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Associations of opioid prescription dose and discontinuation with risk of substance-related morbidity in long-term opioid therapy

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Abstract

Efforts to reduce opioid-related harms have decreased opioid prescription but have provoked concerns about unintended consequences, particularly for long-term opioid therapy (LtOT) recipients. Research is needed to address the knowledge gap regarding how risk of substance-related morbidity changes across LtOT and its discontinuation. The present study used nationwide commercial insurance claims data and a within-individual design to examine associations of LtOT dose and discontinuation with substance-related morbidity. We identified 194 839 adolescents and adults who initiated opioid prescription in 2010–2018 and subsequently received LtOT. The cohort was followed for a median of 965 days (interquartile range, 525–1550), of which a median of 176 days (119–332) were covered by opioid prescription. During follow-up, there were 17 582 acute substance-related morbidity events, defined as claims for emergency visits, inpatient hospitalizations, and ambulance transportation with substance use disorder or overdose diagnoses. Relative to initial treatment, risk was greater within individual during subsequent periods of >60–120 (adjusted odds ratio [OR], 1.29; 95% CI, 1.12–1.49) and >120 (OR, 1.48; 95% CI, 1.24–1.76) daily morphine milligram equivalents. Risk was also greater during days 1–30 after

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discontinuations than during initial treatment (OR, 1.19; 95% CI, 1.05–1.35). However, it was no greater than during the 30 days before discontinuations, indicating that the risk may not be wholly attributable to discontinuation itself. Results were supported by a negative control pharmacotherapy analysis and additional sensitivity analyses. They suggest that LtOT recipients may experience increased substance-related morbidity risk during treatment subsequent to initial opioid prescription, particularly in periods involving higher doses.

1. Introduction

The US has witnessed decades of exponential growth in drug overdose mortality [39]. Beyond risks associated with illicit opioid use [28,64], it is clear that the rise in opioid prescription for non-cancer pain has been associated with this public health crisis [70,71]. Guidelines and other responses, largely focusing on reducing adverse effects of long-term opioid therapy (LtOT) [17], have contributed to decreasing prescription rates since 2012 [4,29].

There is growing concern, however, about unintended consequences of efforts to reduce opioid prescription, particularly for individuals discontinuing LtOT [12,16,43,57]. As reviews for the National Academy of Medicine [63] and the Veterans Affairs Evidence Synthesis Program [51] have documented, empirical evaluations of the consequences of continuing *and* discontinuing LtOT must be strengthened to inform evidence-based policy. Inadequate confounder control [61,66] and lack of attention to outcomes beyond opioid overdose (e.g., polysubstance use) [10,13] represent major limitations in the existing observational opioid literature. Indeed, meta-analyses show extensive cross-study heterogeneity in estimates of overdose, opioid use disorder, and mortality among opioid recipients, precluding clear guidance for patients or policy [1,36,45]. This uncertainty has been amplified by emerging research suggesting greater risk of adverse outcomes among patients who discontinue LtOT [3,11,25,33,40,53,56], although whether any such risk is caused by discontinuation itself is not yet clear [5]. Thus, whereas recipients of higher prescribed opioid doses, for example, experience greater risk of overdose and related harms [6,9,18,22,24,30,34,69], the extent to which these associations reflect acute or longer-term pharmacologic effects or other underlying factors is uncertain [61].

This study used up-to-date, nationwide healthcare data to examine associations of opioid therapy dose and discontinuation with risk of broadly defined substance-related morbidity among LtOT recipients. To address previously identified evidence gaps [61], we applied a novel within-individual design that tracked risk from initial prescription through dose changes during LtOT and eventual discontinuations. By treating each recipient as their own control, this approach ruled out confounding from all time-stable factors [48]. We augmented our analysis with time-varying confounder adjustment and a negative control exposure (i.e., a pain-management pharmacotherapy that would not be expected to affect risk).

2. Methods

2.1 Cohort

We used data from the IBM® MarketScan® Commercial (“MarketScan”) database [32]. MarketScan includes inpatient, outpatient, and filled prescription claims for individuals aged up to approximately 65 years with employer-based insurance nationwide, as well as their spouses and dependents. The data consist of records from all reimbursed healthcare encounters, as well as prescriptions dispensed by pharmacies. To examine recent trends [61], we analyzed opioid prescription from January 1, 2010 through December 31, 2018. During that period, MarketScan included approximately 130 million unique enrollee observations. The Indiana University and University of Chicago Institutional Review Boards determined that the study was exempt.

Our cohort comprised non-cancer LtOT recipients aged ≥14 years at opioid prescription initiation. To ensure incident use, we required recipients to be enrolled for ≥12 consecutive calendar months prior to first opioid prescription fill [60]. We additionally required that participants have at least some continuous follow-up enrollment beginning at initiation and no cancer diagnosis or hospice care within 1 year before initiation. We excluded individuals with difficult-to-calculate opioid doses (i.e., analgesic buprenorphine products, spray formulations, or non-integer fentanyl patch quantities), invalid prescription data (e.g., days supply <1 or >90), or potentially improbable opioid doses (i.e., >99th percentile of daily dose during follow-up or >180 morphine milligram equivalents on the initiation day). To focus on LtOT, we required that participants receive ≥90 cumulative days of opioid therapy during follow-up [20,60]. eTable 1, Supplemental Digital Content, details the complete inclusion criteria. We followed participants until first disenrollment (a month with no enrolled days with prescription drug coverage, per annual enrollment records), cancer, hospice, or December 31, 2018.

2.2 Opioid Prescription

We calculated participants’ daily dose in morphine milligram equivalents (MME/D) from filled prescriptions of non-buprenorphine opioid analgesics (eTable 2, Supplemental Digital Content) [55]. We assumed that prescriptions began on the fill date and covered the days supply, except that we assumed fentanyl patches were worn 1 at a time sequentially for 3 days each [55]. When two prescriptions for the same drug (e.g., long-acting oxycodone) overlapped, we assumed that the supply of the second prescription began the day after the first ended. However, we permitted prescriptions for differing opioid drugs to overlap, summing to obtain daily dose. Consistent with previous studies, we categorized dose as ≤60 MME/D, >60–120 MME/D, or >120 MME/D [9,20].

2.3 Substance-Related Morbidity Events

To capture time-specific events rather than recurring services for ongoing problems, we assessed acute substance-related morbidity from claims for emergency visits, inpatient hospitalizations, and ambulance transportation with diagnoses of non-tobacco substance use disorder (SUD) or drug/medication overdose (eTable 3, Supplemental Digital Content) [26,27,58]. For each included day, we defined substance-related events as present or absent.

We assumed that claims separated by less than 2 days represented the same event (e.g., overnight hospitalizations) [9,46].

2.4 Statistical Analysis

After preliminarily describing substance-related event rates across the year before and after opioid initiation and discontinuation, we examined risk of events as a function of daily prescription status (i.e., with the person-day as the unit of analysis). Specifically, to model change over the course of LtOT, we examined the extent to which risk of substance-related events during later treatment differed from that during initial treatment as a baseline comparison (Figure 1). This strategy allowed us to examine subsequent risk among the minority of initiators who persist into LtOT [59,65], while avoiding an inappropriate (pre-treatment or post-discontinuation) baseline [52]. Based on preliminary analyses, we defined the initial treatment baseline as medicated time within 30 days after initiation, assuming that substance-related events on the initiation date were premorbid. For periods after treatment episodes, we distinguished discontinuation days 1–30 and 31–90 from later days [56], where discontinuation was defined as ≥7 days with no opioid supply. For shorter gaps, we carried the previous dose forward. We excluded days when patients were in inpatient facilities, except days that were substance-related events [68]. Because the outcomes were defined as repeatable events separated by ≥2 days, we excluded days considered as an extension of a prior event, as well as the 2 days following each event (because a new discrete event would not have been permitted).We analyzed data in SAS, version 9.4 (SAS Institute, Inc).

We first examined differences in risk across treatment periods using discrete-time logistic regression at the population level [9,23]. We estimated relative risk with odds ratios [14], adjusting for sex and time-varying age, calendar year, and prescription of benzodiazepines, gabapentinoids, z-hypnotics, and pharmacotherapies for SUD (eTable 4, Supplemental Digital Content). We adjusted standard errors to account for the non-independence of days within individuals.

These population-level models were susceptible, however, to unmeasured confounders that differed between individuals. Thus, to rule out all time-stable confounding (i.e., from factors that did not vary among treatment periods within individuals) [48], we estimated within-individual comparisons using conditional logistic regression [2,58]. These models asked whether, relative to a given individual's risk during initial treatment, that specific individual experienced greater risk when they subsequently received categorized doses in LtOT or discontinued treatment. Because the models capitalized on within-individual variation, only discordant individuals (i.e., those varying in substance-related events and at least one predictor variable) were informative. We did not include age or calendar year as covariates given the relatively short time elapsed during included follow-up. To further focus on the period immediately before and after discontinuation, we constructed additional within-individual models comparing risk during the 30 days before treatment discontinuation (counting medicated days only) with that during the 30 days after discontinuation (censoring at any subsequent prescription). We focused on individuals' first discontinuations in order to limit these additional models to 1 discontinuation per individual. To account for differences

by episode duration, the models examined first discontinuations of discrete treatment episodes of 1–30, 31–90, or >90 days.

Finally, sensitivity analyses examined the robustness of our results to alternative specifications. First, and critically, we evaluated the specificity of the associations to LtOT rather than to processes associated with chronic pain management in general. Specifically, we used cyclic antidepressants as a negative control medication [49,62], repeating the adjusted within-individual analysis for incident cyclic antidepressant receipt within our analytic cohort [58]. Additionally, to examine opioid prescription assumptions, we estimated associations without altering exposure dates for overlapping prescriptions and, separately, with exposure defined as beginning the day after prescription fills. To examine assumptions about discontinuation, we estimated associations when varying the minimum gap considered as a discontinuation to more extreme boundaries (1 or 30 days) and when excluding individuals who discontinued prescription during hospitalizations. To examine outcome assumptions, we estimated associations when including emergency department events only, when increasing the minimum gap between events from 2 to 10 days, and when censoring follow-up at the change to ICD-10-CM (September 30, 2015). To examine outcome specificity, we separately examined overdose, non-overdose, and non-self-harm (i.e., events not accompanied by a diagnosis of intentional self-harm or injury of undetermined intent [35]) outcomes. Finally, we examined whether associations varied as a function of pre-existing SUD in stratified analyses.

3. Results

We identified 22 099 792 MarketScan enrollees who filled a first opioid prescription in 2010–2018 (eTable 1). Sequential exclusion due to initiation age <14 years (743 760), non-incident prescription (11 264 768), non-enrollment at initiation (28 080), prior cancer or hospice (884 448), unusable or improbable opioid data (332 866), fewer than 90 medicated follow-up days (8 650 028), and unusable covariate and other follow-up data (1003) yielded an included cohort of 194 839 incident, non-cancer LtOT recipients (51.4% female; Table 1). At initiation, 89.8% (N, 174 927) received doses ≤60 MME/D. There were 17 582 substance-related events among 8972 individuals (4.6%) during follow-up after initiation (2.41 events per 1000 person-months).

3.1 Substance-Related Events at Opioid Initiation and Discontinuation

Across the year before and after first opioid receipt, substance-related event rates peaked during the month and days immediately *prior* to the day of initiation (Figure 2). Following initiation, however, rates stabilized rapidly and were comparable to that in the 31–60 days before initiation. This pattern supported our use of days 1–29 following initiation as the initial treatment reference period.

Relative to the rate prior to discontinuations, the substance-related event rate was slightly greater in the month after all discontinuations of discrete 1–30 day treatment episodes (Figure 3). However, the opposite was apparent for longer treatment episodes: Event rates were greater immediately prior to discontinuations relative to after discontinuations.

3.2 Association between Opioid Dose and Substance-Related Events

Relative to initial treatment (2.61 events per 1000 person-months), risk of substance-related events was greater during subsequent treatment periods of >60–120 MME/D (5.77 per 1000 person-months; adjusted OR, 1.66; 95% CI, 1.41–1.95) and especially during periods of >120 MME/D (7.31 per 1000 person-months; OR, 1.92; 95% CI, 1.59–2.32; Table 2). In the within-individual comparison that ruled out all time-stable confounding, these associations were smaller in magnitude but persisted (>60–120 MME/D: OR, 1.29; 95% CI, 1.12–1.49; >120 MME/D: OR, 1.48; 95% CI, 1.24–1.76). eTable 5, Supplemental Digital Content, shows within-individual informative participants (i.e., those discordant on substance-related events and at least one predictor). eTables 6 and 7, Supplemental Digital Content, show unadjusted results and adjusted-model covariates, respectively.

3.3 Association between Opioid Discontinuation and Substance-Related Events

Unadjusted risk of substance-related events decreased across discontinuation days 1–30 (2.53 per 1000 person months), days 31–90 (2.26 per 1000 person-months), and days >90 (2.11 per 1000 person-months; Table 2). In the within-individual comparison, risk was modestly greater during discontinuation days 1–30 than during initial treatment (OR, 1.19, 95% CI, 1.05–1.35). Risk during later discontinuation days did not differ from that in initial treatment.

In models analyzing just the 30 days before and after discontinuation, however, we found no statistically significant evidence of greater risk immediately after—relative to immediately before—discontinuation. Risk actually decreased immediately after discontinuations of longer episodes (1–30 day episodes: OR, 1.21; 95% CI, 0.98–1.50; 31–90 day episodes: OR, 0.95; 95% CI, 0.80–1.12; >90 day episodes: OR, 0.81; 95% CI, 0.68–0.96).

3.4 Negative Control

We repeated the within-individual analysis with cyclic antidepressants as a negative control exposure. Among our cohort, 22 132 individuals initiated cyclic antidepressants (eTable 8, Supplemental Digital Content). Relative to initial treatment, subsequent cyclic antidepressant periods were associated with lower risk of substance-related events (OR, 0.74; 95% CI, 0.62–0.88). Risk of substance-related events was also lower during all discontinuation periods, although not statistically significantly during discontinuation days 1–30. That is, the pattern of associations observed over the course of LtOT differed from that for a different chronic pain pharmacotherapy.

3.5 Sensitivity Analyses

Sensitivity analyses largely supported the within-individual results (eTables 9–11, Supplemental Digital Content). We found commensurate dose associations across varying exposure and outcome assumptions, with the exception that associations were somewhat stronger when excluding individuals with in-hospital discontinuations. Associations with discontinuation were weaker and not statistically significant when extending the permitted minimum treatment gap to 30 days and when varying outcome assumptions, which was consistent with the limited support in the primary analysis. For specific substance-related outcomes, dose associations were stronger and discontinuation associations weaker when

examining rarer overdose events but not the other outcomes. Finally, among those with pre-existing substance-related morbidity, both dose and discontinuation associations were weaker and not statistically significant.

4. Discussion

This study used 9 years of nationwide healthcare data on 194 839 LtOT recipients to examine change in risk of substance-related morbidity from initial opioid prescription through subsequent treatment and its discontinuation. Unadjusted substance-related event rates were more than doubled during later treatment periods involving doses >60 MME/D. Although these associations attenuated in within-individual comparisons with measured time-varying covariates, they remained positive and statistically significant. Specifically, individuals experienced 29% and 48% relatively greater risk of substance-related events in subsequent treatment periods involving >60–120 MME and >120 MME, respectively. These results were supported by a range of sensitivity analyses, including a negative control analysis suggesting that the LtOT results were not explained by general processes in pharmacologic chronic pain management. Although no single observational study can determine a true adverse medication effect, our results are consistent with dose-related increases in risk of substance-related events during LtOT [1,6,34]. Considered with evidence of lack of clinical improvement with opioid dose escalation [54], as well as no greater benefit beyond that provided by non-opioid pain medications [42], our results further support the need for caution in initiating and continuing LtOT.

At the same time, interpretations of our results should also consider the magnitude of substance-related event risk. During initial treatment, substance-related events occurred in 1 of every 384 person-months of prescription (2.61 events per 1000). Even at later doses >120 MME, the unadjusted rate was 1 in 137 person-months, and dose-related differences attenuated substantially with adjustment. That is, for many LtOT recipients, the likelihood of substance-related events was quite low. Direct comparisons between our results and those of prior studies are not straightforward, both because we captured broader polysubstance-involved outcomes [10] and because prior estimates have been highly heterogeneous [1,36,45]. Even so, our within-individual dose-related associations appear substantially smaller in magnitude than previous meta-analytic summaries. Thus, our findings may call into question very large associations in studies with less adjustment for confounding [1,36]. They underscore the need for careful confounding control (e.g., pre-existing mental health conditions, additional psychoactive pharmacotherapies) [19,61]. Nevertheless, even a small absolute risk of overdose or other morbidity should not be dismissed.

Since the US opioid prescription rate peaked in 2012, decreases appear to have been driven by reductions in opioid initiation as well as reductions in prescriptions of shorter days supply [29], perhaps reflecting challenges associated with successful discontinuation of ongoing LtOT [21,43,44]. Moreover, recent research suggests that individuals who discontinue LtOT may experience greater risk of overdose mortality [56]. In our within-individual approach, we found less support for the hypothesis that discontinuation increases risk of substance-related morbidity. Rather, given findings of greater concurrent risk during LtOT, our discontinuation results are consistent with the possibility that any elevated risk

observed after LtOT ends may at least in part reflect substance-related morbidity that had already escalated prior to discontinuation. Indeed, recent studies suggest that discontinuation is mostly due to clinicians' concern about misuse or aberrant opioid-related behavior [38,50]. However, our within-individual results do not provide direct evidence regarding whether discontinuation would resolve or otherwise affect risk for all patients. Figure 3 shows that risk persisted longer after discontinuations of >90 day treatment episodes, although this pattern should be interpreted with caution given the relatively small number of observed events.

We note that risk of substance-related events actually peaked immediately *prior* to first prescription. This pattern may indicate that opioids were initiated, for some, in response to substance-related events (e.g., substance-involved injuries). More broadly, greater risk during the pre-initiation period has been observed for other psychoactive medications, outcomes, and healthcare data sources [8,37,52]. It may be important to consider in future opioid research when, for example, identifying baseline risk prior to LtOT. Indeed, when we limited our analysis to individuals with substance-related morbidity recorded prior to initiation, we found no statistically significant changes in risk of substance-related events later in LtOT. We caution that this result may reflect imprecise outcome timing during the premorbid vs. baseline periods, as well as regression to the mean induced by selecting participants with prior substance-related morbidity. Consistent with their greater event rate throughout follow-up (20.54 substance-related events per 1000 person-months, or 1 in 49 person-months), these individuals may simply have experienced persistently higher risk.

Our findings should be interpreted considering their strengths and limitations. First, we combined a within-individual design with time-varying statistical covariates and a negative control analysis. However, we could not rule out unmeasured time-varying confounders (e.g., pain-related distress, stressful life events) and thus could not definitively establish the magnitude of any adverse effect [61]. Second, when we specifically examined the period immediately before and after opioid prescription discontinuation, we limited our analysis to participants' first discontinuations. Further research is needed to understand the interplay between recurrent discontinuations and risk of substance-related morbidity. Third, although we analyzed nationwide data, we do not know the extent to which the observed associations would generalize to those with non-employer-based (or no) insurance [41], cancer pain, or other specific clinical characteristics. Fourth, we assessed LtOT from filled prescriptions claims, meaning that we could not identify prescriptions written but not filled, filled but not used, or paid out-of-pocket (which appears rare) [7,47]. Fifth, our dose categories relied on assumptions about opioid equivalence and did not consider differential associations for long-acting formulations; they should not be interpreted as providing thresholds for harm [66]. Sixth, in order to examine time-specific outcomes, we focused on acute substance-related events [58]. We also included a broad range of substance-related morbidity, including overdose and problems related to diverse substances. However, other outcomes, including those not recognized clinically or resulting in unreimbursed care, would be omitted [67]. A complete evaluation of potential harms associated with LtOT should include additional substance-related morbidity (e.g., misuse, illicit use, criminal justice involvement), outcomes (e.g., diversion, suicidal behavior, hyperalgesia, broader functioning), and treatment characteristics (e.g., duration of LtOT) [66]. Seventh,

any benefits associated with patient-centered dose tapering (e.g., minimizing withdrawal, facilitating transition to opioid use disorder management) would be beyond the scope of this study [15], consistent with previous research [56]. However, this practice appears relatively rare in real-world care to date [31,53].

4.1 Conclusions

This study illustrated the importance of addressing measured and unmeasured confounding in estimating risk of substance-related morbidity from initiation through discontinuation of LtOT. We found that higher-dose periods were independently associated with greater risk of substance-related morbidity, albeit in smaller magnitudes than have been found in some studies. Although we found less support for increased risk due to discontinuation, our results suggest that the period around LtOT discontinuation warrants careful clinical monitoring and continued research on potential harms and benefits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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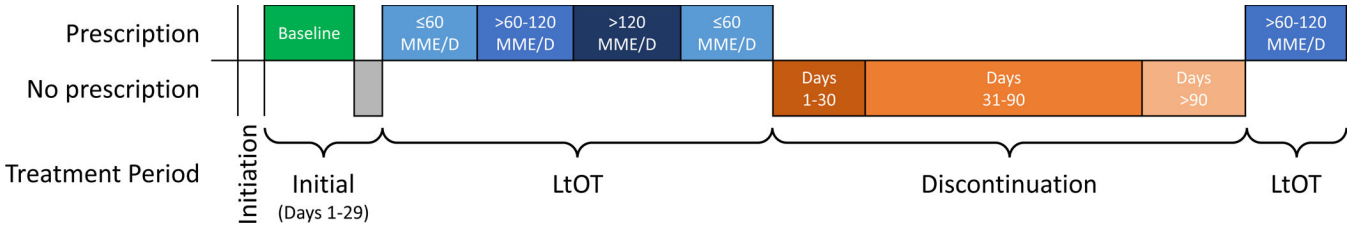

Figure 1.

Study design. Depiction of study design (for an example individual) to examine associations of opioid dose and discontinuation with substance-related events from prescription initiation through course of long-term opioid therapy (LtOT). Green segment indicates initial treatment baseline period, which served as the reference condition for statistical comparisons. Grey segment indicates prescription gap during initial period (days 1–29), which would be excluded from analysis. Blue segments indicate opioid dose in morphine milligram equivalents per day (MME/D), which could vary on a daily basis during treatment. Orange segments indicate time after last opioid treatment during discontinuations. Covariates (sex and time-varying age, calendar year, and prescription of substance use disorder medications, benzodiazepines, gabapentinoids, and z-hypnotic medications) not shown. Time-varying covariates were defined on a daily basis throughout all included treatment periods.

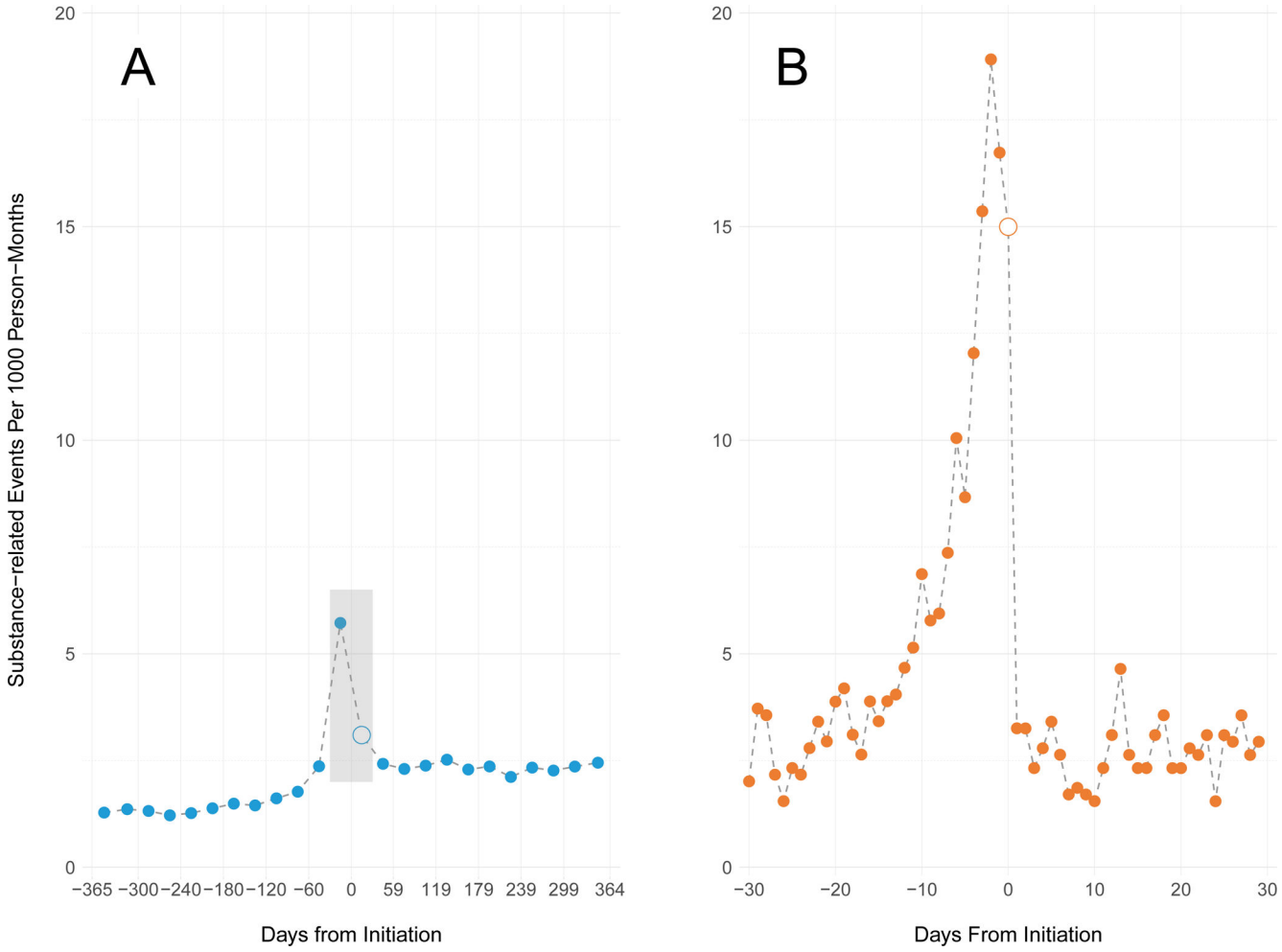

Figure 2.

Opioid therapy initiation and substance-related events. Substance-related events by month within 1 year of first initiation (Panel A) and by day within 30 days of first initiation (Panel B). Open circles include the date of initiation.

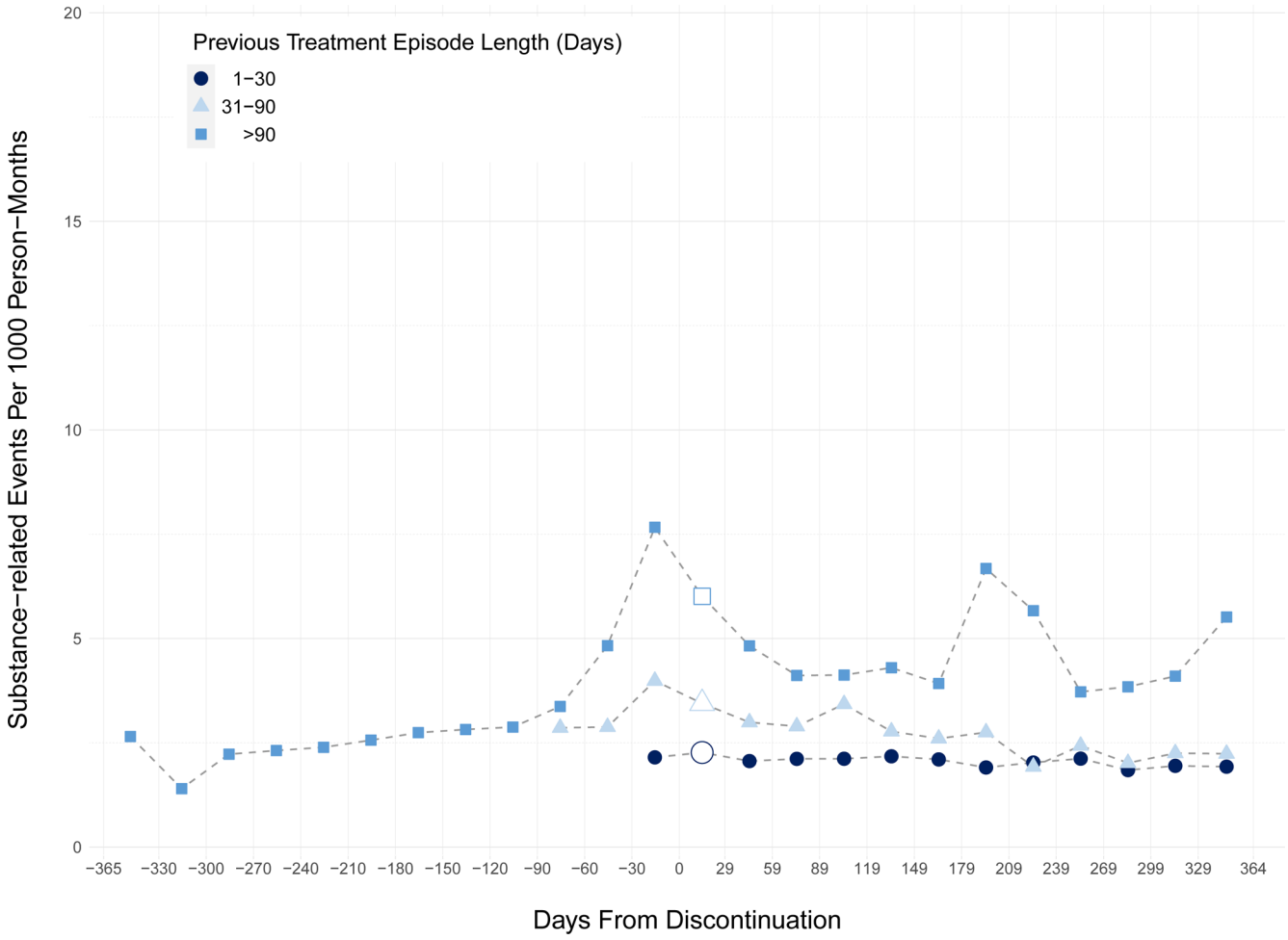

Figure 3.

Opioid therapy discontinuation and substance-related events. Substance-related events by month within 1 year of all discontinuations following any opioid therapy periods of 1–30, 31–90, or 91 or more consecutive days. Open symbols include dates of discontinuations.

Table 1.

Descriptive Statistics for 194 839 Long-Term Opioid Therapy Recipients

Variable	n	%
Included individuals	194 839	
Female	100 122	51.4%
Age at initiation		
14–18	3036	1.6%
19–25	8954	4.6%
26–35	24 535	12.6%
36–45	41 516	21.3%
46–55	65 401	33.6%
56–65	51 397	26.4%
Dose at initiation		
> 0 to 60 MME/D	174 927	89.8%
> 60 to 120 MME/D	16 448	8.4%
> 120 MME/D	3464	1.8%
Maximum dose during follow-up		
0 MME/D[a]	1	0.0%
> 0 to 60 MME/D	100 056	51.4%
> 60 to 120 MME/D	63 593	32.6%
> 120 MME/D	31 189	16.0%
Substance-related events during follow-up		
0	185 867	95.4%
1	5974	3.1%
2–5	2557	1.3%
6–10	317	0.2%
≥ 11 (max, 93)	124	0.1%
Median follow-up days (IQR)	965 (525 – 1550)	
Median prescribed days during follow-up (IQR)	176 (119 – 332)	

[a]All prescribed days were excluded from analysis for 1 individual.

MME/D, morphine milligram equivalents per day.

Table 2.

Substance-Related Event Rates by Opioid Treatment Period among 194 839 Long-Term Opioid Therapy Recipients

Period	Substance-Related Events	Person-Months	Events / 1000 Person-Months	Population[a] OR (95% CI)	Within-Individual[b] OR (95% CI)
Initial Treatment Baseline Period [reference]	279	107 013.17	2.61	[1]	[1]
Dose during LtOT					
> 0 to 60 MME/D	4173	1 639 387.07	2.55	0.88 (0.76–1.01)	1.09 (0.96–1.23)
> 60 to 120 MME/D	754	130 714.43	5.77	1.66 (1.41–1.95)	1.29 (1.12–1.49)
> 120 MME/D	373	51 023.67	7.31	1.92 (1.59–2.32)	1.48 (1.24–1.76)
Treatment Discontinuations					
1–30 days after treatment	2890	1 142 935.43	2.53	0.99 (0.86–1.13)	1.19 (1.05–1.35)
31–90 days after treatment	2549	1 128 966.00	2.26	0.90 (0.78–1.03)	1.04 (0.91–1.18)
> 90 days after treatment	6564	3 109 773.80	2.11	0.81 (0.71–0.93)	1.02 (0.90–1.15)

Month defined as 30 days. 398 394.63 months with 17 582 events among 8972 informative (discordant) individuals in within-individual comparisons.

LtOT, long-term opioid therapy. MME/D, morphine milligram equivalents per day. OR, odds ratio.

[a]Adjusted for sex, age, calendar year, and prescription of substance use disorder medications, benzodiazepines, gabapentinoids, and z-hypnotic medications.

[b]Adjusted for prescription of substance use disorder medications, benzodiazepines, gabapentinoids, and z-hypnotic medications.