Reducing Prescription Opioid Dose and Duration to Reduce Risk of Opioid Use Disorder Among Patients With Musculoskeletal Pain

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Background: We estimated the extent to which the risk of developing opioid use disorder or overdose over 15 months of follow-up would be affected by applying prescription opioid dose and duration reductions to subsets of newly diagnosed musculoskeletal pain patients, defined in terms of the "riskiness" level of their initial opioid prescription.

Methods: We studied a cohort of nonpregnant Medicaid patients, aged 19–63 years, without cancer nor on palliative care, who were opioid-naive, newly diagnosed with musculoskeletal pain, and were prescribed an opioid within 3 months from the diagnosis date (N = 324,389). We applied a novel statistical approach to estimate the effects of local modified treatment policies (a generalization of the average treatment effect on the treated). Specifically, we estimated the expected difference in risk of developing opioid use disorder or opioid overdose by sequential 3-month follow-ups among patients with different levels of opioid prescribing had those patients had their prescription opioid dose and/or duration decreased by 20% versus no hypothetical intervention, and had they remained uncensored.

Results: We estimated clinically modest effects on absolute opioid use disorder risk when universally reducing opioid prescription dose and duration by 20% across the cohort. In contrast, we estimated much larger, clinically relevant reductions in absolute risk of one percentage point or greater when assessing the localized effects of: (1) a 20% reduction in dose among individuals with doses ≥90 morphine milligram (mg) equivalents, (2) a 20% reduction in days supplied among individuals with >30 days supplied, and (3) 20% reductions in both dose and duration among those with ≥50 morphine mg equivalents and >7 days supplied.

Conclusions: We estimate that reductions in opioid prescribing may have a limited impact on the risk of opioid use disorder when applied broadly but possibly meaningful reductions in risk when applied to those with riskier prescriptions.

Keywords: Local causal effect; Modified treatment policy; Musculoskeletal pain; Opioid use disorder

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Musculoskeletal pain, defined as pain affecting bones, muscles, ligaments, joints, tendons, or nerves,[1,2] is estimated to affect more than half of the US adult population,[3] and negatively impacts quality of life (e.g., in terms of decreased mobility and diminished economic prospects).[4–8] Recommended treatments for musculoskeletal pain include nonpharmacologic interventions such as physical therapy[9,10] and pharmacologic treatments such as nonsteroidal anti-inflammatory drugs.[10–12] Although not recommended as a first-line treatment,[12] opioids remain commonly prescribed, even at the initial medical encounter for musculoskeletal pain,[10,13] despite known risks of misuse, development of opioid use disorder, and possible overdose.[12] For example, an analysis of National Ambulatory Medical Care Survey data (2007–2015) estimated that 21.5% of chronic musculoskeletal pain patients had opioids prescribed at the initial visit.[10] To reduce risks associated with using prescription opioids for pain management, the US Centers for Disease Control and Prevention (CDC) published opioid prescribing guidelines, most recently in 2022, which recommended initiating opioids at the lowest effective dose for the shortest required time.[12,14] These guidelines are backed by findings that high doses pose an increased risk of opioid-related harms and are generally no more effective at controlling pain than lower doses; for example, (1) doses ≥50 morphine milligram (mg) equivalents may not substantially benefit pain management compared with lower doses and (2) prescriptions longer than 7 days are likely unnecessary except in cases of severe traumatic injury.[12]

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The Medicaid TAF data used in the study are available upon application to the Centers for Medicare & Medicaid Services. Computing code to replicate the data cleaning and analyses is available at https://github.com/CI-NYC/everything-local-lmtp.

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However, the CDC guidelines do not consider two sources of nuance. First, the guidelines do not consider dose strength and prescription duration as a joint exposure. Considering dose and duration jointly may result in a more accurate understanding of prescription opioid risks if the two components interact.[15] For example, it could be that opioid dose has little effect on risk if the duration of the prescription is a single day, but higher doses may have an outsized impact on risk at longer prescription durations. Second, the guidelines are written as applying "to all persons."[12] However, it is plausible that the majority of opioid prescribing poses little risk and therefore, is not in need of intervention. Rather, it could be that the portion of the population being prescribed opioids at the highest levels is responsible for the majority of risk, and that substantial opioid use disorder risk reduction could be realized by applying prescribing guidelines only to these patients. The potential for additional nuance in the CDC's opioid prescribing guidelines, coupled with continued opioid prescribing at high-risk levels for musculoskeletal pain patients, motivates the current study. In this article, we consider a large cohort of newly diagnosed, opioid-naive musculoskeletal pain patients enrolled in Medicaid, and estimate the effects of modest reductions in opioid dose and duration prescribing practices (considered as a joint exposure) on the risk of developing opioid use disorder over 15 months among subsets of patients with different prescribing levels.

METHODS

Data and Cohort

This study was approved by the Columbia University Institutional Review Board. We conducted a retrospective cohort study with data from Medicaid T-MSIS Analytic Files (TAF): Demographics, Other Services, Inpatient, and Pharmacy claims (2016–2019).

We studied a cohort of nonpregnant Medicaid patients, aged 19–63 years, without cancer nor on palliative care, who were opioid-naive, newly diagnosed with musculoskeletal pain, and were prescribed an opioid within 3 months from the diagnosis date. We included the following 26 states that implemented Medicaid expansion under the Affordable Care Act in or before 2014: ND, VT, NH, CA, OR, MI, IA, NV, OH, IL, NY, MD, MA, RI, HI, WV, WA, KY, DE, AZ, NJ, MN, NM, CT, CO, AR[16] (but excluded patients from MD due to unreliable diagnosis codes[17]). We considered a patient's first diagnosis of musculoskeletal pain on or after 1 January 2016 and on or before 31 December 2019. We characterized the exposure start date as the first date an opioid for pain was prescribed within 3 months following the initial musculoskeletal pain diagnosis. We followed beneficiaries for a maximum of 24 months (i.e., a 6-month washout period, a 3-month exposure period, and up to 15 months of follow-up). We chose this follow-up time because many patients with musculoskeletal pain qualify for Medicaid based on Social Security Disability Insurance (e.g., patients with diseases of the musculoskeletal system and connective tissue comprised the largest diagnostic group, over 30%, of those awarded Social Security Disability Insurance in 2019[18]); these individuals would transition to Medicare being the primary payer after 24 months.[19] We considered the 6 months preceding the first opioid prescription following musculoskeletal pain diagnosis to be the washout period, which we used to determine cohort eligibility. We required patients to be continuously enrolled during the washout period. We excluded patients with any of the following during this washout period: opioid use disorder (see the Outcome subsection for further details), overdose, any medications for opioid use disorder, probable opioid misuse,[20] or any opioid prescription. We did not include patients who were dual eligible with Medicare, as we do not have access to Medicare claims. We excluded patients who were institutionalized. A study timeline is shown in Figure 1, and the cohort exclusion/inclusion criteria are shown in eFigure 1; https://links.lww.com/EDE/C265.

Measures

Exposures

The exposures of interest were prescription opioid maximum dose and duration during the patient's first opioid prescription episode following their new-onset musculoskeletal diagnosis. Time zero was the start date of this initial opioid prescription, and the musculoskeletal pain diagnosis needed to occur in the 3 months before this date, during the washout period. The first opioid prescription episode starts on day 0 and extends until there is a gap in the opioid prescription longer than 7 days (30 days in a sensitivity analysis), in alignment with prior work,[21,22] and does not extend past month 3.

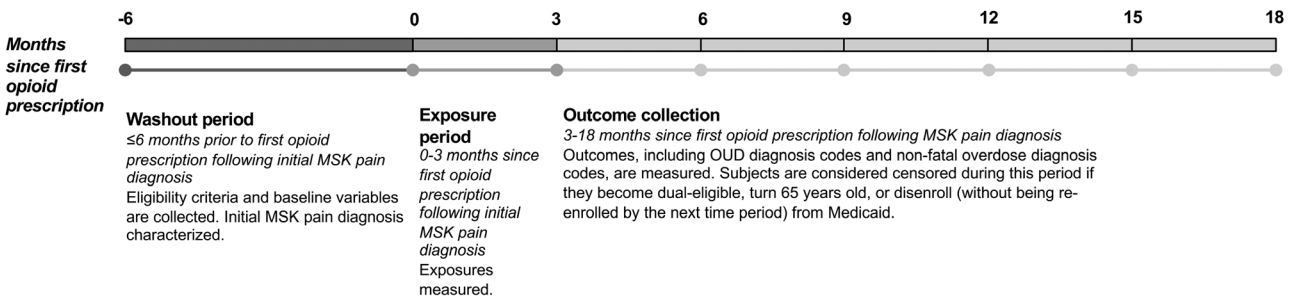

FIGURE 1. Study measures characterization timeline.

Using this period of continuous opioid use, we measured the two exposures: maximum daily opioid dose (in morphine mg equivalents) and number of days supplied (e.g., if an individual had a 3-day opioid prescription followed by an 8-day break, then another 4-day prescription followed by a 55-day break, then this individual would have a days supply of 3 days in the primary analysis and 7 days in the sensitivity analysis).

Due to the presence of extreme morphine mg equivalent doses in some patients, we truncated the maximum daily opioid dose at 200 morphine mg equivalents (this affected 0.50% and 0.59% of the cohort in the primary and sensitivity analyses, respectively).

Outcome

The outcome was presence versus absence of having either an opioid use disorder diagnosis defined by abuse or dependence (International Classification of Diseases, 10th Revision, Clinical Modification diagnosis codes F11.x)[23] or a nonfatal, unintentional opioid overdose (International Classification of Diseases, 10th Revision, Clinical Modification diagnosis codes listed in the Github repository) by follow-up period t.[24] We measured the outcome in five separate 3-month periods ($t \in \{1,..,5\}$) starting 3 months after time $t = 0$. We considered this as a survival-type outcome in the sense that once the outcome was positive in one of these periods, it was positive for the remainder.

We censored patients at the point of any of the following: end of 2019, disenrollment from Medicaid (without reenrollment by the next outcome period; see eFigure 2; https://links.lww.com/EDE/C265), 65th birthday, or otherwise becoming Medicare-eligible.

Covariates

We characterized the following baseline covariates for each beneficiary using the 6-month washout period: age (years), sex, race/ethnicity, English as their primary language, marriage/partnership status, household size, veteran status, income likely >133% of the Federal Poverty Level, any inpatient or outpatient diagnosis of bipolar disorder, any anxiety disorder, attention deficit hyperactivity disorder, any depressive disorder, or other mental disorder (e.g. anorexia, personality disorders).[23] Additionally, we included an indicator of having an average of ≥2 emergency department visits for pain not resulting in hospitalization or surgery per month over the first opioid prescription episode. For individuals with a first opioid prescription episode shorter than 1 month long, we used the 1-month period before their opioid prescription episode end date. We controlled for this variable to serve as an imperfect proxy for uncontrolled pain.

We imputed missing values with the mode and included indicator variables for any covariates with missing values.

Statistical Analysis

We assume observed data $\mathbf{O} = (\mathbf{W}, \mathbf{A}, C_1, C_1Y_1, ..., C_5, C_5Y_5)$, where: $\mathbf{W}$ represents covariates measured during the 6-month washout period; $\mathbf{A} = (A_1, A_2)$, where A_1 represents maximum daily opioid dose (in morphine mg equivalents) and A_2 represents days supplied in the opioid prescription, measured during the 3 months following an initial musculoskeletal pain diagnosis; C_t is an indicator of remaining uncensored by time t (discretized into 3-month intervals) for $t \in \{1, ..., 5\}$; and Y_t represents a binary outcome of incident opioid use disorder or opioid overdose by time t, observed among those who remain uncensored.

We used exposure variables to define the following subsets of the cohort based on opioid prescribing risk:

1. Defined by dose: $\mathcal{B}1_j = \{A_1 \geq x_j \text{ morphine mg equivalents}\}$ for $j \in \{1,2\}$, where $(x_1, x_2) = (50, 90)$ for those with more "risky" prescribing and $\mathcal{B}1_0 = \{A_1 \leq 20 \text{ morphine mg equivalents}\}$ for those with "nonrisky" prescribing[12];
2. Defined by duration: $\mathcal{B}2_j = \{A_2 > z_j \text{ days}\}$ for $j \in \{1,2\}$, where $(z_1, z_2) = (7, 30)$ for those with more "risky" prescribing and $\mathcal{B}2_0 = \{A_2 \leq 7 \text{ days}\}$ for those with "nonrisky" prescribing;
3. Defined by both dose and duration: $\mathcal{B}3_j = \{A_1 \geq x_j \text{ morphine mg equivalents} \cap A_2 > z_j \text{ days}\}$ for $j \in \{1,2,3,4\}$, where $(x_1, x_2, x_3, x_4) = (50, 90, 50, 90)$ and $(z_1, z_2, z_3, z_4) = (7, 7, 30, 30)$ for those with more "risky" prescribing and $\mathcal{B}3_0 = \{A_1 \leq 20 \text{ morphine mg equivalents} \cap A_2 \leq 7 \text{ days}\}$ for those with "nonrisky" prescribing.

We chose the risky cutoffs to either correspond to CDC guidance on what constitutes risky opioid prescribing[12] or, at the more extreme values, to reflect US state laws that restrict days' supply to 30 days (HI, IL),[25] or for requiring co-prescription of an opioid antagonist in the presence of prescriptions ≥ 90 morphine mg equivalents per day (NY).[26]

For each of the above-defined risk-based subsets (defined by [1] dose, [2] duration, or [3] both, $\mathcal{B}k$ for $k \in \{1,2,3\}$), we were interested in a type of causal effect called a modified treatment policy that considers the effect of hypothetically intervening on the natural value of treatment.[27] In this case, we consider a hypothetical intervention that would reduce patients' natural values of opioid prescription dose and/or duration by 20%; we denote these hypothetically reduced exposure variables as $\mathbf{A}^{\mathrm{d}k} = \mathrm{d}k(\mathbf{A})$, indicating that we apply the hypothetical reduction $\mathrm{d}k$ to the patients' exposure values $\mathbf{A}$. Specifically, we consider the causal effect $\theta_{t,k,j} = \mathrm{E}[Y_t(\mathbf{A}^{\mathrm{d}k}, \bar{C} = \bar{1}) - Y_t(\mathbf{A}, \bar{C} = \bar{1}) \,|\, \mathbf{A} \in \mathcal{B}k_j]$, where we sometimes denote $\mathrm{d}k(\mathbf{A})$ as $\mathrm{d}k$ for simplicity, and where we use an overbar to denote variable history. In words, this is the expected difference in risk of developing opioid use disorder or opioid overdose by the t^{th} 3-month follow-up among patients in $\mathcal{B}k_j$, had those patients had their prescription opioid dose and/or duration decreased by 20% according to policy $\mathrm{d}k$ versus no hypothetical intervention, and had they remained uncensored. This type of causal effect is called the effect of a local modified treatment policy, as it is the effect of a modified treatment policy, $\mathrm{d}k$, among the subsets for whom the policy would be relevant, based on their treatment status.[28] This causal effect is identified under consistency, positivity, and sequential exchangeability.

In this case, positivity means that $\mathrm{P}(\mathbf{A} = \mathbf{A}^{\mathrm{d}k}|W) > 0$ for any pair $(\mathbf{a}, w)$ such that $\mathrm{P}(W = w|\mathbf{a} \in \mathcal{B}k_j) > 0$ and that $\mathrm{P}(C_t = 1|\mathbf{A}, W, \bar{C}_{t-1} = \bar{1}, \bar{Y}_{t-1}) > 0$ for all $\mathrm{P}(w, \bar{c}_{t-1} = \bar{1}, \bar{y}_{t-1}|\mathbf{a} \in \mathcal{B}k_j) > 0$. In words, positivity means that: (1) there is a positive probability of observing the shifted dose and/or duration specified by dk conditional on the baseline covariate values observed among those in the specified subgroup $\mathcal{B}k_j$, and (2) there is a positive probability of remaining uncensored by each follow-up time conditional on the past history and among those with dosages in the specified subgroup $\mathcal{B}k_j$. In this case, sequential exchangeability means that, for all $t \in \{1, ..., 5\}$, $Y_t\left(\mathbf{A}^{\mathrm{d}k}, \bar{C}_t = \bar{1}\right) \perp\!\!\!\perp \mathbf{A}|W$ and $Y_t\left(\mathbf{A}^{\mathrm{d}k}, \bar{C}_t = \bar{1}\right) \perp\!\!\!\perp C_t|\mathbf{A}, W, \bar{C}_{t-1} = \bar{1}, \bar{Y}_{t-1}$. In words, sequential exchangeability means that: (1) dosage, $\mathbf{A}$, is independent of the counterfactual outcome had dosage been shifted under dk conditional on covariates, and (2) censoring at each time t is independent of the counterfactual outcome conditional on the past.

We considered the following three modified treatment policies, dk for $k \in \{1, 2, 3\}$:

$\mathrm{d1}(\mathbf{A}) = (0.8A_1, A_2)$, reduce dose by 20 % ;

$\mathrm{d2}(\mathbf{A}) = (A_1, 0.8A_2)$, reduce duration by 20 % ;

$\mathrm{d3}(\mathbf{A}) = (0.8A_1, 0.8A_2)$, reduce dose and duration by 20 % .

We note that these 20% reductions stay within the support of the observed data when applied to the subsets of patients with risky prescribing. We slightly modify the above dk's when applying the shifts to the entire cohort or the subsets with nonrisky prescribing, such that values would be kept at their observed levels if a 20% reduction would be outside the support of the data; these updated modified treatment policies are given in eAppendix 1; https://links.lww.com/EDE/C265. Consequently, all shifts we consider satisfy the positivity assumption stated above and in Susmann et al.[28] We chose a 20% reduction, because this represents a likely clinically achievable shift in prescribing. In this cohort, a 20% reduction in morphine mg equivalents corresponds to approximately 6.8 morphine mg equivalents, and a 20% reduction in prescribed days corresponds to approximately 2.3 days. Average shifts among the cohort and within each subset defined based on prescribing risk are presented in eTable 1; https://links.lww.com/EDE/C265. We used targeted minimum loss-based estimation with cross-fitting (two-folds, which we believe is sufficient due to low variation in results across seeds [see eFigure 4; https://links.lww.com/EDE/C265]) to estimate the above-specified causal effects. Targeted minimum loss-based estimation is a semiparametric substitution estimator; the implementation we used is robust to misspecification of certain nuisance parameters, as described in Susmann et al.[28] When using targeted minimum loss-based estimation, nuisance parameters can be estimated using flexible machine-learning algorithms while maintaining theoretically valid inference.[29] We estimated outcome regression nuisance parameters using a stacked ensemble[30] of: an intercept-only model, a main-effects generalized linear model, multivariate adaptive regression splines,[31] and light gradient boosting machines.[32] We estimated nuisance parameters associated with the hypothetical interventions (dose, duration, and censoring) using Riesz regression.[33] Specifically, we used a feed-forward neural network, with the Adam optimizer, composed of an ensemble of three multilayer perceptrons with increasing hidden layers; we utilized early stopping and $\ell 2$ regularization. Analyses were conducted using R (version 4.4.1)[34] with the *lmtp*,[35,36] *mlr3superlearner*,[37] and *torch*[38] packages. All code for the analysis is available at https://github.com/CI-NYC/everything-local-lmtp.

RESULTS

Our cohort included N = 324,389 patients (see Table 1 and eTables 2–4; https://links.lww.com/EDE/C265). The cohort was majority female (63%). The median age was slightly higher among those prescribed opioids for >7 days (44 years) compared with those who were prescribed opioids for ≤7 days (37 years). Most patients (76.1%) received only a single opioid prescription in the exposure period in the primary analysis.

Unadjusted incidence of opioid use disorder or overdose was greatest among those prescribed opioids with a maximum morphine mg equivalents ≥90 for >30 days at 18.1% by the end of the study. Incidence of opioid use disorder or overdose by the end of the study was much lower among those with less "risky" prescribing levels of opioids at 3.1% among those with a maximum morphine mg equivalents ≤20 for ≤7 days.

Row 1 of Figures 2 and 3 illustrates the estimated cumulative risk of opioid use disorder or overdose by 3-month period t for the observed opioid prescribing practices, as well as under each of the three strategies (d1 and d2 in Figure 2 and d3 in Figure 3) among the "risky" and "nonrisky" subsets and cohort in the primary analysis. Row 2 of the figures depicts the differences in risks of opioid use disorder or overdose (absolute risk differences, RD) comparing each of the dosing strategies to the observed prescribing, along with their associated 95% confidence intervals (CIs) for each timepoint t.

By the end of the 15th-month follow-up, all three treatment regimes statistically significantly reduced the risk of opioid use disorder or overdose as compared to the risk under observed prescribing. However, the extent to which risk was reduced varied markedly depending on the subset of patients for which the treatment regimen was applied. We observed larger effects among people with riskier opioid prescribing compared with those observed among the entire cohort or among people with nonrisky prescribing. For example, reducing both maximum daily dose and days supplied by 20% decreased absolute risk of opioid use disorder or overdose by 3.33 (95% CI = 2.77, 3.89) percentage points by the end of the study among those with opioid prescriptions of both maximum morphine mg equivalents ≥90 and days supplied >30

TABLE 1. Descriptive Statistics of Cohort and Select Prescribing Groups

Baseline Demographics[a]	Cohort	MME ≥90	Days >30	MME ≥50, Days > 7
	N = 324,389	N = 10,453	N = 16,515[a]	N = 20,060
Age	39 (29, 50)	41 (31, 52)	45 (35, 54)	43 (33, 53)
Sex				
Female	203,087 (63%)	5,433 (52%)	8,933 (54%)	10,520 (52%)
Race/Ethnicity				
AIAN, non-Hispanic	5,362 (2.0%)	171 (1.9%)	176 (1.3%)	257 (1.5%)
Asian, non-Hispanic	11,283 (4.1%)	228 (2.6%)	327 (2.4%)	464 (2.7%)
Black, non-Hispanic	50,868 (19%)	1,417 (16%)	2,379 (17%)	2,690 (16%)
Hawaiian/Pacific Islander	2,021 (0.7%)	*[b]	*[b]	*[b]
Hispanic, all races	64,265 (24%)	1,340 (15%)	2,629 (19%)	2,819 (17%)
Multiracial, non-Hispanic	239 (<0.1%)	*[b]	*[b]	*[b]
White, non-Hispanic	138,797 (51%)	5,561 (63%)	8,267 (60%)	10,552 (62%)
Unknown	51,554	1,669	2,673	3,171
Primary Language English	254,631 (90%)	8,700 (95%)	13,117 (94%)	16,118 (94%)
Unknown	42,279	1,323	2,512	2,983
Married/partnered	21,115 (18%)	656 (16%)	923 (14%)	1,440 (18%)
Unknown	205,107	6,440	9,875	12,274
Probable high income	7,703 (2.4%)	232 (2.2%)	279 (1.7%)	452 (2.3%)
Household size				
1	57,384 (65%)	2,926 (72%)	2,868 (69%)	4,301 (69%)
2	11,202 (13%)	464 (11%)	526 (13%)	743 (12%)
2+	20,344 (23%)	702 (17%)	737 (18%)	1,192 (19%)
Unknown	235,459	6,361	12,384	13,824
Veteran	471 (0.6%)	19 (0.8%)	26 (0.6%)	35 (0.7%)
Unknown	247,625	7,924	12,364	14,827
TANF benefits	37,012 (14%)	940 (11%)	1,553 (12%)	2,213 (14%)
Unknown	58,877	2,091	3,903	4,214
SSI benefits				
Mandatory or optional	7,919 (5.2%)	223 (5.4%)	612 (8.4%)	520 (6.3%)
Not applicable	143,824 (95%)	3,892 (95%)	6,713 (92%)	7,726 (94%)
Unknown	172,646	6,338	9,190	11,814
Average of 2+ ED visits	75,480 (23%)	1,208 (12%)	325 (2.0%)	2,337 (12%)
Baseline psychiatric conditions				
Bipolar	11,683 (3.6%)	486 (4.6%)	748 (4.5%)	904 (4.5%)
Anxiety	68,868 (21%)	3,547 (34%)	3,712 (22%)	5,889 (29%)
ADD/ADHD	4,600 (1.4%)	230 (2.2%)	257 (1.6%)	408 (2.0%)
Depression	37,823 (12%)	1,552 (15%)	2,221 (13%)	2,869 (14%)
Other mental illness	19,278 (5.9%)	792 (7.6%)	974 (5.9%)	1,420 (7.1%)
Exposures				
Maximum daily MME dose	30 (19, 40)	113 (94, 150)	40 (20, 75)	75 (60, 96)
Days' supply	4 (3, 8)	13 (5, 40)	72 (46, 89)	20 (11, 48)
Number of opioid prescriptions	1 (1, 2)	3 (2, 5)	4 (3, 5)	3 (2, 5)
Cumulative OUD*2* or overdose				
OUD/overdose by period 1	1,859 (0.7%)	198 (2.2%)	332 (2.3%)	334 (1.9%)
Censored	51,845	1,412	1,823	2,521
OUD/overdose by period 2	3,373 (1.4%)	342 (4.1%)	572 (4.2%)	578 (3.6%)
Censored	76,336	2,085	2,844	3,825
OUD/overdose by period 3	4,595 (2.0%)	452 (5.9%)	744 (5.9%)	766 (5.1%)
Censored	99,139	2,761	3,885	5,103
OUD/overdose by period 4	5,652 (2.8%)	546 (7.7%)	891 (7.7%)	919 (6.7%)
Censored	121,171	3,368	4,871	6,268
OUD/overdose by period 5	6,555 (3.7%)	616 (9.6%)	1,027 (9.7%)	1,057 (8.5%)
Censored	145,035	4,056	5,904	7,591

[a]Median (IQR); n (%).
[b]Suppressed due to small cell size.
ADD/ADHD, attention deficit (hyperactivity) disorder; AIAN, American Indian and Alaska Native; ED, emergency department; MME, Morphine Milligram Equivalents; OUD, opioid use disorder; SSI, supplemental security income; TANF, temporary assistance for needy families.

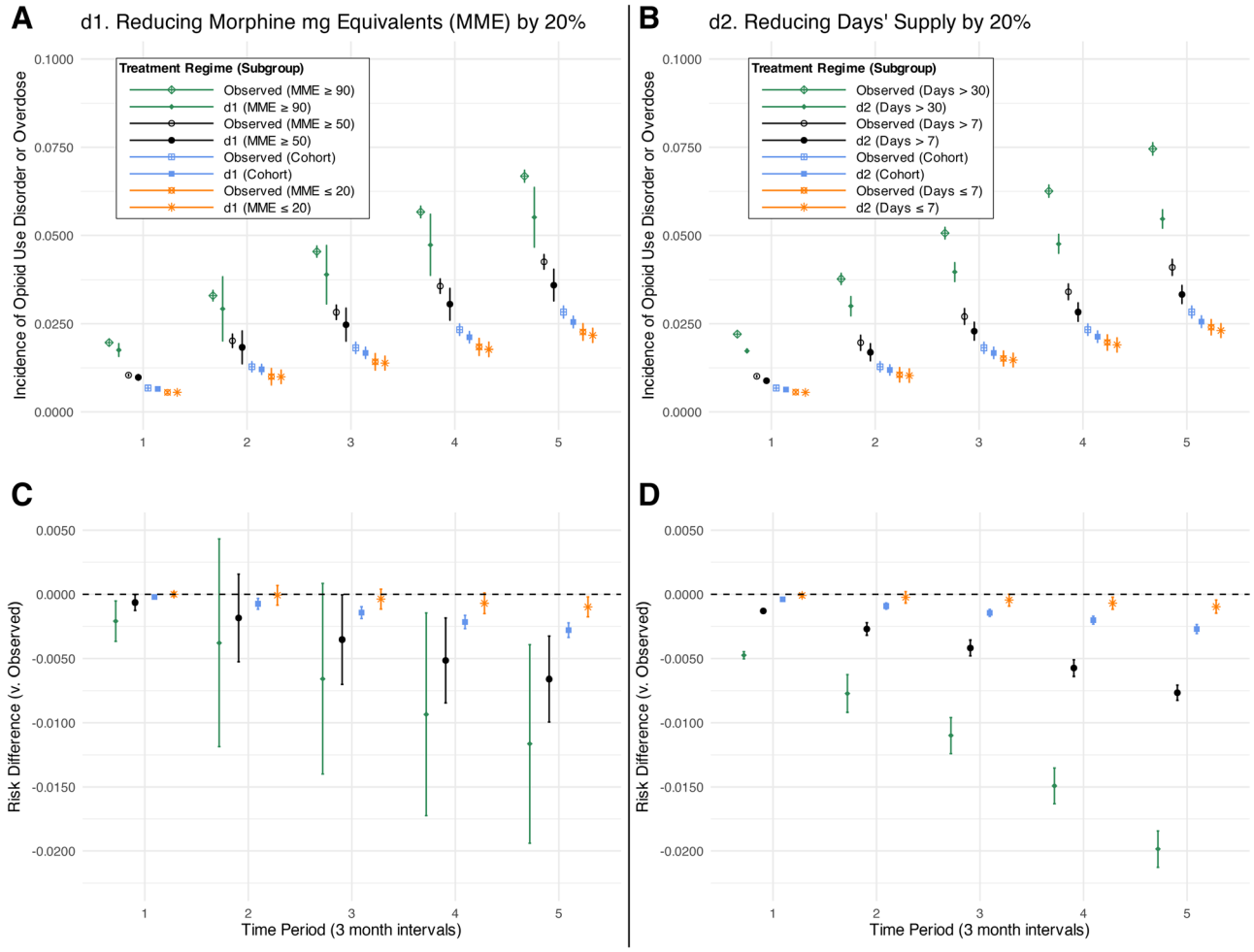

FIGURE 2. Opioid use disorder or overdose incidence by period when reducing either dose (d1, A and C) or duration (d2, B and D) alone.

days, whereas it only reduced risk by 0.13 (95% CI = 0.05, 0.21) percentage points among those with prescriptions ≤20 morphine mg equivalents and ≤7 days.

We estimated smaller reductions in risk from decreasing either dose or duration by 20%, but observed the same pattern in terms of the magnitude increasing for those with higher doses and longer durations. Reducing dose by 20% was estimated to decrease risk of opioid use disorder or overdose by 1.17 percentage points (95% CI = 0.39, 1.94) by the end of the study among those with opioid prescriptions ≥90 morphine mg equivalents, but only by 0.10 percentage points (95% CI = 0.02, 0.17) among those with prescriptions ≤20 morphine mg equivalents. Slightly larger risk reductions were estimated when decreasing prescription duration by 20%: 1.98 percentage points (95% CI = 1.84, 2.13) by the end of the study among those with opioid prescriptions >30 days, but only 0.10 percentage points (0.05, 0.15) among those with opioid prescriptions ≤7 days.

Findings were similar in the sensitivity analysis in which we limited continuous use of opioids to a maximum gap of 30 days in the exposure period (See eFigures 5 and 6; https://links.lww.com/EDE/C265).

We provide point estimates and 95% CIs for all primary results in eTable 5; https://links.lww.com/EDE/C265.

DISCUSSION

We quantified the extent to which modest reductions in opioid dose and duration would reduce opioid use disorder risk for musculoskeletal pain patients with different levels of opioid prescribing. Among musculoskeletal pain patients with an opioid prescription ≤20 morphine mg equivalents and ≤7 days, hypothetically reducing the dose and duration by 20% was estimated to have no meaningful effect on the risk of opioid use disorder or overdose across 15 months, reducing risk by only one-tenth of one percent. Rather, we found, as others have, that high-dose and/or long-duration opioid prescriptions confer more clinically meaningful risk.[12,20,21,39–41] Among musculoskeletal pain patients with an opioid prescription ≥90 morphine mg equivalents and >30 days, reducing the dose

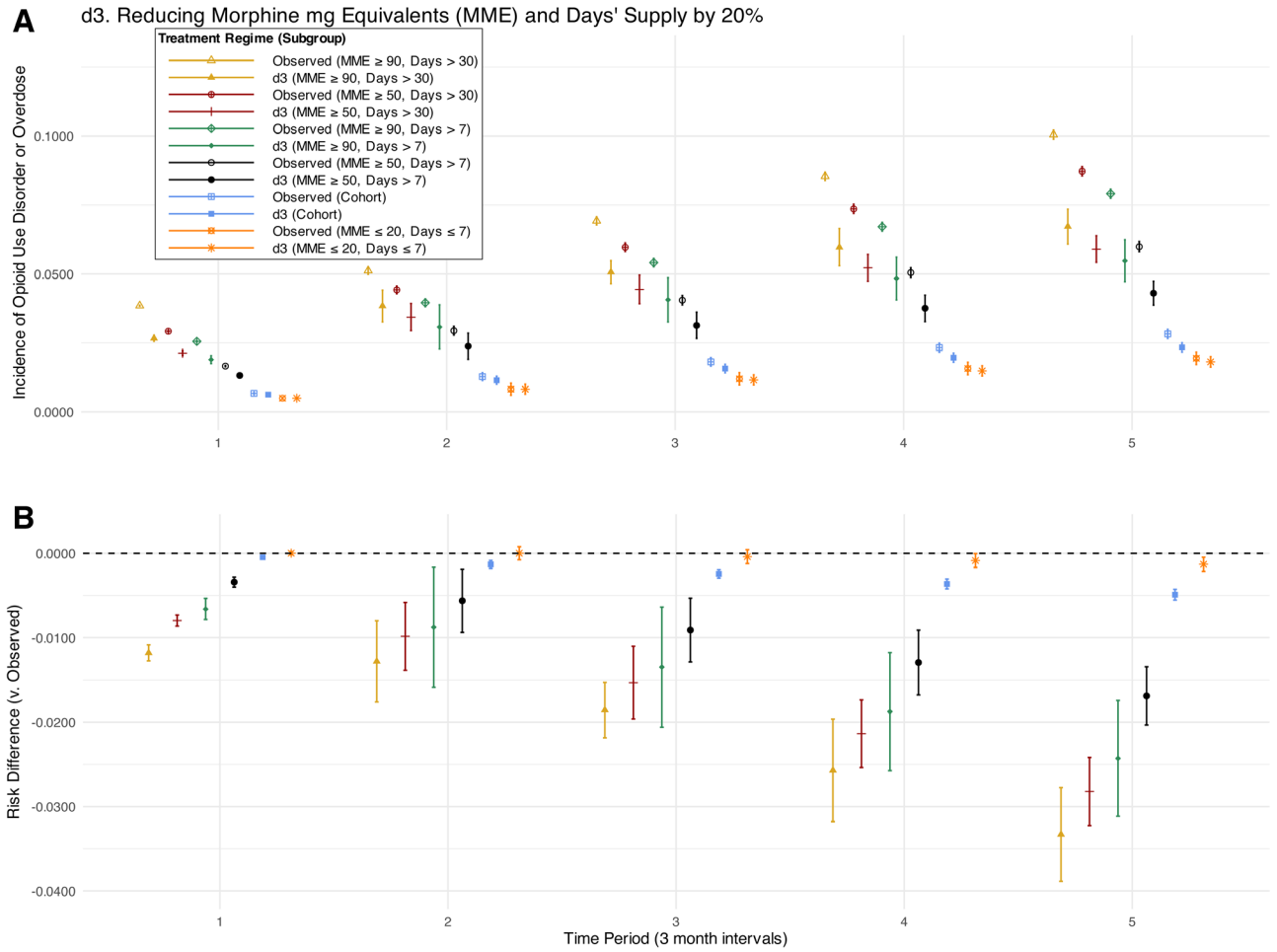

FIGURE 3. Opioid use disorder or overdose incidence by period when jointly reducing both dose and duration (d3).

and duration by 20% was estimated to reduce 15-month risk by 3.33 percentage points—a relative risk reduction of 33.1%. Reducing dose and duration by 20% for the entire cohort was estimated to reduce the risk of opioid use disorder or overdose by 15 months by 0.49 percentage points, the same order of magnitude as the risk reduction estimated among those with non-risky prescribing.

Given the above findings, applying opioid prescribing guidelines or policies to encourage universal reductions in dose and duration may have little effect on reducing opioid-related harms, and, plausibly, may even be counterproductive to the extent that their universal application results in uncontrolled pain. In contrast, applying opioid prescribing guidelines or policies to target patients with high-dose and/or long-duration opioid prescriptions would be expected to yield much larger benefits in terms of opioid-related harm reduction. For example, if one considered a one percentage point absolute risk reduction over 15 months as clinically relevant (though this is just an example, as no such threshold exists), then this would suggest targeting interventions to reduce opioid prescription dose and duration to those patients with both doses ≥50 morphine mg equivalents and durations >7 days or reduce opioid prescription dose only to patients with doses ≥90 morphine mg equivalents. However, if one considered a two percentage point absolute risk reduction over 15 months as clinically relevant, then this would suggest targeting interventions to reduce opioid prescription dose and duration to those patients with doses ≥90 morphine mg equivalents and durations >7 days or those with doses ≥50 morphine mg equivalents and durations >30 days. Broadly, these results add to a body of literature demonstrating the effectiveness of targeting patients with risky opioid prescribing practices to reduce opioid-related harms[41–43] and are aligned with policies that have done so.[44,45]

Our study was limited in several respects. First, we lack a measure of pain severity or persistence in Medicaid claims data. Such a variable may function as both an unobserved confounder and an unobserved mediator in that the pain treatments prescribed to patients may be influenced by their level of pain and may also influence their level of pain. Although we attempt to control for uncontrolled pain using claims for pain-related emergency department visits, identifying an

appropriate proxy for pain severity and persistence in claims data is the subject of our future work. Second, the optimal reduction in opioid prescription dose and duration for a given level of prescribing remains an open question. We chose a 20% reduction as this represents a modest, clinically realistic reduction and allows us to stay within the bounds of the observed data, such that we are protected against drawing conclusions based on extrapolation. A third limitation is that although our approach of estimating effects within subsets receiving risky opioid prescriptions allows for more nuanced estimates, it may not be straightforward to identify which *new* opioid users should be targeted for reductions. The method we use is premised on the so-called "natural value" of treatment(s), which in this example would be defined as the prescription opioid dose and duration that a patient would receive in the absence of any intervention.[27] How to identify who would receive risky opioid prescriptions for the first time is an important and complex practical consideration, which we discuss next.

One potential, expert-recommended[46] way to integrate evidence-based opioid prescribing recommendations into clinical practice is through clinical decision support systems.[47] For example, when a provider inputs an opioid prescription that falls into one of the risky categories into an electronic health record,[47] a prompt could suggest a new prescription that reflects a 20% reduction in dose and/or duration, also providing the scientific rationale.[47–49] Such a hypothetical clinical decision support system is somewhat analogous to the Veteran's Health Administration's Stratification Tool for Opioid Risk Mitigation (STORM) initiative, which identified patients currently prescribed opioids who were at-risk for opioid-related misuse and required provider review of their treatment plan.[50] Recent evaluations of STORM found that it effectively reduced mortality.[42] Another limitation is that we do not account for other pain-related treatments that the patients may be taking. In particular, it is possible that other prescription medications may interact with prescription opioids to place patients at particular risk of developing opioid use disorder or overdose.[51] Learning subsets of patients defined by the natural values of multiple co-occurring treatments whose risk is particularly affected by dose reductions is an important area for future work.

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