, so death certificates for casualties involving it - especially escalating so quickly - are subject to misclassification. That could partially explain

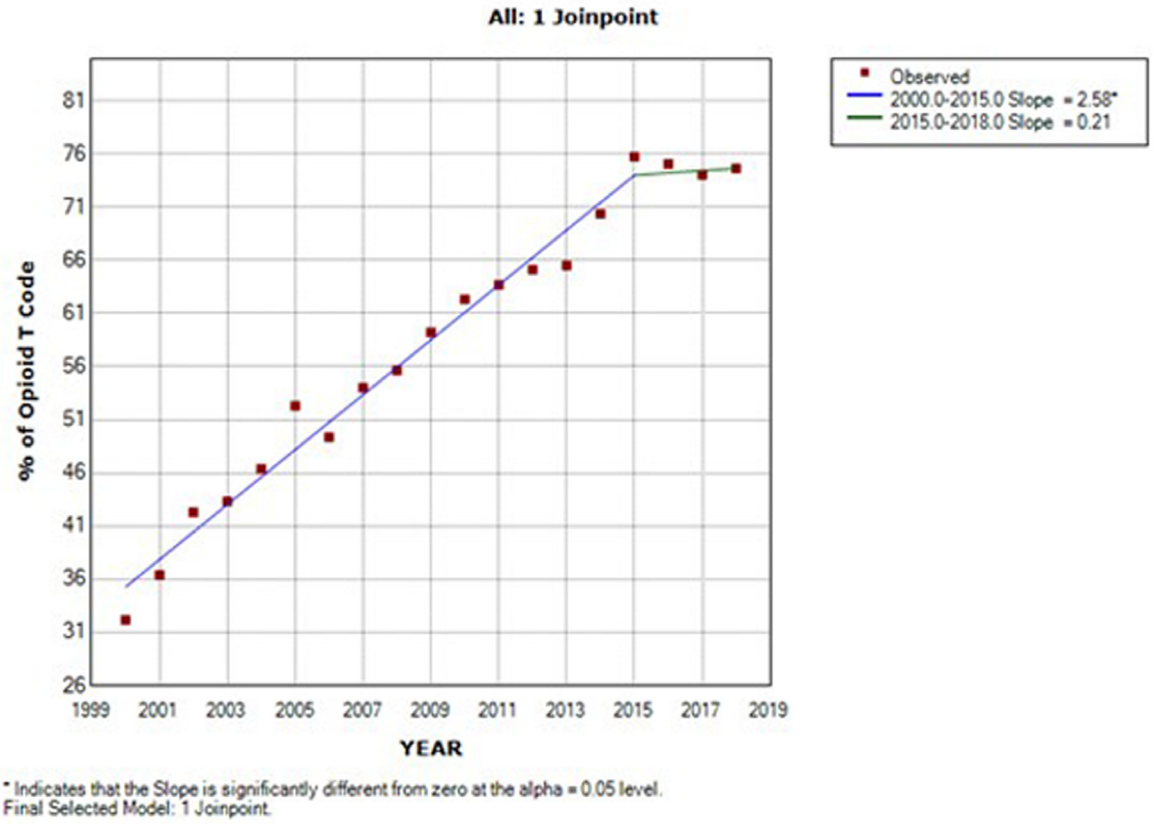

Figure 3. Joinpoint regression model with proportion of deaths involving a concurrent opioid T code among deaths involving a T42.6/T42.7 ICD code deaths from 2000 to 2018 in the USA (Y-axis truncated for best visualization).

why the participation of opioids in deaths with a T42.6/T42.7 ICD code have not grown after 2015.

Compared to the overall population who died from an overdose between 2000 and 2018 with a T code, the subset with a T42.6/T42.7 ICD code had a higher share of women, higher educational background, higher proportion of whites, and more intentional overdoses compared to the overall overdose casualties. These findings align with results from a populational cross-sectional study about medical and non-medical users of z-drugs.[18] In previous population-based studies, both gabapentinoids[39] and z-drugs[40] have been associated with suicidal behaviors. Among gabapentinoids, pregabalin and gabapentin were associated with higher and lower hazards, respectively.[39] Concerning the link between gender and overdoses, it is notable that despite the FDA's 2013 recommendation that women should be prescribed low doses of zolpidem to start, in 2012, only 5% of women were prescribed low doses.[41] Even though factors such as higher prevalence of insomnia among women[42] are important to explain the gender disparities observed in our findings, lack of caution by prescribers could also have contributed. This gender-specific increase seems to be a trend in other parts of the world as well. In a Scotland study looking at gabapentinoid prescribing and associated deaths, women were found to be especially likely to receive prescriptions compared to men.[43] Against the backdrop of an increase in prescribing from 2006 to 2016, gabapentinoids contributing to drug-related death causes in women in Scotland is in line with our findings. Though there is limited data on the relationship between educational attainment and overdose deaths, a study examining people with opioid use disorder highlighted that higher educational attainment was associated with gabapentin use.[44] As such, overall our findings were in-line with prescribing practices and misuse that point to demographic characteristics that put those in specific categories at more risk for overdose-related deaths.

Notwithstanding our findings of increased overdose deaths, including gabapentinoids and z-drugs over the last two decades, there is sparse literature and data on the subject. There is more focus towards simultaneous usage of Z-drugs and gabapentinoids with other substances, for which there is widespread agreement that this is a dangerous practice.[11,20,45] We found that the concurrent poisoning by a drug represented by the T42.6 or T42.7 ICD codes and any other drug increased

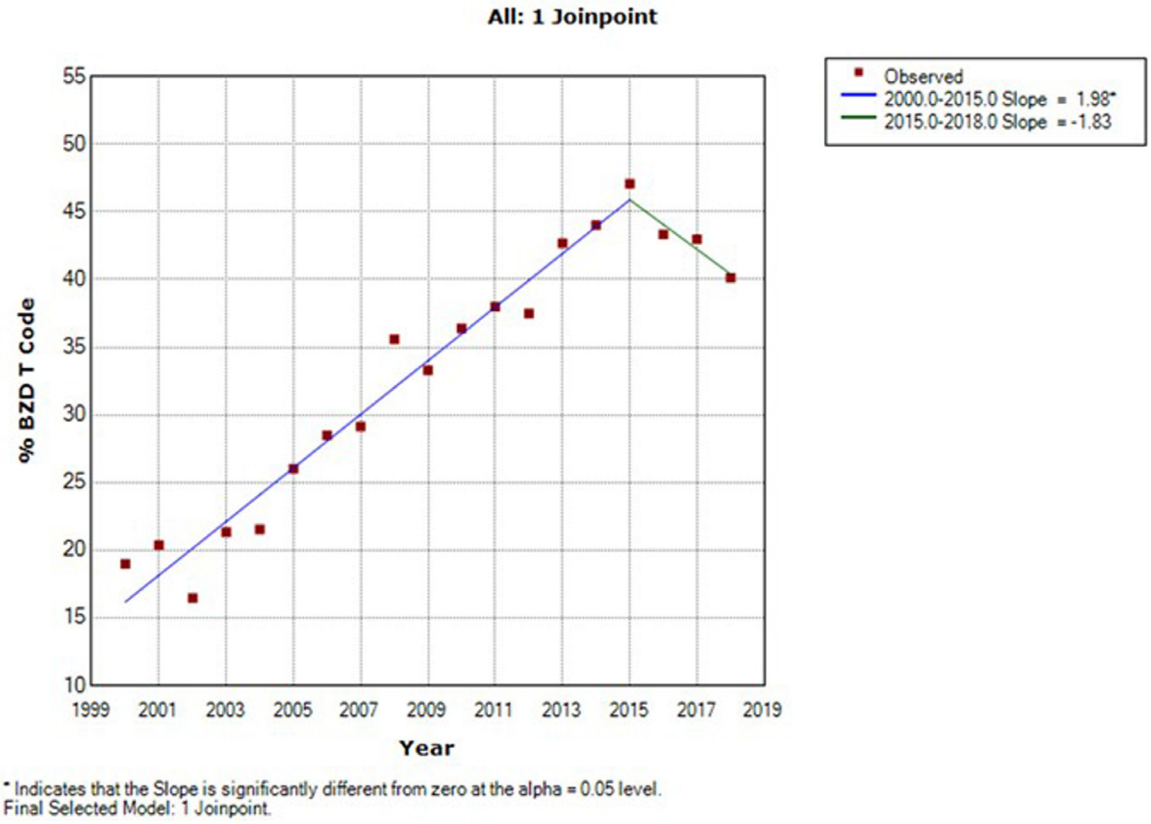

Figure 4. Joinpoint regression model with proportion of deaths involving a concurrent benzodiazepine T code among deaths involving a T42.6/T42.7 ICD code deaths from 2000 to 2018 in the USA (Y-axis truncated for best visualization).

markedly, as have specific concurrent poisonings by opioids and benzodiazepines. This mirrors findings from a study that found almost half of the clinical visits involving the combination of benzodiazepines and Z-drugs resulted in death, patient transfer, or hospitalization.[11] Gabapentinoids can also become lethal, especially when used with other substances of abuse, especially opioids and sedatives.[45] Conversely, this trend was not accompanied by concurrent alcohol poisonings, though other literature indicates that increasing fatalities with gabapentinoid involvement also pointed to co-usage of several substances, including alcohol. Nonetheless, the proportion of fatalities were not broken down by the concurrent substance types.[11]

The proportion of opioid-related deaths among all overdose deaths was 70.6% in 2019. Our data shows that 67.4% of those who died from overdoses with a T42.6/42.7 ICD code were also opioid-related deaths. Could this mean that these drugs are just adding up to opioids rather than mitigating their harms? Despite the introduction of z-drugs and gabapentinoids aiming to replace benzodiazepines and opioids as safer alternatives to treat insomnia and pain, there exists sufficient evidence that users of one often intake the intended replacement as well, a dangerous and often fatal practice. Pregabalin has been reported to be used by 3–12% of people with opioid dependence, for example, with such simultaneous use potentially increasing overdose risk, as found by a study where opioids were found in more than 90% of deaths associated with pregabalin use among pregabalin abusers.[20] This is especially important considering that pure overdoses of gabapentinoids are relatively safe but potentially lethal when used along with other psychoactive drugs, especially opioids and sedatives.[11] Similarly, with Z-drugs, there is evidence that clinical visits involving individuals taking benzodiazepines and Z-drugs simultaneously are more associated with having a serious disposition than clinical visits regarding other sedative-hypnotics.[45] The combination of Z-drugs and opioids can also be notably harmful, due to the former further adding to the depressing respiratory effects of opioids.[20] Evidence, both from our analysis and that of other literature, clearly indicates the issue of simultaneous substance usage. Though meant to mitigate the effects of opioids and benzodiazepines by acting as a replacement, Z-drugs and gabapentinoids seemingly contribute to overdose death and harm users more than reducing the same.

Limitations are noted. As stated, it is not possible to determine which other medication classes are included in the T42.6/42.6 ICD codes as these are intended to encompass medications not otherwise specified. As

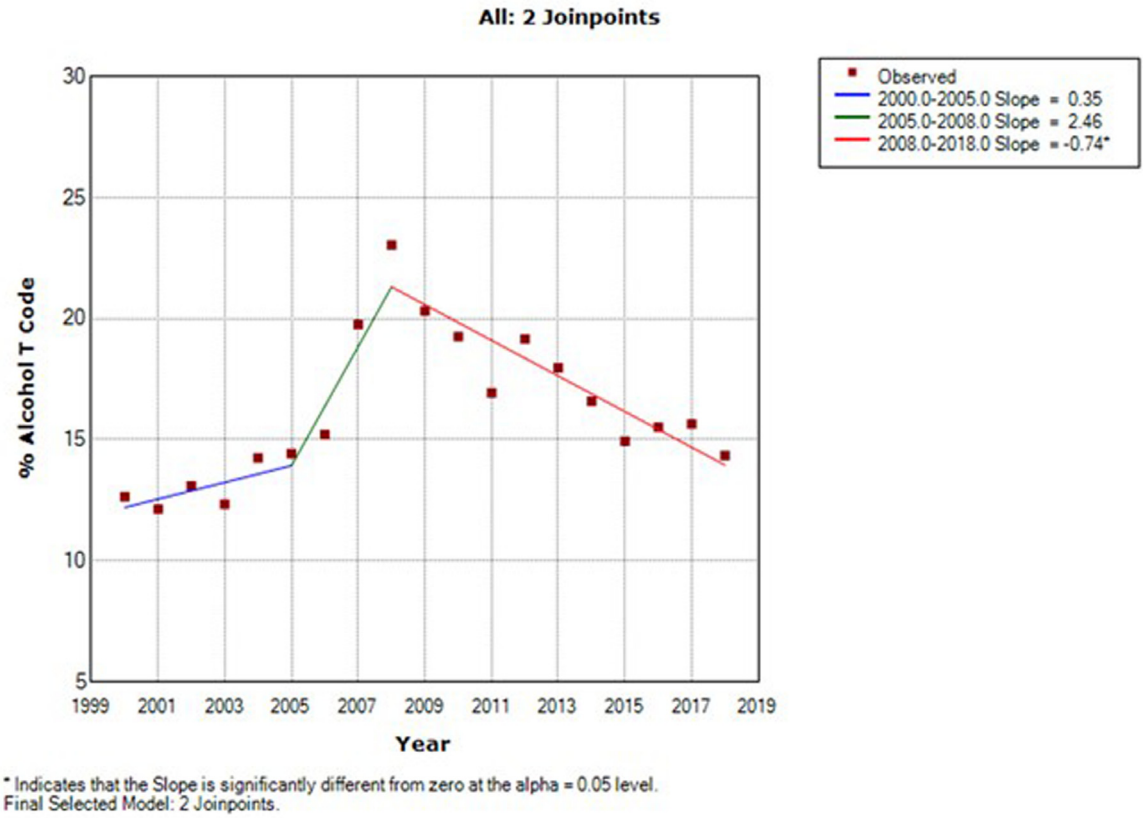

Figure 5. Joinpoint regression model with proportion of deaths involving a concurrent alcohol T code among deaths involving a T42.6/T42.7 ICD code deaths from 2000 to 2018 in the USA (Y-axis truncated for best visualization).

such, medications other than z-drugs and gabapentinoids may contribute to this rising trend, even though data on prescription rates strongly suggested these medications classes played a significant role in fuelling the overdose rates, including the given codes. Furthermore, studies that rely on data from death certificates are always subject to misclassification. Nevertheless, the quality of data from death certificates has been improving over time.[46]

Another potential limitation is including poisonings by suicide and accident. We included ICD codes for drug poisoning (unintentional: X40-X44; intentional: X60-X64; undetermined intent: Y10-Y14; alcohol-related: X45 [unintentional], X65 [intentional], and Y15 [undetermined]). This is a similar approach to that used by other studies about overdose deaths, including CDC reports.[38] Data from death certificates are very subject to misclassification,[47] and even more when assessing intentionality. As such, including overdose deaths with all intentionality status is a safe approach to avoid missing or distorting available information.

Conclusion

There was an alarming increase in deaths due to z-drugs and gabapentinoids over the last two decades. While gabapentinoids are often prescribed to avoid or replace benzodiazepines and opioids, these medications are not risk-free and pose harm. Moreover, rates of concurrent overdose deaths with opioids and benzodiazepines are startling and suggest that gabapentinoids and z-drugs could add risk to non-medical users of benzodiazepines and opioids rather than minimize it. As such, gabapentinoids and z-drugs should always be prescribed with caution. Clinicians and primary care doctors should take a thorough history of potential risky behaviors prior to prescribing these drugs and educate their patients about potential interactions between gabapentinoids and z-drugs with opioids, alcohol, and other sedative drugs.

Contributors

VST: study conception, literature search, data analysis, data interpretation, writing, figures

MCMB: study conception, data collection, data analysis, figures

RP: literature search, figures, writing

LES: study design, figures, data interpretation, writing

JMCM: data collection, study design, data interpretation, writing

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Data sharing statement

The data used for this article is publicly available on https://wonder.cdc.gov/.

Declaration of interests

The authors have no conflict of interest to declare.

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