OPIOIDS & SUBSTANCE USE DISORDERS SECTION

Reasons for Opioid Discontinuation and Unintended Consequences Following Opioid Discontinuation Within the TOPCARE Trial

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Abstract

Objective. To identify reasons for opioid discontinuation and post-discontinuation outcomes among patients in the Transforming Opioid Prescribing in Primary Care (TOPCARE) study. **Design.** In TOPCARE, an intervention to improve adherence to opioid prescribing guidelines, randomized intervention primary care providers (PCPs) received nurse care manager support, an electronic registry, academic detailing, and electronic tools, and control PCPs received electronic tools only. **Setting.** Four Boston safety net primary care practices. **Subjects.** Patients in both TOPCARE study arms who discontinued opioid therapy during the trial. **Methods.** Through chart review, we examined the reason for discontinuation and post-discontinuation outcomes: one or more PCP visits, one or more pain-related emergency department (ED) visits, evidence of opioid use disorder (OUD), and referral for OUD treatment. **Results.** Opioid discontinuations occurred in 83/586 (14.2%) intervention and 42/399 (10.5%) control patients ($P = 0.09$). Among patients who discontinued opioids, 81 (65%) discontinued for misuse, with no difference by group ($P = 0.38$). Aberrancy in monitoring (e.g., discordant urine drug test results) was the most common type of misuse prompting discontinuation (occurring in 51/83 [61%] of intervention patients vs 19/42 [45%, $P = 0.08$] of control patients). Intervention patients who discontinued opioids had less PCP follow-up (65% vs 88%, $P < 0.01$) compared with control patients. We found no differences between groups for pain-related ED visits, evidence of OUD, or OUD treatment referral following discontinuation. **Conclusions.** The decreased follow-up among TOPCARE intervention patients who discontinued opioids highlights the need to understand unintended consequences of involuntary opioid discontinuations resulting from interventions to reduce opioid risk.

Key Words: Opioids; Chronic Pain; Discontinuation; Discontinuing; Taper; TOPCARE

Introduction

In 2014, physicians prescribed chronic opioid therapy to an estimated one in 20 US adults [1]. In an effort to curb the ongoing opioid crisis, medical organizations and government agencies recommend close monitoring for patients prescribed chronic opioid therapy [2–4]. Monitoring is intended to help determine if the

risk–benefit ratio of opioid therapy becomes unfavorable, which would prompt potential therapeutic changes including opioid discontinuation and identification and treatment of opioid use disorder (OUD) [4].

Some researchers suggest that public health initiatives aimed at limiting opioid prescription may have unintentionally resulted in an increase in heroin overdose deaths

[5]. Nationally, rates of opioid prescribing stabilized from 2010 to 2012 [6], but deaths from heroin overdoses nearly doubled during this period [7]. Whether or not there is a link between policies and practices to reduce opioid prescribing and increases in heroin overdose is subject of much debate [8], with few data to support either side [5,9–11].

To our knowledge, clinical studies have not examined the unintended consequences of interventions designed to mitigate risks of opioid prescribing. A recent systematic review found that it may be possible to taper or discontinue chronic opioid therapy without worsening, while perhaps improving, pain, function, and quality of life. However, the studies included were low quality and limited by voluntary subject participation in tapering interventions [12]. We are not aware of published data on outcomes following involuntary tapers, particularly in the setting of suspected opioid misuse.

To identify consequences of monitoring, we analyzed data from the Transforming Opioid Prescribing in Primary Care (TOPCARE) study, a cluster randomized controlled trial of a multicomponent intervention (nurse care management, an electronic registry, academic detailing, and electronic decision tools for opioid prescribing; www.mytopcare.org) [13]. The study aimed to improve primary care provider (PCP) adherence to guidelines for patients on chronic opioid therapy for chronic pain. The intervention resulted in a significant improvement in the proportion of patients who had opioid treatment agreements, urine drug testing, and guideline-concordant care compared with the control group [13].

We conducted a subgroup analysis among patients in both arms of the TOPCARE study who were discontinued from chronic opioid therapy to determine 1) whether the study groups differed in reasons for discontinuation and 2) whether the study group or reason for discontinuation affected post-discontinuation outcomes of PCP follow-up, pain-related emergency department (ED) visits, evidence of OUD, or referrals for OUD treatment. We hypothesized that opioid misuse would be the most frequent reason for opioid discontinuation, with the intervention group having more patients discontinued for misuse. We also hypothesized that the groups would be similar in terms of PCP follow-up and ED utilization and that the intervention group would have more patients referred to treatment for OUD.

Methods

Study Design and Setting

We performed a post hoc exploratory analysis through a retrospective chart review of patients who were discontinued from chronic opioid therapy during the TOPCARE trial. TOPCARE is a cluster randomized trial conducted at four primary care practices in Boston, Massachusetts: one urban safety net hospital primary

care practice and three community health center primary care practices. Details of the TOPCARE trial have been published elsewhere [13]. Briefly, the trial randomized 53 PCPs to either an intervention arm consisting of nurse care management of patients prescribed chronic opioid therapy, an electronic registry, academic detailing, and electronic tools (www.mytopcare.org) or a control arm with electronic tools only [13]. Data collection for each site was conducted over the course of a year. We received approval for this study from the Boston University Medical Center Institutional Review Board.

Inclusion and Exclusion Criteria

Patient inclusion criteria for the TOPCARE study included 1) age ≥ 18 years, 2) one or more completed visits to the primary care practice in the past year, 3) chronic opioid treatment (three or more opioid prescriptions written at least 21 days apart within six months) at the start of the intervention period, 4) an ICD-9-CM diagnosis for musculoskeletal or neuropathic pain, and 5) an opioid prescription 60 days before the start of the intervention. The TOPCARE study excluded patients if they were currently receiving care for cancer, except nonmelanoma skin cancer.

We identified opioid discontinuation in two steps. First, we identified patients who met the TOPCARE study definition for opioid discontinuation: They did not receive opioids in the final 60 days of the 12-month intervention period. From this group, we identified patients for whom the medical record documentation confirmed an explicit decision to discontinue opioid therapy (made by either the patient or the PCP). Our sample excluded patients who discontinued opioids for the following reasons: lost to follow-up (defined as no explicit reason for discontinuation other than patient not returning to clinic for appointments), death due to non-opioid-related causes, transfer of care for non-opioid-related reasons, and receipt of opioids from an outside provider.

Data Source

We obtained electronic health record (EHR) data from the main TOPCARE trial analysis using Boston Medical Center's clinical data warehouse, a repository of electronic health record data. We used this data to generate a list of patients meeting criteria for opioid discontinuation, along with the date of opioid discontinuation (the last day of opioid supply from the final opioid prescription).

Data Abstraction

We conducted a chart review of the EHR at the four study sites using a standard chart abstraction form that included data on the following variables: a) reasons for discontinuation, b) PCP follow-up visits, c) ED visits, d) evidence of OUD, and e) treatment for OUD. We reviewed all data including the free text of the clinical

notes from three months before and six months after the opioid discontinuation date. One author (JH) abstracted data for all charts. Blinding of intervention status was not possible as TOPCARE nurse care manager involvement is readily identifiable in the patient chart. Two additional authors (ML and JML) reviewed 10 charts to assess interrater reliability. Interrater reliability revealed 100% agreement (Kappa [κ] = 1.00) for reason for discontinuation (dichotomized as “presumed misuse” vs “other reason for discontinuation”) (see Table A1 in the Appendix for interrater reliability for all subcategories of reason for discontinuation), 80% agreement for PCP follow-up (κ = 0.62) and ED visits for pain (κ = 0.41), and 90% agreement for evidence of OUD (κ = 0.62) and referral for OUD (κ = 0.62).

Outcomes

Our primary outcome was reason for opioid discontinuation, dichotomized into the mutually exclusive categories of 1) presumed misuse and 2) other reasons for discontinuation. The presumed misuse category included patients whose opioid prescriptions were terminated by their PCP due to history suggesting misuse (e.g., “She initially denied getting any outside pain meds – however when pressed she admitted to going to [outside hospital] looking for percocet and tramadol”) or through objective evidence such as aberrancy in monitoring results of urine drug testing, pill counts, or the state prescription drug monitoring program (PDMP). The other category included patients who discontinued opioids for a) pain resolution, b) inadequate analgesia, c) adverse effects, or d) unknown. If a patient had multiple reasons for discontinuation, we selected the most pertinent reason for this mutually exclusive category, according to a predetermined hierarchy of reasons for discontinuation in the following order: 1) presumed misuse (most pertinent), 2) adverse effects, 3) inadequate analgesia, 4) pain resolution, 5) unknown (least pertinent).

We also subcategorized specific types of presumed misuse into the following non-mutually exclusive categories: a) using more opioids than prescribed, b) use of illicit opioids, c) use of nonprescribed opioid analgesics, d) misuse of non-opioid substances, e) diversion, f) prescriptions from multiple providers, and g) aberrancy in monitoring (as evidenced by urine drug testing, pill counts, or the state PDMP).

We assessed the following outcomes in the six months after opioid discontinuation: a) attendance at at least one follow-up appointment with the PCP who prescribed the patient’s opioids, b) one or more ED visits for musculoskeletal or neuropathic pain, c) one or more ED visits for opioid-related harm (overdose, intoxication, and intravenous drug use-related infections), d) evidence of OUD, e) referral for OUD treatment. Of note, a six-month PCP follow-up appointment was not a requirement of the trial.

In the three months before and six months after the opioid discontinuation date, we assessed evidence of

OUD, defined as 1) presence of “opioid use disorder,” “opioid/opiate dependence,” or “opioid/opiate abuse” on the problem list or 2) presence of two or more criteria for opioid use disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [14]. We evaluated criteria for OUD from all clinical documentation available in the EHR, including notes by the PCP, nurse care manager, and specialists, as well as ED and inpatient providers.

We recorded referrals to and initiation of the following treatments for OUD: a) buprenorphine, b) methadone, c) naltrexone, d) psychosocial treatments, e) detoxification, and f) residential treatment.

We obtained data on patient demographics (gender, race), number of risk factors for opioid misuse (age <45 years; drug use disorder, alcohol use disorder, tobacco use, and mental health disorder [defined by ICD-9 diagnosis and billing codes]), and morphine equivalent daily opioid medication dose in the 30 days before the start of the intervention (MED).

Statistical Analysis

We conducted between-group comparisons using *t* tests of means for continuous variables and chi-square tests for categorical variables. We used *P* values of <0.05 to determine statistical significance. We analyzed data using SAS, version 9.4 (SAS Institute Inc).

Results

Participants

The TOPCARE study included 586 participants in the intervention and 399 in the control group. Of these participants, 125 in the intervention group and 67 in the control group met TOPCARE study criteria for opioid discontinuation. After excluding participants without documentation of a confirmed opioid discontinuation, the analytic cohort consisted of 83 participants in the intervention and 42 in the control group (Figure 1). Age, race, average number of risk factors, and MED in the 30 days before the start of the study were similar in the intervention and control groups (Table 1).

In the entire TOPCARE study population (N = 985), 83/586 (14.2%) of those in the intervention group had confirmed opioid discontinuations, compared with 42/399 (10.5%) of the control group (*P* = 0.09). Of those whose opioids were confirmed to be discontinued, 81 (65%) were discontinued for presumed misuse, compared with 44 (35%) for other reasons, with no differences between the intervention and control groups (*P* = 0.38) (Table 2).

Of those patients whose opioids were discontinued for presumed misuse, the most common reasons for discontinuation were aberrancy in monitoring results (70/81, 86%), misuse of nonopioid substance (36/81, 44%), and using more opioids than prescribed (29/81, 36%).

Figure 1. Flow diagram for selection of subjects. *TOPCARE was a randomized controlled trial (RCT) aiming to improve adherence to opioid-prescribing guidelines. The current study is a subgroup analysis of the TOPCARE RCT. †TOPCARE defined discontinuation as no opioids in the final 60 days of the 12-month intervention. ‡The current study refined this definition to require a deliberate decision to discontinue opioids noted in the chart. §Patients excluded in the “not discontinued” category were found to still be receiving opioids from an outside provider. f/u = follow-up.

Table 1. Baseline characteristics of patients with confirmed discontinuation of long-term opioid therapy, by study group

Patient Characteristics	Total (N = 125)	Intervention (N = 83)	Control (N = 42)	P Value
Age, mean (SD), y	52.3 (12.0)	51.8 (11.5)	53.4 (13.1)	0.48
Female, No. (%)	58 (46)	38 (46)	20 (48)	0.85
Race, No. (%)				0.76
Non-Hispanic white	68 (54)	43 (52)	25 (60)	
Non-Hispanic black	43 (34)	30 (36)	13 (31)	
Hispanic	12 (10)	9 (11)	3 (7)	
Other	2 (2)	1 (1)	1 (2)	
Mean No. (SD) of opioid misuse risk factors*	1.8 (1.1)	1.8 (1.0)	1.8 (1.3)	0.94
Daily morphine equivalent dosage, No. (%)†				0.65
<50 mg	95 (76)	64 (77)	31 (74)	
50–100 mg	19 (15)	11 (13)	8 (19)	
>100 mg	11 (9)	8 (10)	3 (7)	

*Risk factors were identified in the 12 months before intervention start and included age <45 years, drug use diagnosis, alcohol use diagnosis, tobacco use diagnosis, and mental health diagnosis (diagnoses identified using ICD-9 codes).

†Average daily morphine equivalent dosage in the 30 days before the start of the intervention.

Aberrancy in monitoring occurred in 51/83 (61%) of the intervention patients, compared with 19/42 (45%, $P=0.08$) of the control patients. The frequency of other subcategories of misuse or aberrancy was similar between groups (Table 2).

Of those whose opioids were discontinued for reasons other than presumed misuse, 19 (43%) were discontinued for pain resolution, 10 (23%) for inadequate analgesia, 10 (23%) for adverse effects, and five (11%) for unknown reasons. Again, there were no differences between groups ($P=0.73$) (Table 2).

Most patients (91/125, 73%) returned to their PCP's office for a follow-up visit within six months of opioid discontinuation. Follow-up visits were less common for patients in the intervention group (65%) compared with the control group (88%, $P<0.01$). ED visits for pain within six months of opioid discontinuation occurred in 14/125 (11%) of subjects, with no difference between intervention

(12/83, 15%) and control (2/42, 5%) patients ($P=0.10$). ED visits for opioid-related harm occurred in two patients (2%) in the intervention group (both for opioid detoxification) and one patient (2%) in the control group (overdose). We identified evidence for opioid use disorder in 30/125 (24%) subjects (see Table 3 for examples of the DSM-V criteria used to identify patients with OUD). OUD was more frequent in patients discontinued for presumed misuse (25/81, 31%) compared with other reasons for discontinuation (5/44, 11%, $P=0.01$). Overall, 16/125 (13%) of patients were referred for treatment of OUD (Table 4).

Discussion

Confirmed discontinuations occurred in 13% of patients on chronic opioid therapy over 12 months, with a trend toward more discontinuations in the group of patients randomized to the TOPCARE intervention. Presumed

Table 2. Reasons for opioid discontinuation for all patients and by study group

Reason for Discontinuation, No. (%)	Total (N = 125)	Intervention (N = 83)	Control (N = 42)	P Value
Presumed misuse*	81 (65)	56 (67)	25 (60)	0.38
Aberrancy in monitoring	70 (56)	51 (61)	19 (45)	0.08
Misuse of nonopioid substance	36 (29)	23 (28)	13 (31)	0.71
Using more than prescribed	29 (23)	22 (27)	7 (17)	0.22
Nonprescribed opioid analgesic	13 (10)	8 (10)	5 (12)	0.69
Multiple prescribers	7 (6)	4 (5)	3 (7)	0.59
Illicit opioid use	3 (2)	2 (2)	1 (2)	0.99
Diversion	3 (2)	3 (6)	0 (0)	–
Other†	44 (35)	27 (33)	17 (40)	0.73
Resolution of pain	19 (15)	12 (15)	7 (17)	0.97
Inadequate analgesia	10 (8)	7 (8)	3 (7)	0.80
Adverse effects	10 (8)	6 (7)	4 (10)	0.66
Unknown	5 (4)	2 (2)	3 (7)	0.20

*Subcategories of presumed misuse are not mutually exclusive, and column totals may add to more than 100%. *P* values are from chi-square tests of pairwise comparisons for each subcategory.

†Subcategories of other reasons for opioid discontinuation are mutually exclusive, and column totals that do not equal 100% are due to rounding. *P* values represent chi-square test for distribution among all subcategories.

Table 3. DSM-5 diagnostic criteria for opioid use disorder and examples from chart review; a problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period

OUD Diagnostic Criteria	Example from Chart Review
1. Opioids are often taken in larger amounts or over a longer period than was intended.	"She was prescribed oxycodone 20 mg BID on discharge but taking at least 4-6 times a day, plus dilaudid 4 mg every 4 hrs."
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.	"Calls to report that she started suboxone yesterday afternoon... Pt states 'I won't be back to pick up narcotics ever again.'"
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.	"She initially denied getting any outside pain meds – however when pressed she admitted to going to [outside hospital] looking for percocet and tramadol."
4. Craving, or a strong desire or urge to use opioids	"Feels has lost mental/emotional control to opioids, dependent, clock watching to the next dose, not getting true relief or increased function, just taking more and more."
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home	Example not found in chart review.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids	"Pt states he is at Police Station at this time as he was charged with STEALING."
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.	Example not found in chart review.
8. Recurrent opioid use in situations in which it is physically hazardous	"Twice in past 4 mos or so pt has been hospitalized w apparent OD opioids +/- illicit."
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance	"Percocet, d/w goal to taper on f/u, esp given pt calling frequently for early refills, and has had mult recent falls and I am concerned that polypharmacy is contributor."
10. Tolerance	"She said sometimes her pain meds don't help and she has to use opiates on the street to manage pain."
11. Withdrawal	"For last utox, admits that was out of meds for few days, felt worse pain and sweats, unwell, a friend gave him 'a chip' of suboxone, which helped with these symptoms."

opioid misuse accounted for the majority of opioid discontinuations, with monitoring aberrancies being the most common reason for presumed misuse. Although most patients who discontinued opioids returned to see their PCP within six months, intervention group patients were less likely to do so.

We are unaware of prior studies that have examined the outcomes of PCP follow-up and ED visits for patients with chronic pain who were discontinued from chronic opioid

therapy. Our findings are consistent with Lovejoy et al. [15], who also found that aberrant behavior (most often misuse of other substances) was the most common reason for long-term opioid therapy discontinuation in a population of veterans with chronic pain. Consistent with Nugent et al. [16], our study also shows low rates of referral for addiction treatment following opioid discontinuation.

We found a trend toward higher rates of discontinuation due to monitoring aberrancies in the intervention

Table 4. Outcomes in the six months following opioid discontinuation, overall and stratified by study group and reason for discontinuation

Outcome	Total (N = 125)	Intervention (N = 83)	Control (N = 42)	P Value	Misuse or Aberrancy (N = 81)	Other (N = 44)	P Value
≥1 follow-up PCP visit	91 (73)	54 (65)	37 (88)	<0.01	57 (71)	34 (77)	0.41
≥1 ED visit for pain	14 (11)	12 (15)	2 (5)	0.10	11 (14)	3 (7)	0.25
Evidence of OUD	30 (24)	22 (27)	8 (19)	0.36	25 (31)	5 (11)	0.01
Treatment referral for OUD	16 (13)	13 (16)	3 (7)	0.18	13 (16)	3 (7)	0.14

OUD = opioid use disorder; PCP = primary care provider.

group. Although this finding did not meet the a priori level of statistical significance, our post hoc exploratory analysis was not powered to detect this difference. This difference in discontinuation could reflect the increased attention to guideline-recommended treatment monitoring in the TOPCARE group [13]. In addition, nurse care managers may have facilitated interpretation of and response to aberrant monitoring.

Our study identified a potential unintended consequence of the TOPCARE trial, that intervention group patients were less likely to return to their primary care office for follow-up. It is possible that the use of nurse care managers negatively affected the PCP–patient relationship and led to more patients intentionally ceasing follow-up after opioid termination. Outcomes beyond six months after discontinuation for these patients are unknown and merit further study. Of particular importance is determining the degree to which patients engage in “doctor shopping” to find a different PCP to continue opioid prescribing or turn to illicit opioids after their opioid prescription is terminated. We did not have access to data from other health systems where patients may have received opioids or care related to illicit opioid use. Through review of documentation within our EHR, we identified three patients (Figure 1) who continued to receive opioids from a provider outside our health system, which was not recorded in our EHR medication list. We also identified seven patients whose reason for discontinuation was receiving opioids from multiple prescribers concurrently (Table 2). The state PDMP may help physicians identify patients who are inappropriately receiving opioids from other prescribers.

Opioid discontinuation can be challenging for PCPs due to concerns about untreated pain or addiction or loss to follow-up. Unfortunately, evidence to guide clinicians through this process is limited. Cohort studies show that discontinuation of chronic opioid therapy occurs at relatively low rates, ranging from 8% to 35% [17,18]. Another cohort study showed that among patients with nonfatal overdose on chronic opioid therapy, almost all (91%) continued to receive prescription opioids after overdose [18].

Given the increased risk of overdose associated with chronic opioid therapy, in the setting of an opioid overdose epidemic, targeting at-risk patients for opioid dose reduction or discontinuation is a worthy public health

goal. Recent evidence suggests against long-term opioid therapy being an effective treatment for chronic pain [19]. The SPACE RCT compared opioid with nonopioid alternatives for patients with chronic pain and found that pain intensity was lower in the nonopioid group over 12 months. Furthermore, patients in the nonopioid group suffered fewer adverse effects [19]. Some chronic pain patients may actually show clinical benefit from tapering off opioids. A recent systematic review concluded that pain, function, and quality of life may improve following opioid dose reduction or discontinuation [12]. However, these data were comprised of low-quality studies with uncontrolled designs and heterogeneous interventions.

Our findings highlight the potential for unintended consequences of opioid discontinuation and the need for physicians to improve management of patients who have their opioids terminated. Strategies to keep patients engaged in primary care following opioid discontinuation may include using protocols for tapering, ensuring that patients continue to receive pain treatment, and linking patients to substance use disorder treatment.

Our study has several limitations. First, this was a post hoc exploratory analysis. Because the randomized controlled trial was not designed to assess outcomes related to discontinuation, our study could be underpowered. Second, we only had access to data within the EHR of the patient’s primary care practice and the affiliated hospital ED. Thus, data from patient visits outside of the hospital system were not available. Study outcomes were based on subjective assessments with unblinded data that could introduce bias, such as possible misclassification of outcomes. We assessed interrater reliability based on a small sample of charts with both kappa statistics and percentage agreement. The primary outcome of reason for discontinuation (misuse vs other) resulted in perfect interrater reliability. Most of the secondary outcomes (PCP follow-up, evidence of OUD, and referral for OUD treatment) resulted in kappa statistics with substantial agreement ($\kappa = 0.62$ – 0.71); however, the outcome of one or more ED visits for pain showed only moderate agreement ($\kappa = 0.41$). Lastly, the study was conducted in an urban safety net hospital–based primary care practice and three affiliated community health centers; therefore, our findings may not be generalizable to other populations.

In conclusion, we found that of the few primary care patients who discontinued chronic opioid therapy, most did so due to presumed misuse, largely found through monitoring aberrancies. A nurse care manager–driven intervention that increased monitoring may have increased loss to follow-up for patients who discontinued opioids. Policy-makers should consider the unintended consequences of increased scrutiny of patients taking chronic opioid therapy when implementing national policies on opioid monitoring. Discontinuation of opioids may carry risks that should be thoughtfully assessed and managed.

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Appendix

Table A1. Interrater reliability for outcomes

Outcome	Interrater Agreement, %	Kappa Value
Dichotomous reason for discontinuation (presumed misuse vs other)	100	1.00
Using more than prescribed	90	0.74
Illicit opioid use	100	*
Use of nonprescribed opioid analgesics	100	1.00
Misuse of nonopioid substance	100	*
Diversion	100	*
More than one opioid prescriber	100	1.00
Aberrancies in monitoring	100	1.00
Pain resolved	90	0.74
Inadequate analgesia	100	1.00
Adverse effects	100	*
Unknown reason	90	*
One or more follow-up PCP visits	80	0.62
One or more ED visits for pain	80	0.41
Evidence of OUD	90	0.62
Referral for OUD treatment	90	0.62

ED = emergency department; OUD = opioid use disorder; PCP = primary care provider.

*Kappa could not be calculated because only one reviewer coded this outcome. Kappa can only be calculated if each reviewer uses each response at least once.