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Ann Intern Med. Author manuscript; available in PMC 2019 March 18.

Published in final edited form as:

Ann Intern Med. 2018 September 18; 169(6): 367–375. doi:10.7326/M18-1243.

Opioid Prescribing in the United States Before and After the Centers for Disease Control and Prevention's 2016 Opioid Guideline

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Abstract

Background: In response to adverse outcomes from prescription opioids, the Centers for Disease Control and Prevention (CDC) released the *Guideline for Prescribing Opioids for Chronic Pain* in March 2016.

Objective: To test the hypothesis that the CDC guideline release corresponded to declines in specific opioid prescribing practices.

Design: Interrupted time series analysis of monthly prescribing measures from the IQVIA transactional data warehouse and Real-World Data Longitudinal Prescriptions population-level estimates based on retail pharmacy data. Population size was determined by U.S. Census monthly estimates.

Setting: United States, 2012 to 2017.

Patients: Persons prescribed opioid analgesics.

Measurements: Outcomes included opioid dosage, days supplied, overlapping benzodiazepine prescriptions, and the overall rate of prescribing.

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Statistical expertise: G.P. Guy.

Administrative, technical, or logistic support: G.P. Guy, J.L. Losby.

Collection and assembly of data: G.P. Guy.

Publisher's Disclaimer: Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the official position of the CDC.

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-1243.

Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Available from Dr. Guy (e-mail, gguy@cdc.gov). *Data set:* Available via licensing agreements with IQVIA.

Current author addresses and author contributions are available at Annals.org.

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Results: The rate of high-dosage prescriptions (≥90 morphine equivalent milligrams per day) was 683 per 100 000 persons in January 2012 and declined by 3.56 (95% CI, −3.79 to −3.32) per month before March 2016 and by 8.00 (CI, −8.69 to −7.31) afterward. Likewise, the percentage of patients with overlapping opioid and benzodiazepine prescriptions was 21.04% in January 2012 and declined by 0.02% (CI, −0.04% to −0.01%) per month before the CDC guideline release and by 0.08% (CI, −0.08% to −0.07%) per month afterward. The overall opioid prescribing rate was 6577 per 100 000 persons in January 2012 and declined by 23.48 (CI, −26.18 to −20.78) each month before the guideline release and by 56.74 (CI, −65.96 to −47.53) per month afterward.

Limitation: No control population; inability to determine the appropriateness of opioid prescribing.

Conclusion: Several opioid prescribing practices were decreasing before the CDC guideline, but the time of its release was associated with a greater decline. Guidelines may be effective in changing prescribing practices.

Primary Funding Source: CDC.

Harms due to opioid medications increased dramatically during the 2000s and early part of the 2010s in the United States. Fatal overdoses from natural and semisynthetic opioids increased from 1.0 per 100 000 adults in 1999 to 4.4 per 100 000 in 2016 (1). Concurrent increases occurred in opioid-related emergency department visits (2), the prevalence of opioid use disorders (3), and opioid prescribing for chronic pain (4), but nonmedical prescription opioid use decreased (3). Data from patients prescribed opioids (5–9) indicate a connection between prescribing practices and opioid-related harms and a need to optimize opioid prescribing.

A common strategy for changing clinician behavior is the release of practice guidelines. Prominent examples of medication-focused guidelines are the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (10) and the Veterans Health Administration's Opioid Safety Initiative (11, 12). However, the ability of guidelines to change behavior may be limited (13), with cross-condition reviews indicating that practice changes in response to guidelines vary widely (14) and that limited implementation efforts often hamper effectiveness (15).

The Centers for Disease Control and Prevention (CDC) released the *Guideline for Prescribing Opioids for Chronic Pain* in March 2016 (16). The CDC guideline recommends evidence-based practices for opioid use for treating chronic pain–excluding cancer treatment, palliative care, and end-of-life care–in patients aged 18 years and older in primary care settings. Compliance is entirely voluntary. Compared with previous guidelines (17), the CDC guideline is broad reaching, as the result of a CDC-coordinated implementation strategy (18, 19). The purpose of this analysis was to assess temporal changes in opioid prescribing since the CDC guideline was released.

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Methods

Study Design

This study consisted of interrupted time series analyses examining changes in opioid prescribing. This method is commonly used to determine whether the time at which a new policy or program was implemented is associated with changes in an outcome, which is measured continuously over time (20). It may be particularly useful for evaluating population-level interventions, such as in cases in which no control or comparison group is available. Each model tested whether the point at which the CDC guideline was released (March 2016) was associated with immediate increases or decreases (a change in the intercept) at the time of "interruption," a change in the trajectory over time (the slope) of prescribing metrics originating at the interruption, or both. This study was exempt from human subjects review.

Data Source

The CDC obtained access to the complete database of opioid prescriptions for 2012 to 2017 from the IQVIA transactional data warehouse and for 2015 to 2017 from Real-World Data Longitudinal Prescriptions, which are based on data provided by pharmacies nationally. During the study period, the number of reporting pharmacies increased from approximately 38 500 in 2012 to approximately 50 400 in 2017, representing 74% and 90% of retail pharmacy prescriptions and 256.4 million and 193.5 million opioid prescriptions, respectively. We used the nationally projected estimates produced by IQVIA that account for pharmacy coverage. The IQVIA data do not include opioids obtained through mail order or dispensed directly by providers, including methadone or buprenorphine dispensed by opiate treatment programs. We excluded cold and cough products and buprenorphine formulations used to treat addiction. For 2 specific patient outcomes, IVQIA provided prescription-level data with patient numbers, linkable within month. Analysts at the CDC used patient identification numbers to construct patient-level outcomes.

Included data represented opioids dispensed between January 2012 and December 2017. Previous work indicates that 2012 was when opioid prescribing peaked (21). For patient-level outcomes, data covered January 2015 to December 2017. U.S. Census estimates for the national population per month were used for the denominator of rates (22).

Outcomes

Outcomes were based on specific recommendations (16). In total, the CDC guideline contains 12 recommendations within the areas of patient selection, treatment and follow-up, and risk mitigation. Although the guideline focuses on opioid prescribing for chronic pain, it also recommends prescribing no more than necessary for acute pain. This evaluation assessed outcomes related to 6 of the 12 recommendations. Others, such as use of prescription drug monitoring programs and development of a treatment plan and goals, could not be assessed in the data source.

We measured several outcomes at the prescription level. For dosages in morphine milligram equivalents (MME) per day, prescriptions were converted on the basis of published ratios

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(23). Information on quantity prescribed and days supplied was used to calculate dosages in MME per day. For these outcomes, prescriptions were attributed only to the month in which they were dispensed, even if the days supplied covered days in the next month or months.

The prescription-level outcomes and the rationale for their selection are as follows:

1a. High-dosage opioid prescribing rate (primary measure 1). The number of opioid prescriptions written to total at least 90 MME/d from that fill alone was calculated per 100 000 persons in the population.

1b. Average MME per capita. The total of all MME prescribed was divided by the monthly population size, resulting in an average amount dispensed per person.

1c. Average daily MME per prescription. For each opioid fill, the MME per day and then the average per month were calculated.

Rationale: Outcome measures 1a to 1c are related to recommendation 5, which advises against titrating dosages above 90 MME/d. We hypothesized that these outcomes would decrease after the CDC guideline was released.

2a. Percentage of prescriptions with no more than 3 and no more than 7 days supplied (primary measure 2).

2b. Average number of days supplied per opioid prescription.

Rationale: These measures are related to recommendation 6, which advises that for acute pain, “prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.” According to the recommendation, a 3-day supply is often sufficient and more than a 7-day supply is rarely needed. We hypothesized that the percentage of prescriptions with no more than 3 and with no more than 7 days supplied would increase after the CDC guideline release, reducing the average days supplied.

3. Overall opioid prescribing rate. The number of opioid prescriptions dispensed per 100 000 persons.

Rationale: Recommendations may have led to an increase in the use of nonopioid therapies as preferred options (recommendation 1) as well as the number of patients discontinuing opioid therapy because of a lack of benefit (recommendation 7). We hypothesized that this outcome would decrease after the CDC guideline release.

We examined 2 measures in data linked at the patient level (patient-level outcomes):

1. Percentage of patients with overlapping opioid and benzodiazepine fills. Prescriptions were classified as overlapping if an opioid and a benzodiazepine prescription both covered at least 1 day in common, regardless of dispensing date. For all patients prescribed opioids, we measured the proportion with an overlapping benzodiazepine prescription within each calendar month. For both medications, we assumed that use started on the date the

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prescription was filled and continued for the number of days supplied, without interruption (5).

Rationale: This measure is related to recommendation 11, which advises against concurrent use of opioids and benzodiazepines. We hypothesized that this metric would decrease after the CDC guideline release.

2. Percentage of opioid-naive patients prescribed an extended-release or long-acting (ER/LA) opioid. Opioid-naive patients were defined as those who had an opioid fill without any opioid treatment in the previous 45 days. For these patients, we calculated the proportion of new prescriptions for drugs classified as ER/LA opioids, as determined by a National Drug Code list maintained by the CDC (23).

Rationale: This measure corresponds to recommendation 4, which advises initiating opioid therapy with an immediate-release formula. We hypothesized that this outcome would decrease after the guideline release.

Comparator Medication

In the absence of a U.S. control group unexposed to the CDC guideline, we used benzodiazepines as a comparator to reflect secular trends in overall prescribing practice outside the guideline's scope. Like opioids, benzodiazepines have psychoactive effects and increase the risk for overdose (6) and other injuries (24). We calculated the overall rate of benzodiazepine prescriptions using the same method we used for the overall opioid prescribing rate.

Statistical Analysis

The analysis took the form of an interrupted time series with segmented regressions (25, 26) using monthly repeated measures. The following equation was used for the regression:

$$Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \varepsilon_t,$$

where Y_t is the aggregated outcome variable measured at each equally spaced time point t, T_t is the time since the start of observation (in months), X_t is a dummy (indicator) variable representing the guideline release (pre–March 2016 periods = 0, post-March 2016 periods = 1), and $X_t T_t$ is an interaction term. The models were parameterized to test for both a one-time change immediately at the time of implementation (intercept; β_2) and the difference in the pre- and postguideline trends (slope; β_3). All analyses were performed with Stata, version 14.2 (StataCorp). We used coefficients from the interrupted time series regressions to estimate comparisons of key outcomes relative to expected outcomes, assuming pre–CDC guideline trends continued unchanged (that is, the counterfactual) (27).

We used Prais–Winsten regression with the Cochrane–Orcutt transformation and robust SEs to adjust for first-order serial autocorrelation. We examined the Durbin–Watson statistic to ensure that our models adequately corrected for first-order autocorrelation. Values of the Durbin–Watson statistic close to 2.0 indicated the absence of serial autocorrelation. After

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correction, the average deviation from 2 across the various models was 0.04, compared with 0.49 before the correction.

We estimated several additional sets of models. First, to examine benzodiazepines as a comparison medication, we created a data set with overall rates for both opioids and benzodiazepines and an indicator of medication type. A multiple-group interrupted time series analysis (25, 26) used interaction terms with medication type to test whether the size of the intercept or change in slope at March 2016 was statistically significantly different between medications. Second, we considered a second date of implementation. The draft CDC guideline was announced for public comment in December 2015, and this month was selected as an alternative time of implementation. Third, we conducted sensitivity analyses to determine the effect on inferences, relative to the primary analyses, when models excluded the time between December 2015 and March 2016 to account for possible gradual guideline effects on practice, and when potential seasonal effects were adjusted for by using a covariate for quarter (28).

Role of the Funding Source

This study was supported by the CDC via employment, an intergovernmental personnel agreement, and costs associated with data acquisition. Authors who are CDC employees were involved in the design, analysis, and decision to submit the manuscript. Experts on CDC subject matter provided feedback for accuracy and clarity but were not otherwise involved in the study.

Results

An average of 19.1 million opioid prescriptions were written each month. In January 2012, 6577 opioid prescriptions were dispensed per 100 000 persons, decreasing to 4240 by December 2017. Likewise, the number of opioid prescriptions written for at least 90 MME/d was 683 per 100 000 persons in January 2012 and decreased to 356 per 100 000 by December 2017.

Before the CDC guideline release, the overall opioid prescribing rate, all measures of opioid dosages, concurrent benzodiazepine use, and initiation with an ER/LA opioid were declining, as indicated by their pre–CDC guideline slopes in Table 1. The change in slope at March 2016 indicates that the overall opioid prescription rate ($P < 0.001$), MME per capita ($P < 0.001$), high-dosage prescribing rate ($P < 0.001$), and percentage of patients with overlapping benzodiazepines ($P < 0.001$) decreased faster after March 2016 than before. The immediate change at March 2016 was statistically significant only for the high-dosage prescribing rate, indicating that, in general, no immediate shifts occurred. The rate of therapy initiation with an ER/LA opioid did not change. Figures 1 to 3 display patterns over time for each measure.

Before March 2016, mean days supplied was increasing by 0.04 days per month, and the proportions of fills for no more than 3 and for no more than 7 days similarly were declining (Table 1). After March 2016, the rate of increase in mean days supplied slowed relative to before March 2016 ($P = 0.012$). The proportion of fills for no more than 3 and for no more

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than 7 days became steady (that is, the slope was not statistically different from 0) after March 2016. To understand these trends in a broader context, we repeated the modeling for prescribing rates by days supplied for fewer than 30 and for 30 or more days (Appendix Figure 1, available at Annals.org). Prescriptions for fewer than 30 days supplied were declining before March 2016 and decreased at a significantly faster rate after March 2016 (β for change in slope, −13.89 [95% CI, −20.83 to −6.94]). Prescriptions for 30 or more days supplied were steady before March 2016 and then began to decline (β for change in slope, −19.56 [CI, −22.89 to −16.22]).

Table 2 reports these averages and the total reductions in each metric for the period between April 2016 and December 2017 after accounting for decreases that would be expected if pre-March 2016 trends had continued unchanged. We estimated that approximately 14.2 million fewer opioid prescriptions, including about 1.3 million high-dosage prescriptions, were filled from March 2016 to December 2017 than would have been expected if pre-CDC guideline trends continued. In addition, 1.1 million fewer patients received concurrent benzodiazepines and opioids during March 2016 to December 2017 than would have been expected.

Comparator Medication: Benzodiazepines

We estimated models for benzodiazepine use during January 2015 to December 2017. Appendix Figure 2 (available at Annals.org) displays the monthly overall prescribing rates, and Table 3 provides model results. The first estimate of −5.80 (CI, −20.86 to 9.26) indicates that the pre–March 2016 rate of decline was similar for both medications. The second estimate of −3.25 (CI, −172.66 to 166.17) indicates that any intercept change immediately at March 2016 was the same for both medications. Finally, the third estimate of −19.17 (CI, −36.31 to −2.02) indicates that the rate of decrease for opioid prescribing was greater than for benzodiazepine prescribing after March 2016.

Analysis for December 2015 as the Implementation Date

We analyzed December 2015, when a draft of the CDC guideline was made public, as the point of implementation (Appendix Table 1, available at Annals.org). Inferences were unchanged for the slope effect for the overall prescribing rate, MME per capita, high-dosage prescribing rate, average days supplied, the proportion of prescriptions for no more than 3 and for no more than 7 days, and the percentage of patients with overlapping opioid and benzodiazepine fills. For several outcomes, significant effects of the intercept, indicating a change just at December 2015, were found here that were not found in the primary analyses. This was true for MME per capita, average MME per prescription, and percentage of patients with overlapping opioid and benzodiazepine prescriptions.

Sensitivity Analyses

Appendix Table 2 (available at Annals.org) reports models in which the months of December 2015 to March 2016 were excluded from analysis. Inferences were unchanged relative to the primary models. Analyses adjusting for seasonal effects (Appendix Table 3, available at Annals.org) also did not demonstrate any meaningful differences from the primary analyses.

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Discussion

Since 2012, opioid prescribing in the United States has steadily declined in terms of the overall number of prescriptions written and the frequency of specific risky prescribing practices. The time of the CDC's release of the *Guideline for Prescribing Opioids for Chronic Pain* was associated with a statistically significantly faster rate of decline in several key opioid prescribing practices. Decreases were observed in the overall rate of opioid prescribing, the rate of high-dosage opioid prescriptions, and the percentage of patients with overlapping benzodiazepine and opioid prescriptions.

Some of the declines observed both before and after the CDC guideline was released were probably a response to accumulating evidence about the risk for overdose associated with specific practices (9, 29, 30). Nonetheless, the guideline release was associated with an increased rate of decline that was greater than the rate observed for benzodiazepines. However, the decreases in most outcomes before the CDC guideline and the nature of the intervention (national scope, lack of a sharply demarcated inflection point) raise the possibility of false-positive findings.

Earlier opioid guidelines were published by Chou and colleagues (31) and by the Management of Opioid Therapy for Chronic Pain Working Group for the U.S. Department of Veterans Affairs and Department of Defense (32). A systematic review synthesized evaluations of these and other opioid-related guidelines and found that they are associated with reductions in risky prescribing patterns (33). The present study provides evidence that a guideline intended for a broad, national audience can change clinician behavior, albeit with relatively small percent changes in monthly rates but sizeable cumulative effects on opioid prescriptions.

We found that the proportion of prescriptions written for no more than 3 and for no more than 7 days was declining before the CDC guideline release and was stable afterward, contrary to our hypothesis. Likewise, the mean days supplied was increasing before the guideline release, and the rate of increase slowed afterward. Supplementary analysis demonstrated that prescriptions for 30 or more days began to decrease after March 2016, but at a slower rate than for those for fewer than 30 days. Given that prescribing for 30 or more days at a time is typical for chronic pain, it is possible that opioid sparing for acute pain occurred more often than for chronic pain, increasing, over time, the average days supplied.

Analysis of December 2015, when the CDC guideline draft was released for public comment, provided further insight into these changes. Findings were similar for most analyses, suggesting that the changes observed for March 2016 may reflect general changes during the time the guideline was developed, made public, and revised, rather than a clear effect tied to its release. One of the primary purposes of the CDC guideline is to increase public awareness, which has affected other health outcomes (34, 35). This mechanism of effect probably occurred gradually, and determining whether the public's heightened awareness was caused by the guideline or by other factors would be difficult. In addition, these findings may suggest that prescribing rates generally were trending downward and that

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the statistically significant changes in March 2016 may not indicate a meaningful inflection point.

The CDC carried out several activities to support the guideline's implementation (18), including translation and communication, with such products as fact sheets and posters. Clinical education incorporated online modules and continuing medical education training. Health system interventions that were part of the strategy included quality improvement metrics that assessed performance relative to the recommendations. Finally, the CDC suggested that payers develop strategies to improve coverage of nonopioid and nonpharmacologic pain treatments and provide reimbursement for time spent monitoring risks and providing relevant counseling.

This study benefited from a data set representing opioid prescribing for the entire United States, as well as its ability to control for temporal trends, but it had several notable limitations. Without a comparison population, the interrupted time series with segmented regression to control for trends is considered an "intermediate" design in terms of strength of evidence (36). Increased federal and state focus on the problem during this period probably affected prescribing in ways that are challenging to distinguish from any potential effect of the CDC guideline. Plans for releasing the guideline attracted some national press attention before December 2015, and pre– and post–CDC guideline periods are difficult to define distinctly. Further, the CDC used several implementation strategies, which makes examining the potential effects of specific activities a challenge. In addition, estimates of dispensed prescriptions do not include the small proportion dispensed directly or via mail order.

Data were not collected for research, and information on patients and providers was fairly limited. Indications for opioid use, such as acute pain, chronic pain, cancer, and palliative care, were not available, and we could not assess the appropriateness of prescribing for individual patients. We also could not separately examine prescriptions that fell outside the scope of the CDC guideline, such as those for cancer pain or palliative care. It is possible that some of the reductions in opioid prescribing observed here were the result of a decrease in appropriate opioid use in these patient groups and others and represent less optimal, rather than improved, care. The outcomes of greatest interest to public health related to opioid use, namely overdose, nonmedical use, and opioid use disorder, cannot be measured in this data source. The declines in these opioid prescribing metrics, whether because of the CDC guideline, other efforts, or secular trends, have not been followed by decreases in opioid overdoses. Instead, overdoses due to illegal opioids (heroin, illicitly manufactured fentanyl) have increased (37).

Clinical practice guidelines, including those for which compliance is voluntary, may be able to change clinician behavior. Our findings demonstrated that the CDC guideline release was associated with decreases in key metrics of inappropriate opioid prescribing patterns. Additional research is needed on specific CDC guideline recommendations that could not be assessed in this data source, as well as the possibility that the guideline had stronger or weaker effects on specific groups of patients. Research should explore potential unintended consequences for patients, such as abrupt tapering; transition to illicit opioids, such as

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heroin; overdose; and suicide. Studies comparing locations with known differences in implementation might strengthen the ability to draw causal inferences.

The opioid overdose epidemic is a complex crisis that requires a response from several sectors, including public health, health care, and public safety. System-level interventions should be implemented in the context of a comprehensive approach targeting the drivers of the epidemic. This study demonstrated changes in national opioid prescribing trends during the past several years, with a greater rate of improvement in several metrics after the CDC guideline was released. These findings suggest that the guideline release may have contributed to better prescribing behaviors.

Acknowledgment:

The authors thank Dr. Grant Baldwin of the CDC, who made important contributions to a draft of this manuscript.

Financial Support: This study was supported by the CDC via employment of Drs. Guy and Losby, an intergovernmental personnel agreement with Dr. Bohnert, and costs associated with data acquisition.

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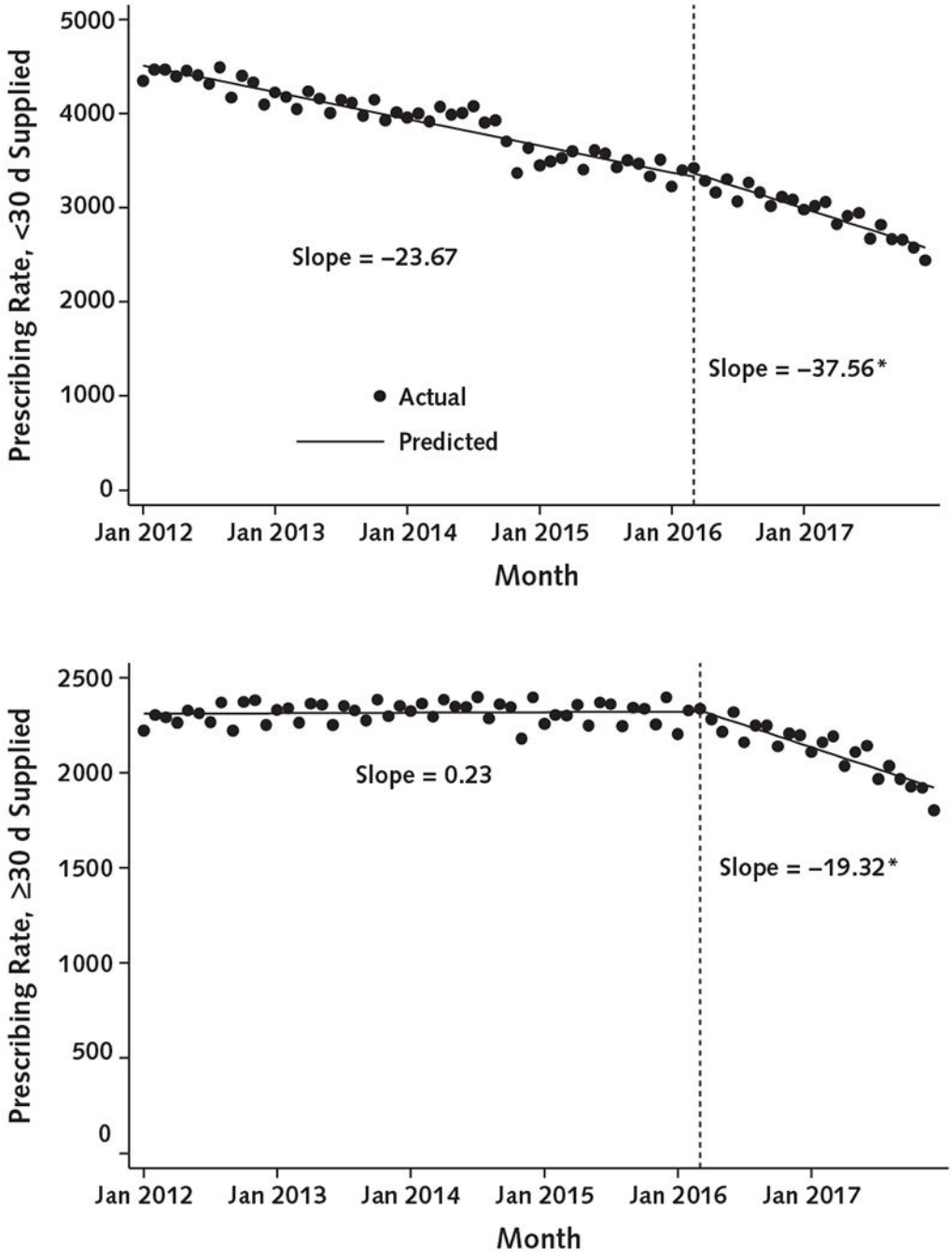
Appendix



Appendix Figure 1.

Rate of prescribing per 100 000 persons before and after release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* in March 2016, stratified by days supplied.

Dashed vertical lines represent the month of CDC guideline implementation (March 2016).

CDC = Centers for Disease Control and Prevention. Top. Rate of prescriptions dispensed

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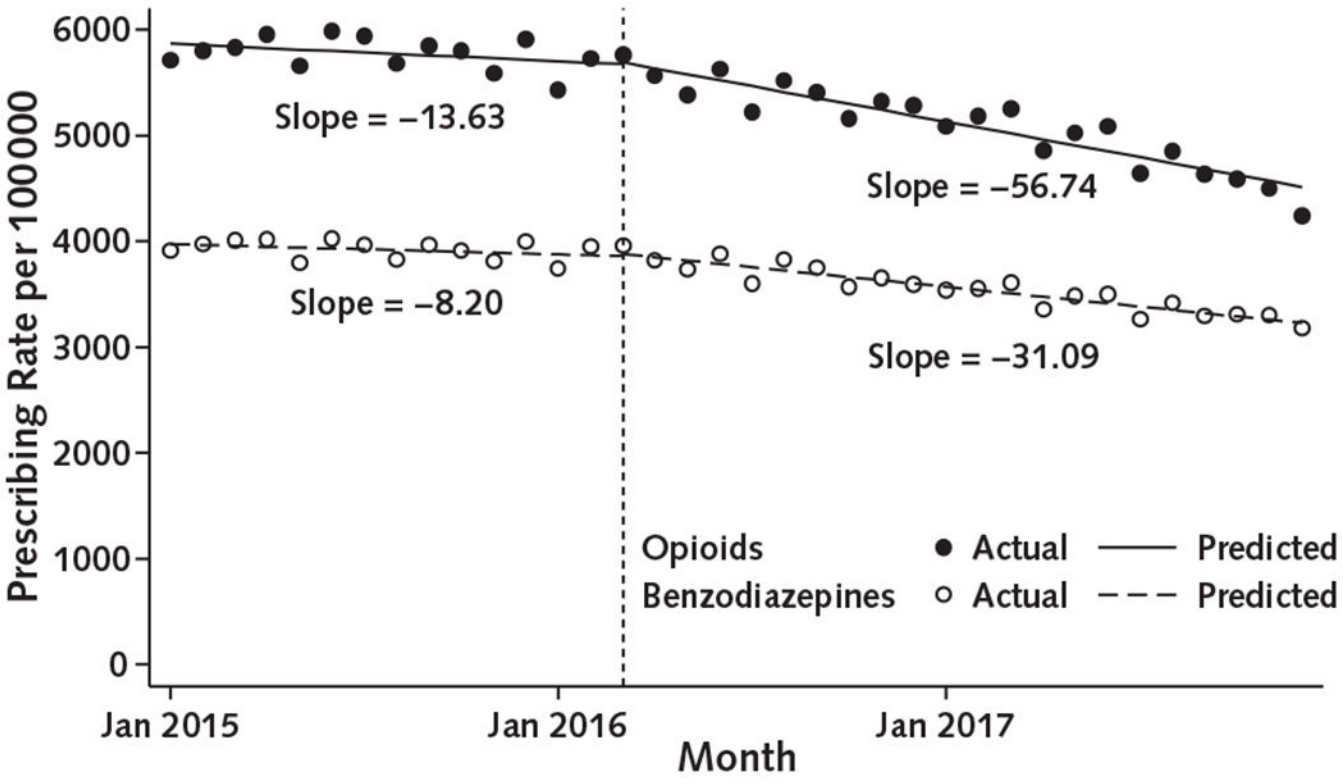
with <30 d supplied per 100 000 persons. Bottom. Rate of prescriptions dispensed with ≥30 d supplied per 100 000 persons.

* Change in slope (i.e., rate of decline per month) from before to after the CDC guideline release was statistically significant at $P < 0.001$.



Appendix Figure 2.

Count of prescriptions dispensed per month, per 100 000 persons, for opioid and benzodiazepine medications before and after release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* in March 2016.

Dashed vertical line represents the month of CDC guideline implementation (March 2016).

CDC = Centers for Disease Control and Prevention.

Appendix Table 1.

Interrupted Time Series Regression Analysis of Opioid Prescribing Measures Before and After Release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* for Public Review in December 2015 *

Variable	Preguideline Trend		Postguideline Trend		Change Associated With Guideline Release			
	Slope (95% CI)	*P* Value	Slope (95% CI)	*P* Value	Immediate Change (95% CI)	*P* Value	Change in Slope (95% CI)	*P* Value
Prescription-level outcomes								

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Variable	Preguideline Trend		Postguideline Trend		Change Associated With Guideline Release			
	Slope (95% CI)	*P* Value	Slope (95% CI)	*P* Value	Immediate Change (95% CI)	*P* Value	Change in Slope (95% CI)	*P* Value
Prescriptions dispensed per 100 000 population	−22.937 (−26.071 to −19.803)	<0.001	−51.457 (−60.310 to −42.604)	<0.001	69.003 (−88.555 to 226.561)	0.39	−28.520 (−37.913 to −19.128)	<0.001
Dosage outcomes								
Total MME prescribed per capita	−0.222 (−0.239 to −0.205)	<0.001	−0.569 (−0.629 to −0.509)	<0.001	1.605 (0.690 to 2.520)	0.001	−0.347 (−0.410 to −0.284)	<0.001
Average daily MME per prescription	−0.103 (−0.117 to −0.088)	<0.001	−0.131 (−0.162 to −0.100)	<0.001	0.390 (0.121 to 0.659)	0.005	−0.029 (−0.069 to 0.011)	0.158
Number of prescriptions written for ≥90 MME/day per 100 000 population	−3.693 (−3.930 to −3.455)	<0.001	−7.433 (−8.096 to −6.769)	<0.001	30.124 (18.950 to 41.297)	<0.001	−3.740 (−4.449 to −3.031)	<0.001
Days supplied outcomes								
Mean days supplied per prescription	0.038 (0.034 to 0.041)	<0.001	0.023 (0.015 to 0.031)	<0.001	0.003 (−0.102 to 0.108)	0.95	−0.015 (−0.025 to −0.005)	0.004
Proportion of fills for a ≤3-day supply	−0.054 (−0.064 to −0.044)	<0.001	−0.013 (−0.032 to 0.007)	0.21	0.161 (−0.151 to 0.474)	0.31	0.041 (0.017 to 0.066)	0.001
Proportion of fills for a ≤7-day supply	−0.107 (−0.121 to −0.094)	<0.001	−0.033 (−0.064 to −0.003)	0.032	−0.058 (−0.553 to 0.436)	0.82	0.074 (0.038 to 0.110)	<0.001
Patient-level outcomes								
Percentage of patients with overlapping opioid and benzodiazepine fills	−0.034 (−0.066 to −0.002)	0.039	−0.072 (−0.077 to −0.067)	<0.001	0.284 (0.084 to 0.485)	0.007	−0.038 (−0.071 to −0.005)	0.024
Percentage of opioid-naive patients prescribed an ER/LA opioid	−0.026 (−0.044 to −0.008)	0.007	−0.009 (−0.012 to −0.006)	<0.001	0.046 (−0.021 to 0.112)	0.172	0.017 (−0.003 to 0.037)	0.096

CDC = Centers for Disease Control and Prevention; ER/LA = extended-release or long-acting; MME = morphine milligram equivalents.

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*The preguideline period was January 2012 to November 2015 for all outcomes except patient-level outcomes, which included only January 2015 to November 2015. The postguideline period was December 2015 to December 2017 for all outcomes. Slopes represent the change in the indicated variable per month.

†Immediate change represents the intercept, a 1-month increase or decrease at March 2016 that is distinct from ongoing trends.

Appendix Table 2.

Interrupted Time Series Regression Analysis of Opioid Prescribing Measures Before and After Release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* in March 2016, Excluding December 2015–March 2016*

Variable	Preguideline Trend		Postguideline Trend		Change Associated With Guideline Release			
	Slope (95% CI)	*P* Value	Slope (95% CI)	*P* Value	Immediate Change (95% CI)	*P* Value	Change in Slope (95% CI)	*P* Value
Prescription-level outcomes								
Prescriptions dispensed per 100 000 population	−22.864 (−26.125 to −19.603)	<0.001	−56.070 (−66.841 to −45.298)	<0.001	−20.024 (−184.850 to 144.802)	0.81	−33.205 (−44.460 to −21.951)	<0.001
Dosage outcomes								
Total MME prescribed per capita	−0.221 (−0.238 to −0.203)	<0.001	−0.613 (−0.683 to −0.542)	<0.001	0.357 (−0.587 to 1.301)	0.45	−0.392 (−0.464 to −0.320)	<0.001
Average daily MME per prescription	−0.104 (−0.119 to −0.090)	<0.001	−0.139 (−0.176 to −0.101)	<0.001	0.424 (−0.183 to 1.031)	0.168	−0.034 (−0.075 to 0.006)	0.097
Number of prescriptions written for ≥90 MME/day per 100 000 population	−3.679 (−3.920 to −3.437)	<0.001	−7.926 (−8.688 to −7.164)	<0.001	16.960 (5.223 to 28.368)	0.005	−4.247 (−5.046 to −3.448)	<0.001
Days supplied outcomes								
Mean days supplied per prescription	0.037 (0.034 to 0.041)	<0.001	0.020 (0.009 to 0.032)	<0.001	−0.024 (−0.209 to 0.161)	0.80	−0.017 (−0.029 to −0.005)	0.006
Proportion of fills for a ≤3-day supply	−0.054 (−0.064 to −0.043)	<0.001	−0.013 (−0.038 to 0.013)	0.33	0.363 (−0.110 to 0.835)	0.130	0.041 (0.014 to 0.069)	0.004
Proportion of fills for a ≤7-day supply	−0.106 (−0.119 to −0.092)	<0.001	−0.015 (−0.055 to −0.025)	0.46	0.006 (−0.646 to 0.658)	0.99	0.091 (0.049 to 0.133)	<0.001
Patient-level outcomes								
Percentage of patients with overlapping opioid and	−0.030 (−0.060 to 0.0004)	0.053	−0.078 (−0.084 to −0.071)	<0.001	0.113 (−0.218 to 0.444)	0.49	−0.048 (−0.079 to −0.017)	0.004

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Variable	Preguideline Trend		Postguideline Trend		Change Associated With Guideline Release			
	Slope (95% CI)	*P* Value	Slope (95% CI)	*P* Value	Immediate Change (95% CI)	*P* Value	Change in Slope (95% CI)	*P* Value
benzodiazepine fills								
Percentage of opioid-naive patients prescribed an ER/LA opioid	−0.027 (−0.048 to −0.007)	0.011	−0.009 (−0.011 to −0.006)	<0.001	0.145 (−0.068 to 0.358)	0.173	0.018 (−0.002 to 0.039)	0.078

CDC = Centers for Disease Control and Prevention; ER/LA = extended-release or long-acting; MME = morphine milligram equivalents.

*The preguideline period was January 2012 to November 2015 for all outcomes except patient-level outcomes, which included only January 2015 to November 2015. The postguideline period was April 2016 to December 2017 for all outcomes. Slopes represent the change in the indicated variable per month.

†Immediate change represents the intercept, a 1-month increase or decrease at March 2016 that is distinct from ongoing trends.

Appendix Table 3.

Interrupted Time Series Regression Analysis of Opioid Prescribing Measures Before and After Release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* in March 2016, Adjusting for Potential Season Effects*

Variable	Preguideline Trend		Postguideline Trend		Change Associated With Guideline Release			
	Slope (95% CI)	*P* Value	Slope (95% CI)	*P* Value	Immediate Change (95% CI)	*P* Value	Change in Slope (95% CI)	*P* Value
Prescription-level outcomes								
Prescriptions dispensed per 100 000 population	−23.320 (−25.867 to −20.773)	<0.001	−55.627 (−64.946 to −46.309)	<0.001	24.571 (−116.789 to 165.930)	0.73	−32.307 (−41.824 to −22.791)	<0.001
Dosage outcomes								
Total MME prescribed per capita	−0.219 (−0.234 to −0.204)	<0.001	−0.615 (−0.679 to −0.550)	<0.001	0.746 (−0.122 to 1.614)	0.091	−0.396 (−0.461 to −0.330)	<0.001
Average daily MME per prescription	−0.097 (−0.112 to −0.081)	<0.001	−0.132 (−0.179 to −0.085)	<0.001	−0.045 (−0.214to 0.124)	0.60	−0.035 (−0.091 to 0.021)	0.21
Number of prescriptions written for ≥90 MME/day per 100 000 population	−3.568 (−3.789 to −3.347)	<0.001	−8.047 (−8.791 to −7.302)	<0.001	19.213 (8.554 to 29.872)	0.001	−4.478 (−5.248 to −3.712)	<0.001
Days supplied outcomes								

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Variable	Preguideline Trend		Postguideline Trend		Change Associated With Guideline Release			
	Slope (95% CI)	*P* Value	Slope (95% CI)	*P* Value	Immediate Change (95% CI)	*P* Value	Change in Slope (95% CI)	*P* Value
Mean days supplied per prescription	0.037 (0.035 to 0.040)	<0.001	0.021 (0.010 to 0.032)	<0.001	−0.022 (−0.136 to 0.092)	0.70	−0.016 (−0.028 to −0.005)	0.006
Proportion of fills for a ≤3-day supply	−0.051 (−0.058 to −0.044)	<0.001	−0.006 (−0.029 to 0.018)	0.63	0.186 (−0.0891 to 0.460)	0.181	0.045 (0.019 to 0.071)	0.001
Proportion of fills for a ≤7-day supply	−0.104 (−0.112 to −0.096)	<0.001	−0.016 (−0.055 to −0.022)	0.39	−0.061 (−0.571 to 0.449)	0.81	0.088 (0.048 to 0.127)	<0.001
Patient-level outcomes								
Percentage of patients with overlapping opioid and benzodiazepine fills	−0.025 (−0.039 to −0.012)	0.001	−0.079 (−0.085 to −0.073)	<0.001	0.126 (−0.005 to 0.256)	0.058	−0.054 (−0.068 to −0.039)	<0.001
Percentage of opioid-naive patients prescribed an ER/LA opioid	−0.015 (−0.028 to −0.003)	0.019	−0.007 (−0.010 to −0.003)	<0.001	−0.034 (−0.078 to 0.009)	0.117	0.009 (−0.006 to 0.023)	0.23

CDC = Centers for Disease Control and Prevention; ER/LA = extended-release or long-acting; MME = morphine milligram equivalents.

*The preguideline period was January 2012 to February 2016 for all outcomes except patient-level outcomes, which included only January 2015 to February 2016. The postguideline period was March 2016 to December 2017 for all outcomes. Slopes represent the change in the indicated variable per month.

†Immediate change represents the intercept, a 1-month increase or decrease at March 2016 that is distinct from ongoing trends.

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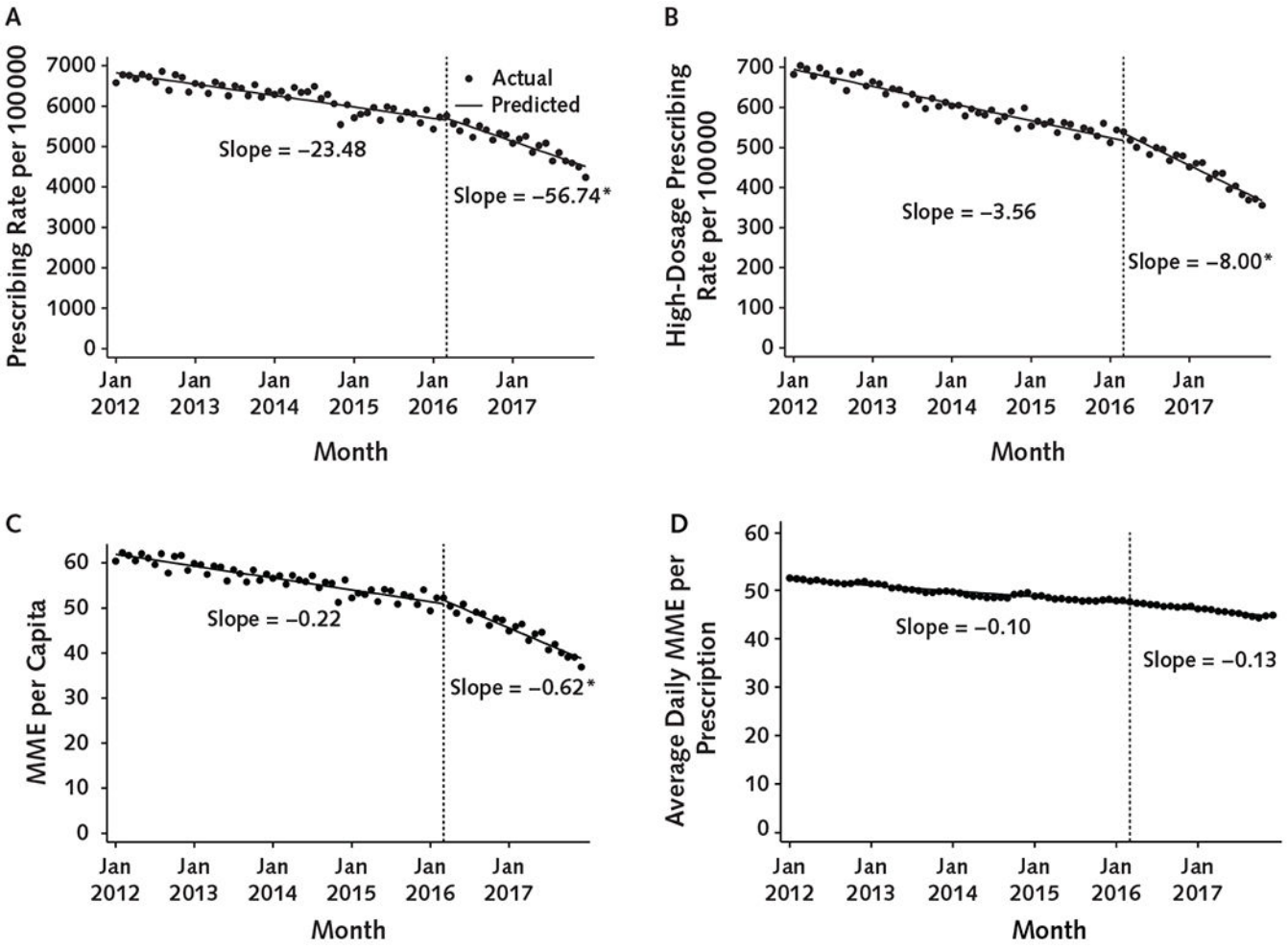

Figure 1.

Overall prescribing rate and dosage-related outcomes before and after release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* in March 2016.

Denominators in panels A to C are based on total U.S. population size. Dashed vertical lines represent the month of CDC guideline implementation (March 2016). CDC = Centers for Disease Control and Prevention; MME = morphine milligram equivalents. **A.** Count of all opioid prescriptions dispensed in a month, per 100 000 persons. **B.** Number of opioid prescriptions dispensed in a month to total a daily dosage >90 MME, per 100 000 persons. **C.** Total of all MME dispensed in a month, per person. **D.** Average daily dosage (in MME) per prescription, for all opioid prescriptions written in a month.

* Change in slope (i.e., rate of decline per month) from before to after the CDC guideline release was statistically significant at $P < 0.001$.

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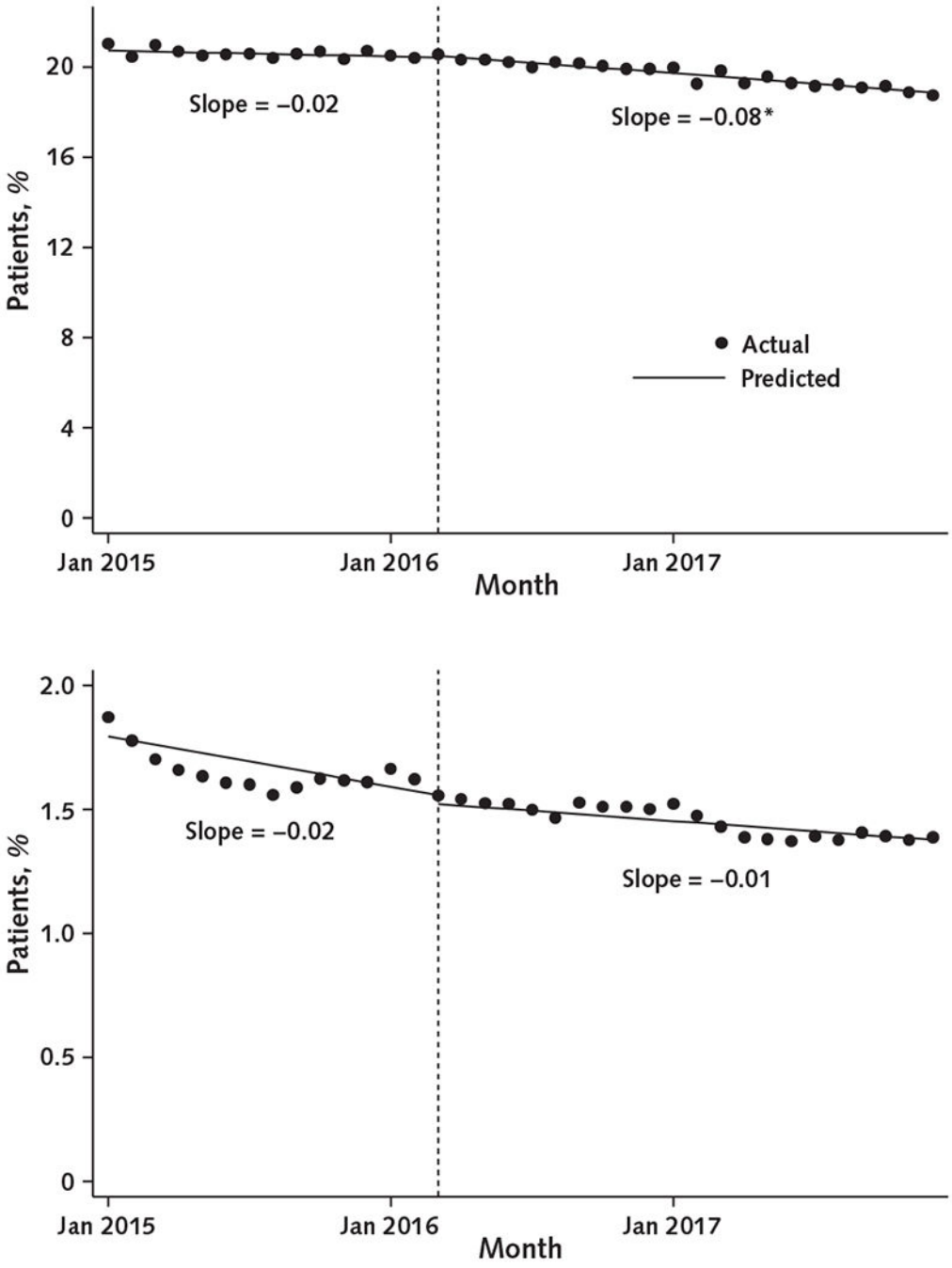

Figure 2.

Patient-level outcomes before and after release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* in March 2016.

Dashed vertical lines represent the month of CDC guideline implementation (March 2016). CDC = Centers for Disease Control and Prevention; ER/LA = extended-release or long-acting. Top. Percentage of patients with an opioid and a benzodiazepine prescription overlapping by ≥1 d. Bottom. Percentage of opioid-naive patients filling an ER/LA opioid prescription.

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* Change in slope (i.e., rate of decline per month) from before to after the CDC guideline release was statistically significant at $P < 0.001$.

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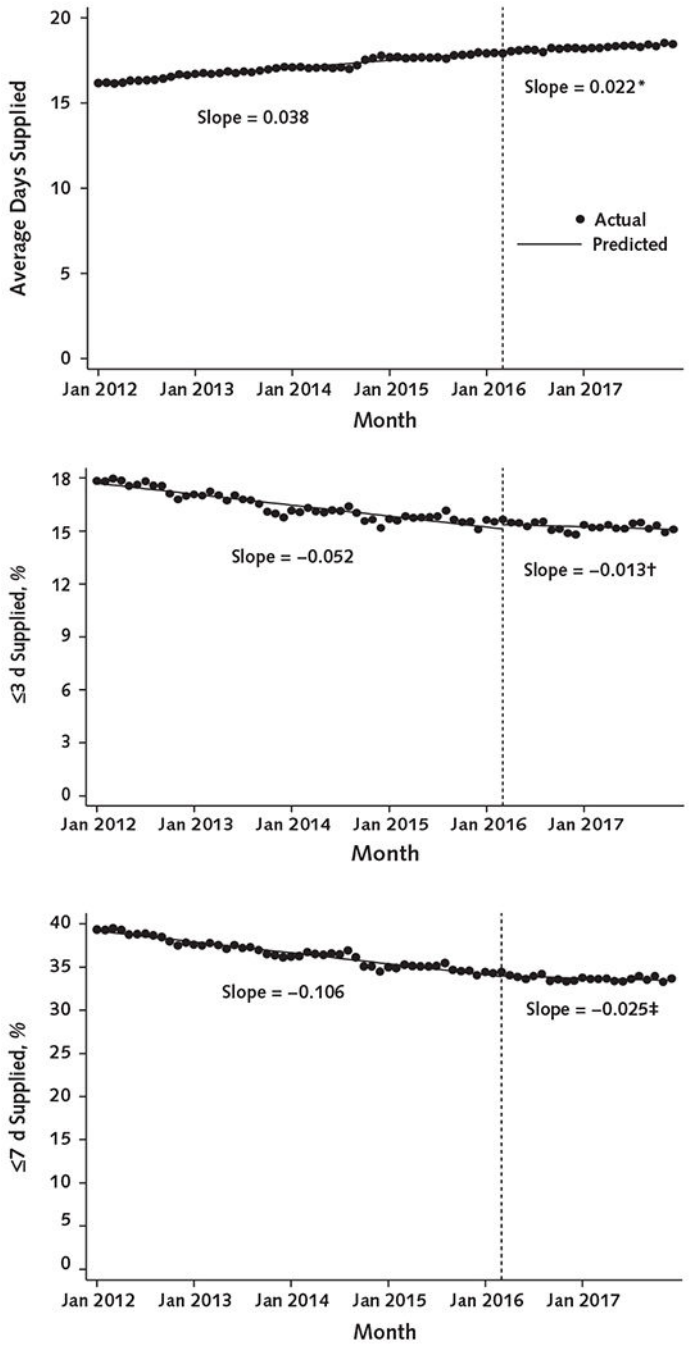

Figure 3.

Outcomes regarding days supplied before and after release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* in March 2016.

Dashed vertical lines represent the month of CDC guideline implementation (March 2016). CDC = Centers for Disease Control and Prevention. Top. Average days supplied for all prescriptions dispensed in a month. Middle. Percentage of opioid prescriptions dispensed in a month with ≤3 d supplied. Bottom. Percentage of opioid prescriptions dispensed in a month with ≤7 d supplied.

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* $P = 0.012$.
† $P = 0.005$.
‡ $P < 0.001$.

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Table 1.

Interrupted Time Series Regression Analysis of Opioid Prescribing Measures Before and After Release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* in March 2016*

Variable	Preguideline Trajectory		Postguideline Trajectory		Change Associated With Guideline Release			
	Slope (95% CI)	*P* Value	Slope (95% CI)	*P* Value	Immediate Change (95% CI)†	*P* Value	Change in Slope (95% CI)	*P* Value
Prescription-level outcomes								
Prescriptions dispensed per 100 000 persons	−23.477 (−26.179 to −20.774)	<0.001	−56.744 (−65.957 to −47.531)		44.720 (−94.393 to 183.832)	0.52	−33.267 (−42.833 to −23.701)	<0.001
Dosage outcomes								
Total MME prescribed per capita	−0.220 (−0.234 to −0.205)	<0.001	−0.618 (−0.679 to −0.556)	<0.001	0.792 (−0.045 to 1.629)	0.063	−0.398 (−0.461 to −0.335)	<0.001
Average daily MME per prescription	−0.097 (−0.112 to −0.081)	<0.001	−0.126 (−0.167 to −0.085)	<0.001	−0.051 (−0.235 to 0.133)	0.58	−0.029 (−0.079 to 0.021)	0.26
Number of prescriptions written for ≥90 MME/d per 100 000 persons	−3.556 (−3.789 to −3.324)	<0.001	−8.000 (−8.686 to −7.314)	<0.001	18.052 (6.648 to 29.155)	0.002	−4.444 (−5.164 to −3.724)	<0.001
Days supplied outcomes								
Mean days supplied per prescription	0.038 (0.035 to 0.040)	<0.001	0.022 (0.012 to 0.033)	<0.001	−0.038 (−0.146 to 0.071)	0.49	−0.015 (−0.027 to −0.003)	0.012
Proportion of fills for a ≤3-d supply	−0.052 (−0.061 to −0.042)	<0.001	−0.013 (−0.035 to 0.010)	0.26	0.249 (−0.043 to 0.541)	0.093	0.039 (0.012 to 0.066)	0.005
Proportion of fills for a ≤7-d supply	−0.106 (−0.117 to −0.095)	<0.001	−0.025 (−0.064 to 0.015)	0.22	0.060 (−0.472 to 0.592)	0.82	0.081 (0.038 to 0.124)	<0.001
Patient-level outcomes								
Percentage of patients with overlapping opioid and benzodiazepine fills	−0.021 (−0.035 to −0.008)	0.003	−0.077 (−0.083 to −0.072)	<0.001	0.071 (−0.061 to 0.202)	0.28	−0.056 (−0.070 to −0.042)	<0.001
Percentage of opioid-naive patients prescribed an ER/LA opioid	−0.017 (−0.031 to −0.002)	0.024	−0.007 (−0.012 to −0.002)	0.007	−0.036 (−0.079 to 0.007)	0.097	0.010 (−0.007 to 0.027)	0.25

CDC = Centers for Disease Control and Prevention; ER/LA = extended-release or long-acting; MME = morphine milligram equivalents.

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[*] The preguideline period was January 2012 to February 2016 for all outcomes except patient-level outcomes, which included only January 2015 to February 2016. The postguideline period was March 2016 to December 2017 for all outcomes. Slopes represent the change in the indicated variable per month.

[†] Immediate change represents the intercept, a 1-month increase or decrease at March 2016 that is distinct from ongoing trends.

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Table 2.

Estimated Change per Month in Opioid Prescribing Metrics Before and After Release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* in March 2016

Variable	Average per Month*		Estimated Total Reduction Above Preguideline Trends, March 2016-December 2017 (95% CI)†
	Before Guideline Release	After Guideline Release	
Overall opioid prescribing			
Rate per 100 000 persons	6250.03	5099.69	–
Prescriptions, *n*	20 120 806	16 827 635	14 195 471 (5 714 193–22 676 769)
High-dosage (≥90 MME/d) opioid prescribing			
Rate per 100 000 persons	607.88	450.99	–
Prescriptions, *n*	1 956 356	1 487 890	1 283 074 (626 426–1 939 724)
Patients with overlapping opioid and benzodiazepine fills			
Percentage	20.6	19.7	–
Number	2 269 812	2 021 741	1 094 492 (534 795–1 654 188)

CDC = Centers for Disease Control and Prevention; MME = morphine milligram equivalents.

*The preguideline period was January 2012 to February 2016 for overall and high-dosage opioid prescribing and January 2015 to February 2016 for overlapping opioid and benzodiazepine fills. The postguideline period was March 2016 to December 2017 for all outcomes.

†Indicates the total reductions in each metric for the postguideline period that may be attributed to the guideline release after accounting for decreases that would be expected if pre–March 2016 trends had continued unchanged.

Ann Intern Med. Author manuscript; available in PMC 2019 March 18.

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Table 3.

Comparison of Opioid and Benzodiazepine Prescriptions per 100 000 Persons Before and After Release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* in March 2016*

Outcome Measure	Preguideline Trend: Difference in Slope Between Opioids and Benzodiazepines		Differences Between Opioids and Benzodiazepines in Size of Changes at March 2016			
	Slope (95% CI)	*P* Value	Immediate Change (95% CI)†	*P* Value	Change in Slope (95% CI)	*P* Value
Prescribing rate for opioids compared with that for benzodiazepines	−5.799 (−20.855 to 9.256)	0.44	−3.246 (−172.664 to 166.172)	0.97	−19.165 (−36.313 to −2.017)	0.029

CDC = Centers for Disease Control and Prevention.

*Calculated with interaction terms between medication type (opioids/benzodiazepines) and the intercept and slope; the rate of decline was similar for both medications before March 2016 but grew steeper for opioids after March 2016. Slopes represent the change in the indicated variable per month.

†Immediate change represents the intercept, a 1-month increase or decrease at March 2016 that is distinct from ongoing trends.