ARTICLE

Opioid Prescribing and Suicide Risk in the United States

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Objective: This study estimates associations of regional change in opioid prescribing with total suicide deaths and suicide overdose deaths involving opioids.

Methods: A panel analysis was performed with 2009–2017 U.S. national IQVIA Longitudinal Prescription Database data and National Center for Health Statistics mortality data aggregated into commuting zones (N=886), which together span the United States. Opioid prescription exposures included opioid prescriptions per capita and percentages of patients with any opioid prescription, with high-dose prescriptions (>120 mg of morphine equivalents), with long-term prescriptions (≥60 consecutive days), and with prescriptions from three or more prescribers. Linear regression models were used with year and commuting zone fixed effects.

Results: Suicide deaths were significantly positively associated with opioid prescriptions per capita (β=0.045), having any opioid prescription (β=0.069), having high-dose prescriptions (β=0.024), having long-term prescriptions (β=0.028), and having three or more opioid prescribers (β=0.046). Similar significant associations were observed between each of the five opioid prescription measures and suicide overdose deaths involving opioids (β range, 0.029–0.042). However, opioid prescriptions per capita, having any opioid prescription, and having three or more opioid prescribers were each negatively associated with unintentional opioid-related deaths in people in the 10- to 24-year and 25- to 44-year age groups.

Conclusions: In this retrospective study of U.S. commuting zone–level opioid prescriptions and mortality, regional decreases in opioid prescriptions were consistently associated with declines in total suicide deaths, including suicide overdose deaths involving opioids. For some opioid prescribing measures, negative associations were observed with unintentional overdose deaths involving opioids among younger people. Individual-level inferences are limited by the ecological nature of the analysis.

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Reducing access to highly lethal suicide methods has been associated with substantial declines in suicide deaths (1). Because of their respiratory depression effects and narrow therapeutic window, opioids pose a greater risk than any other drug class of an intentional overdose proving to be lethal (2), and approximately 40% of overdose suicide deaths in the United States involve opioids (3). However, the relationship between opioid prescribing and suicide risk is complex. When people have their opioids tapered, they can become desperate if their pain becomes uncontrolled (4) or if they experience serious withdrawal symptoms (5), no matter why they received opioids. Long-term opioid exposure can also promote depression, which in turn increases the risk of suicide by any method. Given these complexities, uncertainty surrounds the connection between opioid prescribing and suicide risk, including opioid and non-opioid suicide deaths.

It is not known whether certain opioid prescribing patterns, such as high-dose or long-term prescriptions or having multiple opioid prescribers, are associated with particularly elevated suicide risk. A case-control study of veterans with chronic non-cancer pain found that opioid prescriptions had a significant dose-dependent relationship with risk of suicide, including suicide by overdose (6). However, a population-based cohort study of adults in Denmark, which may have been inadequately powered, did not reveal a significant association between long-term use of prescription opioids and risk of suicide (7).

Alongside concerns that some opioid prescribing patterns may directly contribute to suicide risk in susceptible individuals, there are competing concerns that tapering or discontinuing opioids in adults with chronic pain could increase their risk of suicidal behavior (2). In a cohort study of patients with stable high-dose opioid prescriptions, tapering was associated with an increased risk of medically treated suicide attempts (8). A second cohort study found that stopping opioid therapy for chronic pain, especially after longer periods of opioid therapy, was significantly associated with a

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composite measure that included death by suicide or any overdose (9). Symptoms of depression may also emerge or worsen during tapering of long-term opioid therapy (10). In the previously mentioned study of veterans, however, the suicide rate among patients who discontinued prescribed opioids was similar to the rate among patients who received low-dose opioids and was lower than that among patients who received high-dose opioids. These findings are not consistent with the hypothesis that opioid discontinuation contributes to suicide risk (2).

In efforts to reduce opioid overdose deaths in the United States, several policies have been implemented to restrain prescription of opioids (11–13), and they have coincided with a decline in opioid prescribing (14). Several (15–17) but not all (18) population-level studies have reported that lower opioid prescribing is correlated with lower overdose deaths involving prescription opioids. This research has generally focused on unintentional overdoses. One study from Ontario, Canada, however, reported that the regional rate of opioid prescriptions was not significantly related to concurrent opioid-related suicide deaths for men and was only weakly associated for women (14). Because regions vary in several factors that could contribute to suicide risk, the extent to which local opioid prescribing policies contribute to population-level suicide risk remains unclear.

Given uncertainties surrounding opioid prescribing and suicide risk, we evaluated changes in regional opioid prescribing in relation to changes in overall suicide deaths, including suicide deaths involving opioids. We also examined opioid prescribing in relation to unintentional and undetermined opioid-related overdose deaths. We used fixed-effects models in which geographic regions served as their own controls to evaluate regional changes in total suicide deaths and suicide deaths involving opioids in relation to changes in several measures of opioid prescribing. A greater understanding of these associations might help inform opioid prescription surveillance and clinical practice.

METHODS

Sources of Data

Data were derived from four sources. For opioid-related death data, the National Center for Health Statistics 2009–2017 Multiple Cause of Death Research Files (All Counties) were used (19). These files, which contain individual-level information on decedents in the United States, include cause of death, age, sex, and county of occurrence.

For opioid prescription data, we used the IQVIA Longitudinal Prescription Database (LRx) from January 2009 to December 2017, excluding buprenorphine formulations approved for the treatment of opioid addiction. The IQVIA LRx is a longitudinal database of prescriptions from retail and nonretail pharmacies for individuals followed across years, pharmacies, and payment sources. The estimated proportion of the U.S. population covered in the data set increased from 76.5% in 2009 to 92.0% in 2017.

For geographic aggregation, we used states and commuting zones as defined by the U.S. Department of Agriculture (USDA) (20). Commuting zones, which are based on journey-to-work data, are county clusters with strong commuting ties. Because counties were too small for trend analyses of opioid-related deaths, commuting zones (hereafter "regions") were selected as the geographic level of population aggregation (N=886). U.S. Census Bureau data were used to derive population-based rates of the opioid prescribing and opioid-related mortality measures at the regional level (21).

Opioid Prescribing Measures

Five opioid prescription measures were calculated for each study year and region. The first metric, which is used by the Centers for Disease Control and Prevention to communicate national opioid prescribing trends (22), was the number of filled opioid prescriptions per capita. Because the volume of opioid prescribing is unevenly distributed among patients (23), we also included annual percentage of patients with at least one prescription. In order to evaluate whether quality-of-care metrics (24) track more closely with overdose mortality, we also considered percentage with at least one prescription with a daily dose >120 mg of morphine equivalents (high-dose opioid prescriptions), which has been associated with an increased risk of overdose death (25). Because length of opioid prescribing is strongly associated with persistent opioid use (26), we included a measure of percentage with opioid prescriptions for ≥60 consecutive days (long-term opioid prescriptions). Finally, because of an association between having multiple opioid prescribers and opioid overdose risk (27), we defined a multiple prescriber measure as percentage with three or more opioid prescribers during a year.

Mortality Measures

Total suicide deaths was identified in the mortality data using ICD-10-CM codes X60–X84, Y87.0, and U03. Drug overdose deaths involving opioids were identified among suicide (X60–X64), unintentional (X40–X44), or undetermined (Y10–Y14) overdose deaths that also included opioid-related codes (T40.0–T40.4, T40.6).

Statistical Analysis

We first generated maps of opioid-related unintentional and suicide deaths for 2009 and 2017 by applying 2009 distributions and creating quintiles for regional rates of total suicide deaths, opioid-related suicide deaths, and opioid-related unintentional deaths per 100,000 persons. Regions were defined using states and USDA Economic Research Service (20) commuting zone areas. Similar procedures were followed for regional opioid prescriptions per capita, percentage with any opioid prescriptions, and percentage with high-dose opioid prescriptions. We then calculated mean population-weighted regional rates per 100 persons in 2009 and 2017 of the five opioid prescribing measures for the total sample, four age groups (10–24, 25–44, 45–64, and ≥65 years), and males and females. Similar procedures were

followed to calculate, on an annual per-100,000-person basis, mean regional suicide deaths, opioid-related overdose suicide deaths, opioid-related unintentional deaths, and opioid-related undetermined deaths. We then used data from all years (2009–2017) to calculate linear regression estimates using z-scored values of prescribing and mortality variables so that coefficients (β) represented the effect of a one-standard-deviation change in the prescribing variable on standard deviation units of mortality. The coefficients represent relative changes within regions. For example, if regions with larger than average decreases in opioid prescribing also tended to have smaller than average increases (or larger than average decreases) in suicide rates, the resulting correlation coefficient would be positive, whereas if the same regions tended to have the smaller than average increases (or smaller than average decreases) in suicide rates, the coefficient would be negative. Z-scores were calculated using means and standard deviations specific to each group by age and sex in separate models. These values were pooled in analyses of the whole population. In all models, year and state/commuting zone fixed effects were included so that estimates reflect temporal changes in prescribing within commuting zones. In pooled models, controls for sex and age group were also included. The model can be expressed as

$$M^z_{astg} = \alpha_a + \gamma_s + \delta_t + \eta_g + \beta P^z_{astg} + \epsilon_{astg},$$

where M^z is the z-scored mortality rate in age group a, sex s, year t, and commuting zone g; P^z is the z-scored prescribing variable, and α, γ, δ, and η are, respectively, the age, sex, year, and commuting-zone fixed effects. In a post hoc analysis, we modeled the estimated percentage change in total suicide deaths and opioid-involved suicide deaths that would have occurred had there been no change in opioid prescribing between 2009 and 2017. We also evaluated whether the strength of associations between the prescribing metrics and regional suicide rates varied across the four U.S. Census Regions. Confidence intervals were corrected to account for heteroskedasticity caused by correlation of error terms across observations from the same region (28). Analyses were weighted by population in the state/commuting zone areas. To protect from type I error, a Bonferroni correction for an alpha of 0.05 was applied to each block of seven age and sex linear regression analyses ($p<0.0071$). The analyses were performed in Stata, version 17.0.

All data were de-identified and exempted from consent by the Institutional Review Board of New York State Psychiatric Institute.

RESULTS

Trends in Opioid Prescribing

Each of the five opioid prescribing measures declined during the 2009–2017 period. Regional opioid prescriptions per 100 persons declined from 70.19 to 61.63; percentage with at least one opioid prescription, from 26.40 to 20.27; percentage filling high-dose prescriptions, from 2.01 to 1.60; percentage filling long-term prescriptions, from 1.24 to 0.96; and percentage filling prescriptions from three or more prescribers, from 3.18 to 2.26 (see Tables S1 and S2 and Figures S1–S3 in the online supplement).

Suicide Deaths

Between 2009 and 2017, the regional rate of total suicide deaths increased from 13.80 to 16.36 per 100,000 persons (difference=2.56, 95% CI=2.05, 3.07) (see Tables S1 and S2 in the online supplement). Change in total regional suicide deaths was positively associated with change in all five opioid-prescribing measures (Table 1; see also Figure S4 in the online supplement). If there had been no decrease between 2009 and 2017 in opioid prescriptions per capita, we estimate that, ceteris paribus, there would have been 3.0% more suicide deaths in 2017. In addition, there would have been an estimated 8.2%, 1.5%, 0.5%, and 4.8% more suicide deaths in 2017, respectively, had there been no decrease in the percentage with at least one opioid prescription, high-dose prescriptions, long-term prescriptions, and three or more opioid prescribers.

For opioid prescriptions per capita, the association with change in suicide deaths was significantly stronger in the West than in the East or the Midwest. For percentage with at least one opioid prescription and with three or more opioid prescribers, the associations were stronger in the West than elsewhere and stronger in the South than in the Midwest or the East (see Table S3 in the online supplement).

For males and females, change in regional suicide deaths was also positively associated with change in each opioid-prescribing measure. For the two youngest and the oldest age groups, however, change in regional suicide deaths was not significantly related to change in any of the prescribing measures. Among individuals in the 45- to 64-year age group, change in regional suicide deaths was positively associated with change in regional opioid prescriptions per capita (β=0.054, p=0.0001) and change in percentage with at least one opioid prescription (β=0.061, p=0.0004).

Suicide Deaths Involving Opioids

During the study period, the annual regional rate did not significantly change for suicide deaths involving opioids (from 0.64 to 0.66 per 100,000 persons; difference=0.02, 95% CI=−0.04, 0.08) (see Tables S1 and S2 in the online supplement). Similar to the associations with total suicide deaths, change in regional suicide deaths involving opioids was significantly related to change in each opioid-prescribing measure in the total population and separately among males and females (Table 1; see also Figure S5 in the online supplement). If opioid prescribing per capita had held constant from 2009 to 2017, there would have been an estimated 10.5% more suicide deaths involving opioids in 2017. The corresponding estimated percentage increases in opioid-related suicide deaths were 14.7%, 8.6%, 8.6%, and 18.8%, respectively, for percentage with at least one opioid prescription, high-dose prescriptions, long-term

TABLE 1. Associations of regional change in prescription opioid use measures with all suicide deaths and with suicide deaths involving opioids, by age group and sex[a]

	Opioid Prescriptions per Capita		Percentage With ≥1 Opioid Prescription		Percentage With High-Dose Prescriptions		Percentage With Long-Term Prescriptions		Percentage With ≥3 Prescribers	
Characteristic	β	p	β	p	β	p	β	p	β	p
All deaths by suicide										
Total	0.045	<0.0001	0.069	<0.0001	0.024	<0.0001	0.028	<0.0001	0.046	<0.0001
Male	0.066	<0.0001	0.089	<0.0001	0.031	0.0001	0.056	<0.0001	0.057	<0.0001
Female	0.050	<0.0001	0.057	<0.0001	0.037	<0.0001	0.05	<0.0001	0.053	<0.0001
Age group (years)										
10–24	−0.011	0.31	−0.0004	0.98	−0.003	0.36	−0.012	0.06	−0.017	0.06
25–44	−0.012	0.42	0.036	0.02	−0.003	0.77	−0.026	0.03	−0.016	0.15
45–64	0.054	0.001	0.061	0.0004	0.033	0.03	0.015	0.40	0.026	0.06
≥65	0.007	0.55	0.004	0.72	−0.002	0.86	−0.017	0.32	0.004	0.66
Deaths by suicide involving opioid overdose										
Total	0.040	<0.0001	0.039	<0.0001	0.029	<0.0001	0.033	<0.0001	0.042	<0.0001
Male	0.033	<0.0001	0.044	<0.0001	0.020	0.0007	0.022	0.006	0.032	<0.0001
Female	0.039	<0.0001	0.032	0.0006	0.033	<0.0001	0.035	<0.0001	0.047	<0.0001
Age group (years)										
10–24	0.010	0.46	0.013	0.46	0.016	0.007	0.015	0.08	−0.001	0.97
25–44	0.040	0.004	0.038	0.03	0.039	0.0002	0.032	0.01	0.027	0.05
45–64	0.047	0.01	0.036	0.06	0.048	0.005	0.051	0.002	0.028	0.10
≥65	0.002	0.86	0.006	0.66	0.008	0.50	0.015	0.33	0.006	0.62

[a] All deaths by suicide were defined with ICD-10-CM codes X60–X84, Y87.0, and U03 as the underlying cause of death. Deaths by suicide involving opioid overdose were defined with an ICD-10-CM code for intentional overdose (X60–X64) and a code for opioids (T40.0–T40.4, T40.6).

prescriptions, and three or more opioid prescribers. For each prescribing metric, the association with change in suicide deaths involving opioids was significantly stronger in the West than in the South or the Midwest. For percentage with at least one prescription and percentage with three or more prescribers, the associations were stronger in the West than in the East (see Table S3 in the online supplement).

For all except the oldest age group, change in regional suicide deaths involving opioids was significantly associated with change in percentage with high-dose opioid prescriptions. Among individuals in the 25- to 44-year age group, change in regional suicide deaths was also positively associated with change in opioid prescriptions per capita (β=0.040, p=0.004). In addition, among individuals in the 45- to 64-year age group, change in suicide deaths involving opioids was positively associated with change in long-term opioid prescriptions (β=0.051, p=0.002). For the oldest age group, change in suicide deaths involving opioids was not related to any of the opioid-prescribing measures.

Unintentional Deaths Involving Opioids

Over the study period, the annual regional rate of unintentional overdose deaths involving opioids increased from 6.56 to 15.62 per 100,000 persons (difference=9.05, 95% CI=8.18, 9.92) (see Tables S1 and S2 in the online supplement). Change in total unintentional deaths involving opioids was positively associated with change in opioid prescriptions per capita (β=0.074, p=0.007) and change in percentage with high-dose opioid prescriptions (β=0.050, p=0.007) (Table 2). However, neither of these correlations was significant in analyses stratified by sex. Among individuals in the 10- to 24-year and 25- to 44-year age groups, the change in unintentional deaths involving opioids was negatively associated with opioid prescriptions per capita, percentage with at least one opioid prescription, and percentage with three or more opioid prescribers. Among individuals age 65 and older, the change in regional unintentional deaths involving opioids was positively correlated with change in percentage with high-dose opioid prescriptions (β=0.086, p=0.0001).

Undetermined Deaths Involving Opioids

The annual regional rate of opioid overdose deaths of undetermined intent was little changed, from 0.73 in 2009 to 0.93 per 100,000 persons in 2017 (difference=0.20, 95% CI=−0.14, 0.54) (see Tables S1 and S2 in the online supplement). Change in total undetermined deaths involving opioids was significantly and positively associated with change in all of the prescribing measures except percentage with at least one opioid prescription (β=0.011, p=0.57) (Table 3). Among females, change in undetermined deaths involving opioids was positively correlated with change in opioid prescriptions per capita and percentage with long-term opioid prescriptions. For individuals age 65 and older, change in undetermined deaths involving opioids was also positively associated with change in opioid prescriptions per capita as well as with percentage with at least one opioid prescription and percentage with three or more opioid prescribers.

DISCUSSION

In the United States, geographic regions with the greatest declines in people filling opioid prescriptions also tended to

TABLE 2. Associations of regional change in prescription opioid use measures with unintentional deaths involving opioids, by age group and sex[a]

	Opioid Prescriptions per Capita		Percentage With ≥1 Opioid Prescription		Percentage With High-Dose Prescriptions		Percentage With Long-Term Prescriptions		Percentage With ≥3 Prescribers	
Characteristic	β	p	β	p	β	p	β	p	β	p
Total	0.074	0.007	0.037	0.27	0.050	0.007	0.02	0.41	−0.016	0.53
Sex										
Male	0.059	0.09	0.01	0.83	0.026	0.3	0.001	0.99	−0.065	0.09
Female	0.017	0.53	−0.018	0.56	0.048	0.009	−0.012	0.65	−0.036	0.16
Age group (years)										
10–24	−0.12	0.006	−0.157	0.002	0.016	0.59	−0.007	0.79	−0.188	<0.0001
25–44	−0.238	0.001	−0.317	<0.0001	−0.096	0.11	−0.117	0.04	−0.399	<0.0001
45–64	0.069	0.15	−0.103	0.09	0.09	0.05	0.02	0.73	−0.098	0.06
≥65	0.51	0.02	0.004	0.89	0.086	0.0001	0.068	0.03	−0.011	0.73

[a] Deaths with underlying ICD-10-CM cause of unintentional overdose (X40–X44) involving opioids (T40.0–T40.4, T40.6).

TABLE 3. Associations of regional change in prescription opioid use measures with undetermined deaths involving opioids, by age group and sex[a]

	Opioid Prescriptions per Capita		Percentage With ≥1 Opioid Prescription		Percentage With High-Dose Prescriptions		Percentage With Long-Term Prescriptions		Percentage With ≥3 Prescribers	
Characteristic	β	p	β	p	β	p	β	p	β	p
Total	0.047	0.002	0.011	0.57	0.025	0.004	0.036	0.004	0.024	0.006
Sex										
Male	0.053	0.008	0.016	0.38	0.021	0.008	0.034	0.004	0.018	0.08
Female	0.038	0.001	0.014	0.48	0.032	0.009	0.037	0.002	0.023	0.12
Age group (years)										
10–24	0.023	0.26	0.008	0.75	0.001	0.92	0.030	0.05	0.026	0.18
25–44	0.03	0.20	−0.035	0.41	0.012	0.45	0.018	0.36	−0.009	0.71
45–64	0.05	0.07	−0.06	0.41	0.038	0.16	0.035	0.21	−0.015	0.71
≥65	0.062	0.0005	0.053	0.002	0.035	0.05	0.035	0.03	0.044	0.003

[a] Deaths with underlying ICD-10-CM cause of undetermined overdose (Y10–Y14) involving opioids (T40.0–T40.4, T40.6).

have the greatest declines in total suicide deaths, including suicide overdoses involving opioids. These associations, which were robust across all five measures of opioid prescribing and tended to be strongest in the Western United States, provide population-level evidence linking opioid prescribing to suicide risk. We estimate that, other things being equal, had the national decline in per capita opioid prescriptions between 2009 and 2017 not occurred, there would have been 3.0% more suicide deaths overall in the United States in 2017, and 10.5% more suicide deaths involving opioids. These estimates may reflect not only the high lethality of opioid overdose events (2) but also the exceptionally high risk of suicide by all methods among individuals with opioid use disorder (29, 30). For four of five prescribing measures, decreasing regional opioid prescriptions were also related to declining total opioid-related overdose deaths of undetermined intent. Conversely, for three opioid prescription measures, regional declines in opioid prescribing were associated with significant increases in unintentional opioid-related overdose deaths in the two youngest age groups.

Regional associations connecting decreasing opioid prescriptions to declining suicide deaths are consistent with clinical research suggesting that opioid prescriptions can contribute to suicide risk in susceptible individuals (3). In a postmortem study, people who died of intentional overdoses were more likely than those who died of unintentional drug overdoses to have had prescriptions for opioids prior to death (31). In addition to the direct risks related to intentional overdoses involving opioids, longer durations of opioid prescriptions have been related to increased risk of new-onset and recurrent depression (32, 33), which may mediate increased suicide risk. Although the present population-level research cannot establish that opioid prescriptions cause deaths by suicide, the results are consistent with the view that opioid prescription policies and practices should give careful attention to possible connections between prescription opioids and suicide risk.

While the results support consideration of local opioid prescribing practices in suicide prevention initiatives, these ecological-level analyses do not shed light on the clinical pathways connecting local opioid prescribing to individual opioid overdose suicide deaths. In order to assess the effects of opioid prescriptions on an individual's risk of suicide, it is necessary to analyze prescription records that are linked to death records at the individual level. In line with our population-level results, a patient-level case-control study of veterans with chronic non-cancer pain conditions

reported that higher-dose opioid prescriptions were associated with increased suicide risk (6). Interestingly, the strength of the association of opioid dosage with overall suicide mortality was similar to its strength with suicide overdose deaths.

In evaluating the results of this panel analysis, it is important to consider the potential for confounding factors to bias the correlation coefficients. For example, overdose deaths have been related to several population-level variables, including poverty, unemployment, lower educational attainment, income inequality, and lower social capital (34–36), while similar regional factors have been correlated with rates of opioid prescribing (37, 38). However, a key advantage of fixed-effects models is that they control for all variables that vary across regions but are constant over time.

The present findings contrast with a weak relationship of local opioid prescribing and prescription opioid suicide overdose deaths previously reported from an analysis of 89 local health areas in British Columbia (15). Because the Canadian study and the present analysis differ in analytic design, power, location, and study period, it is not possible to determine the primary reason for the divergent findings.

For four of the five prescribing measures, there was a significant positive association of opioid prescribing with unintentional overdose deaths involving opioids. Because suicide overdose deaths are particularly prone to be misclassified as undetermined deaths (39), it is possible that the observed correlation between opioid prescribing and undetermined opioid-related overdose deaths, which was most apparent among older adults, is partially attributable to misclassified suicide deaths. This hypothesis is supported by research with electronic health records indicating similarities between suicide and undetermined overdose deaths in their pattern of mental health diagnoses, toxicological data, and recent stressors (40, 41). In a sample of inpatients in treatment for opioid use disorder, most (58.5%) of the inpatients reported at least some desire to die before their most recent overdose, and over one-third (35.8%) expressed a strong desire to die (42).

For the two youngest age groups, significant negative associations were identified between three regional opioid prescribing measures and unintentional opioid-related overdose deaths. In regions with falling rates of opioid prescriptions, it is possible that some individuals, including younger adults with opioid dependence, turn to heroin and other illicitly obtained or manufactured opioids that pose greater risks of unintentional overdose. For example, there were negative associations between having three or more opioid prescribers and unintentional opioid deaths in the younger age groups. Opioid prescription "doctor shopping," which peaks around age 30 (43), is associated with opioid dependence and low rates of treatment seeking (44). Facing local declines in the availability of prescription opioids via multiple opioid prescribers or other sources, some individuals may initiate use of nonprescription illicit opioids.

The present analysis has several limitations. First, as an observational ecological study, this analysis cannot establish cause and effect. Because of potential confounding by time-varying factors within each commuting zone, we cannot infer that the local changes in opioid prescribing caused the coincident changes in the various mortality outcomes. Second, as stated above, it is difficult to classify overdose events according to intent, and this may be particularly true for fatal events (40). Third, the analysis only captured changes in prescription opioids and lacked a means of measuring illicitly obtained opioids that are directly involved in a large proportion of overdose deaths (45). Fourth, due to incomplete population coverage of the IQVIA prescription data, there is uncertainty associated with the opioid prescription measurement. Finally, because the opioid crisis has evolved from being closely tied to prescribed opioids to being related to illicit heroin and fentanyl (46), and because the COVID-19 pandemic may have had population-level effects on suicide risk (47), results from the 2009–2017 period may not directly apply to contemporary conditions.

Because opioids pose a greater risk than any other drug class that an intentional overdose will prove to be lethal (2), it is not surprising that regional declines in opioid prescribing were found to ameliorate local trends in suicide deaths. These findings reinforce the importance of safe opioid prescribing practices and proper disposal of unused opioids. In managing patients with pain, physicians should evaluate whether adequate relief can be achieved with nonpharmacological interventions (48). While some patients with pain need and benefit from opioids without risk, those for whom opioids are prescribed should be evaluated and, if necessary, treated for co-occurring mental health disorders that might otherwise increase their risk of suicide. Finally, despite the epidemiological linkage between regional decreases in opioid prescribing and lowered suicide risk, some patients who are physically dependent on opioids develop serious withdrawal symptoms that may include suicide when the opioid medications are suddenly discontinued or the dosage is quickly decreased (49).

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Examination Questions for Opioid Prescribing and Suicide Risk in the United States

1. **In the United States, geographic regions with greatest declines in people filling opioid prescriptions also tended to have the greatest:**
   A. Increases in total suicide deaths and increases in suicide deaths involving opioids.
   B. Decreases in total suicide deaths but decreases in suicide deaths involving opioids.
   C. Decreases in total suicide deaths but increases in suicide deaths involving opioids.
   D. Decreases in total suicide deaths and decreases in suicide deaths involving opioids.
2. **Which best characterizes the association between regional change in opioid prescriptions per capita and regional change in unintentional deaths involving opioids?**
   A. Change in opioid prescriptions per capita is not associated with change in total unintentional deaths involving opioids.
   B. Change in opioid prescriptions per capita is positively associated with change in total unintentional deaths involving opioids.
   C. Change in opioid prescriptions per capita is negatively associated with change in total unintentional deaths involving opioids.
   D. Change in opioid prescriptions per capita is negatively associated with change in unintentional deaths involving opioids among men, but not among women.
3. **Which best characterizes age variation in the association between regional change in opioid prescriptions per capita and regional change in unintentional deaths involving opioids?**
   A. Change in opioid prescriptions per capita is positively associated with unintentional deaths involving opioids for older, but not younger, adults.
   B. Change in opioid prescriptions per capita is positively associated with unintentional deaths involving opioids for younger, but not older adults.
   C. Change in opioid prescriptions per capita is negative associated with unintentional deaths involving opioids for older, but not younger, adults.
   D. Change in opioid prescriptions per capita is negative associated with unintentional deaths involving opioids for younger, but not older, adults.