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Nonrandomized Intervention Study of Naloxone Coprescription for Primary Care Patients Receiving Long-Term Opioid Therapy for Pain

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Background: Unintentional overdose involving opioid analgesics is a leading cause of injury-related death in the United States.

Objective: To evaluate the feasibility and effect of implementing naloxone prescription to patients prescribed opioids for chronic pain.

Design: 2-year nonrandomized intervention study.

Setting: 6 safety-net primary care clinics in San Francisco, California.

Participants: 1985 adults receiving long-term opioid therapy for pain.

Intervention: Providers and clinic staff were trained and supported in naloxone prescribing.

Measurements: Outcomes were proportion of patients prescribed naloxone, opioid-related emergency department (ED) visits, and prescribed opioid dose based on chart review.

Results: 38.2% of 1985 patients receiving long-term opioids were prescribed naloxone. Patients prescribed higher doses of opioids and with an opioid-related ED visit in the past 12 months were independently more likely to be prescribed naloxone. Patients who received a naloxone prescription had 47% fewer opioid-related ED visits per month in the 6 months after receipt of the prescription (incidence rate ratio [IRR], 0.53 [95% CI, 0.34 to 0.83]; $P = 0.005$) and 63% fewer visits after 1 year (IRR, 0.37 [CI, 0.22 to 0.64]; $P < 0.001$) compared with patients who did not receive naloxone. There was no net change over time in opioid dose among those who received naloxone and those who did not (IRR, 1.03 [CI, 0.91 to 1.27]; $P = 0.61$).

Limitation: Results are observational and may not be generalizable beyond safety-net settings.

Conclusion: Naloxone can be coprescribed to primary care patients prescribed opioids for pain. When advised to offer naloxone to all patients receiving opioids, providers may prioritize those with established risk factors. Providing naloxone in primary care settings may have ancillary benefits, such as reducing opioid-related adverse events.

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In the United States, the opioid analgesic overdose death rate increased from 1.4 to 5.4 per 100 000 adults from 1999 to 2011 (1). Efforts to manage this increase in mortality have focused on modifying the prescribing practices of providers (2). Mandated urine testing, pain agreements, and inspections of prescription drug monitoring program data have become standard practice, yet few data support a link between such interventions and reduced opioid-related morbidity or mortality. In fact, whereas opioid analgesic deaths have recently plateaued, heroin use and overdose deaths have skyrocketed, suggesting possible unintended consequences of opioid stewardship initiatives (3, 4).

Many communities have used the targeted distribution of naloxone, the short-acting opioid antagonist, to address opioid-related mortality (5). Provision of naloxone to those likely to witness or experience an opioid overdose, principally illicit drug users, has been associated with substantial reductions in community-level opioid overdose mortality relative to communities that did not implement naloxone distribution (6). Other observational and ecologic analyses have demonstrated marked reductions in opioid overdose mortality in communities that distributed naloxone, including Chicago, Illinois (7); New York City (8); and Scotland (9). A meta-analysis demonstrated a higher likelihood of survival in overdose situations when naloxone was administered by laypersons (10). Naloxone distribution to heroin users is remarkably cost-effective (11).

In San Francisco, California, implementation and expansion of a targeted naloxone distribution program were temporally associated with a decline in heroin overdose deaths from as high as 180 per year to as few as 10 through 2012. The number of deaths attributed to opioid analgesics, however, exceeded 100 annually from 2010 to 2012 (12). Most of these decedents had received primary care in safety-net clinics, and most had received long-term opioid therapy for pain. However, literature to support naloxone prescribing to this population is limited to early descriptive analyses (13) and anecdotal reports (14). At U.S. Army Fort Bragg, overdoses seen in the emergency department (ED) declined from 8 per month to 0 after naloxone coprescription was started (14, 15); this finding suggests that naloxone prescription may have affected the overdose event rate by influencing patient and/or provider behavior, rather than simply being available as a reversal agent. These results are consistent with some data indicating that heroin users who receive naloxone reduce heroin use (16).

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In response to these data, we developed and coordinated a standardized naloxone coprescribing program at primary care clinics in a safety-net system in San Francisco. To inform the larger-scale implementation of naloxone prescribing for patients prescribed opioid medications, we assessed the feasibility of introducing and scaling up naloxone coprescribing in these primary care clinics and conducted analyses to assess the association of naloxone coprescribing with ED use and prescribed opioid dose.

METHODS

Naloxone for Opioid Safety Evaluation (NOSE) staff coordinated the clinical program and conducted the evaluation. The study was approved by the Committee on Human Research of the University of California, San Francisco (CHR#13-11168).

Clinical Program

The clinical program was implemented in a rolling fashion from February 2013 to April 2014 at 6 clinics where patients had died of opioid overdose from 2010 to 2012. All clinics accepted only publicly insured or uninsured patients, and 2 were resident training sites. Onsite leaders were selected, and a consistent protocol was implemented across sites, beginning with training in naloxone prescribing for providers (physicians, nurse practitioners, and physician assistants) and staff (see **Appendix** and **Appendix Table 1**, available at www.annals.org, for implementation plan and process outcomes). Training covered rationale and indications for prescribing naloxone (anyone who uses opioids long term or is otherwise at risk for witnessing or experiencing an opioid overdose), language to approach patients (for example, use such phrases as "bad reaction" instead of "overdose"), naloxone formulations, and pharmacy/payer coverage. Additionally, providers and staff were trained on how to educate patients on naloxone use, how to assemble the intranasal device (the U.S. Food and Drug Administration has since approved a device requiring no assembly [17]), and ensuring that caretakers know how and when to administer naloxone (**Appendix Figure 1**, available at www.annals.org).

Initial training was provided to all sites approximately 30 days preceding initiation of naloxone coprescription; after initiation, additional training was provided and at least 1 reminder e-mail was sent to providers (**Appendix Figure 2**, available at www.annals.org). Because most providers opted to prescribe the intranasal formulation of naloxone and the mucosal atomization device was not readily available from pharmacies, clinics could order the device and patient brochures (**Appendix Figure 3**, available at www.annals.org) in zipper-seal plastic bags from the clinic system's central pharmacy. NOSE staff assisted with any logistic problems, and a clinical pharmacist educated any pharmacies that encountered problems ordering, dispensing, or billing for naloxone (**Appendix Figure 4**, available at www.annals.org).

Data Sources and Data Abstraction

Feasibility was assessed through chart reviews of all patients receiving long-term opioid therapy by prescription. Patients receiving sufficient opioids to take at least 1 pill daily for more than 3 months were added to a pain management registry (PMR) by staff at each clinic. This list was downloaded every 3 months during the intervention period, and a merged list of 3138 patients with demographic data was generated in March 2015. A manual chart review was conducted to determine whether patients were valid PMR entrants during the study period and to collect the following data: 1) opioid type, dose, quantity per 30 days, and date prescribed at 2 clinic visits (the visit closest to the baseline date [start of naloxone coprescribing at the given clinic or the date the patient was added to the PMR, whichever was later] and the last visit at the clinic before chart review [that is, follow-up date]); 2) the date of initial naloxone prescription; and 3) dates of all ED visits at the county hospital and opioid-relatedness.

The ED visits were coded as "opioid-related" in accordance with documentation for establishing drug-relatedness of ED visits from the Drug Abuse Warning Network (18). Visits were opioid-related if the documenting physician considered them to be primarily due to an adverse event from an opioid or to opioid-seeking behavior; a subset of visits was coded as "oversedation" if the assessment was an opioid poisoning or other complication attributed by the documenting physician to opioid-induced sedation. Staff reviewing charts included a physician who trained other staff and reviewed uncertain cases; 62.5% of charts were independently assessed by at least 2 reviewers (see **Appendix** for details). Death information was extracted from the California Electronic Death Record System on 14 July 2015.

Feasibility Analysis

We assessed bivariate relationships between all demographic and clinical characteristics presented in **Table 1** and the receipt of naloxone during the study period using chi-square, Fisher exact (for comparisons with cell sizes <5), and Wilcoxon rank-sum tests. Morphine equivalent daily dose in milligrams (MEQ) was calculated for each patient at baseline and subsequent follow-up dates by using standard conversion ratios from the literature (19, 20).

We fit a normal-logistic regression model, with random effects for providers, to assess both patient- and provider-level predictors of naloxone prescription. All baseline patient characteristics assessed in bivariate analyses were included in the model, except for opioid type; the latter was excluded because relevant elements of formulations (such as presence of acetaminophen or duration of action) do not necessarily correspond to opioid type. Only baseline history of any opioid-related ED visit was included in the model because this category of visit was hypothesized to be most relevant to naloxone prescribing. The model also included provider type (attending physician or fellow, resident physician, or other provider) and the size of

Table 1. Demographic and Clinical Characteristics of PMR Patients, by Receipt of Naloxone Prescription

Characteristic	Received Naloxone		Total
	No	Yes	
Total, *n* (%)	1226 (61.8)	759 (38.2)	1985 (100.0)
Sex, *n* (%)			
Female	503 (61.2)	319 (38.8)	822 (41.4)
Male	723 (62.2)	440 (37.8)	1163 (58.6)
Mean age (SD), *y**	57.3 (10.8)	55.7 (10.7)	56.7 (10.8)
Race/ethnicity, *n* (%)†			
White	338 (55.8)	268 (44.2)	606 (30.5)
Black	622 (64.8)	338 (35.2)	960 (48.4)
Hispanic/Latino	175 (66.0)	90 (34.0)	265 (13.4)
Other	91 (59.1)	63 (40.9)	154 (7.8)
Clinic, *n* (%)†			
A	431 (68.8)	195 (31.2)	626 (31.5)
B	313 (69.9)	135 (30.1)	448 (22.6)
C	165 (48.7)	174 (51.3)	339 (17.1)
D	199 (67.5)	96 (32.5)	295 (14.9)
E	98 (44.5)	122 (55.5)	220 (11.1)
F	20 (35.1)	37 (64.9)	57 (2.9)
MEQ daily dose, *n* (%)†			
≤20 mg	418 (72.8)	156 (27.2)	574 (28.9)
21–60 mg	338 (66.9)	167 (33.1)	505 (25.4)
61–120 mg	165 (56.5)	127 (43.5)	292 (14.7)
121–200 mg	109 (54.2)	92 (45.8)	201 (10.1)
201–400 mg	113 (49.6)	115 (50.4)	228 (11.5)
≥400 mg	83 (44.9)	102 (55.1)	185 (9.3)
Prescribed opioid, *n* (%)			
Codeine	130 (67.4)	63 (32.6)	193 (9.7)
Hydrocodone†	361 (70.0)	155 (30.0)	516 (26.0)
Oxycodone†	523 (57.0)	394 (43.0)	917 (46.2)
Morphine†	269 (53.6)	233 (46.4)	502 (25.3)
Methadone†	106 (53.3)	93 (46.7)	199 (10.0)
Hydromorphone	33 (54.1)	28 (45.9)	61 (3.1)
Fentanyl*	20 (41.7)	28 (58.3)	48 (2.4)
Other‡	12 (63.2)	7 (36.8)	19 (1.0)
Opioid dose change during study period*†			
Mean dose change in MEQ (SD), *mg*	−21.6 (197.6)	−44.9 (228.2)	−31 (210.0)
Median dose change in MEQ (IQR), *mg*	0.0 (−15.0 to 5.0)	0.0 (−50.0 to 3.0)	0.0 (−25.0 to 4.5)
Increase, *n* (%)	340 (62.7)	202 (37.3)	542 (27.3)
No change, *n* (%)	415 (65.7)	217 (34.3)	632 (31.8)
Reduction, *n* (%)	279 (53.4)	243 (46.6)	522 (26.3)
Discontinuation, *n* (%)	192 (66.4)	97 (33.6)	289 (14.6)
ED visits during 12 mo before baseline date, *n* (%)			
Any visit†	390 (58.3)	279 (41.7)	669 (33.7)
Any opioid-related visit†	59 (46.5)	68 (53.5)	127 (6.4)
Any oversedation visit	14 (46.7)	16 (53.3)	30 (1.5)
ED visits between 1 January 2013 and end of follow-up, *n* (%)			
Patients with any visit	644 (60.7)	417 (39.3)	1061 (53.5)
Patients with any opioid-related visit†	130 (52.8)	116 (47.2)	246 (12.4)
Patients with any oversedation visit†	31 (46.3)	36 (53.7)	67 (3.4)
Mean annual ED visit rate between 1 January 2013 and end of follow-up (SD)			
Mean rate of any type of visit	0.87 (2.0)	0.99 (2.0)	0.91 (2.0)
Mean rate of opioid-related visits*	0.11 (0.6)	0.13 (0.6)	0.12 (0.6)
Mean rate of oversedation visits*	0.017 (0.1)	0.024 (0.1)	0.020 (0.1)
Deaths during study period, *n* (%)			
All-cause	40 (67.8)	19 (32.2)	59 (3.0)
Opioid poisoning§	3 (60.0)	2 (40.0)	5 (0.3)

ED = emergency department; IQR = interquartile range; MEQ = morphine equivalent; PMR = pain management registry.
* $P < 0.05$ from Wilcoxon rank-sum test.
† $P < 0.05$ from chi-square or Fisher exact test.
‡ Other opioids included buprenorphine for pain and meperidine.
§ Bivariate relationship assessed with Fisher exact test because of small cell sizes.

each provider's panel of PMR patients, while controlling for time in days from 1 February 2013 (the earliest program initiation date) to patient baseline date, as well as time between the baseline and follow-up visit dates.

To characterize residual differences among providers in naloxone prescription rates, we calculated the odds ratio for the difference between the 25th and 75th percentile values of the random provider effect. A descriptive summary of the PMR panel size, number of patients prescribed naloxone, and percentage of patients prescribed naloxone per provider is presented in Appendix Table 2 (available at www.annals.org).

Analysis of ED Use

In our prespecified plan to assess the association of naloxone receipt with opioid-related ED visits, numbers of opioid-related ED visits were calculated for each patient in each month between January 2013 and the date of chart review (March to October 2015). For patients who died during the study period (n = 59), follow-up ended at the date of death.

We then developed a multivariable Poisson regression model for the monthly number of opioid-related ED visits, using an offset to account for days of exposure in each month (ranging from 1 to 31 with an average of 30.0). This model used generalized estimating equations with exchangeable working correlation and robust SEs to account for clustering by patient, as well as overdispersion. The effect of receipt of a naloxone prescription was assessed by using 2 time-dependent covariates: The first, an indicator for all months after the first naloxone prescription, models the immediate effect; and the second, the number of months since first naloxone prescription, captures subsequent increases or decreases in the prescription effect; this has value 0 before receipt of naloxone. Patients never prescribed naloxone were assigned values of 0 for both covariates.

The model adjusted for age, race/ethnicity, sex, MEQ at baseline date, history of any opioid-related ED visit between 1 January 2012 and 31 December 2012, and clinic. The model also flexibly controlled for secular trends in ED use by using a 3-knot restricted cubic spline in calendar month, starting from January 2013; as a result, effect estimates for having received a naloxone prescription are net of any underlying secular trend.

To illustrate the estimated naloxone effects, we plotted the expected number of ED visits in each month for 2 patients (1 who received naloxone and 1 who did not), with the time scale for both trajectories centered on the median month of naloxone prescription; for both patients, expected values were evaluated at the mean values of all covariates. Similar plots stratified by clinic and models allowing modification of both the immediate naloxone prescription effect and subsequent changes in the effect over time by clinic are presented in Appendix Figure 5 (plots) and Appendix Table 3 (regression results) (available at www.annals.org).

In a sensitivity analysis, we counted opioid overdose deaths that occurred during the study period (n = 5) as an event. In a second sensitivity analysis, we adjusted for whether the patient ever received naloxone during the study period in order to control for unmeasured differences between individuals who were and were not prescribed naloxone that may not have been accounted for by the included demographic and clinical covariates. In a third sensitivity analysis, we excluded the variable indicating a history of any opioid-related ED visit between 1 January 2012 and 31 December 2012.

Analysis of Opioid Dose

We fit an adjusted generalized estimating equation negative binomial model for the baseline and follow-up total MEQ values, set up in essentially the same way as the model for opioid-related ED visits. Negative binomial models accommodate severe right skewness and also 0 values, observed at follow-up among participants whose opioids were discontinued. Specifically, we used the same 2 time-dependent covariates to model the immediate effect of having received a naloxone prescription as well as changes in this effect, net of the secular effect modeled using a 3-knot restricted cubic spline in months since 1 February 2013 (the earliest program initiation date), and controlling for age, sex, race/ethnicity, history of any opioid-related ED visit, and clinic. However, in line with our sensitivity model for ED visits, we included an indicator for naloxone group as a fixed effect (that is, whether the patient ever received naloxone during the study period), to capture the systematically higher total MEQ at baseline in the group that went on to receive a naloxone prescription; this difference could not be adequately controlled by the covariates available to us. This is analogous to an analysis of pre- and posttreatment values in a randomized trial using group, time, and their interaction, with the main effect for group capturing any baseline between-group differences.

Finally, as indicated by exploratory analysis, we allowed this baseline group effect to vary by clinic, using an interaction term. As in the analysis of ED visits, we illustrate the estimated naloxone effects by plotting expected MEQ dose for 2 patients, 1 of whom received naloxone, both with typical covariate levels, and the time scale centered on the median month of naloxone prescription. Similar plots stratified by clinic and models allowing modification of both the immediate naloxone prescription effect and subsequent changes in the effect over time by clinic are presented in Appendix Figure 6 (plots) and Appendix Table 4 (regression results) (available at www.annals.org).

Motivated by the hypothesis that naloxone prescription could lead providers to decrease total MEQ for some patients and increase it for others, we also categorized the change in prescribed opioid dose between the baseline and follow-up clinic visits as increased, decreased/discontinued, or unchanged and used a multinomial logistic regression model to assess the association of naloxone prescription with this 3-level outcome, with no change in dose as the reference level of the outcome (Appendix).

Role of the Funding Source

The funder, the National Institute on Drug Abuse, had no role in the design, conduct, or reporting of this study or the decision to publish the manuscript.

RESULTS

Patient Characteristics

A total of 3138 patient chart reviews identified 1985 patients prescribed opioids for long-term pain management from the clinics during the time of naloxone prescribing (Table 1). The excluded patients consisted of those who, at the start of naloxone prescribing, were no longer in care at the clinics (n = 600), were not prescribed opioids (n = 447), were deceased (n = 21), or were prescribed opioids only for opioid use disorder treatment (n = 85). There were more men than women, and blacks accounted for the plurality of patients. Baseline opioid dose ranged from 2 to 4200 MEQ/d, with a median dose of 53 MEQ/d. Nearly three quarters received more than 20 MEQ/d, and nearly 10% received more than 400 MEQ/d. Oxycodone was the most commonly prescribed opioid, followed by hydrocodone and morphine. Patient characteristics stratified by clinic are presented in Appendix Table 5.

Feasibility of Naloxone Prescribing

During the study period, naloxone was prescribed to 759 pain patients (38.2%) over 2254 patient-years. Patients who received naloxone accounted for 19 of 59 (32.2%) deaths during the study period and 2 of 5 (40%) opioid poisoning deaths. Our logistic regression model assessing predictors of naloxone prescription included only the 1805 (90.9%) patients for whom provider data were available. In this analysis, patients who were receiving a higher dose of opioids or seen in the county ED for an opioid-related visit in the 12 months preceding their baseline date were more likely to receive a naloxone prescription (Table 2).

Older patients had lower odds of being prescribed naloxone. Receiving a naloxone prescription was also dependent on which clinic patients attended, with 3 clinics (including 1 of 2 resident training sites) prescribing naloxone to a substantially lower proportion of patients than the other clinics. Although statistically insignificant (P > 0.05), there were trends toward lower odds of being prescribed naloxone among black patients than among white patients and greater odds of prescribing naloxone among resident physicians compared with attending physicians and fellows. The odds ratio for the difference between the 25th and 75th percentiles of the provider random effect (our measure of residual between-provider variability in naloxone prescription rates not accounted for by the fixed effects in the model) was 5.06 (95% CI, 3.45 to 6.9).

Opioid-Related ED Visits

There were a total of 4322 ED visits during the study period, 471 of which were opioid-related and 95 which were attributed to opioid-induced oversedation. On average, patients had 6% fewer opioid-related ED visits with each additional month since the receipt of a naloxone prescription (incidence rate ratio [IRR], 0.94 [CI, 0.89 to 0.998]; P = 0.044), after adjustment for all demographic and clinical covariates and secular trends in ED use (Table 3). This monthly decrease in opioid-related ED visits after the receipt of a naloxone prescription corresponds to a 47% reduction in opioid-related ED visits per month 6 months after receipt of the prescription (IRR, 0.53 [CI, 0.34 to 0.83]; P = 0.005) and a 63% reduction after 1 year (IRR, 0.37 [CI, 0.22 to 0.64]; P < 0.001).

Figure 1 shows the pattern of expected ED visit rates for 2 typical patients, 1 of whom received naloxone. Results were essentially unchanged when the 5 opioid poisoning deaths that occurred during the study period were included as events (IRR, 0.95 [CI, 0.89 to 1.00]; P = 0.050) and in our sensitivity analysis adjusting for ever receiving a naloxone prescription (IRR, 0.94 [CI, 0.89 to 1.00]; P = 0.039). In our final sensitivity analysis excluding history of any opioid-related ED visit, the evidence for the relationship between months since naloxone prescription and the monthly number of ED visits was marginally insignificant (IRR, 0.94 [CI, 0.88 to 1.01]; P = 0.080).

Prescribed Opioid Dose

In the generalized estimating equation negative binomial model for expected MEQ, the baseline secular

Table 2. Multivariable Logistic Regression Model Assessing Odds of Naloxone Prescription (n = 1805 Patients)*

Variable	Adjusted Odds Ratio (95% CI)	P Value
Age (5-y units)	0.94 (0.89–1.00)	0.036
Race/ethnicity		
White	Reference	
Black	0.77 (0.58–1.03)	0.078
Hispanic/Latino	0.74 (0.49–1.13)	0.162
Other	0.74 (0.45–1.22)	0.239
Sex		
Female	Reference	
Male	0.99 (0.77–1.27)	0.945
Log MEQ daily dose	1.73 (1.57–1.92)	<0.001
ED visit during 12 mo before baseline date†	2.54 (1.54–4.18)	<0.001
Provider type		
Attending physician/fellow	Reference	
Resident physician	1.84 (0.98–3.45)	0.058
Other provider	0.83 (0.41–1.68)	0.606
Number of PMR patients seen by provider	1.00 (0.98–1.02)	0.691

ED = emergency department; MEQ = morphine equivalent; PMR = pain management registry.
* Adjusted for patient clinic, number of days elapsed between the earliest date of program initiation (1 February 2013) and patient baseline date and number of days elapsed between patient baseline date and subsequent follow-up date.
† Includes only opioid-related ED visits.

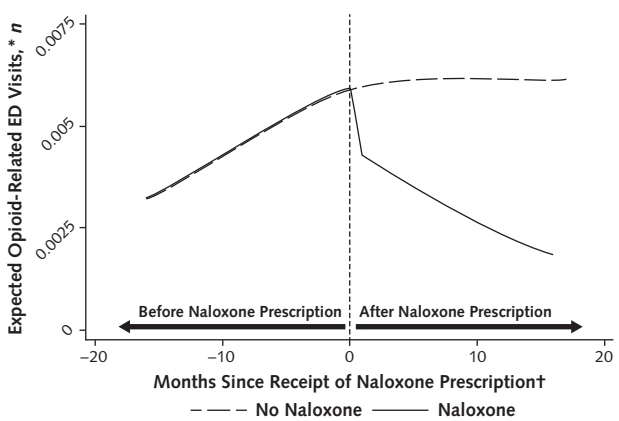
Table 3. Multivariable Poisson Regression Model Fit With Generalized Estimating Equations Assessing Count of Opioid-Related ED Visits per Month (n = 1985 Patients)*

Variable	IRR (95% CI)	*P* Value
Immediate naloxone effect	0.76 (0.42–1.36)	0.355
Naloxone trend effect per additional month after naloxone receipt	0.94 (0.89–0.998)	0.044
Age (5-y units)	0.94 (0.85–0.97)	0.003
Race/ethnicity		
White	Reference	
Black	0.91 (0.50–1.66)	0.769
Hispanic/Latino	1.21 (0.46–3.17)	0.702
Other	1.40 (0.63–3.10)	0.415
Sex		
Female	Reference	
Male	1.61 (1.09–2.37)	0.017
Log MEQ daily dose	1.25 (1.04–1.51)	0.017
ED visit between 1 January and 31 December 2012†	9.65 (5.68–16.40)	<0.001

ED = emergency department; IRR = incidence rate ratio; MEQ = morphine equivalent.
* Adjusted for patient clinic and a cubic spline of the sequential count of patient-months starting with a value of 1 for January 2013.
† Includes only opioid-related ED visits.

trend showed a rapid decrease followed by leveling off (P < 0.0005 for both the overall effect and its nonlinearity), as well as strong baseline differences between the 2 groups, in particular at 2 of the 6 clinics. After controlling for demographic and clinical characteristics and secular trend, we found a nominal 15% decrease in total MEQ at the time of naloxone prescription (IRR, 0.85 [CI, 0.67 to 1.08]; P = 0.191), followed by 1% monthly increases in dose (IRR, 1.01 [CI, 0.996 to 1.03]; P = 0.154), resulting in an estimated net effect at 18 months of nil (IRR, 1.03 [CI, 0.91 to 1.27]; P = 0.61) (Table 4). These effects are illustrated for 2 typical patients in Figure 2.

Figure 1. Expected number of opioid-related ED visits per month, by receipt of naloxone prescription.



ED = emergency department.
* Expected number of ED visits per month calculated for 2 patients (1 who received a naloxone prescription and 1 who did not), both with mean values of all covariates.
† For both trajectories, time was uniformly centered on April 2014, the median month of receipt of naloxone prescription during the study period among patients who received naloxone.

Table 4. Multivariable Negative Binomial Regression Model Fit With Generalized Estimating Equations Assessing Opioid Dose at Baseline and Follow-up (n = 1985 Patients)*

Variable	IRR (95% CI)	*P* Value
Immediate naloxone effect	0.85 (0.67–1.08)	0.191
Naloxone trend effect per additional month after naloxone receipt	1.01 (1.00–1.03)	0.154
Age (5-y units)	0.99 (0.97–1.02)	0.725
Race/ethnicity		
White	Reference	
Black	0.83 (0.71–0.98)	0.031
Hispanic/Latino	0.63 (0.50–0.79)	<0.001
Other	0.45 (0.35–0.58)	<0.001
Sex		
Female	Reference	
Male	1.19 (1.04–1.37)	0.012
ED visit during 12 mo before baseline date†	1.43 (1.11–1.83)	0.005

ED = emergency department; IRR = incident rate ratio.
* Adjusted for patient clinic, a naloxone group indicator (i.e., whether patient ever received naloxone during the study period), and a cubic spline in months since 1 February 2013 (the earliest program initiation date). The model allowed for the effect of the naloxone group indicator to vary by clinic, using an interaction term.
† Includes only opioid-related ED visits.

In our additional analysis using multinomial logistic regression, having received a naloxone prescription was associated with a decrease or discontinuation in opioid dose (relative risk reduction, 1.47 [CI, 1.17 to 1.86]; P = 0.001) but not significantly associated with an increase in dose (relative risk ratio, 1.18 [CI, 0.92 to 1.52]; P = 0.198) (Appendix Table 6, available at www.annals.org).

DISCUSSION

This nonrandomized intervention study found that primary care providers prescribed naloxone to a substantial proportion of patients receiving long-term opioid therapy for pain management. When advised to offer naloxone to all patients receiving long-term opioids, clinicians were more likely to prescribe to those who were probably at higher risk for overdose, including patients receiving higher doses of opioids and those who have had opioid-related ED visits in the past. In the absence of guideline-based indications for naloxone coprescribing, these may be reasonable metrics upon which to prioritize prescription of naloxone. In fact, the Centers for Disease Control and Prevention recently released guidelines on opioid prescribing that recom-

mend considering naloxone prescription for patients with a history of overdose, a history of a substance use disorder, an opioid dose greater than 50 MEQ, or concurrent benzodiazepine use (21).

Nonetheless, there may be hazards to risk-stratifying patients for naloxone prescription, including stigma, medico-legal concerns about acknowledging a patient's elevated risk for overdose, and failure to reach the high proportion of potential decedents who access intentionally or unintentionally diverted opioids (22). Finally, there may be a behavioral effect of naloxone coprescription in which patients become more aware of the hazards of these medications and engage in efforts to improve medication safety—a benefit hinted at by our analyses.

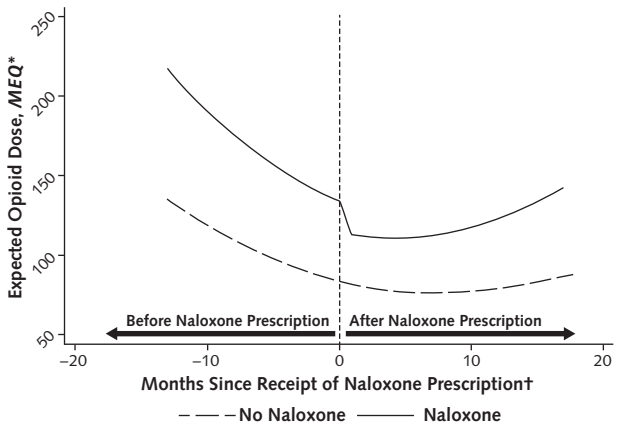
The proportion of patients prescribed naloxone varied substantially both by clinic and by provider. In addition, older patients were less likely to receive naloxone prescriptions, and weak evidence suggested the same for black patients. There are several possible explanations for this variation. Because prescribing naloxone was not considered standard practice and lacked the wealth of data supporting most other routine preventive medical interventions, some providers may have opted not to follow the recommendations for naloxone prescribing, and vocal "champions" at selected clinics may have been able to substantially influence other providers. With regard to patient-level factors, the median age of opioid overdose death in San Francisco is 50 years (12), suggesting unmet need for naloxone among older patients. Similarly, blacks were overrepresented among PMR patients in the safety-net clinics (particularly in 2 of the low-prescribing clinics, representing 88.4% and 42.5% of patients at those clinics, respectively), as well as among opioid overdose decedents, relative to the San Francisco population (12). Changes in clinic protocols and additional provider education may be needed to ensure access to naloxone to patients most at risk.

Receipt of naloxone was independently associated with a reduction in opioid-related ED visits over time, raising the possibility that providing naloxone affected patient behavior with respect to opioids. This finding is consistent with prior observations of similar benefits with naloxone receipt among patients prescribed opioids at U.S. Army Fort Bragg (14, 15) and among some heroin users trained in overdose prevention (16). Such a change was not found in an interrupted time series of community distribution of naloxone (6), suggesting that any associated behavioral modification may depend on the mode of intervention delivery. In addition, we found no net effect of naloxone receipt on opioid dose over time and a possible reduction in dose in an alternative analysis, alleviating potential concerns that providing naloxone could result in risk compensation via increased use of opioids. These potential benefits of naloxone provision should be targets for future research.

This study had several limitations. First, we cannot definitively infer causality from this observational study. Second, data collected by chart review may vary by documentation patterns; however, the size of our sample should reduce the effect of such variation. Third, our data do not confirm that patients filled their naloxone prescriptions. Fourth, we were unable to ascertain whether patients sought care outside of the safety-net system. In addition, we could not assess details of patients' history of substance use or incarceration, factors that may influence naloxone prescribing and overdose risk. Finally, results may not be generalizable outside of safety-net clinical care settings.

In summary, we demonstrated that naloxone can be successfully prescribed to a substantial proportion of patients receiving opioids for chronic pain in primary care practices. Naloxone coprescribing was associated with reduced opioid-related ED visits, suggesting a possible ancillary benefit of reducing opioid-related adverse events, and no net change in opioid dose. Naloxone prescribing is now more straightforward, with the U.S. Food and Drug Administration's recent approval of naloxone devices designed for lay persons (17).

Figure 2. Expected opioid dose, by receipt of naloxone prescription.



MEQ = morphine equivalent.
* Expected MEQ daily dose in milligrams in 2 patients (1 who received a naloxone prescription and 1 who did not), both with mean values of all covariates.
† For both trajectories, time was uniformly centered on April 2014, the median month of receipt of naloxone prescription during the study period among patients who received naloxone.

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Appendix: Methods

Clinical Program

NOSE staff provided initial and ongoing training at each clinic and provided ongoing support throughout the pilot. NOSE staff conducted onsite naloxone prescribing and education training at each clinic before program initiation and provided additional training intermittently throughout the study (Appendix Table 1). Clinic-wide staff received information about the program at least once through in-person meetings and staff-wide e-mails; providers, nurses, and medical assistants received additional specialized education through group-specific meetings and one-on-one training.

Meetings with providers focused on technical aspects of naloxone prescribing, including entering the prescription into the electronic medical record, interfacing with pharmacies, delegating naloxone prescribing and education tasks, and fielding provider questions and concerns. These trainings also covered nonstigmatizing language to present naloxone to patients. Trainings were often conducted at provider-wide meetings or smaller provider "huddles," which varied in size and length. Provider trainings included 5 to 30 providers and lasted 5 to 60 minutes.

The nursing and medical assistant staff also received one-on-one training to discuss educating patients who were receiving naloxone prescriptions. These sessions were designed to ensure familiarity with the naloxone device, including its formulation, assembly, and indications for when and how to use it, and to ensure comfort with the education guidelines, as described in Appendix Figure 1. This training included role-plays and lasted 5 to 15 minutes.

After rollout, NOSE staff remained engaged with clinic activities and were available to provide technical support, such as addressing problems with pharmacy access to naloxone and access to naloxone kit supplies (for example, the atomizer and brochure).

Support for all 6 clinics combined required on average approximately 20% full-time effort per year provided by midlevel nonclinical staff.

Data Sources and Data Abstraction

Review of 3138 charts identified 1985 patients eligible for inclusion in the study. Patients were excluded if, at the start of naloxone prescribing, they were not in care (n = 600), were not prescribed opioids (n = 447), were receiving opioids for opioid use disorder treatment only (n = 85), or were deceased (n = 21). At least 1241 (62.5%) of the 1985 eligible charts were assessed by 1 or more additional reviewers. These additional assessments occurred in several different ways. First, reviewers were instructed to mark "review" on any charts for which there was uncertainty about any data elements, resulting in a second assessment of at least 908 charts (an unquantified number of additional charts were assessed by a second reviewer in real time when the initial reviewer had questions). Second, at the conclusion of data collection, to ensure that charts assessed early in the process were consistent with interpretations made later in the process, a second reviewer assessed all 339 charts from the first clinic reviewed. Third, at the conclusion of data collection, a second reviewer assessed the 409 charts assessed by reviewers who had assessed less than 20% of the total charts. Finally, at the conclusion of data collection, 63 additional charts not reassessed through any of the prior processes were randomly selected for a final assessment. Data were not collected with regard to changes made during secondary reviews, with the exception of the final random review of 63 charts, which resulted in no changes to any data elements. The total number of repeated assessments exceeds the total number of charts that were reassessed because some charts marked for "review" were later selected for reassessment.

Analysis of Opioid Dose

In an additional analysis, motivated by the hypothesis that naloxone prescription could lead providers to decrease total MEQ for some patients and increase it for others depending on current dose as well as unmeasured patient characteristics, we categorized the change in prescribed opioid dose between the first and final clinic visits as increased, decreased/discontinued, or unchanged. We then used multinomial logistic re-

gression to assess the association of naloxone prescription with this multinomial 3-level outcome, with no change in dose as the reference level of the outcome, and controlling for patient age, race/ethnicity, sex, and history of an opioid-related ED visit in the year before the baseline date. The model also flexibly adjusted for a linear secular trend as the time in days from 1 February 2013 (the earliest program initiation date) to patient baseline date, as well as time between the baseline and follow-up visits. Adjustment for baseline MEQ could induce collider-stratification bias if this potentially important confounder is a common effect of both unmeasured confounders and measurement error in both the baseline and follow-up dose (23); as result, we omitted baseline MEQ from the model. The results from this analysis are presented in Appendix Table 6.

Web-Only Reference

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Appendix Table 1. Implementation Plan and Process Outcomes for Naloxone Coprescribing at Safety-Net Clinics

Activity	Occurrence, *n*	Time Frame	Purpose	Personnel	Number Done at Clinics					
					A Start-date 12/1/13	**B Start-date 2/1/13**	**C Start-date 2/1/13**	**D Start-date 4/1/14**	**E Start-date 3/1/14**	**F Start-date 11/1/13**
NOSE introduction meeting	1	2-3 months prior to program initiation	Introduce program to clinic leaders and discuss rollout logistics	NOSE study staff, clinic director, nurse manager and "champions"	1	1	1	1	1	1
Clinic-wide staff training	≥1	1-2 months preinitiation	Introduce/review program with all staff, disseminate naloxone education checklist*	NOSE study staff, all clinic staff	3	1	1	4	3	2
Naloxone kit material procurement, kit creation and site storage	Ongoing	2 months preinitiation; 1 month preinitiation determine communal location for kit storage; restock and assemble kits on ongoing basis when supplies are low	Obtain and assemble naloxone prescribing materials for "kit" including: atomizers, plastic bags, and patient education brochures	Designated clinic staff	NA	NA	NA	NA	NA	NA
Provider trainings	≥1	0-1 months preinitiation	Answer questions related to provider-specific activities and remind providers of protocol	NOSE study staff, clinic providers (MD, NP, PA)	2	6*	11†	1	1	1
Nurse/MEA trainings	≥1	0-1 months preinitiation	Answer questions related to nurse/MEA-specific activities; Nurses/MEAs 1-on-1 role plays	NOSE study staff, clinic nurses and MEAs	4	0	2	2	2	1
Staff-wide e-mails‡	≥2	At rollout; 3-4 months after initiation	Alert clinic staff of program start and refresh on protocol and purpose	Clinic director	2	2	2	2	2	1
Ongoing technical support	Ongoing	Ongoing	Provide technical assistance	NOSE study staff	NA	NA	NA	NA	NA	NA

MEA = medical educator and assistant; NA = not available; NOSE = Naloxone for Opioid Safety Evaluation.
* Five of these trainings included 5-10 providers each in preclinic "huddles."
† Ten of these trainings included 5-10 chief residents (5) or 5-10 providers in preclinic "huddles" (5).
‡ E-mail template provided by NOSE staff.

Appendix Figure 1. Checklist for clinic staff to train patients receiving naloxone.

Intranasal Naloxone Patient Education Checklist

5- to 10-min Trainings

Causes of Opioid Overdose

☐ Opioids can lower or stop your breathing, especially when:

- Used with medications like alcohol, benzodiazepines, or other drugs
- Changing the dose of or how often opioids are used

Recognizing Opioid Overdose

☐ You can tell someone has overdosed when you can't wake them up with stimulation like rubbing knuckles on breastbone

[OPTIONAL] Other signs include:

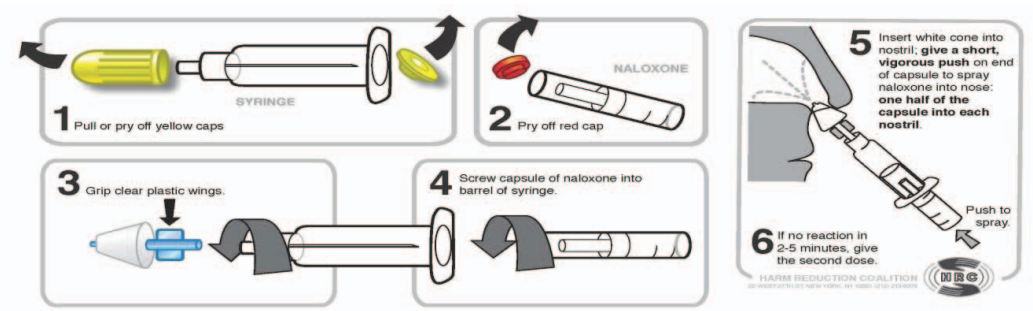
- Slow breathing, gasping for air, snoring, or gurgling
- Pale or bluish skin (especially lips and fingernails)
- Slow heartbeat, weak pulse

What To Do If Someone Overdoses

☐ Call 911

☐ Give naloxone

- Assemble naloxone kit (see diagram)
- Demonstrate with demonstration kit
- **Spray half up EACH nostril**



☐ Follow 911 dispatcher's directions, which may include: CPR, rescue breathing, or chest compressions

Rescue Breathing:

- Make sure nothing is in their mouth
- Tilt head back, lift chin, pinch nose
- Make a tight seal over their mouth and give 1 breath every 5 seconds

[OPTIONAL] Aftercare

- Continue rescue breathing if they're not breathing on their own
- Give another 2 sprays of naloxone (one in each nostril) after **3 minutes** if they're still having trouble breathing or if they still won't wake up
- Naloxone wears off in 30-90 minutes so the overdose may return
- Stay with the them until the paramedics arrive

Now That You Have Naloxone

☐ **Make sure to tell someone where your naloxone is and when/how to use it!**

CPR = cardiopulmonary resuscitation.

Appendix Figure 2. E-mail template to remind providers about naloxone prescribing.

To: [Clinic] Providers
Subject: Remember to prescribe Naloxone!

Dear **[Clinic]** Providers,

This is an email reminder that **[clinic]** is offering intra-nasal **naloxone** (Narcan®) to patients on chronic opioid therapy.

This is one part of the greater movement towards Safe Opioid Prescribing at **[Clinic]**. Unfortunately, many of our patients do have risk factors for unintentional overdose, so this is a potentially life-saving medication for them to have.

If you have been trained on how to prescribe, terrific! Remember that the atomizers are in the **precepting room** in the back – one ziplock bag needs to be given to the patient in addition to sending the prescription to the pharmacy (the ziplock bag also tells you how to write the prescription in ECW).

If you have not heard about this, please let me know and I can give you a brief introduction on how to do this and why it is important. Here's a quick overview:

How:

- Identified a patient you want to prescribe naloxone to and tell a nurse or medical assistant, "I would like a naloxone kit, please"
- The nurse or medical assistant will provide you with
  - A teaching kit for demonstrating intranasal administration
  - A dispensing kit with atomizers and an educational brochure
- The kits have instructions on them describing how to prescribe naloxone in the LCR
- The educational brochure contains instructions for assembling the atomizer
- Show the patient how to assemble the atomizer and encourage the patient to tell his or her friends and family about the kit and where it is kept
- After distributing the dispensing kit and faxing your prescription, return the teaching kit to the nursing station

Patients can only pick up naloxone at the following pharmacies:

- **[List of pharmacies your patients frequently use to fill prescriptions]**

Please email: **[contact]** at **[email]** or **[phone #]** with any questions.

Best,
[Signature]

ECW = eClinicalWorks; LCR = lifetime clinical record.

Appendix Figure 3. Naloxone for opioid safety patient brochure.

What is an opioid overdose?

Opioids can cause bad reactions that make your breathing slow or even stop. This can happen if your body can't handle the opioids that you take that day.

TO AVOID AN ACCIDENTAL OPIOID OVERDOSE:

- Try not to mix your opioids with alcohol, benzodiazepines (Xanax, Ativan, Klonopin, Valium), or medicines that make you sleepy.
- Be extra careful if you miss or change doses, feel ill, or start new medications.

Now that you have naloxone…

Tell someone where it is and how to use it.

Common opioids include:

GENERIC	BRAND NAME
Hydrocodone	Vicodin, Lorcet, Lortab, Norco, Zohydro
Oxycodone	Percocet, OxyContin, Roxicodone, Percodan
Morphine	MSContin, Kadian, Embeda, Avinza
Codeine	Tylenol with Codeine, TyCo, Tylenol #3
Fentanyl	Duragesic
Hydromorphone	Dilaudid
Oxymorphone	Opana
Meperidine	Demerol
Methadone	Dolophine, Methadose
Buprenorphine	Suboxone, Subutex, Zubsolv, Bunavail, Butrans

* Heroin is also an opioid.

For patient education, videos and additional materials, please visit **www.prescribetoprevent.org**

SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH

Opioid safety and how to use naloxone

A GUIDE FOR PATIENTS AND CAREGIVERS

SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH

Appendix Figure 3–Continued.

How to identify an opioid overdose:

Look for these common signs:

- The person won't wake up even if you shake them or say their name
- Breathing slows or even stops
- Lips and fingernails turn blue or gray
- Skin gets pale, clammy

In case of overdose:

1 Call 911 and give naloxone
If no reaction in 3 minutes, give second naloxone dose

2 Do rescue breathing or chest compressions
Follow 911 dispatcher instructions

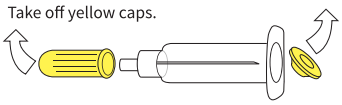
3 After naloxone
Stay with person for at least 3 hours or until help arrives

How to give naloxone:

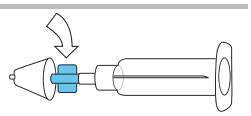
There are 3 ways to give naloxone. Follow the instructions for the type you have.

Nasal spray naloxone

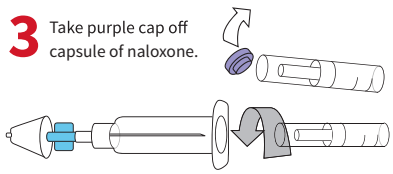
1 Take off yellow caps.



2 Screw on white cone.

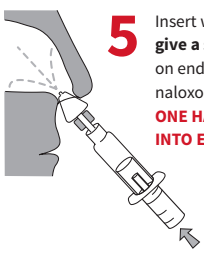


3 Take purple cap off capsule of naloxone.



4 Gently screw capsule of naloxone into barrel of syringe.

5 Insert white cone into nostril; **give a short, strong push** on end of capsule to spray naloxone into nose: **ONE HALF OF THE CAPSULE INTO EACH NOSTRIL.**



Push to spray.

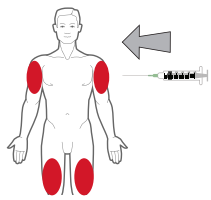
6 If no reaction in 3 minutes, give second dose.

Injectable naloxone

1 Remove cap from naloxone vial and uncover the needle.

2 Insert needle through rubber plug with vial upside down. Pull back on plunger and take up 1 ml.

3 Inject 1 ml of naloxone into an upper arm or thigh muscle.



4 If no reaction in 3 minutes, give second dose.

Auto-injector

The naloxone auto-injector is FDA approved for use by anyone in the community. It contains a speaker that provides instructions to inject naloxone into the outer thigh, through clothing if needed.

Appendix Figure 4. Informational sheet for pharmacists on ordering, dispensing, counseling, and billing for naloxone.

City and County of San Francisco

Edwin M Lee, Mayor

Department of Public Health

Community Behavioral Health Sciences
Community Oriented Primary Care
San Francisco General Hospital

INTRANASAL NALOXONE PATIENT COUNSELING

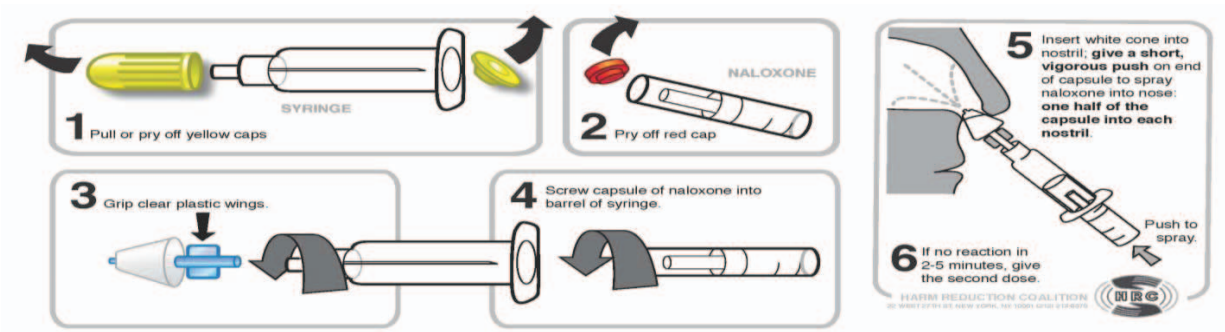
COMMON BRAND NAMES: Narcan

USES: This medication is used to treat an opioid overdose. Naloxone works by reversing the effects of opioids.

SIGNS OF AN OPIOID OVERDOSE: Slow or shallow breathing, blue or gray lips and fingernails, pale and/or clammy skin, unable to wake up or respond.

HOW TO USE: If you suspect someone has overdosed on opioids:

1. Call 911
2. Give naloxone:



3. Give second dose of naloxone in 2-3 minutes if no response to first
4. Perform rescue breathing if comfortable doing so

Patients should be instructed to tell family/friends where naloxone is stored and how to administer it in case of an overdose.

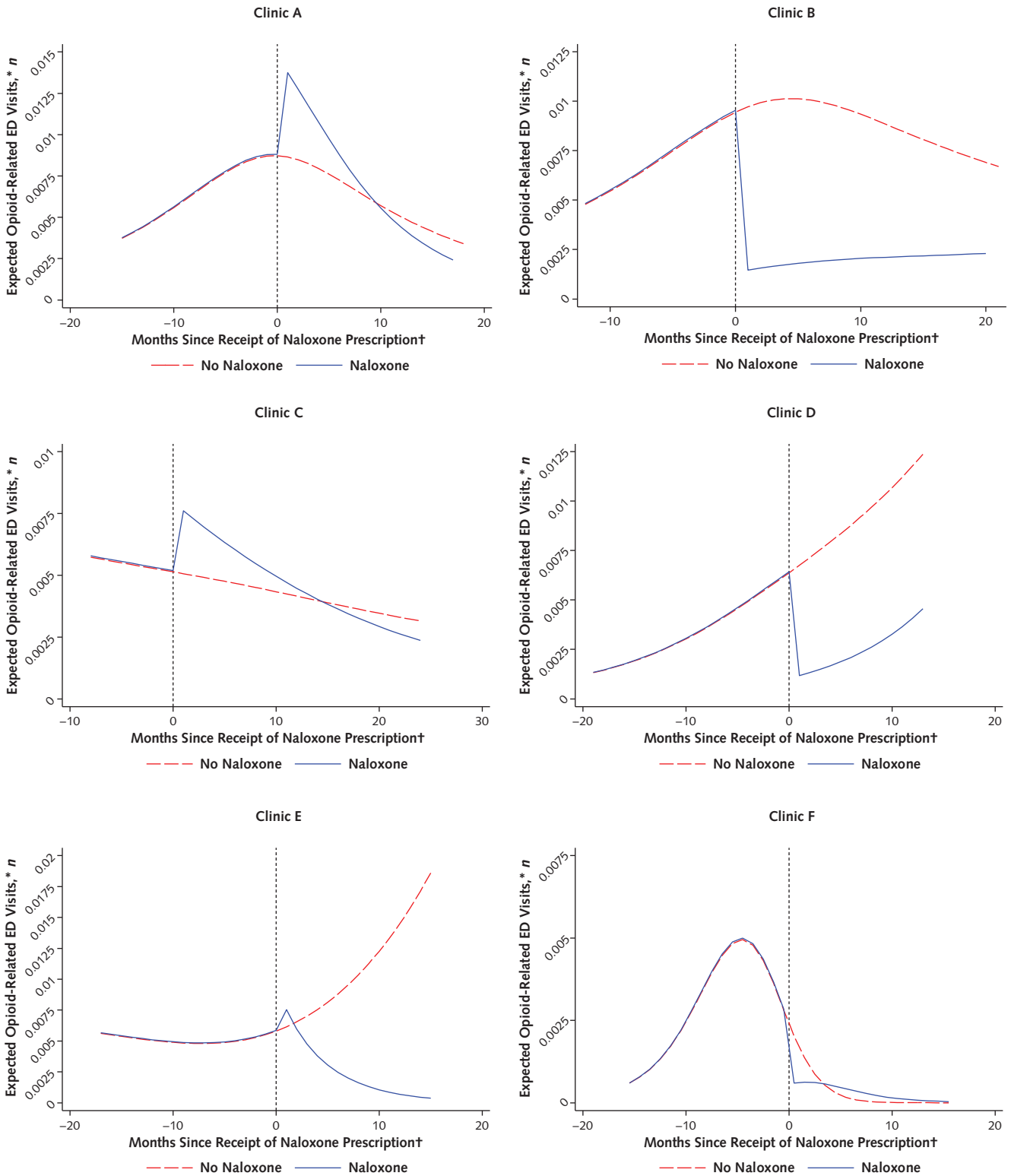
SIDE EFFECTS: Anxiety, sweating, nausea/vomiting, shaking may occur. Talk to your doctor if these occur. A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of serious allergic reaction, including: itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing. This is not a complete list of possible side effects. If you notice other effects not listed, contact your doctor or pharmacist.

Appendix Table 2. Provider-Level Data on Total Number of Patients, Number of Patients Prescribed Naloxone, and Percentage of Patients Prescribed Naloxone

	All Providers	Providers by Quartiles of Total Number of Patients			
		1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Number of providers	186	63	34	45	44
Number of PMR patients per provider					
Mean (SD)	9.7 (14.6)	1.4 (0.5)	3.4 (0.5)	6.8 (1.7)	29.3 (19.4)
Median (IQR)	4 (2–10)	1 (1–2)	3 (3–4)	7 (5–8)	23 (13–44)
Range	1–93	1–2	3–4	5–10	11–93
Number of patients prescribed naloxone per provider					
Mean (SD)	3.8 (7.2)	0.6 (0.6)	1.7 (1.1)	2.6 (2.1)	11.1 (11.9)
Median (IQR)	1 (1–4)	1 (0–1)	2 (1–2)	2 (1–4)	7 (5–11)
Percentage of patients prescribed naloxone					
Mean (SD)	42.4 (34.9)	43.7 (43.5)	50.7 (33.8)	38.5 (29.6)	38.3 (25.2)
Median (IQR)	38.8 (12.5–66.7)	50 (0.0–100.0)	58.3 (25–66.7)	33.3 (14.3–85.7)	27.6 (19.2–58.9)

IQR = interquartile range; PMR = pain management registry.

Appendix Figure 5. Expected number of opioid-related ED visits per month by receipt of naloxone prescription, by clinic.



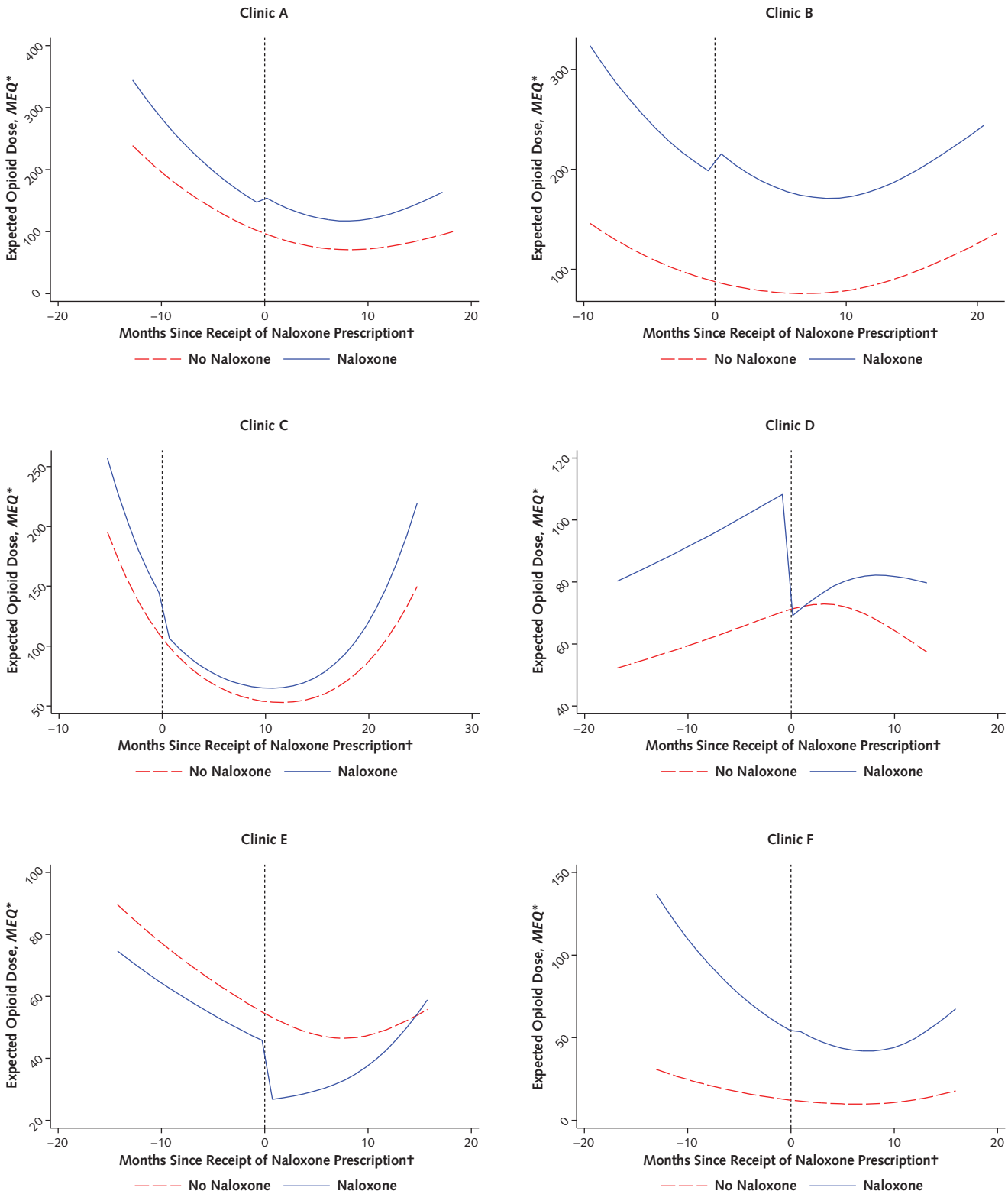
ED = emergency department.
* Expected number of ED visits per month in 2 patients (1 who received a naloxone prescription and 1 who did not), both with mean values of all covariates and stratified by clinic.
† For both trajectories, time was uniformly centered on April 2014, the median time of receipt of naloxone prescription during the study period among patients who received naloxone.

Appendix Table 3. Clinic-Specific Incidence Rate Ratio Values for Post–Naloxone Receipt and Months Since Naloxone Receipt on Count of Opioid-Related Emergency Department Visits per Month*

Clinic	Post-Naloxone Receipt			Months Since Naloxone Receipt		
	IRR (95% CI)	*P* Value	Overall *P* Value†	IRR (95% CI)	*P* Value	Overall *P* Value†
Clinic A	1.49 (0.43–5.14)	0.525	0.040	0.92 (0.81–1.04)	0.170	0.093
Clinic B	0.15 (0.03–0.63)	0.010		1.03 (0.93–1.15)	0.550	
Clinic C	1.29 (0.48–3.43)	0.615		0.93 (0.87–0.99)	0.030	
Clinic D	0.26 (0.07–0.96)	0.044		1.08 (0.93–1.25)	0.302	
Clinic E	1.58 (0.50–4.95)	0.433		0.78 (0.62–0.97)	0.025	
Clinic F	0.63 (0.17–2.28)	0.481		0.94 (0.83–1.07)	0.354	

IRR = incidence rate ratio.
* Calculated from multivariable Poisson regression, fit with generalized estimating equations, assessing count of opioid-related emergency department visits per month. Model adjusts for age, race/ethnicity, sex, log morphine-equivalent daily dose, patient clinic, history of opioid-related emergency department visit, and a cubic spline of the sequential count of patient-months starting with a value of one for January 2013. The model includes interaction terms between patient clinic and the post–naloxone receipt indicator variable as well as between patient clinic and the months since naloxone receipt continuous variable.
† Corresponds to global tests for significance of the interaction terms between clinic and either post-naloxone receipt or months since naloxone receipt.

Appendix Figure 6. Expected opioid dose by receipt of naloxone prescription, by clinic.



MEQ = morphine equivalent.
* Expected MEQ daily dose in milligrams in 2 patients (1 who received a naloxone prescription and 1 who did not), both with mean values of all covariates and stratified by clinic.
† For both trajectories, time was uniformly centered on April 2014, the median time of receipt of naloxone prescription during the study period among patients who received naloxone.

Appendix Table 4. Clinic-Specific Incidence Rate Ratio Values for Post–Naloxone Receipt and Months Since Naloxone Receipt on Opioid Dose at Baseline and Follow-up*

Clinic	Post-Naloxone Receipt			Months Since Naloxone Receipt		
	IRR (95% CI)	*P* Value	Overall *P* Value†	IRR (95% CI)	*P* Value	Overall *P* Value†
Clinic A	0.84 (0.56–1.27)	0.415	0.166	1.00 (0.98–1.04)	0.755	0.548
Clinic B	1.50 (1.04–2.19)	0.032		0.99 (0.96–1.01)	0.217	
Clinic C	0.96 (0.42–2.21)	0.928		1.01 (0.98–1.05)	0.458	
Clinic D	0.74 (0.33–1.66)	0.465		1.00 (0.93–1.07)	0.945	
Clinic E	0.51 (0.21–1.23)	0.134		1.05 (0.98–1.13)	0.172	
Clinic F	1.01 (0.52–1.97)	0.980		1.00 (0.94–1.06)	0.917	

IRR = incidence rate ratio.

* Calculated from multivariable negative binomial regression, fit with generalized estimating equations, assessing opioid dose at baseline and follow-up. Model adjusts for age, race/ethnicity, sex, patient clinic, history of opioid-related emergency department visit, a naloxone group indicator (i.e., whether the patient ever received naloxone during the study period), and a cubic spline in months since 1 February 2013 (the earliest program initiation date). The model includes interaction terms between patient clinic and the naloxone group indicator variable, the post-naloxone receipt indicator variable, and months since naloxone receipt continuous variable.

† Corresponds to global tests for significance of the interaction terms between clinic and either post-naloxone receipt or months since naloxone receipt.

Appendix Table 5. Number of Providers and Demographic and Clinical Characteristic of Patients, by Clinic*

Characteristic	Clinic A	Clinic B	Clinic C	Clinic D	Clinic E	Clinic F
Total number of providers	22	85	75	12	11	6
Total number of patients	626	448	339	295	220	57
Prescribed naloxone	195 (31.2)	135 (30.1)	174 (51.3)	96 (32.5)	122 (55.5)	37 (64.9)
Sex						
Female	211 (33.7)	181 (40.4)	181 (53.4)	124 (42.0)	99 (45.0)	26 (45.6)
Male	415 (66.3)	267 (59.6)	158 (46.6)	171 (58.0)	121 (55.0)	31 (54.4)
Age						
Mean age (SD), *y*	56.4 (9.1)	57.7 (11.5)	54.6 (12.6)	58.7 (10.3)	56.3 (10.5)	57.2 (12.6)
Race/ethnicity						
White	269 (43.0)	129 (28.8)	103 (30.4)	26 (8.8)	49 (22.3)	30 (52.6)
Black	266 (42.5)	203 (45.3)	121 (35.7)	249 (84.4)	111 (50.5)	10 (17.5)
Hispanic/Latino	59 (9.4)	82 (18.3)	74 (21.8)	11 (3.7)	34 (15.5)	5 (8.8)
Other	32 (5.1)	34 (7.6)	41 (12.1)	9 (3.1)	26 (11.8)	12 (21.1)
MEQ daily dose						
≤20 mg	165 (26.4)	96 (21.4)	90 (26.5)	109 (36.9)	91 (41.4)	23 (40.4)
21–60 mg	148 (23.6)	119 (26.6)	78 (23.0)	81 (27.5)	59 (26.8)	20 (35.1)
61–120 mg	101 (16.1)	66 (14.7)	45 (13.3)	43 (14.6)	30 (13.6)	7 (12.3)
121–200 mg	77 (12.3)	44 (9.8)	34 (10.0)	24 (8.1)	19 (8.6)	3 (5.3)
201–400 mg	84 (13.4)	58 (12.9)	40 (11.8)	31 (10.5)	14 (6.4)	1 (1.8)
≥400 mg	51 (8.1)	65 (14.5)	52 (15.3)	7 (2.4)	7 (3.2)	3 (5.3)
Prescribed opioid						
Codeine	52 (8.3)	36 (8.0)	43 (12.7)	29 (9.8)	27 (12.3)	6 (10.5)
Hydrocodone	125 (20.0)	93 (20.8)	109 (32.2)	109 (36.9)	63 (28.6)	17 (29.8)
Oxycodone	221 (35.3)	281 (62.7)	165 (48.7)	122 (41.4)	102 (46.4)	26 (45.6)
Morphine	214 (34.2)	115 (25.7)	77 (22.7)	56 (19.0)	28 (12.7)	12 (21.1)
Methadone	84 (13.4)	20 (4.5)	43 (12.7)	23 (7.8)	22 (10.0)	7 (12.3)
Hydromorphone	17 (2.7)	22 (4.9)	10 (2.9)	5 (1.7)	7 (3.2)	0 (0.0)
Fentanyl	13 (2.1)	17 (3.8)	12 (3.5)	3 (1.0)	3 (1.4)	0 (0.0)
Other†	9 (1.4)	1 (0.2)	4 (1.2)	3 (1.0)	2 (0.9)	0 (0.0)
Opioid dose change during study period						
Mean dose change in MEQ daily dose (SD)	−34.8 (202.5)	−38.4 (216.1)	−58.2 (327.2)	−9.0 (73.8)	5.7 (102.2)	−7.1 (64.5)
Median dose change in MEQ daily dose (IQR)	0.0 (−33.8, 7.5)	0.0 (−45.0,-5.0)	−3.3 (−45.0, 2.5)	0.0 (−15.0, 0.0)	0.0 (−2.3, 0.8)	0.0 (0.0, 2.3)
Increase	183 (29.2)	127 (28.3)	89 (26.3)	73 (24.7)	55 (25.0)	15 (26.3)
No change	172 (27.5)	134 (29.9)	72 (21.2)	114 (38.6)	110 (50.0)	30 (52.6)
Reduction	166 (26.5)	127 (28.3)	120 (35.4)	63 (21.4)	38 (17.3)	8 (14.0)
Discontinuation	105 (16.8)	60 (13.4)	58 (17.1)	45 (15.3)	17 (7.7)	4 (7.0)
ED visits during 12 mo prior to baseline date						
Any visit	189 (30.2)	186 (41.5)	112 (33.0)	103 (34.9)	66 (30.0)	13 (7.0)
Any opioid-related visit	36 (5.8)	34 (7.6)	17 (5.0)	13 (4.4)	21 (9.5)	6 (7.0)
Any oversedation visit	11 (1.8)	11 (2.5)	4 (1.2)	3 (1.0)	1 (0.5)	0 (7.0)

(*continued on following page*)

Appendix Table 5–Continued

Characteristic	Clinic A	Clinic B	Clinic C	Clinic D	Clinic E	Clinic F
ED visits between 1 January 2013 and end of follow-up						
Patients with any visit	301 (48.1)	276 (61.6)	179 (52.8)	161 (54.6)	122 (55.5)	22 (38.6)
Patients with any opioid-related visit	70 (11.2)	61 (13.6)	41 (12.1)	32 (10.8)	35 (15.9)	7 (12.3)
Patients with any oversedation visit	22 (3.5)	23 (5.1)	9 (2.7)	9 (3.1)	4 (1.8)	0 (0.0)
Annual ED visit rate						
Mean rate of any type of visit (SD)	0.73 (1.46)	1.30 (2.72)	0.81 (1.74)	0.93 (2.06)	0.90 (1.93)	0.44 (1.00)
Mean rate of opioid-related visits (SD)	0.09 (0.38)	0.13 (0.60)	0.07 (0.23)	0.13 (0.82)	0.23 (1.06)	0.07 (0.19)
Mean rate of oversedation visits (SD)	0.02 (0.15)	0.03 (0.17)	0.01 (0.06)	0.02 (0.11)	0.01 (0.09)	0.00 (0.00)
Deaths during study period						
All-cause	18 (2.9)	26 (5.8)	10 (2.9)	4 (1.4)	1 (0.5)	0 (0.0)
Opioid poisoning	2 (0.3)	2 (0.4)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

ED = emergency department; IQR = interquartile range; MEQ = morphine equivalent.
* Values are numbers (percentages) unless otherwise indicated.
† Included buprenorphine for pain and meperidine.

Appendix Table 6. Multinomial Logistic Regression Model Assessing Odds of Increase in Opioid Dose and Decrease in Opioid Dose Relative to No Change in Opioid Dose (n = 1985 Patients)*

Variable	Increase in Opioid Dose Relative to No Change in Dose		Decrease in Opioid Dose Relative to No Change in Dose	
	RRR (95% CI)	*P* Value	RRR (95% CI)	*P* Value
Naloxone receipt	1.18 (0.92-1.52)	0.198	1.47 (1.17-1.86)	0.001
Age (5-y units)	0.90 (0.85-0.95)	<0.001	0.91 (0.87-0.96)	0.001
Race/ethnicity				
White	Reference		Reference	
Black	0.97 (0.73-1.29)	0.835	1.24 (0.95-1.61)	0.115
Hispanic/Latino	1.03 (0.70-1.52)	0.865	0.94 (0.66-1.35)	0.749
Other	1.17 (0.73-1.86)	0.517	0.99 (0.63-1.55)	0.966
Sex				
Female	Reference		Reference	
Male	1.05 (0.82-1.34)	0.696	1.00 (0.80-1.25)	0.990
ED visit during 12 mo prior to baseline date†	1.89 (1.16-3.08)	0.011	1.39 (0.86-2.25)	0.182

ED = emergency department; RRR = relative risk ratio.
* Adjusted for patient clinic, number of days elapsed between the earliest date of program initiation (1 February 2013) and patient baseline date, and number of days elapsed between patient baseline date and subsequent follow-up date.
† Includes only opioid-related ED visits.