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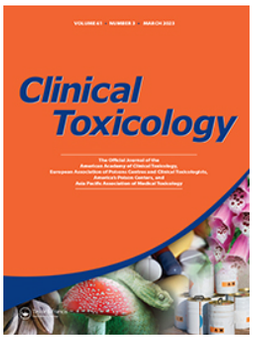

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POISON CENTRE RESEARCH

Trends in concomitant and single opioid and benzodiazepine exposures reported to the California Poison Control System following the Centers for Disease Control and Prevention release of opioid guidelines in 2016

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ABSTRACT

Introduction: In March 2016, the Centers for Disease Control and Prevention released the Guideline for Prescribing Opioids for Chronic Pain, intended for primary care clinicians. One recommendation advised against concurrent prescription of opioids and benzodiazepines. Although existing research suggests a reduction in co-prescribing of these drug classes by clinicians after guideline release, there are limited data assessing its possible effect on patient medical outcomes, such as overdoses.

Methods: This retrospective observational study analyzed opioid and benzodiazepine exposures, alone or in combination, reported to the California Poison Control System from January 2012 to June 2021. Interrupted time series analyses identified the difference in monthly call volume between pre- and post-guideline release. For exposures resulting in serious medical outcomes, additional analyses assessed trends and identified associated variables.

Results: There was no significant change in concomitant opioid and benzodiazepine exposures reported to California Poison Control System between pre- and post-guideline release. Compared to pre-guideline release, exposures to a single opioid or to a single benzodiazepine significantly decreased by 1.07 (95% CI: −1.62, −0.51) and 1.82 (95% CI: −2.33, −1.31) calls per month, respectively, after the guideline release. For exposure calls associated with serious medical outcomes, there was a significant increase of 0.11 (95% CI: 0.04, 0.18) and 0.2 (95% CI: 0.05, 0.34) calls per month for concomitant opioid and benzodiazepine and single opioid exposures, respectively, following guideline release.

Discussion: The guideline release appeared to have a variable association with exposures to single opioid, single benzodiazepines, and concomitant opioid and benzodiazepine cases reported to California Poison Control System. Although exposures to opioids or benzodiazepines alone significantly decreased after guideline release, there was no significant change in concomitant exposures. Additionally, for exposures associated with serious medical outcomes, concomitant exposures, and single opioid exposures significantly increased following guideline release.

Conclusion: Our results suggest that the guideline was not associated with a corresponding decrease in the number of concomitant poisoning exposures reported to California Poison Control System. Additional interventions may be needed to reduce concomitant exposures to opioids and benzodiazepines.

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Introduction

From 1999 to 2019, nearly 500,000 of the 841,000 drug overdose deaths in the United States (US) involved prescription and illicit opioids [1]. In 2019 alone, opioids accounted for 49,860, or 71%, of 70,630 drug overdose deaths [2]. The concurrent use of benzodiazepines and opioids increases the risk of opioid overdose and death [3,4]. Both opioids and benzodiazepines can potentiate the effect of the other and result in adverse effects, such as sedation and respiratory depression [5]. A 2016 study conducted in North Carolina found overdose death rates to be 10-fold higher in patients co-prescribed opioid and benzodiazepines than those given opioids alone [6].

These findings resulted in interventions to promote the safer use of opioids. In the US, the Food and Drug Administration (FDA) required *Boxed Warnings* on prescription opioid and benzodiazepine labels as a strategy to warn of the potential dangers of the concomitant use of these drugs [7]. The 2016 US Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain consisted of twelve recommendations—one of which advised against the concurrent prescription of opioids and benzodiazepines [8].

Two studies suggested a decrease in co-prescription of opioid and benzodiazepines following the 2016 CDC Guideline release [9,10]. However, these studies primarily focused on clinician practices and did not assess possible changes in health outcomes. We sought to address this gap in research on health outcomes by conducting a retrospective analysis of exposures reported to the California Poison

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Control System. Analysis of exposure calls reported to poison centers make it possible to assess changes in exposures to opioids and benzodiazepines, including those associated with serious outcomes. We evaluated changes in monthly call volume of opioid or benzodiazepine exposures, alone or in combination, reported to the California Poison Control System before and after the March 2016 CDC Guideline release. We hypothesized that monthly opioid, benzodiazepine, and concomitant exposures reported to California Poison Control System would decrease following the recommendation to reduce co-prescription.

Methods

Design

This retrospective observational study analyzed trends in opioid and benzodiazepine exposures, alone or in combination, reported to California Poison Control System between 1 January 2012 and 30 June 2021. Pre-intervention included the dates before 1 March 2016, while post-intervention included the period from 1 March 2016 until 30 June 2021.

Data source and collection

Data were obtained from the California Poison Control System, a network of four poison-center sites (San Francisco, Sacramento, San Diego, and Madera/Fresno) that collectively serve a state population of 39 million persons. We used the following inclusion criteria: calls reporting an exposure to both opioid and benzodiazepine (concomitant) or to an opioid or benzodiazepine alone. For single opioid or single benzodiazepine cases, no other types of drugs were reported. Specifically, we defined "single" exposures as calls involving only one substance; exposure calls involving more than one opioid and no other substances were not included as single opioid cases, and exposure calls involving more than one benzodiazepine and no other substances were not included as single benzodiazepine cases. Exposures involved calls in which there was "actual or suspected contact with any substance which has been ingested, inhaled, absorbed, applied to, or injected into the body, regardless of toxicity or clinical manifestation" [11]. The selected drugs in each class included the most commonly prescribed opioids and benzodiazepines in the US [12,13]. For opioids, these included oxycodone, codeine, tramadol, hydrocodone, morphine, hydromorphone, methadone, buprenorphine, pethidine (meperidine), and combination products. For benzodiazepines, these included diazepam, alprazolam, clonazepam, lorazepam, triazolam, chlordiazepoxide, clorazepate, and halazepam. Exposure cases involving illicit opioids, such as heroin or fentanyl, were excluded, as were calls originating from outside of California, involving animal exposures or calling for information but did not report an exposure. We used total human exposures calls as a measure given that the total number of calls made to California Poison Control System for all types of exposures showed no consistent time trend (see Supplement).

Measures

Variables extracted from each de-identified California Poison Control System record included call date, age, gender, reason for exposure, and medical outcome. The number of substances involved in each exposure was also extracted for concomitant opioid and benzodiazepine cases, given that cases could also involve exposure to other substances. Exposures were categorized as involving a minor ($<$18 years old) or an adult ($\geq$18 years old). The reason for exposure was coded by California Poison Control System in accordance with the America's Poison Centers National Poison Data System (NPDS) coding manual and included: unintentional, intentional (suspected suicide, misuse, abuse, unknown), adverse reaction, other (malicious or contamination/tampering), and unknown reason [14]. Known medical outcomes included: uncertain effect, no effect, minor effect (minimally bothersome or self-limiting symptoms), moderate effect (pronounced, prolonged symptoms), major effect (life-threatening symptoms), and death [14]. For analysis, we defined serious medical outcomes as those that resulted in moderate effects, major effects, or death.

Analytical strategy

We reviewed the characteristics of exposure calls for concomitant exposures overall and separately as pre- and post-guideline release.

Our primary analysis relied on interrupted time series analyses. We assessed the risk of delayed implementation (using "actest" for autocorrelation) and identified a lag of one month for our analyses of time trends. The regression model, assuming the form of $Yt = \beta 0 + \beta 1Tt + \beta 2Xt + \beta 3XtTt + \epsilon t$, tested for several parameters which included: $\beta 0$, the intercept or initial level; $\beta 1$, the trend before the intervention; $\beta 2$, the immediate change following an intervention; and $\beta 3$, the difference in the trend of pre- and post-intervention periods [15]. The outcome variable was the count of total monthly exposures to our drug(s) of interest: opioid, benzodiazepine, or concomitant opioid and benzodiazepine. Our intervention was the release of the CDC Guideline in March 2016, meaning that exposures occurring before that month were regarded as pre-intervention while exposures occurring after were post-intervention.

Secondary analyses (1) assessed trends in exposures to opioid, benzodiazepine, or concomitant opioid and benzodiazepine associated with a serious outcome using interrupted time series analyses, and (2) calculated odds ratios between exposure characteristics and serious medical outcomes associated with exposure to either or both drug classes before and after the guideline release. We identified potential predictor variables to generate a multivariable logistic regression model, which simultaneously analyzed potential associations between serious medical outcomes and being a minor (reference: adults), female (reference: male), and reason for exposure (reference: other). All analyses were conducted using Stata v17.

Ethical approval

The University of California at San Francisco Institutional Review Board granted the study exempt status on 30 December 2021 (#21-35769) on the grounds that the study would not adversely affect the right and welfare of the individuals and would involve no more than minimal risk to their privacy.

Results

From 1 January 2012 to 30 June 2021, California Poison Control System received calls reporting a total of 9594 concomitant opioid and benzodiazepine exposures, 37,354 single opioid exposures, and 24,427 single benzodiazepine exposures. We excluded 809 concomitant, 2926 opioid, and 540 benzodiazepine exposures for including illicit opioids, originating from outside of California, involving animal exposures, or for requesting information rather than reporting exposures.

Of the remaining 8785 concomitant exposures, 4850 cases occurred before and 3935 occurred after the intervention. Concomitant exposure reports were 62% female and 94% adult. The mean age was 42.2 years. Reasons for exposure were 12% unintentional and 84% intentional; the latter consisted of 68% suspected suicide, 6% misuse, 7% abuse, and 3% unknown. Sixty-nine percent of the concomitant exposures were associated with no effect or minor effect, while 13% involved a serious medical outcome. Characteristics of concomitant exposures are further provided as before, after, and overall subgroups in Table 1.

Trends in all exposures

Before the guideline release, concomitant opioid and benzodiazepine exposures reported to California Poison Control System were decreasing (see Figure 1 for trendlines and Table 2 for rates and 95% CIs) at a rate of 0.67 calls per month. Although monthly exposure calls continued to decrease at a rate of 0.57 calls per month after guideline release, this increase of 0.094 (95% CI: −0.14, 0.33) calls per month was not significant. In contrast, pre-guideline release single opioid exposures were decreasing at a rate of 0.96 calls per month, and post-guideline release the rate of decline in single opioid exposures increased to 2.02 fewer monthly exposure calls. This difference of −1.07 (95% CI: −1.62, −0.51) calls per month was significant. Similarly, single benzodiazepine monthly exposures pre-guideline release increased by 0.27 calls per month, and after guideline release decreased at a rate of 1.55 exposure calls per month. The decrease of −1.82 (95% CI: −2.33, −1.31) calls per month was significant. Figure 1 depicts the count of exposure calls per month over time and Table 2 provides a summary of trends.

Trends in exposures to serious medical outcomes

Among cases with serious medical outcomes, concomitant opioid and benzodiazepine exposure calls as well as single opioid exposure calls significantly increased after the guideline release (see Figure 2 for trendlines and Table 2 for rates and 95% CIs). Reported concomitant opioid and benzodiazepine exposure cases with a serious medical outcome were decreasing at a rate of 0.12 calls per month before the guideline release whereas after guideline release, it decreased at a rate of 0.004. This translated to a significant increase of 0.11 (95% CI: 0.04, 0.18) calls per month. For opioid-only exposures with a serious medical outcome, monthly exposure cases decreased by 0.06 calls per month before the guideline release; afterward, exposures increased at a rate of 0.14 calls per month, translating to a significant increase of

Table 1. Characteristics of cases of concomitant exposures to opioids and benzodiazepines.

Characteristic	Overall ($n = 8785$)	Before ($n = 4850$)	After ($n = 3935$)	*P*-Value for difference between groups
Categorical variables				
Female	5419 (62%)	3036 (63%)	2383 (61%)	0.057
Adults (18 years and greater)	8248 (94%)	4587 (95%)	3661 (93%)	0.003
Reason for exposure				
Unintentional	1048 (12%)	517 (11%)	531 (13%)	<0.001
Intentional	7377 (84%)	4147 (85%)	3230 (82%)	<0.001
Intentional—suspected suicide	5959 (68%)	3438 (71%)	2521 (64%)	<0.001
Intentional—misuse	497 (6%)	264 (5%)	233 (6%)	0.335
Intentional—abuse	625 (7%)	324 (7%)	301 (8%)	0.079
Intentional—unknown	296 (3%)	121 (2%)	175 (4%)	<0.001
Other	215 (2%)	106 (2%)	109 (3%)	0.078
Unknown	145 (2%)	80 (2%)	65 (2%)	0.993
Outcome of exposure				
Non-toxic: no effect	1646 (19%)	921 (19%)	725 (18%)	0.500
No effect	2128 (24%)	1153 (24%)	975 (25%)	0.275
Minor effect	2242 (26%)	1249 (26%)	993 (25%)	0.580
Severe outcome	1158 (13%)	609 (13%)	549 (14%)	0.056
Moderate effect	1030 (12%)	543 (11%)	487 (12%)	0.087
Major effect	66 (1%)	35 (1%)	31 (1%)	0.721
Death	62 (1%)	31 (1%)	31 (1%)	0.408
Uncertain effect	1611 (18%)	918 (19%)	693 (17%)	0.032
Continuous variables				
Age, years	42.2 (17.7)	42.1 (16.9)	42.4 (18.7)	0.045
Number of substances taken	3.4 (1.8)	3.6 (1.9)	3.2 (1.5)	<0.001

Data are *n* (%) or mean (*SD*). Before is defined as 1 January 2012 to 29 February 2016, the period prior to the release of the Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain, and after is defined from 1 March 2016 to 30 June 2021.

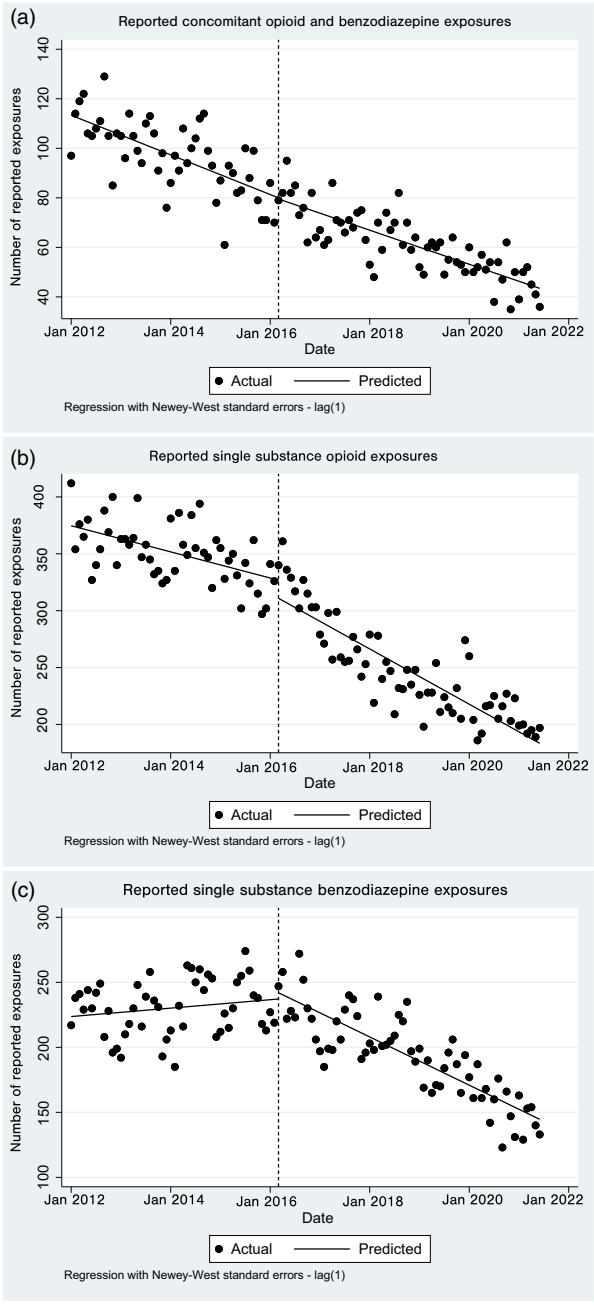

Figure 1. Interrupted time series analysis of exposures from January 2012 to June 2021. The intervention time point is March 2016, the month of the Centers for Disease Control and Prevention Guideline release. Figures display exposures over time for: (a) concomitant opioid and benzodiazepine (no significant change, $P = 0.423$); (b) single opioid (decrease, $P < 0.001$); and (c) single benzodiazepine (decrease, $P < 0.001$).

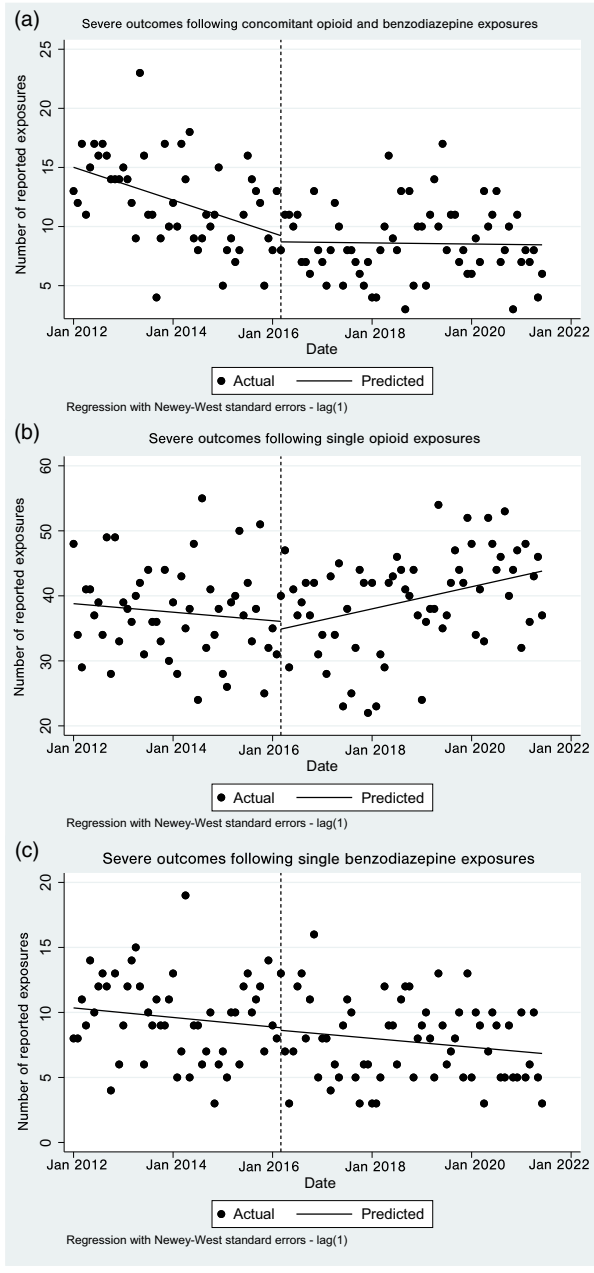

Figure 2. Interrupted time series analysis of exposures resulting in serious outcomes from January 2012 to June 2021. The intervention time point is March 2016, the month of the Centers for Disease Control and Prevention Guideline release. Figures display exposures over time for: (a) concomitant opioid and benzodiazepine (increase, $P = 0.003$); (b) single opioid (increase, $P = 0.007$); and (c) single benzodiazepine (no significant change, $P = 0.947$).

Table 2. Slope and confidence intervals for drug exposure trend lines before and after release of 2016 Centers for Disease Control and Prevention opioid guidelines.

	Before			After				
Drug(s) of interest	Initial level	Slope	95% CI	Slope	95% CI	Difference	95% CI	*P*-Value
Exposures leading to all outcomes								
Concomitant	113.34	−0.67	−0.88, −0.46	−0.57	−0.67, −0.47	0.094	−0.14, 0.33	0.423
Opioids	374.68	−0.96	−1.38, −0.53	−2.02	−2.38, −1.67	−1.07	−1.62, −0.51	<0.001
Benzodiazepine	223.68	0.27	−0.17, 0.71	−1.55	−1.80, −1.29	−1.82	−2.33, −1.31	<0.001
Exposures leading to severe outcomes								
Concomitant	15.01	−0.12	−0.18, −0.05	−0.004	−0.04, 0.03	0.11	0.04, 0.18	0.003
Opioids	38.8	−0.06	−0.17, 0.06	0.14	0.06, 0.22	0.20	0.05, 0.34	0.007
Benzodiazepine	10.35	−0.03	−0.08, 0.02	−0.03	−0.07, 0.02	0.002	−0.07, 0.07	0.947

95% CI: confidence interval. The initial level is defined as the number of monthly exposure calls at the beginning of the study period. The slope is defined as the change in the number of monthly exposure calls (rate) reported to California Poison Control System in the specified intervention period. The difference is the change in trend between the pre- and post-intervention period.

Table 3. Associations between serious health outcomes and individual characteristics.

	Before		After	
Variables	Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval
Concomitant				
Minors (younger than 18 years)	0.56*	0.33, 0.94	1.06	0.75, 1.50
Female	1.02	0.85, 1.22	0.78*	0.65, 0.95
Reason for exposure: unintentional	0.45**	0.25, 0.82	0.45**	0.26, 0.80
Reason for exposure: intentional	1.17	0.58, 2.32	1.49	0.83, 2.68
Intentional—suspect suicide	1.11	0.65, 1.90	0.83	0.55, 1.23
Intentional—misuse	0.25**	0.11, 0.58	0.28**	0.15, 0.55
Intentional—abuse	0.68	0.36, 1.31	1.14	0.71, 1.84
Opioids				
Minors (younger than 18 years)	0.60**	0.51, 0.71	0.74**	0.64, 0.85
Female	0.87**	0.79, 0.97	0.88**	0.80, 0.96
Reason for exposure: unintentional	0.30**	0.24, 0.38	0.22**	0.18, 0.27
Reason for exposure: intentional	3.50**	2.55, 4.80	2.69**	2.09, 3.46
Intentional—suspect suicide	0.72*	0.55, 0.95	0.76*	0.61, 0.94
Intentional—misuse	0.30**	0.23, 0.41	0.35**	0.27, 0.45
Intentional—abuse	0.75	0.56, 1.01	1.43**	1.13, 1.81
Benzodiazepines				
Minors (younger than 18 years)	0.44**	0.35, 0.54	0.55**	0.44, 0.69
Female	1.02	0.84, 1.24	0.88	0.73, 1.06
Reason for exposure: unintentional	4.44**	2.33, 8.47	1.35	0.93, 1.96
Reason for exposure: intentional	0.39	0.08, 1.79	0.29**	0.13, 0.65
Intentional—suspect suicide	1.73	0.42, 7.08	1.52	0.71, 3.27
Intentional—misuse	2.34	0.54, 10.1	1.23	0.52, 2.94
Intentional—abuse	1.52	0.31, 7.39	1.7	0.73, 3.94

Using multivariate logistic regression, we assessed the likelihood that different individual characteristics were associated with a serious medical outcome, while simultaneously controlling for the other characteristics. The baseline categories for minor, female, and reason for exposure were adults, male, and other reason, respectively. ** denotes $P < 0.01$ and * denotes $P < 0.05$.

0.2 (95% CI: 0.05, 0.34). In comparison, monthly benzodiazepine-only exposure calls with a serious medical outcome did not change significantly (95% CI: −0.07, 0.07) pre- and post-intervention.

Characteristics associated with serious medical outcomes: concomitant exposures

Before the guideline release, characteristics significantly associated with reduced likelihood of severe outcomes following concomitant drug exposures were being a minor (OR = 0.56; 95% CI: 0.33, 0.94), unintentional exposure (OR = 0.45; 95% CI: 0.25, 0.82), and intentional misuse (OR = 0.25; 95% CI: 0.11, 0.58) as shown in Table 3. After the guideline release, characteristics significantly associated with reduced likelihood of severe outcomes were self-reporting as female (OR = 0.78; 95% CI: 0.65, 0.95), unintentional exposure (OR = 0.45; 95% CI: 0.26, 0.80), and intentional misuse (OR = 0.28; 95% CI: 0.15, 0.55).

Characteristics associated with serious medical outcomes: single opioid exposures

Before the guideline release, all but one characteristic analyzed was significantly associated with serious medical outcomes following single opioid exposures: being a minor (OR = 0.6; 95% CI: 0.51, 0.71), self-reporting as female (OR = 0.87; 95% CI: 0.79, 0.97), unintentional exposure (OR = 0.3; 95% CI: 0.24, 0.38), intentional overall (OR = 3.5; 95% CI: 2.55, 4.8), intentional—suspected suicide (OR = 0.72; 95% CI: 0.55, 0.95), and intentional—misuse (OR = 0.30; 95% CI: 0.23, 0.41) After the guideline release, all characteristics were significantly associated with a serious medical outcome: being a minor (OR: 0.74; 95% CI: 0.64, 0.85), self-reporting as female (OR: 0.88; 95% CI: 0.8, 0.96), unintentional exposure (OR: 0.22; 95% CI: 0.18, 0.27), intentional overall (OR = 2.69; 95% CI: 2.09, 3.46), intentional—suspected suicide (OR = 0.76; 95% CI: 0.61, 0.94), intentional—misuse (OR = 0.35; 95% CI: 0.27, 0.45), and intentional—drug abuse (OR = 1.43; 95% CI: 1.13, 1.81) were significantly associated with severe medical outcomes.

Characteristics associated with serious medical outcomes: single benzodiazepine exposures

Before the guideline release, those who were minors (OR = 0.44; 95% CI: 0.35, 0.54) were significantly less likely to experience a serious medical outcome following a single benzodiazepine exposure while those who were unintentionally exposed (OR = 4.44; 95% CI: 2.33, 8.47) were significantly more likely to experience a serious medical outcome. After the guideline release, those who were minors (OR = 0.55; 95% CI: 0.44, 0.69) and those who were exposed intentionally (OR = 0.29; 95% CI: 0.13, 0.65) were significantly less likely to experience a serious outcome following a single benzodiazepine exposure.

Discussion

Our study analyzed California Poison Control System data of reported exposures to opioids and benzodiazepines, either alone or concomitantly, between January 2012 and June 2021 to determine whether the release of the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain was associated with changes in exposures reported to California Poison Control System. Contrary to our hypothesis, we identified no significant change in the trend of concomitant exposures reported to California Poison Control System following the guideline release.

We were unable to identify any previous studies analyzing the association between the guideline release and health outcomes for prescription opioids. However, previous research has found that the proportion of people with an overlapping opioid and benzodiazepine prescriptions significantly declined after the guideline release [9,10], whereas the intensity of co-prescription, or the fraction of days where both drugs were available, had no significant change [9]. Together with our results, these findings suggest that although co-prescription may be less prevalent after the guideline release, those who had been co-prescribed opioids and benzodiazepines in the past continued to have access to both drugs and remained at risk for some kind of adverse exposure. In contrast, we found that exposures to opioids alone and benzodiazepines alone decreased significantly after the guideline release. As the CDC guidelines contained twelve recommendations aimed at safer opioid prescribing, including considering nonopioid and non-pharmacological alternatives [8], these findings are consistent with our original hypothesis that the guideline could be associated with reduced adverse health outcomes. This is also consistent with previous literature, which has identified a significant decrease in opioid prescribing rate, independent of co-prescribing, after the guideline release [10,16].

In addition to analyzing overall exposures following opioid, benzodiazepine, and concomitant exposures, we considered a subset of exposures that were followed by a serious medical outcome. Our results were not consistent across drugs; relative to pre-guideline release, we found a significant increase in concomitant opioid and benzodiazepine as well as single opioid exposures associated with a serious medical outcome after the guideline release. However, we found no change in exposure for benzodiazepines alone. Our results parallel those from previous studies and national databases [1]. The annual number of overdose deaths involving any opioids has either remained steady or increased annually in the past two decades [17], and research has suggested that these deaths likely involve illicit opioids, such as heroin and illicitly manufactured fentanyl [18,19]. Since our dataset excluded illicit opioids, our findings suggest that although guideline release may have decreased opioid prescribing [10,16], it may have had unintended consequences, such as an increase in the misuse of prescription opioids resulting in adverse health outcomes. On the other hand, benzodiazepine-involved overdose deaths decreased from 2017 to 2019 but have since increased and often involve both a benzodiazepine and an opioid rather than a benzodiazepine alone [20].

Lastly, we analyzed characteristics associated with serious medical outcomes following an opioid, benzodiazepine, or concomitant exposure before and after the guideline release. Before the intervention, both intentional exposure to opioids and unintentional exposure to benzodiazepines were significantly associated with serious medical outcomes. After the CDC guideline release, only intentional exposures to opioids continued to be significantly associated with serious medical outcomes. One possible explanation may be that despite a decrease in opioid prescribing after guideline release [10,16], those intentionally using opioids continue to remain at risk *via* other avenues, such as abuse of prescription opioids. On the contrary, those unintentionally exposed to benzodiazepines no longer remain at risk, likely due to its decreased availability as supported by decreased overall benzodiazepine exposures reported to California Poison Control System after guideline release. People who self-reported as females were less likely to experience a serious medical outcome after an exposure to the drugs of interest, or there was no significant association. This finding is consistent with literature that has found disproportionate opioid overdose deaths in males [21].

Strengths and limitations

Our analysis evaulated poison center data from a single state, California, which may limit the application to other states or nationally. However, California is the largest state and largest poison system in the US, and past research has found that results from California are consistent with those in other states, as well as nationally [22,23]. Another strength is that our findings provide context to prior research that suggests that co-prescribing rates declined but did not assess the association between co-prescribing rates and health outcomes.

This study also has limitations. Reported exposures do not represent all true exposures since reporting to poison centers is voluntary, and as result may not be representative. Additionally, California Poison Control System toxicologists often do not have access to a complete medical history, meaning that we were unable to filter for exposures in adults with a chronic pain diagnosis, the intended patient population of the CDC Guideline. As a result, it is possible our findings may have underestimated the guideline's effect. By analyzing the trend of exposures to opioids and benzodiazepines as a class, we lost data granularity in the trend of exposures to each drug itself (for example, if exposures to one kind of opioid declined but exposures to another increased). Future research could improve upon both of these aspects.

In addition, given the time frame of the study, other factors may have influenced shifts in exposures, such as the effects of the COVID-19 pandemic and the 2016 updates to California's prescription drug monitoring program (automated proactive reports to prescribers and mandatory registration for prescribers and pharmacists, implemented over several months) [24]. Finally, given that the concomitant opioid and benzodiazepine exposure group included exposures to other potentially dangerous substances in addition to the drugs of interest, medical outcomes may have been influenced by the other substances. This meant that we could only identify associations and not infer that the use of these substances led directly to the serious outcomes.

Conclusions

Despite prior findings of decreased co-prescription after the release of the 2016 CDC Opioid Guideline, our results suggest the guideline release was not associated with a corresponding decrease in the number of concomitant poisoning exposures reported to California Poison Control System; on the contrary, it was associated with an increased number of concomitant exposures associated with a severe medical outcome as

reported to California Poison Control System. These changes were intended to address overprescribing, and this appears to have been successful, but were also intended to reduce health harms, and in this respect, the guideline appears to have been less successful. Overall, these findings suggest that further interventions are needed to reduce poisoning associated with opioids and benzodiazepines.

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Author contributions

All authors contributed to the study conception, design, data collection, data analysis, manuscript preparation, and revisions.

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Data availability statement

The data supporting the conclusions of this article are available from the California Poison Control System by submitting a Data Request Form.

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