

# Physician Prescribing of Opioids to Patients at Increased Risk of Overdose From Benzodiazepine Use in the United States

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 Supplemental content

**IMPORTANCE** Recent increases in US opioid-related deaths underscore the need to understand drivers of fatal overdose. The initial prescription of opioids represents a critical juncture because it increases the risk of future opioid use disorder and is preventable.

**OBJECTIVE** To examine new opioid prescribing patterns in US patients at increased risk of overdose from benzodiazepine use.

**DESIGN, SETTING, AND PARTICIPANTS** This study used publicly available data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey from January 1, 2005, through December 31, 2015, to identify adults 20 years or older receiving new opioid prescriptions and concurrently using a benzodiazepine.

**MAIN OUTCOMES AND MEASURES** Population-based rates of new opioid prescriptions stratified by use of benzodiazepines.

**RESULTS** This study analyzed 13 146 visits, representing 214 million visits nationally, with a new opioid prescription. Rates of new opioid prescriptions among adults using a benzodiazepine increased from 189 to 351 per 1000 persons between 2005 and 2010 (rate difference, 162; 95% CI, 29-295;  $P = .02$ ) and decreased to 172 per 1000 persons by 2015 (rate difference, -179; 95% CI, -310 to -48;  $P = .008$ ). New opioid prescriptions in the general population not using benzodiazepines increased nonsignificantly from 78 to 93 per 1000 US persons between 2005 and 2010 (rate difference, 15; 95% CI, -3 to 33;  $P = .10$ ) and decreased nonsignificantly to 79 per 1000 persons by 2015 (rate difference, -14; 95% CI, -38 to 11;  $P = .28$ ). The likelihood of receiving a new opioid prescription during an ambulatory visit remained higher for patients concurrently using benzodiazepines compared with the general population after adjusting for demographic characteristics, comorbidities, and diagnoses associated with pain (adjusted relative risk, 1.83; 95% CI, 1.56-2.15;  $P < .001$ ). Naloxone was coprescribed in less than 1% of visits when a patient concurrently used a benzodiazepine.

**CONCLUSIONS AND RELEVANCE** In 2010, new opioid prescriptions for US adults stopped increasing and began to decrease among higher-risk patients who used benzodiazepines. These patterns suggest that the recent increase in opioid-related deaths may be associated with factors other than physicians writing new opioid prescriptions. Nevertheless, prescribing among higher-risk patients still occurred at rates higher than rates in the general population, representing an important opportunity to improve quality of care for patients experiencing pain.

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Opioids have helped physicians ameliorate suffering experienced by patients with pain, but the increase in opioid-related deaths has called into question physician prescribing patterns and their role in the epidemic.<sup>1-3</sup> In 2015, opioid overdose accounted for 33 000 deaths in the United States (approximately 91 deaths per day), and the US Centers for Disease Control and Prevention (CDC) estimates that nearly half of these deaths involved a prescription opioid.<sup>4</sup> Such data underscore the need to understand the drivers of fatal overdose.<sup>4</sup> Although many social, economic, and cultural factors have influenced the increase in opioid-related deaths, evidence suggests that physician overprescribing has also contributed.<sup>5,6</sup> Such patterns indicate an urgent need to understand the association between clinical practice patterns and risk of opioid-related morbidity and mortality.

The initial prescription of opioids among opioid-naïve patients represents a particularly important juncture in medical decision making because it increases the risk of future opioid use disorder and is preventable. Fatal overdoses seem to cluster among patients who concurrently use benzodiazepines and opioids; these patients are up to 4 times more likely to overdose than patients not concurrently using benzodiazepines.<sup>7-9</sup> Although few policies have been able to curb the increase in opioid-related deaths, access to naloxone is emerging as a strategy to reverse fatal overdose, particularly in patients who are long-term users of opioids.<sup>10-13</sup> However, little guidance exists to inform evidence-based prescribing.

In this context, we estimated US national patterns in new opioid prescribing in patients at increased risk of overdose from benzodiazepine use. We also examined coprescriptions of naloxone to assess the degree to which clinicians are adopting this practice as a strategy to prevent opioid-related death. We hypothesized that although new opioid prescriptions would have decreased in recent years, they would remain disproportionately high for patients at increased risk of fatal overdose and that naloxone use would be low.

## Methods

### Data Collection

We analyzed data from adults 20 years or older from the 2005-2015 National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS; available through 2011), nationally representative surveys of ambulatory care.<sup>14</sup> We included all visits to office-based physicians and hospital-based outpatient clinics. The National Center for Health Statistics (NCHS) and the CDC conduct the NAMCS and NHAMCS in the United States annually. The NAMCS is conducted on a nationally representative sample of visits to office-based physicians, and the NHAMCS is conducted on a nationally representative sample of visits to hospital-based outpatient clinics and emergency departments. For both surveys, data are collected from the medical record on patients' symptoms, comorbidities, and demographic characteristics; physicians' diagnoses; medications ordered or provided; and medical services provided. This study was

### Key Points

**Question** What are the national patterns in physician prescribing of opioids to patients at increased risk of overdose?

**Findings** In this study of 13 146 visits, representing 214 million visits nationally, with a new opioid prescription, rates of initial opioid prescribing to persons using benzodiazepines significantly increased from 2005 to 2010, followed by decreases through 2015. Higher rates of initial opioid prescriptions were seen among patients concurrently taking benzodiazepines compared with the general population.

**Meaning** Decreases in initial opioid prescriptions from 2010 to 2015 suggest that the recent increase in opioid-related deaths may be associated with factors other than physicians writing new opioid prescriptions; nevertheless, prescribing to higher-risk patients still occurred at rates higher than in the general population.

exempt from institutional review board review according to policies of the UCLA Office of the Human Research Protection Program.

### Prescriptions for Opioids and Benzodiazepines

The NAMCS and NHAMCS capture whether a prescription is new or continued. Ambulatory visits with a new drug prescription therefore reflect the national volume of new prescriptions for that medication in ambulatory settings. Using this framework, we estimated the number of new opioid prescriptions by identifying ambulatory visits during which a new opioid prescription was provided to a patient not receiving any other opioids. We also identified whether benzodiazepines or naloxone were reported on the medication list during the same visit. All medications were identified using Multum Lexicon drug codes and NCHS generic codes (eTable 1 in the [Supplement](#)). Visits for outpatient procedures that are frequently performed with sedation (eg, arthroscopy, endoscopy, surgery, and device insertion or removal) were excluded. We also excluded prescriptions for opioid-containing cough medicine and buprenorphine because they are not generally prescribed for pain.<sup>15</sup> A maximum of 8 medications could be recorded for visits between 2005 and 2011, which increased to 10 medications in 2012 to 2013 and 30 medications in 2014 to 2015. To maintain consistency, we limited our accounting to the first 8 medications for each visit across all years but performed a sensitivity analysis in which up to 30 medications were assessed. This sensitivity analysis is presented in eTable 2 in the [Supplement](#) and yielded results similar to those of our primary analyses.

### Pain-Related Reasons for Visit and Diagnoses

We reviewed all reasons for visit from 2005 to 2015 and identified reasons that were associated with pain. We then categorized these reasons for visit as being related to cancer, back pain, headache, injuries, musculoskeletal pain, or other causes of pain. In addition, we identified diagnosis codes for cancer, back pain, and headache. These codes are presented in eTable 3 in the [Supplement](#). The NAMCS and NHAMCS intake materials allowed physicians and staff to record up to 3 reasons for

each visit and 3 diagnoses related to the visit from 2005 to 2013, which increased to 5 reasons for visit and diagnoses from 2014 to 2015. In addition, from 2005 to 2015, several other major comorbid diagnoses were separately captured with checkboxes (coded by NCHS staff using the *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM]).<sup>14</sup>

### Other Measures

To further assess the association of benzodiazepine use with new opioid prescription at the visit level, we extracted information on patient age, sex, race/ethnicity, insurance status (private, Medicare, Medicaid, self-pay or no charge, and other or unknown), US Census region (Northeast, Midwest, South, and West), urban or rural setting, continuity of care, and modified Charlson comorbidity index.<sup>16,17</sup> We considered a patient to have good continuity of care if the patient had been seen before and had at least 1 visit in the practice during the preceding 12 months.<sup>18</sup>

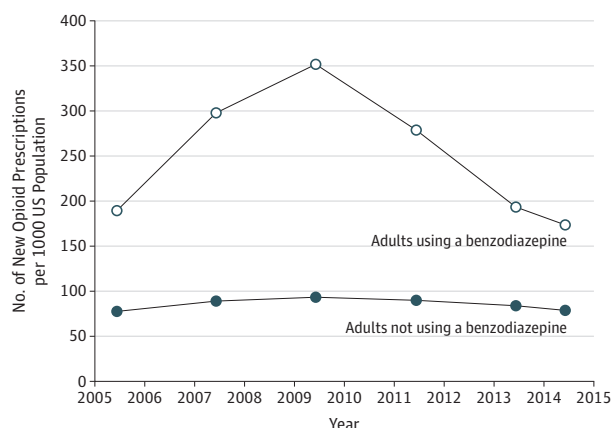
### Adjustment for NHAMCS and Community Health Center Data

Data on community health centers (part of NAMCS) and outpatient hospital departments (part of NHAMCS) were unavailable in 2012 to 2015. However, most ambulatory care is performed in office-based visits and captured by the NAMCS (91% of visits during 2005-2011 occurred in NAMCS office visits rather than in NHAMCS hospital outpatient departments, and of the NAMCS visits, 98% of them occurred outside community health centers). To estimate nationally representative rates of new opioid prescriptions, we adjusted the NAMCS data for the absence of these care sites from 2012 to 2015. Specifically, we calculated total new opioid prescriptions from 2009 to 2011 with and without the NHAMCS or community health center data. We then estimated the ratio of these quantities and used this ratio to adjust NAMCS 2012 to 2015 data for national representativeness. The ratio of total new opioid prescriptions across all sites compared with the NAMCS sites only from 2009 to 2011 was 1.28:1 when a benzodiazepine was reported on the medication list and 1.19:1 when a benzodiazepine was not reported on the medication list. We also performed a sensitivity analysis limiting data to NAMCS only without NHAMCS or community health center data; this analysis is presented in eTable 4 in the [Supplement](#) and yielded results similar to those of our primary analyses.

### Statistical Analysis

The reference populations used for calculating new opioid prescription rates were based on National Health and Nutrition Examination Survey (NHANES) data for 2005 to 2014 (2013-2014 NHANES data were carried forward to 2015 because 2015 data were unavailable). This method of analyzing NAMCS, NHAMCS, NHANES, and US Census Bureau data to generate population estimates has been used in prior research.<sup>19-21</sup> We estimated population rates rather than visit rates of new opioid prescriptions because the former is robust to differences in visit frequency between comparator groups and population estimates have greater US policy relevance. The NHANES

**Figure 1. Rate of New Opioid Prescriptions in the US Population Among All Adults Stratified by Benzodiazepine Use, 2005-2015**



asks participants if they have taken medications in the past 30 days for which they needed a prescription, and we separated patients who reported benzodiazepine use from those who did not. Because of the design of NHANES, our reference populations were defined by the cross-sectional point prevalence of benzodiazepine use rather than the period prevalence (cumulative prevalence) of benzodiazepine use during the year.<sup>22,23</sup>

To evaluate patterns, we estimated the rate difference in population rates of new opioid prescriptions from 2005-2006 to 2009-2010 and 2009-2010 to 2014-2015. The year 2010 was selected as an inflection point based on prior research on national prescribing patterns and visual inspection of our plots.<sup>24</sup> To compare visit rates of new opioid prescribing between patients prescribed or not prescribed benzodiazepines, we estimated generalized linear models using a Poisson distribution and log link function. The models adjusted for patients' clinical and demographic characteristics, insurance, region, and setting using data from 2010 to 2015 (after the inflection point for prescribing patterns). Subgroup analyses with tests for interaction were performed by sex, race/ethnicity, and age. All analyses accounted for the complex sampling design of NAMCS and NHAMCS and were performed using Stata, version 14 (StataCorp).<sup>25</sup> We used a 2-sided  $P < .05$  to assess for statistical significance for all analyses.

## Results

### New Opioid Prescription Patterns

From 2005 to 2015, the annual number of US adults 20 years or older who reported using benzodiazepines increased from 7.3 million to 13.0 million, and the number who reported not using benzodiazepines increased from 202.8 million to 216.1 million. Patterns in new opioid prescriptions among these adults and adults in the general population are shown in **Figure 1**. Rates of new opioid prescriptions among adults using a benzodiazepine increased from 189 to 351 per 1000 US persons between 2005 and 2010 (rate difference, 162; 95% CI, 29-295;  $P = .02$ ) and decreased to 172 per 1000 persons by 2015

Table 1. US Ambulatory Care Visits for Adults Receiving a New Opioid Prescription by Benzodiazepine Use (2010-2015)<sup>a</sup>

Characteristic	Adults Prescribed a Benzodiazepine			Adults Not Prescribed a Benzodiazepine			P Value <sup>b</sup>
	Unweighted Visits, No.	Annual Weighted Visits, No.	Visits, % (SE)	Unweighted Visits, No.	Annual Weighted Visits, No.	Visits, % (SE)	
All visits	15 552	48 311 000	100 (0.0)	223 722	698 800 000	100.0 (0.0)	NA
Age, y							
20-39	3110	9 220 000	19.1 (0.7)	53 476	159 100 000	22.8 (0.4)	.11
40-64	7642	23 085 000	47.8 (0.8)	96 001	300 100 000	42.9 (0.3)	
≥65	4800	16 006 000	33.1 (0.9)	74 245	239 600 000	34.3 (0.4)	
Sex							
Female	10 154	31 754 000	65.7 (0.8)	133 739	419 800 000	60.1 (0.3)	<.001
Male	5398	16 557 000	34.3 (0.8)	89 983	279 000 000	39.9 (0.3)	
Race/ethnicity							
Non-Hispanic white	9653	29 550 000	61.2 (1.2)	119 226	373 000 000	53.4 (0.8)	Reference
Non-Hispanic black	802	2 455 000	5.1 (0.4)	19 581	59 306 000	8.5 (0.4)	<.001
Hispanic	863	3 046 000	6.3 (0.6)	18 581	62 605 000	9.0 (0.4)	<.001
Other/unknown	4234	13 261 000	27.4 (1.2)	66 334	203 900 000	29.2 (0.8)	<.001
Insurance							
Private	6222	20 744 000	42.9 (1.0)	99 380	342 500 000	49.0 (0.5)	Reference
Medicare	5316	16 684 000	34.5 (0.9)	68 395	215 200 000	30.8 (0.4)	<.001
Medicaid	1693	4 023 000	8.3 (0.5)	23 207	52 256 000	7.5 (0.3)	<.001
Other/unknown	1163	2 988 000	6.2 (0.4)	19 439	52 181 000	7.5 (0.4)	<.001
Uninsured	1158	3 873 000	8.0 (0.8)	13 301	36 669 000	5.2 (0.3)	.46
US region							
Northeast	2704	10 086 000	20.9 (1.1)	41 313	148 400 000	21.2 (0.6)	Reference
Midwest	4276	9 946 000	20.6 (0.9)	57 717	133 000 000	19.0 (0.6)	.20
South	5076	17 728 000	36.7 (1.4)	73 303	256 400 000	36.7 (0.9)	.82
West	3496	10 551 000	21.8 (1.1)	51 389	161 000 000	23.0 (0.8)	.64
Setting							
Urban	13 711	43 252 000	89.5 (1.2)	199 242	632 900 000	90.6 (0.8)	.13
Rural	1841	5 059 000	10.5 (1.2)	24 480	65 853 000	9.4 (0.8)	
Charlson comorbidity index							
0	10 671	32 945 000	68.2 (0.9)	154 062	483 100 000	69.1 (0.4)	.17
1	3670	11 397 000	23.6 (0.7)	53 317	164 100 000	23.5 (0.3)	
≥2	1211	3 969 000	8.2 (0.5)	16 343	51 568 000	7.4 (0.2)	
Pain diagnosis							
Cancer	1504	3 786 000	7.8 (0.5)	20 421	53 141 000	7.6 (0.2)	.59
Back pain	1136	3 974 000	8.2 (0.5)	13 214	49 334 000	7.1 (0.3)	.02
Headache	590	1 604 000	3.3 (0.3)	6063	17 892 000	2.6 (0.1)	<.001
Injuries and MSK pain	1911	6 403 000	13.3 (0.6)	33 415	113 400 000	16.2 (0.4)	<.001
Other pain	1152	3 777 000	7.8 (0.4)	19 412	63 097 000	9.0 (0.2)	.008
Good continuity of care	12 764	41 141 000	85.2 (0.6)	164 520	530 900 000	76.0 (0.3)	<.001

Abbreviations: MSK, musculoskeletal; NA, not applicable; NAMCS, National Ambulatory Medical Care Survey; NHAMCS, National Hospital Ambulatory Medical Care Survey.

<sup>a</sup> All analyses account for the complex sampling design of the NAMCS and NHAMCS.

<sup>b</sup> P values calculated with Wald  $\chi^2$  test from simple ordinal (age and Charlson comorbidity index) or binomial or multinomial (sex, race/ethnicity, insurance, setting, and pain diagnosis) logistic regression models comparing patients prescribed vs not prescribed a benzodiazepine.

(rate difference, -179; 95% CI, -310 to -48;  $P = .008$ ). These rates were substantially higher than the rates of new opioid prescription in the general population not using benzodiazepines, which increased nonsignificantly from 78 to 93 per 1000 US persons between 2005 and 2010 (rate difference, 15; 95% CI, -3 to 33;  $P = .10$ ) and decreased nonsignificantly to 79 per 1000 persons by 2015 (rate difference, -14; 95% CI, -38 to 11;  $P = .28$ ). Naloxone was coprescribed in less than 1% of visits made by adults receiving a new opioid prescription and when a patient concurrently used a benzodiazepine.

### Association of Benzodiazepines With New Opioid Prescription

**Table 1** compares the visit characteristics of US adults 20 years or older, stratified by whether these patients used a benzodiazepine. The unadjusted relative risk for initial opioid prescription among patients using a benzodiazepine compared with patients not prescribed a benzodiazepine was 1.74 (95% CI, 1.45-2.09;  $P < .001$ ). The likelihood of receiving an initial opioid prescription remained higher for patients concurrently using benzodiazepines compared with the general popu-

**Table 2. Adjusted RRs of New Opioid Prescription Among 239 274 Adults With US Ambulatory Care Visits, 2010-2015<sup>a</sup>**

Characteristic	Adjusted RR (95% CI)	P Value <sup>b</sup>
Prescribed a benzodiazepine	1.83 (1.56-2.15)	<.001
Sex		
Male	1 [Reference]	NA
Female	0.87 (0.79-0.95)	.003
Race/ethnicity		
White	1 [Reference]	NA
Non-Hispanic black	0.94 (0.77-1.15)	.56
Hispanic	0.77 (0.64-0.92)	.004
Other/unknown	0.97 (0.85-1.11)	.68
Age, y		
20-39	1 [Reference]	NA
40-64	0.87 (0.78-0.98)	.02
≥65	0.57 (0.49-0.67)	<.001
Insurance		
Private	1 [Reference]	NA
Medicare	1.15 (0.99-1.33)	.07
Medicaid	1.27 (1.07-1.51)	.005
Other/unknown	1.22 (1.06-1.40)	.005
Uninsured	1.32 (1.08-1.61)	.007
Urban or rural setting		
Urban	1 [Reference]	NA
Rural	1.33 (1.14-1.55)	<.001
US region		
Northeast	1 [Reference]	NA
Midwest	1.31 (1.04-1.65)	.02
South	1.74 (1.39-2.18)	<.001
West	1.40 (1.10-1.77)	.006
Charlson comorbidity index		
0	1 [Reference]	NA
1	0.90 (0.79-1.02)	.09
≥2	0.89 (0.66-1.18)	.42
Pain diagnosis		
Cancer	1.34 (1.07-1.68)	.01
Back pain	2.88 (2.32-3.58)	<.001
Headache	1.65 (1.33-2.04)	<.001
Injuries and MSK pain	4.24 (3.46-5.19)	<.001
Other pain	2.89 (2.44-3.42)	<.001
Good continuity of care	0.97 (0.85-1.10)	.58

Abbreviations: MSK, musculoskeletal; NA, not applicable; NAMCS, National Ambulatory Medical Care Survey; NHAMCS, National Hospital Ambulatory Medical Care Survey; RR, relative risk.

<sup>a</sup> Reference groups in the Poisson regression models are male sex, white race/ethnicity, age of 20 to 39 years, private insurance, urban setting, Charlson comorbidity index, and no pain-related reason for revisit. All analyses account for the complex sampling design of the NAMCS and NHAMCS.

<sup>b</sup> P values calculated with Wald  $\chi^2$  test from simple ordinal (age and Charlson comorbidity index) or binomial or multinomial (sex, race/ethnicity, insurance, setting, pain diagnosis) logistic regression models comparing patients prescribed vs not prescribed a benzodiazepine.

lation (Table 2) after adjusting for demographic characteristics, comorbidities, and diagnoses associated with pain (adjusted relative risk, 1.83; 95% CI, 1.56-2.15;  $P < .001$ ). In post hoc analyses, there was a significant interaction between

initial opioid prescription among patients using a benzodiazepine and both race/ethnicity and age (Figure 2).

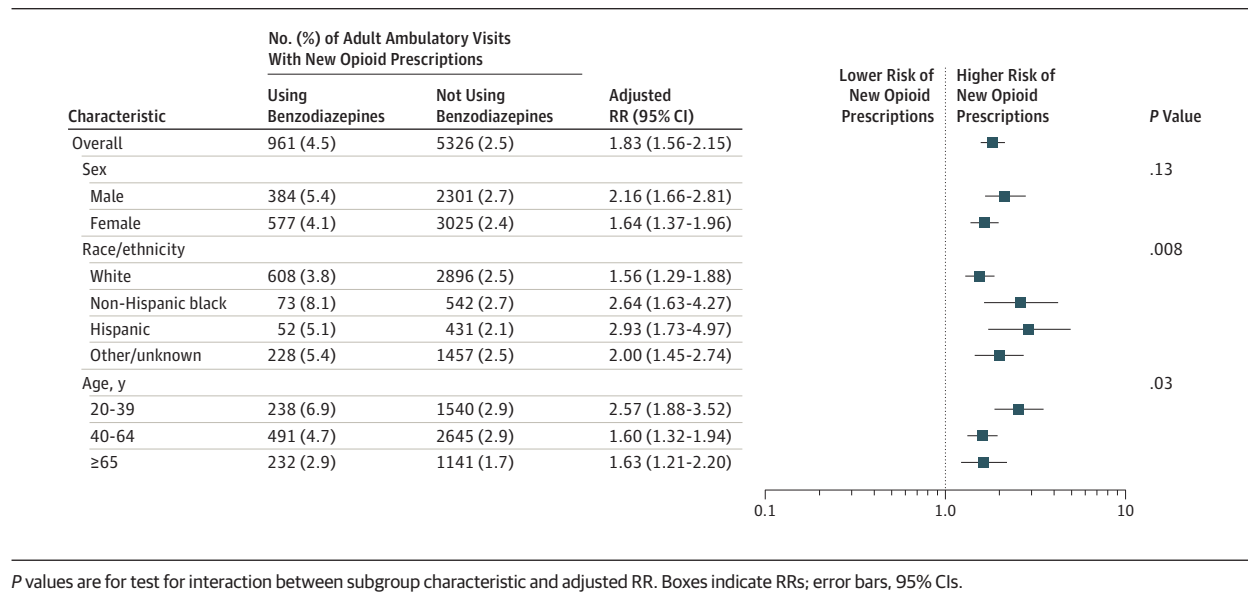
## Discussion

We found that in 2010, new opioid prescriptions for US adults stopped increasing and began to decrease among higher-risk patients who used benzodiazepines, with substantial decreases through 2015. These patterns suggest that the recent increase in opioid-related deaths may be associated with factors other than physicians writing new opioid prescriptions. Nevertheless, prescribing among higher-risk patients occurred at rates higher than rates in the general population. This finding represents an important opportunity to improve the quality of care for patients experiencing pain. These results may be of particular interest to psychiatrists because adults with chronic pain are substantially more likely to have mental illness,<sup>26</sup> and use of benzodiazepines, prescribed to approximately 1 in 12 US adults, is a risk factor for persistent opioid use after an initial prescription.<sup>27-29</sup>

We observed a decrease in new opioid prescriptions from 2010 to 2015, with decreases among patients using a benzodiazepine in particular. This finding suggests that physicians writing new opioid prescriptions are not the primary driver of the recent increase in opioid-related deaths reported by the CDC. Opioid-related deaths have increased from 5 per 100 000 persons in the United States in 2005 to 7 per 100 000 persons in 2010 and 11 per 100 000 persons in 2015.<sup>3</sup> Although new opioid prescriptions increase the risk of opioid use disorder and high rates of new prescriptions before 2010 have likely contributed to current opioid use disorders,<sup>5</sup> overall prescriptions have been decreasing since 2010. Recent CDC data show increases in opioid-related overdose deaths even through 2017.<sup>30</sup> These increases have been associated with an increase in the rate of death from synthetic opioids, such as fentanyl, and a steady increase in heroin-related opioid deaths and deaths from natural and semisynthetic opioids, such as oxycodone.<sup>31</sup> Factors behind these concerning patterns include social networks of friends or relatives sharing opioids, patients with iatrogenic opioid use disorder who unintentionally overdose, and increasing availability of heroin or illicit synthetic opioids, such as illegally synthesized fentanyl.<sup>30</sup> These changes are also occurring against a broader backdrop of widening social, economic, and racial/ethnic disparities.<sup>32-34</sup>

Our findings also show that rates of new prescriptions of opioids to patients prescribed benzodiazepines have remained disproportionately high from 2005 to 2015 compared with the general population receiving opioids alone. Concurrent benzodiazepine prescription with opioids has been associated with up to 4 times the risk of overdose death compared with prescription of opioids alone.<sup>7-9</sup> Because of these data, the CDC Guideline for Prescribing Opioids for Chronic Pain recommends that clinicians avoid prescribing opioids and benzodiazepines concurrently whenever possible.<sup>11-13</sup> Although chronic pain and mental illness frequently coexist, patients may garner greater benefit and less harm from nonbenzodiazepine and nonpharmacologic approaches to mental illness.<sup>26</sup>



**Figure 2. Adjusted Relative Risks (RRs) for New Opioid Prescriptions in US Ambulatory Care Visits Among Adults Using Benzodiazepines Compared With Adults Not Using Benzodiazepines**

P values are for test for interaction between subgroup characteristic and adjusted RR. Boxes indicate RRs; error bars, 95% CIs.

Because of wide variation in physician prescribing of opioids,<sup>35</sup> there are substantial opportunities to improve the quality of care while reducing risk of iatrogenic patient harm in this context. In addition, a recent study<sup>36</sup> demonstrated that the probability of long-term opioid use increased to 13.5% after 8 days of therapy and 29.9% after 31 days of therapy.

In guidelines for chronic pain, the CDC recommends that clinicians consider offering naloxone to patients at increased risk for opioid overdose, including patients with concurrent benzodiazepine use. Many states now allow pharmacies to dispense naloxone without a written prescription, and 2 large national pharmacy chains recently announced that they would stock naloxone nasal spray in response to the increase in opioid overdose deaths.<sup>37</sup> We found that naloxone was rarely coprescribed during visits with an initial opioid prescription. Expanding access to naloxone at the community level may be a cost-effective policy option for reducing the rate of death from opioid overdoses. However, there is limited evidence on the effectiveness of prescribing naloxone for overdose prevention among patients receiving initial opioid prescriptions.

Although the decrease of new opioid prescriptions is a step in the right direction, one danger to this pattern is that patients with chronic pain may lack care for their pain. In this context, our findings highlight an urgent need to reorganize our health care system's approach to managing pain. Multidisciplinary rehabilitation, acupuncture, yoga, and tai chi effectively alleviate chronic low back pain based on results of randomized clinical trials, but access and insurance coverage for such high-value treatments are frequently challenging in daily practice.<sup>38,39</sup> Another approach for pain management is topical nonsteroidal anti-inflammatory pain medicines. Sixty-one randomized clinical trials have proven that these medicines can substantially reduce musculoskeletal pain with minimal risk of iatrogenic harm.<sup>40</sup> Despite this overwhelming evidence, many payers require physicians to complete prior-authorization

applications for such medications while providing no such barriers for drugs such as oxycodone or lorazepam. Lack of insurance coverage may force patients to purchase these medicines out of pocket; generic diclofenac gel's lowest current out-of-pocket market price is approximately \$45 per month compared with approximately \$18 per month for oxycodone and approximately \$9 per month for lorazepam.<sup>41</sup> We challenge policy makers, practice leaders, patients, clinicians, industry, and payers to develop innovative solutions that redesign our ability to deliver evidence-based, multidisciplinary, and low-risk approaches to chronic pain management.

### Limitations

Our study has several limitations. The NAMCS and NHAMCS provide a limited amount of clinical information on each patient visit, and we were unable to robustly account for severity of pain, distinguish patients who received opioids for short-term therapy from those who received opioids in the long term after their initial prescription, or distinguish patients with initial opioid prescriptions who had been treated with opioids in the past from patients who had not. We also did not have access to pharmacy data for the preceding months; thus, some patients with new prescriptions may have previously received opioid prescriptions that were discontinued or expired. The CIs for changes in population rates of new opioid prescriptions were also large because of sample size limitations. Overdose risk increases with benzodiazepine and opioid dose, but dose information was unavailable. Our estimates of medication prescriptions could also underestimate true rates because of underreporting. In addition, data from community health centers and outpatient hospital departments were unavailable from 2012 to 2015; thus, we performed adjustments to account for their absence. However, our findings were changed minimally when these sites were excluded from the analysis.

## Conclusions

New opioid prescriptions for US adults stopped increasing and began to decrease among higher-risk patients who used benzodiazepines from 2010 to 2015. These patterns suggest that

the recent rapid increase in opioid-related deaths is primarily associated with factors other than physicians writing new opioid prescriptions. Nevertheless, prescribing among higher-risk patients still occurred at rates higher than rates in the general population, representing an important opportunity to improve the quality and safety of care for patients with pain.

### ARTICLE INFORMATION

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**Study concept and design:** Ladapo, Larochelle, Chen, Villalon, Mafi.

**Acquisition, analysis, or interpretation of data:** All authors.

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**Statistical analysis:** Ladapo, Vassar, Huang.

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