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Polydrug epidemiology: Benzodiazepine prescribing and the drug overdose epidemic in the United States

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Abstract

Background: Although polydrug incidents comprise a substantial proportion of overdose deaths, scholarly and popular focus has centered on prescription opiates. This study examines the role of benzodiazepine and opioid prescriptions on overdose—both individually and synergistically—using data from Medicare Part D, a source of prescription drug claims for about 35 million Americans.

Methods: Prescribing data from the Medicare Part D Public Use Files for 2013, 2014, and 2015 (approximately 3.5 billion prescription drug claims) are geolocated using the prescriber's national provider identifier to calculate the proportion of claims for opioids and benzodiazepines in each county. These rates are matched with overdose data and controls to compile an analytic dataset of 9105 county-years. Multinomial logistic regression is used to estimate the probability that a county experiences higher rates of overdose fatalities.

Results: A 1% increase in the benzodiazepine proportion of claims is associated with 1.2 odds of high, versus low, overdose ($P < .1$) and 1.4 odds of very high overdose ($P < .05$). Moreover, there was a substantial interaction between opioids and benzodiazepines ($P < .001$). A county with 6% benzodiazepine prescriptions and 12% opioid prescriptions has a .58 predicted probability of very high overdose, significantly higher ($P < .001$) than the .33 probability for a county with 12% opioid prescriptions but 3% benzodiazepine prescriptions.

Conclusion: These findings shed light on the polydrug epidemiology of the overdose epidemic. Overdose deaths are highest where elevated opioid and benzodiazepine claims coexist. Overdose levels may reflect polydrug use and misuse, requiring clinical and policy responses beyond reducing opioid prescriptions.

KEYWORDS

benzodiazepine, ecological, Medicare Part D, overdose, pharmacoepidemiology

1 | INTRODUCTION

By 2011, overdose deaths in the United States reached crisis levels and have since climbed still further.[1-3] Rising drug overdose deaths drive the finding that all-cause mortality rates rose among non-Hispanic middle-aged whites since the late 1990s.[4] The most common classes[5] of drugs in overdose death certificates are opiates (6 of the 10 most common drugs named in death certificates) followed by benzodiazepines (2 of 10). Moreover, most overdose events are polysubstance, frequently including opioids alongside benzodiazepines.[6,7] Benzodiazepines may be implicated in as many as 30% of deaths involving prescription opiates, while 77.2% of death

certificates mentioning benzodiazepines also mention prescription opiates.[8] Concurrent benzodiazepine and opioid prescriptions, which have become increasingly common,[9] are associated with early opioid refills[10,11] and dose-dependent increases in overdose risk.[12] Concurrent users of benzodiazepines and opioids were twice as likely to overdose compared with sole users of opioids.[13] From 2003 to 2012, benzodiazepines constituted the largest increase among psychotropic medications prescribed to older adults in primary care settings.[14]

This paper examines the individual and synergistic impacts of opioid and benzodiazepine prescriptions on county-level overdose mortality using a compilation of publicly available data, chiefly the Public Use Files for Medicare Part D. Medicare Part D, which came

into effect in January 2006, led to a substantial decline in drug costs and an uptake in prescription drug claims among elderly Americans.[15] By 2013, 35.7 million Americans used Medicare Part D, comprising about 70% of all Medicare beneficiaries.[16] Existing literature has demonstrated a link between Medicare Part D prescriptions for opiates on state admissions to substance use treatment facilities and overdose mortality among the population at large[17] and has revealed state variation and trends in opioid prescribing and drug poisonings.[18,19] This study elaborates on the existing literature in 2 ways. First, it uses novel, county-level measures of prescription rates, providing a more granular analysis than the existing state-level studies. Analyses at this level could help inform public health efforts by county governments, which have become important actors in addressing the overdose epidemic.[20] Second, this study analyzes the potentially synergistic effects of benzodiazepine and opiate prescriptions. While clinical studies emphasize the multifactorial and frequently polydrug nature of overdose deaths, epidemiological studies have not taken heed of this result, typically examining the effect of prescription opiates in isolation.[17,21-24]

2 | METHODS

2.1 | Data

This study links county-level variables from the Center for Disease Control and Prevention, Center for Medicare Services, and US Census to analyze how variation in overdose rates changes with prescribing rates of opioids and benzodiazepines. Data sources were matched together according to the US Census's 5-digit Federal Information Processing Specification codes that uniquely identifies counties and year. Physician-level data were matched together using Medicare's national provider information and joined with county-data through the provider's address.

2.2 | Outcome

The outcome of interest is operationalized as annual, county-level age-adjusted death rates per 100 000 people, estimated by 2-stage empirical Bayes smoothing methods, and publicly available from the National Center for Health Statistics.[25] Drug overdoses were defined by ICD-10 underlying cause-of-death codes for fatal poisonings that were intentional (X60-X64), unintentional (X40-X44), of unknown intent (Y10-Y14), and homicides (X85). The chief advantage of this measurement is its comprehensiveness. While overdoses are alarmingly common in the United States, annual overdoses fatalities in less populous counties often fall below privacy suppression limits in other databases, such as CDC Wonder. The smoothing process in the measurement used also stabilizes rates in small counties. The resulting measure is an ordinal 16-point scale, where 1 represents a range of overdose from 0 to 2 deaths per 100 000 and 16 represents more than 30 deaths per 100 000. For ease of interpretation, the upper end of the binned estimate provided by the NCHS is used to create plots and tables with interpretable values—for example, the descriptive statistics shown in Table 1 and the plotted analyses in Figure 1 use an overdose scale ranging from 2 to 32 deaths per 100 000.

KEY POINTS

- Although polydrug incidents comprise a substantial proportion of overdose deaths, scholarly and popular focus has centered on prescription opiates.

- This study examines the role of benzodiazepine and opioid prescriptions on overdose—both individually and synergistically—using data from Medicare Part D from 2013 to 2015.

- Prescribing data, geolocated to counties, indicate that the proportion of claims for opioids and benzodiazepines varies widely across the United States.

- Overdose deaths are highest where elevated opioid and benzodiazepine claims coexist.

- Overdose levels may reflect polydrug use and misuse, requiring clinical and policy responses beyond reducing opioid prescriptions.

For regression analyses, the dependent variable is an overdose metric subdivided into a 4-point scale: "Low Overdose" (less than 10 overdose deaths per 100 000), "Medium Overdose" (10-14 deaths per 100 000), "High Overdose" (14-20 deaths per 100 000), and "Very High Overdose" (more than 20 deaths per 100 000). This scale was chosen so that each bin comprises about one quarter of the data, as shown in Table 1. In practice, the substantive findings reported are not sensitive to the scale of the dependent variable.

2.3 | Primary independent variables

The investigative variables are the percent of Medicare Part D claims for opiates and benzodiazepines in each county. Publicly available Medicare Part D claims for the years 2013, 2014, and 2015 were downloaded as text files from the Center for Medicaid Services, and suppressed values for claims between 1 and 10 were imputed to 5, as suggested in the technical file.[26] These data comprise approximately 3.5 billion drug claims over the 3-year period. To identify opiates among drug claims, generic drug names were string matched to Medicare's "Drug Category Lists." For benzodiazepines, generic drug names were matched to the "Benzodiazepine Equivalence Table" of the Ashton Manual, a clinical guide for benzodiazepine withdrawal.[27] Claims data were aggregated to the physician level and linked with Medicare Part D's Prescribers Table according to each prescriber's unique National Prescribers ID (national provider information) to obtain addresses. These data manipulations were performed in Python 2.7 using the *Pandas* library. Next, using ArcGIS ESRI's Geocoder, a database of addresses in the United States, the addresses of each of the approximately 2.5 million physician-years in the combined datasets were geolocated to retrieve latitude-longitude coordinates; for 2 418 188 addresses (96.3% of cases), the addresses were successfully matched to coordinates. These data were spatially joined with the US Census County Boundaries file and aggregated to the county level

TABLE 1 A, Descriptive statistics. B, Descriptive Statistics by level of Overdose

A

	Mean	Std Dev	Min	Max	Overdose Correlation Coefficient
Overdose	15.56	6.53	2.00	32.0	...
Benzodiazepine	3.01	1.26	0.00	24.5	.3447***
Opioid, %	6.15	2.83	0.00	58.2	.2309***
Income	47.28	12.10	22.6	125.9	−.1742***
Poverty, %	16.77	6.42	3.00	48.3	.1822***
Hispanic, %	8.93	13.35	0.42	96.1	−.0322**
Black, %	9.37	14.58	0.00	86.0	−.1505***
Rural	−0.00	1.38	−1.89	2.49	−.0229*
Less high school	14.59	6.57	1.59	53.72	.1498***
Year	14.00	0.82	13.00	15.00	.1303***
Observations	9106				

B

|	Low overdose				Moderate overdose				High overdose				Very high overdose			
	Mean	Std. dev.	Min	Max	Mean	Std. dev.	Min	Max	Mean	Std. dev.	Min	Max	Mean	Std. dev.	Min	Max
Overdose	8.32	1.94	2.00	10.00	13.00	1.00	12.00	14.00	17.69	1.62	16.00	20.00	26.10	3.71	22.00	32.00
Benzodiazepine, %	2.42	1.12	0.00	15.15	2.93	1.11	0.00	17.60	3.20	1.20	0.00	24.51	3.66	1.35	0.00	16.34
Opioid, %	5.31	3.01	0.00	54.36	5.91	2.14	0.00	53.38	6.46	2.82	0.00	57.14	7.20	3.00	0.00	58.18
Income	49.83	12.80	22.60	122.6	47.63	11.91	23.01	125.9	46.85	11.79	26.10	125.6	43.85	10.90	23.34	99.87
Poverty, %	15.45	7.20	3.40	48.30	16.63	6.16	3.70	45.00	16.90	5.77	3.00	47.40	18.63	6.06	4.50	47.40
Hispanic, %	9.64	15.74	0.50	96.13	9.42	13.57	0.45	94.33	8.21	11.02	0.49	93.46	8.30	12.46	0.42	79.62
Black, %	11.12	18.62	0.00	86.01	11.74	15.16	0.06	78.29	8.37	12.08	0.04	78.33	5.11	8.27	0.00	70.32
Rural	0.17	1.39	−1.89	2.49	−0.12	1.32	−1.89	2.49	−0.12	1.36	−1.89	2.49	0.08	1.42	−1.89	2.49
Less high school, %	13.63	7.52	2.12	53.72	14.43	6.44	2.32	46.72	14.57	5.91	1.59	40.20	16.19	5.92	1.89	40.20
Year	13.87	0.81	13.00	15.00	13.97	0.81	13.00	15.00	14.04	0.81	13.00	15.00	14.17	0.80	13.00	15.00
Observations	2409				2420				2548				1729			

*P < .05.
**P < .01.
***P < .001.
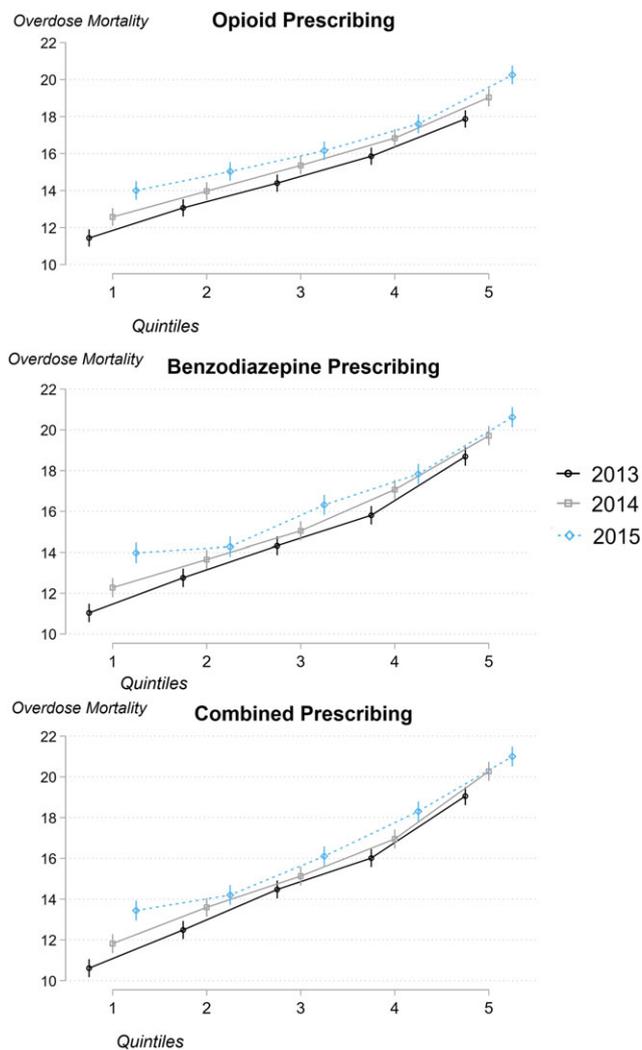
FIGURE 1 Crude association between prescription drug rates and overdose. This figure depicts crude county-level association between annual prescription rate quantiles and average overdose fatalities per 100 000 with 95% confidence intervals calculated using regression. The first panel shows quintiles of opioid claims, the second quintiles of benzodiazepine claims, and the third quintiles of a standardized combination of opioid and benzodiazepine claims. Each graph shows a monotonic increase between quantiles of prescribing and overdose mortality [Colour figure can be viewed at wileyonlinelibrary.com]

using the *SP* and *dplyr* packages in the R programming language. Finally, the total number of benzodiazepine and opioid claims each year were divided by the total number of Medicare Part D claims in the county and multiplied by 100 to generate the percent of total claims comprising opioids or benzodiazepines. Opioids (mean 6.15%) comprised about twice the rate of county-level prescriptions as benzodiazepines (mean 3.01%). Principal component analysis was used to generate an equally weighted, combined measure of prescribing for these drugs for illustrative purposes, used in Figures 1 and 2.

2.4 | Demographic and socioeconomic covariates

To improve the precision of estimates and reduce the likelihood of omitted variable confounding, county-level estimates for income, poverty, education, race, and urbanicity were collected. Income and poverty data originate from the Small Area Income and Poverty

Estimates from the US Census. Race and Hispanic data are from the US Census's Population Estimation Program. Data on educational attainment are from the US Department of Agriculture's Economic Research Service. Finally, principal component analysis was used to construct a continuous urban-rural index from the Census's Rural-Urban County Continuum (a 9-point scale) and its Urban Influence Index (an 11-point scale).

2.5 | Study population

There are 9119 county-years with at least 1 Medicare Part D drug claim, according to the results of the geolocation of prescriber data. A further 12 county-years were absent from the NCHS overdose data (all 12 were county equivalents in Alaska), and 1 county-year had missing demographic data. This left 9106 county-years in the analytic data set.

2.6 | Statistical analyses

The analyses proceed in 3 stages. First, crude associations between overdose mortality and (1) benzodiazepine prescriptions, (2) opioid prescriptions, and (3) a standardized combination of the 2 are plotted during 2013 to 2015. Second, these relationships are visualized using choropleth maps to reveal geographic variation in prescribing rates and spatial overlap between prescribing and overdose. Finally, multinomial logistic regression is used to estimate the average probability of low, medium, high, or very high overdose mortality rate as a function of opiate and benzodiazepine prescribing rates, controlling for a host of socioeconomic and demographic variables. The analyses shown present relative risk ratios of medium, high, or very high overdose, relative to the referent category of lower overdose.

Regression analyses were performed using Stata 13 with standard errors clustered by county to adjust for correlated residuals.

3 | RESULTS

3.1 | Crude associations and mapping

Table 1 displays descriptive statistics for study variables in the aggregate and by level of the outcome variable. Crude, county-level association between annual prescription rate quintiles and average overdose fatalities per 100 000 with 95% confidence intervals were estimated and plotted (Figure 1). The first panel shows quintiles of opioid prescriptions alone, the second for benzodiazepine alone, and the third for a combination of the two. Each plot suggests a significant, monotonic increase between prescription rates and overdose mortality in all years, as well as a rise in average overdose mortality across the 3 years. Additionally, the combined prescribing lines run somewhat steeper than either the opioid or benzodiazepine alone, consistent with a synergistic effect. This is reflected by the improved fit of the combined model, compared with the models containing solely opioids or benzodiazepines. The Bayesian information criterion statistic for the combined model is smaller, indicating better fit, for all 3 years (see Table S1); for example, in 2013, the Bayesian information criterion is 19 028.24 for the combined model, compared with 19 182.04 for the benzodiazepine-only model and 19 358.92 for the opioid-only model.
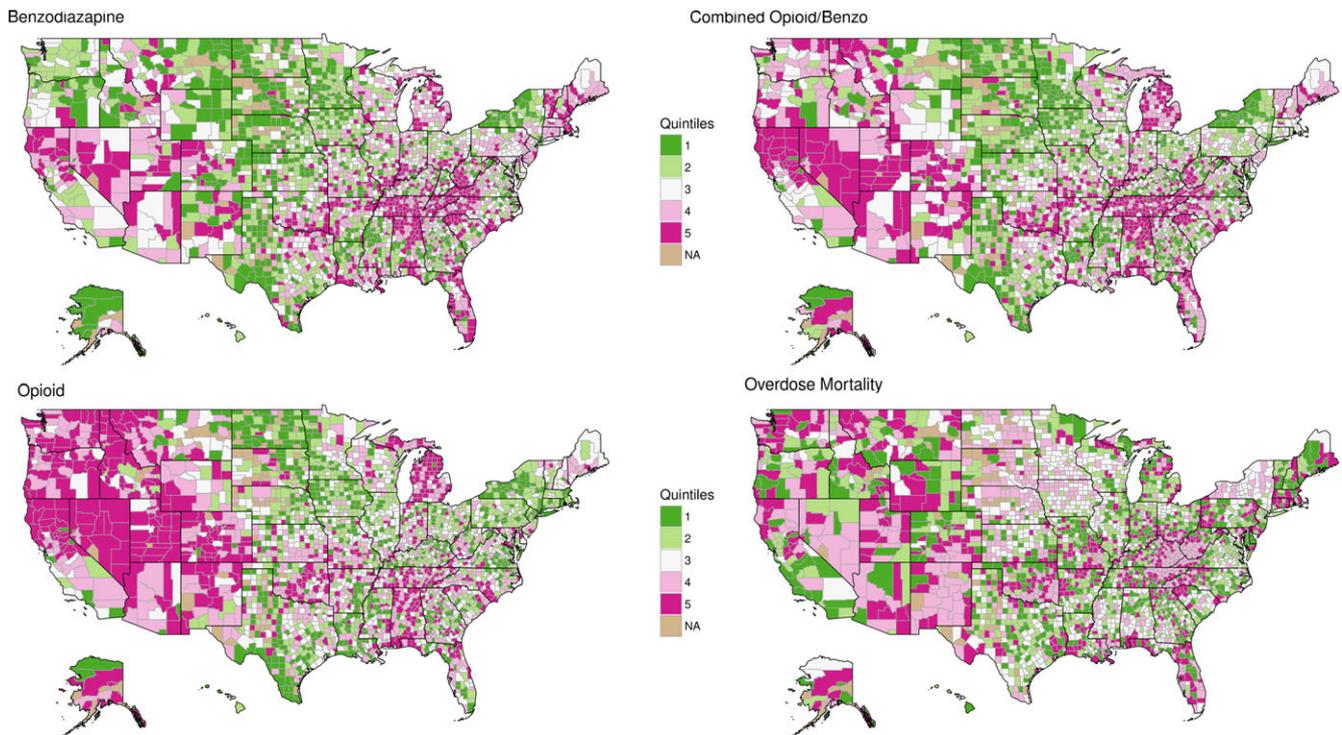
FIGURE 2 Choropleth depiction of prescription drug rates and overdose, 2015. This figure depicts crude county-level association between annual prescription rate quintiles for benzodiazepines alone (top left), opioids alone (bottom left), a standardized combination of the two (top right), and overdose deaths. The scale runs from green (low prescription rates and low overdose) to dark pink (high prescription rates and high overdose). The maps show substantial spatial correlation between opioid prescriptions, benzodiazepine prescriptions, and overdose death. However, they also show that there are counties with relatively high levels of opioid prescriptions alongside relatively low levels of benzodiazepine prescriptions, and vice versa [Colour figure can be viewed at wileyonlinelibrary.com]

Moreover, the places with high levels of prescriptions for both these classes of drugs appear to overlap with the regions with severe overdose mortality. Figure 2 shows crude county-level association between annual prescription rate quintiles for benzodiazepines alone (top left), opioids alone (bottom left), a standardized combination of the two (top right), and overdose deaths. The scale runs from green (low prescription rates and high overdose) to dark pink (high prescription rates and high overdose). The maps show substantial spatial correlation between opioid prescriptions and benzodiazepine prescriptions (Spearman $\rho = .3892$; $P < .001$) and between prescribing for these drugs and overdose (combined drugs and overdose: Spearman $\rho = .4091$; $P < .001$). This is illustrated by swathes of dark pink regions across the southwest United States and Appalachia for each map. However, the maps also show counties where prescribing rates for benzodiazepines and opioids diverge. For example, Washington State combines relatively high levels of opioid prescriptions with relatively low levels of benzodiazepine prescriptions, while southern Florida has high benzodiazepine prescribing rates and relatively few opioid claims.

3.2 | Multinomial regression

Table 2 displays the model parameters of a multinomial regression model including prescriptions data and socioeconomic and demographic controls. Prescriptions for both benzodiazepines and opioids, alone and especially in combination, are associated with higher levels of overdose. Compared with low overdose, a 1% increase in in the percent of Part D prescriptions that are benzodiazepines is associated

with 1.145 odds of medium overdose (not statistically different from 1), 1.2 ($P < .1$) odds of high overdose, and 1.4 ($P < .05$) odds of very high overdose. For opioids, a 1% increase is associated with negligible increased odds of medium overdose, 1.08 ($P < .1$) odds of high overdose, and 1.12 ($P < .01$) odds of very high overdose. Moreover, the interaction term between benzodiazepine and opioids suggests that a 1% increase in the proportion of Part D prescriptions that are benzodiazepines multiplied by opioids is associated with an additional 1.04 ($P < .05$) odds of medium, 1.06 ($P < .01$) odds of high, and 1.08 ($P < .01$) odds of very high overdose, compared with low overdose.

An alternative interpretation of these results is the average changes in the probability of each level of overdose. As Table S2 shows, on average, a 1% increase in the percent of Medicare prescriptions that are benzodiazepines is associated with −.08 decreased probability of low overdose, a .03 increased probability of high overdose, and a .05 increased probability of very high overdose ($P < .001$ for all). A 1-unit increase in the percentage of prescriptions that are opioids is associated with a −.03 decrease in probability of low overdose, a .016 increase in high overdose, and a .02 increase in very high overdose ($P < .001$ for all).

3.3 | Predicted probabilities

To improve the interpretability of these results, the parameters in Table 2 were used to generate average predicted probabilities for each county overdose level at varying levels of benzodiazepine and opioid prescription rates, holding other variables at their observed values.[28]

TABLE 2 Adjusted odds ratios from multinomial regression model[a]

	Med vs Low	High vs Low	V High vs Low
Benzodiazepine, %	1.145 (0.104)	1.208[*] (0.130)	1.356[**] (0.176)
Opioid %	1.015 (0.036)	1.078[*] (0.042)	1.124[***] (0.047)
Benzod, %, * opioid, %	1.044[**] (0.019)	1.061[***] (0.022)	1.077[***] (0.026)
Income	0.991[*] (0.005)	0.999 (0.006)	1.001 (0.007)
Poverty, %	1.024[*] (0.013)	1.065[***] (0.015)	1.128[***] (0.017)
Hispanic, %	0.989[***] (0.004)	0.969[***] (0.005)	0.960[***] (0.006)
Black, %	0.986[***] (0.004)	0.955[***] (0.004)	0.908[***] (0.007)
Rural	0.846[***] (0.030)	0.785[***] (0.032)	0.763[***] (0.037)
Less than high school, %	1.035[***] (0.012)	1.075[***] (0.014)	1.119[***] (0.017)
Year	1.229[***] (0.035)	1.446[***] (0.036)	1.891[***] (0.057)
N	9106		
Pseudo-R^2	0.117		

[a]Adjusted odds ratios; cluster robust standard errors in parentheses.

[*]$P < .10$.

[**]$P < .05$.

[***]$P < .01$.

These estimates are displayed in Figure 3, where each graph is an overdose level, the x-axis represents opioid percent, the y-axis represents predicted probability, and each line type represents a different benzodiazepine percent. The probability that a county falls in the low-overdose category decreases monotonically as rates of opioid and benzodiazepine claims increase. Conversely, the probability of very high overdose increases monotonically with prescribing rates for these drugs. Moreover, reflecting the significant interaction between opioids and benzodiazepines in Table 2, higher levels of benzodiazepines are associated with a sharper increase in the probability of high and very high overdose as well as a sharper decrease in medium and low overdose. A county with 6% benzodiazepine prescriptions and 12% opioid prescriptions has a .58 predicted probability of very high overdose, significantly higher ($P < .001$) than the .33 probability of very high overdose for a county with the same level of opioid prescriptions but just 3% benzodiazepine prescriptions (comparing the pink dashed line in the bottom graph with the blue dotted line).

3.4 | Robustness tests

Robustness tests not shown here confirm that these results are substantively unchanged through other model specifications, such as ordinary least-squares regression, nonparametric regression, ordinal logistic regression, or mixed effects hierarchical modeling; restricting analysis to only rural or urban counties; including state-dummies; and alternative operationalization of the independent variables (eg, quantiles) and dependent variable (eg, original 16-point scale for overdose deaths). They are not sensitive to particular years.

4 | DISCUSSION

These findings indicate a substantial, monotonic relationship between prescription rates of benzodiazepines and opiates and risk of overdose fatality—both individually and synergistically. This ecological finding of combined risk reflects what is known about the individual risks of opioid and benzodiazepine use. Benzodiazepines potentiate the respiratory effects of opioids[29] and are associated with aberrant drug-taking behaviors.[11] Elderly patients are at heightened risk of adverse incidence of overdose and other injuries (such as fractures and falls) from both opioids and benzodiazepines.[30-32] Substantial non-medical use of prescription drugs, especially opioids and sedatives, has been documented among elderly Americans, most worryingly with suicidal intent.[33,34]

While these results pile on to the substantial clinical literature documenting the harmful interaction between these classes of drugs, they also reveal an ecological risk to high levels of benzodiazepine prescriptions, especially alongside elevated rates of opioid prescriptions, that has not yet been documented in the literature. This has important policy implications in part because the average county-level proportion of Medicare Part D prescriptions for benzodiazepines has risen since 2013 (Δ15-13 = 0.258%, $P < .001$), unlike prescriptions for opioids, which declined somewhat between 2013 and 2015 (Δ15–13 = −0.396%, $P < .001$). Moreover, these findings contribute to scholarship of skyrocketing overdose mortality by shedding light on its polydrug epidemiology. While opioid prescribing on the margins is associated with overdose fatalities, overdose deaths are highest where there are both high opioid and benzodiazepine prescription rates, suggesting an ecological potentiation of overdose risk.

5 | LIMITATIONS

5.1 | Measurement error

An important source of measurement error is that some patients likely received prescriptions from doctors located in other counties than their county of residence. About 4% of addresses did not match during
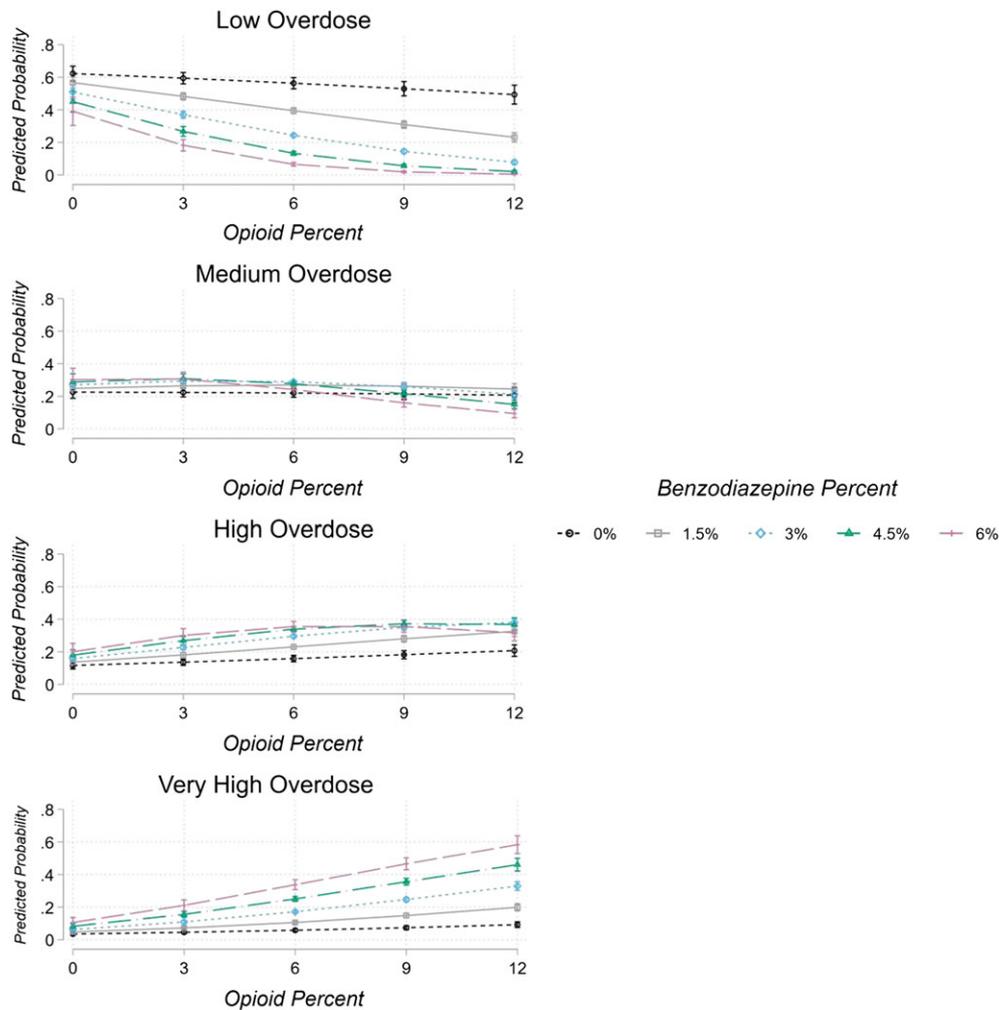
FIGURE 3 Predicted probabilities by opioid and benzodiazepine prescriptions. This figure depicts predicted probabilities for a county falling in each overdose label as a function of opioid and benzodiazepine prescriptions, holding other variables at their actual values. These predicted probabilities are calculated using the model parameters shown in Table 2 [Colour figure can be viewed at wileyonlinelibrary.com]

the geolocation process and were omitted, as were a small portion of counties. Furthermore, the absence of drug dosage information in the Medicare prescribing data is an additional limitation. However, these errors would tend to bias towards a null result, so they may have contributed to an understating the true effect sizes.

5.2 | Ecological limitations

As this paper exploited ecologic variation in county-level prescriptions and overdose rates, the usual reservations about causal inference apply. It is possible that an unobserved, omitted variable explains both high prescriptions of these drugs and high overdose rates along a different causal pathway or in addition to the causal pathway explicated. For example, some underlying geographic susceptibility to drug use not captured by conventional socioeconomic and demographic variables may explain both high prescribing rates for psychotropic drugs and high rates of overdose. However, given the magnitude of the observed relationships, and strong theoretical reasons to believe prescriptions for these drugs play a role in overdose deaths, it seems implausible that unexplained heterogeneity accounted for the all the effect.

6 | CONCLUSION AND IMPLICATIONS

Medicare Part D is an enormous and influential prescription drug program. How Medicare Part D reimburses drugs is a policy choice; indeed, prior to 2013, it did not reimburse benzodiazepines at all—which was demonstrated to affect prescribing patterns for sedatives.[35,36] Decreasing the prescription rates of both benzodiazepines and opiates, especially concurrent prescriptions, may be an important component of reducing overdose deaths.[37] Policymakers, including county governments, could use these results for surveillance purposes, to determine whether local prescribing rates for high-risk drugs exceed peer counties. But any response that does not account for the pain and anxiety that lead to drug taking, medically and otherwise, is incomplete.[38] If overdose deaths are symptomatic of a broader syndrome of midlife distress among certain populations,[4,39] then restricting the supply of psychotropic pharmaceuticals could be offset by substitution with illicit drugs.[40] Thus, policymakers and clinicians should not only identify measures to reduce diversion and overprescribing of these drugs but also foster alternative means of coping—both through nonpharmacological modalities and potentially less harmful drugs.[41] Future clinical and biomedical research could explore variation in harm

within these classes of drugs to inform both clinicians and policymakers about better prescribing practices and identify alternative psychotropic and nonpsychotropic therapies to placate panic and pain.

ETHICS STATEMENT

The author states that no ethical approval was needed.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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