



Contents lists available at ScienceDirect

Journal of Substance Abuse Treatment

journal homepage: www.elsevier.com/locate/jsat

Opioid medication discontinuation and risk of adverse opioid-related health care events

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ARTICLE INFO

Keywords:

Opioid medication discontinuation
Opioid use disorder
Adverse substance-related health care events
Medicaid

ABSTRACT

Background: Between 2012 and 2017, the United States dramatically reduced opioid prescribing rates. While this may be appropriate given the opioid epidemic, there has been little research to guide the clinical practice of discontinuing patients from opioid medications and opioid death rates have continued to increase.

Objective: To determine the relationship between time to opioid discontinuation and the risk of an opioid-related emergency department visit or hospitalization among high dose opioid users.

Design: We applied Cox proportional hazard models to 2013–2017 Medicaid claims data to research this relationship.

Participants: Medicaid beneficiaries in Vermont who filled prescription opioids at high daily doses (at least 120 morphine milligram equivalents) for 90 or more consecutive days and who subsequently discontinued opioid prescriptions (n = 494).

Main measures: The outcome was an opioid-related adverse event defined as an emergency department visit or hospitalization with a primary or secondary diagnosis of opioid poisoning or substance use disorder.

Key results: The median length of time to discontinuation was 1 day indicating that half of patients had no dose reduction prior to discontinuation. 86% of patients discontinued within 21 days (considered rapid tapering in recent clinical guidelines). 49% of members had an opioid-related hospitalization or emergency department visit. After controlling for sociodemographic and clinical factors, each additional week of discontinuation time was associated with a 7% reduction in the probability of having opioid related adverse event ($p < 0.01$). Although 60% of members had a diagnosed substance use disorder prior to tapering, < 1% of beneficiaries were transitioned onto an opioid use disorder medication.

Conclusions: Faster rates of opioid tapering were associated with a greater probability of adverse events and many patients discontinued opioids suddenly, with no dose reduction. Additional clinical guidance, research, and interventions are needed to ensure that patients' opioid prescriptions are discontinued safely.

1. Introduction

The United States opioid prescribing rate grew steadily from 2006 through 2012 where it peaked at a rate of 81.3 prescriptions per 100 persons (Centers for Disease Control and Prevention, 2018). The rise in opioid prescribing was associated with an unprecedented increase in opioid-related deaths which reached 42,000 in 2016 (Centers for Disease Control and Prevention, 2018). To reduce opioid prescribing, misuse, and dependence, Federal and state government agencies issued opioid prescribing guidelines and initiated prescription drug monitoring programs (Dowell, Haegerich, & Chou, 2016). As a result of these efforts, and increased awareness of the dangers of opioids, the national opioid prescribing rate declined from 2012 to 2017, falling to

58.5 prescriptions per 100 persons, the lowest rate it had been in a decade (Centers for Disease Control and Prevention, 2018). Yet still in 2017, opioid pain relievers remained one of the most commonly prescribed medications, with 17.4% of the U.S. population having one or more opioid prescriptions in the past year, and the average person who filled an opioid pain medication prescription receiving 3.4 prescriptions (Centers for Disease Control and Prevention, 2018). Opioid misuse has also remained high, with 4.3% of the population reporting misuse of prescription pain relievers in 2016 (Centers for Disease Control and Prevention, 2018).

The high rate of opioid use, long-term use, misuse and dependence, and the increasing ability of providers to identify patients who may be misusing opioids, has raised important questions of whether and how to

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<https://doi.org/10.1016/j.jsat.2019.05.001>

Received 26 January 2019; Received in revised form 29 April 2019; Accepted 1 May 2019
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discontinue opioid pain prescriptions, particularly among patients who have been taking opioid medications over long periods of time (Dubin, Clarke, & Kahan, 2017). Several organizations have published clinical guidelines that include recommendations for opioid tapering approaches. However, these organizations acknowledge that the guidelines are not supported by high-quality studies comparing the effectiveness of different tapering speeds and tapering approaches (AMDG, 2015; Berna, Kulich, & Rathmell, 2015; Busse et al., 2017). The Centers for Disease Control and Prevention (CDC) Guidelines recommend reducing weekly dosage by 10%–50% per week (Centers for Disease Control and Prevention, 2015). However, the guidelines also state that experts note that tapers slower than 10% per week (e.g., 10% per month) also might be appropriate and better tolerated than more rapid tapers, particularly when patients have been taking opioids for long durations (e.g., for years). The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer recommends that adults with chronic noncancer pain gradually reduce 5% to 10% of the morphine-equivalent dose every 2 to 4 weeks with frequent follow-up. The CDC and Mayo Clinic Guidelines also explain that more rapid tapers, such as over 2 to 3 weeks, might be needed for patient safety under certain circumstances, such as for patients who have experienced overdose on their current dosage, have significant coexisting psychiatric illness, substance use disorders or unstable cardiac conditions.

Organizations offer specific recommendations for tapering opioid pain medications if the patient is identified as having an opioid use disorder. The CDC recommends that if a patient exhibits signs of opioid use disorder, clinicians should arrange for opioid use disorder treatment and consider offering naloxone for overdose prevention. Washington State guidelines recommend that for patients with substance use disorders, opioid medications be immediately discontinued, or rapidly tapered (i.e., over a 2 to 3-week period), and the patient started immediately on methadone or buprenorphine medications along with behavioral therapy.

Despite the development of these clinical guidelines, little is known about how many individuals are tapering off opioid medications, whether observed tapering follows any of the aforementioned guidelines, and the extent to which rapid tapering is associated with negative consequences. The objective of this paper is to begin to fill in this research gap by using insurance claims data to study the association between the time to prescription opioid discontinuation and subsequent opioid-related adverse events. We specifically test whether rapid tapering (i.e., discontinuing prescription opioid use within three weeks) is associated with a higher risk of opioid-related adverse events.

2. Material and methods

2.1. Data

Data were from the Vermont Health Care Uniform Reporting and Evaluation System (VHCURES), which is Vermont's All-Payer claims database. From this database, we extracted data on Medicaid beneficiaries from calendar years 2013 through 2017. These data provided enrollment information as well as medical and pharmacy claims on 100% of Vermont Medicaid enrollees (State of Vermont: Green Mountain Care Board, 2019). Vermont has been aggressive in addressing opioid over-prescribing and misuse. Accordingly, data from this state are ideal for studying the impact of tapering time on opioid-related events.

2.2. Study sample

The study sample was identified by using the Pharmacy Quality Alliance measure: "Using Opioids at High Dosage in Persons Without Cancer" (Pharmaceutical Quality Alliance, 2019). Fig. 1 describes the number of Medicaid beneficiaries who met each of the Pharmacy Quality Alliance measure criteria. Specifically, members had to have at

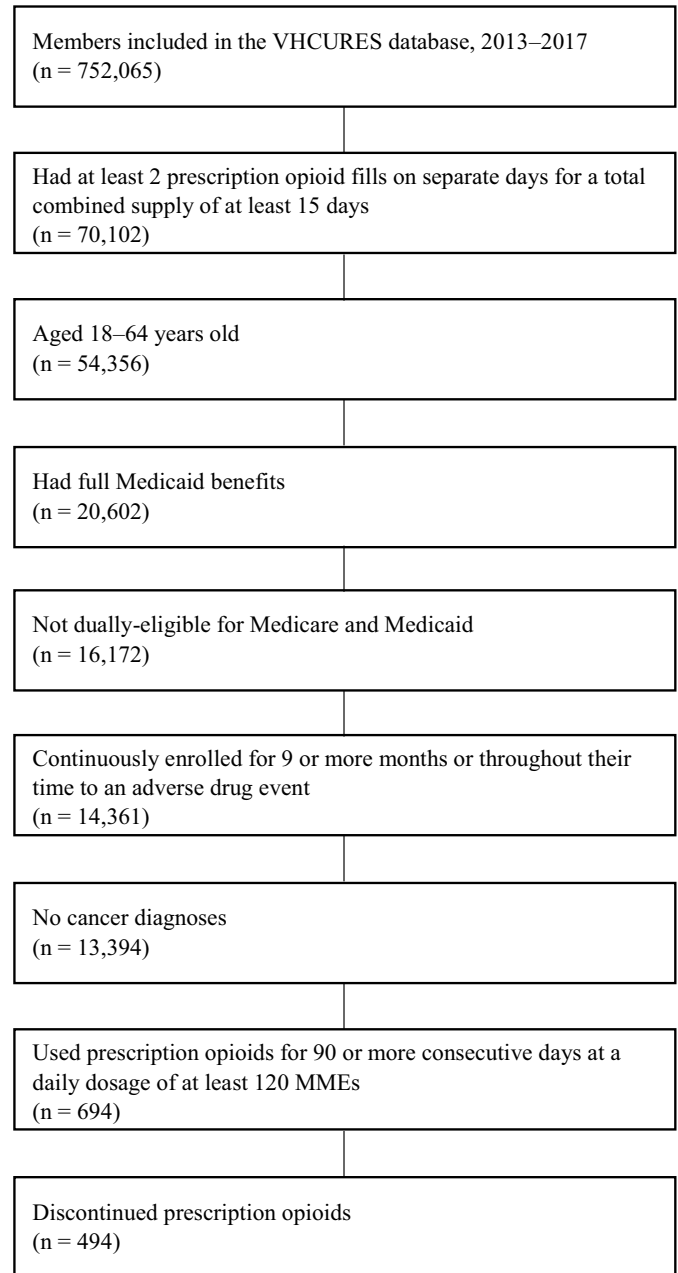


Fig. 1. Inclusion criteria and final sample size.

least two prescription opioid fills on separate days for a total combined supply of at least 15 days (summing days supplied from overlapping prescriptions), had to be aged 18–64, had to have used prescription opioids for 90 or more consecutive days at a daily dose of at least 120 morphine milligram equivalents (MMEs), and not have a cancer diagnosis. In addition, we excluded members who were dually-eligible for Medicare and Medicaid (because we did not have access to Medicare claims on dual-eligibles), who did not have full Medicaid benefits, and who were not continuously enrolled for at least 9 months during their episode. After applying these criteria, we found 694 members who used prescription opioids for 90 or more consecutive days with a daily dosage of at least 120 MMEs, and we identified 494 who then subsequently stopped filling prescriptions for opioid medications. Additional detail regarding the methods can be found in an online appendix.

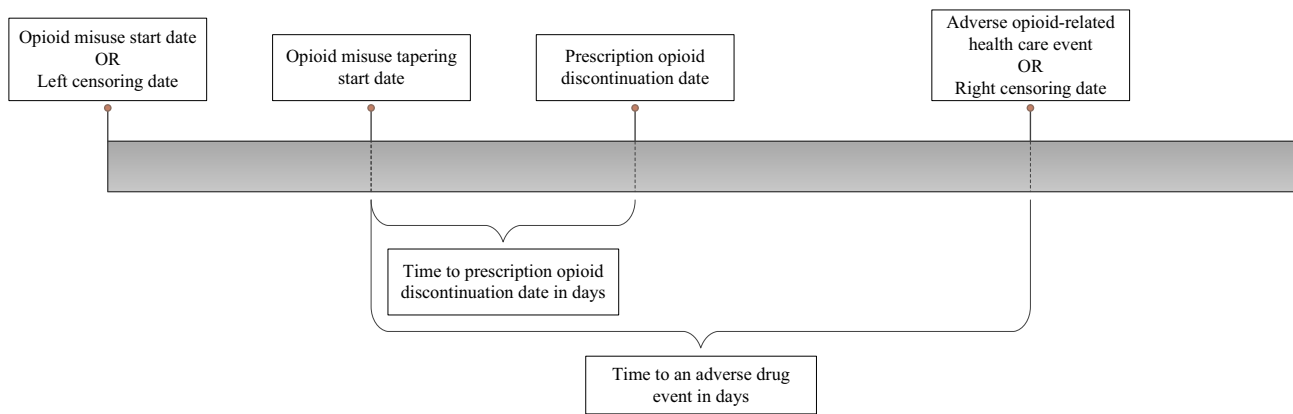


Fig. 2. Illustration of the construction of an opioid misuse tapering to an adverse opioid-related health care event episode.

2.3. Outcome

The outcome measure was the time from the beginning of an opioid taper to an opioid-related adverse event. Opioid-related adverse events were defined as emergency department visits or hospitalizations with a principal or secondary diagnosis of opioid poisoning or a substance use disorder. The beginning of opioid tapering was defined as the first date where the patient filled an opioid prescription for < 120 MMEs (see Fig. 2).

2.4. Independent variables

The primary independent variable of interest was the time from the first opioid prescription for < 120 MMEs (the beginning of opioid tapering) to discontinuation. This measure was defined by the time between: (1) the *opioid tapering start date* and (2) the *opioid discontinuation date* (see Fig. 2). Other control variables included: demographic characteristics (age and gender), opioid prescription drug use patterns (number of days with prescription opioids fills at dosages exceeding 120 MMEs, filling prescription opioids from 4 or more different providers), and an indicator for whether the member was started on medications to treat opioid use disorder after the tapering start date, physical diagnoses (grouped using the major disease classifications in ICD-9/ICD-10), mental health and substance use disorder diagnoses (grouped using the HCUP CCS classification tool). Each of these measures was captured prior to the opioid tapering start date (Fig. 2).

2.5. Statistical analysis

We used a Cox proportional hazard model to test the hypothesis that a longer time to prescription opioid use discontinuation reduces the risk of an opioid-related adverse event, controlling for baseline characteristics. We tested the validity of the proportional hazards assumption by using the Schoenfeld residual statistical test.

3. Results

3.1. Characteristics of the study sample

As shown in Table 1, the median time to opioid discontinuation in days was 1 day, meaning that half of patients did not fill a prescription for a reduced opioid dosage prior to discontinuation. 86% of beneficiaries discontinued filling prescription opioids within 21 days. Only 5% of beneficiaries discontinued prescription opioid fills in > 90 days. 49% of the study sample had an opioid-related adverse event. The median time to those events was 77 days.

On average, beneficiaries in the study sample were 47 years old, 49% were female. On average, beneficiaries used prescription opioids at

or above 120 MMEs for 613 days, and the distribution of days of use at or above 120 MMEs ranged from 111 days at the 5th percentile, 235 days at the 25th percentile, 909 days at the 75th percentile, and 1476 days at the 95th percentile. Additionally, the median number of days using opioids at a high dosage was 510, with a maximum of 1736 days. 24% of beneficiaries who used at or above 120 MMEs for at least 90 days also filled prescriptions for opioids from 4 or more different provider. 60% of beneficiaries had a primary or secondary substance use disorder diagnosis, 27% had a mood diagnosis, and 25% had an anxiety diagnosis. The most common type of substance use disorder diagnosis was opioid use disorder, with almost 50% of the sample having a primary or secondary opioid use disorder. The study population had high rates of physical health comorbidities. Over one third of beneficiaries had diseases/disorders of the nervous system or sense organs, which includes *pain not elsewhere classified*. About a third also had diseases/disorders of the musculoskeletal system and connective tissue, which includes osteoarthritis and other conditions that often are associated with chronic pain. About 32% had endocrine, nutritional, and metabolic diseases and immunity disorders.

3.2. Descriptive analysis

We categorized the primary independent variable of interest as time to discontinue < 21 days, between 21 and 89 days, and equal to or > 90 days. As shown in Fig. 3, persons who had a time to discontinuation of prescription opioids greater than or equal to 90 days had the lowest probability of having an opioid-related adverse event. Persons who had a time to discontinuation of prescription opioids of < 21 had the highest probability of an opioid-related adverse event.

3.3. Cox proportional hazard results

Table 2 reports the adjusted hazard ratios from the Cox proportional hazard models, which are interpreted as the percentage increase or decrease in the risk of an opioid-related adverse event associated with each additional day spent discontinuing opioid use after controlling for demographic characteristics, opioid prescription drug use patterns, physical health comorbidities, and behavioral health comorbidities.

Consistent with the descriptive analysis, a longer time to discontinuation of prescription opioid use was associated with a reduction in the probability of having an opioid-related adverse event. Specifically, the model results indicate that each additional day of tapering time was associated with a 1% reduction in the probability of having an opioid related adverse event ($p < 0.01$). In other words, each additional week of tapering time is associated with a 7% reduction in the risk of having an opioid-related adverse event. Older age was negatively associated with opioid-related adverse events while substance use disorders were positively associated.

Table 1
Summary statistics of the analysis sample.

Measure	Median (Min.-Max.) or %
N	494
Outcome characteristics	
Had an opioid-related adverse health care event, %	49%
Time to an opioid-related adverse health care event in days	77 (1-253)
Type of opioid-related adverse health care event	
Opioid poisoning event	2%
Hospitalization with a SUD diagnosis	7%
ED visit with a SUD diagnosis	91%
Primary independent variable	
Time to prescription opioid use discontinuation in days	1 (1-599)
Time to prescription opioid use discontinuation < 21 days	86%
Time to opioid use discontinuation ≥ 21 and < 90 days	9%
Time to opioid use discontinuation ≥ 90 days	5%
Demographic characteristics	
Mean age in years (standard deviation)	47 (10)
Female	49%
Opioid prescription drug use patterns	
Number of days using prescription opioids at high dosages	510 (90-1736)
Total number of days using prescription opioids (including tapering days)	851 (91-1819)
Calendar year when member began tapering off of high dosage use	
2013	9%
2014	16%
2015	17%
2016	20%
2017	38%
Member filled opioid prescriptions from 4 or more different providers	24%
Member was inducted onto MAT after tapering start date	0.6%
Top ten physical health comorbidities	
Diseases and disorders of the nervous system and sense organs	36%
Diseases and disorders of the musculoskeletal system and connective tissue	33%
Diseases and disorders of the endocrine, nutritional, and metabolic diseases and immunity disorders	32%
Diseases and disorders of the digestive system	30%
Diseases and disorders of the circulatory system	30%
Diseases and disorders of the respiratory system	28%
Infectious and parasitic diseases	19%
Disease and disorders of the blood and blood-forming organs	17%
Diseases and disorders of the genitourinary system	16%
Most frequent behavioral health comorbidities	
Substance use disorder diagnosis (primary or secondary)	60%
Mood disorders (primary diagnoses)	27%
Anxiety disorders (primary diagnoses)	25%

Min. = minimum; Max. = maximum.

3.4. Sensitivity analysis

Because rapid or no tapering is recommended for individuals with substance use disorders under some circumstances, we replicated the analyses described above separately for those with diagnosed substance use disorders and those without diagnosed substance use disorders. The results were nearly identical to those presented above, with a hazard ratio of 0.99 for both subgroups ($p < 0.001$ for those with SUD diagnoses prior to tapering and $p = 0.051$ for those without SUD diagnoses prior to tapering). Full results are available in the online appendix.

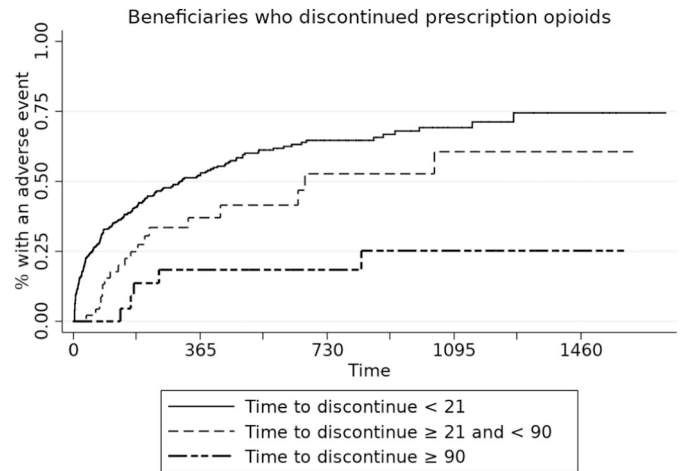


Fig. 3. Kaplan-Meier failure graph comparing opioid-related adverse event probabilities across time to discontinuation categories.

4. Discussion

In recent years, clinicians have grown much more aware of the risk of opioids, have access to more data to alert them to patients who may be misusing opioids, are more cautious about the effectiveness of opioids for chronic pain, and are facing greater oversight and restrictions around opioid prescribing. All of these factors may have accelerated opioid discontinuation. Yet, there has been little research to understand how individuals who have been taking opioids for long periods of time at high doses are being tapered from opioids and their clinical status after opioid medication discontinuation. Moreover, clinical guidelines regarding opioid tapering speed acknowledge that limited research underlies their recommendations. Given that millions of people in the United States receive opioid prescriptions every year and a significant number take opioid medications for long periods of time, research on this topic is critical. The goal of this study was to begin to fill this research gap.

We find that among patients who were receiving high doses of opioids, sudden discontinuation of opioid prescriptions is common and tapering lengths are short. Only 5% of those discontinuing had a tapering period that exceeded 90 days and almost half of patients who were discontinued subsequently experienced an opioid-related hospitalization or emergency department visit. Our findings echo a recent FDA safety announcement that said: "the FDA has received reports of serious harm in patients who are physically dependent on opioid pain medicines suddenly having these medicines discontinued or the dose rapidly decreased. These include serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide." (FDA, 2019).

The FDA noted that they are requiring changes to the prescribing information for opioid medicines to provide expanded guidance to health care professionals on how to safely decrease the dose in patients who are physically dependent on opioid pain medicines when the dose is to be decreased or the medicine is to be discontinued. Discontinuation clearly requires close follow-up and monitoring. Additional research is also warranted to determine whether patients should be discontinued at all from opioid medications.

Our study is limited in that we do not know whether the physician or patient initiated the discontinuation and the reason for the decision. Some of the very rapid discontinuation events may be due to a breakdown in the clinical relationship between physicians and patients. However, recent research by Lovejoy and colleagues, using Veterans Administration medical charts of long-term opioid therapy patients, reported that 85% of patients were discontinued as a result of clinician, rather than patient, decisions (Lovejoy et al., 2017). Lovejoy et al. (2017) also found that clinicians most commonly reporting

Table 2

Model results of the association between time to opioid discontinuation and the risk of an adverse opioid-related event.

Measure	Hazard ratio	95% CI
N	494	
Primary independent variables		
Time to discontinuation in days	0.99**	(0.98, 1.00)
Demographic characteristics		
Age	0.98*	(0.97, 1.00)
Female	0.93	(0.71, 1.21)
Opioid prescription drug use patterns		
Number of days using prescription opioids at high dosages	1.00	(1.00, 1.00)
Member filled opioid prescriptions from 4 or more different providers	1.13	(0.80, 1.59)
Member was started onto opioid use disorder medication after tapering start date	0.90	(0.33, 2.49)
Top physical health comorbidities		
Diseases and disorders of the nervous system and sense organs	0.75	(0.47, 1.19)
Diseases and disorders of the musculoskeletal system and connective tissue	1.19	(0.81, 1.75)
Diseases and disorders of the endocrine, nutritional, and metabolic diseases and immunity disorders	0.94	(0.61, 1.45)
Diseases and disorders of the digestive system	0.97	(0.63, 1.48)
Diseases and disorders of the circulatory system	0.86	(0.58, 1.27)
Diseases and disorders of the respiratory system	1.14	(0.77, 1.68)
Infectious and parasitic diseases	1.14	(0.77, 1.68)
Disease and disorders of the blood and blood-forming organs	1.22	(0.84, 1.79)
Diseases and disorders of the genitourinary system		
Most frequent behavioral health comorbidities		
Substance use disorder diagnosis (primary or secondary)	2.09***	(1.52, 2.89)
Mood disorders (primary diagnoses)	0.94	(0.65, 1.37)
Anxiety disorders (primary diagnoses)	0.94	(0.65, 1.37)

CI = confidence interval.

* $p < 0.05$.** $p < 0.01$.*** $p < 0.001$.

discontinuing opioid prescriptions because of opioid-related aberrant behaviors, such as suspected substance misuse, aberrant urine drug tests, or suspected drug diversion. Even among patients without documented substance use diagnoses, clinicians reported that 68% were discontinued because of concerns about potential misuse. Our study also was limited in that it only looked at patients using at 120 MMEs or more for 90 or more days. We focus on the 120 MME threshold because it is a component of a nationally recognized quality measure and is used by the Centers for Medicare and Medicaid Services (CMS) to monitor and flag potential misuse of prescription opioids. However, additional research on whether rapid taper and adverse events are occurring among individuals using lower doses of opioid medications is needed. Moreover, this study was limited to those with Medicaid coverage and needs to be replicated on those with private health insurance to determine if similar patterns are observed.

If the main reasons why physicians are discontinuing patients from opioid pain medications is concern about opioid misuse, we would have hoped to have seen more connections to opioid misuse treatment following discontinuation. However, we found that < 1% of beneficiaries were transitioned onto an opioid use disorder medication after opioid discontinuation despite the fact that 60% had a documented substance use disorder prior to discontinuation. This is an important missed opportunity that could have greatly reduced the risk of opioid-related adverse events.

Patients who are perceived to be misusing opioids are some of the most complex cases that physicians may encounter (Gallagher, 2018). Pain stemming from chronic medical conditions, opioid dependence from long term use, addiction, and mental illness often co-occur in complex and varying patterns among patients who present in physician's offices with suggested opioid misuse (Walker & Druss, 2018). Physicians' lack of training in addictions and concerns about their ability to effectively treat patients with substance use disorders is well-documented (DeFlavio, Rolin, Nordstrom, & Kazal, 2015; Hutchinson, Catlin, Andrilla, Baldwin, & Rosenblatt, 2014). Moreover, the most commonly prescribed opioid medication – buprenorphine – requires that clinicians undergo training and receive a waiver – only a small

percentage of physicians in the United States are currently buprenorphine-waived.

Our data do not indicate the extent to which patients who discontinued opioid medications were referred to addiction, mental health, and/or pain specialists and to what extent those referrals were successful. Furthermore, our data do not permit us to measure whether patients took advantage of alternative pain treatments which is an important question for future research. Another limitation of the data that we analyzed is that we did not capture suicides or all-cause hospitalizations and ED visits as outcomes. These are likely additional important clinical outcomes that should be measured in future research. In recognition of the difficulty and risks of slow and ineffective transitions to addiction treatment, hospitals have begun to start patients on opioid use disorder medications before they are discharged; consult with addiction and mental health specialists (increasingly leveraging telemedicine) during the hospital stay; employ peer counselors to help connect patients to addiction treatment; and distribute naloxone upon discharge (D'Onofrio et al., 2015; Trowbridge et al., 2017). Expanding these interventions to physician offices could be effective in reducing the risk of adverse opioid events following opioid discontinuation.

The opioid epidemic also has brought into stark relief the lack of integrated care settings that are equipped to address the complex needs of patients who misuse opioids. Addiction specialty providers typically lack medical and mental health staff (Aletaris, Roman, & Pruett, 2017). Mental health specialty providers lack addiction expertise (Druss & Goldman, 2018; Mark, Meinhofer, & Zarkin, 2018). Pain clinics lack both addiction, mental health specialists, and expertise in non-pharmacologic approaches to pain management (Manhapra & Becker, 2018). Almost all medical settings have limited ability to connect patients with social services such as family counseling, transportation, housing, and employment supports. This is a long-term challenge that is not likely to be fixed quickly.

4.1. Conclusion

The United States went through a great “experiment” of expanding

treatment of pain with opioids which has proved to be disastrous for public health. We have entered the next great “experiment” of discontinuing opioid medications among the millions of Americans who are currently taking them. It is important that we monitor the consequences of this discontinuation and research ways to optimally transition individuals off of opioid pain medications when appropriate and into appropriate alternative treatments.

Acknowledgments

This work was supported by internal funding from RTI International, Inc. We thank Elise Hooper for her programming assistance and Gary Zarkin and Alex Cowell for feedback on earlier version of the manuscript.

This work has not been previously presented.

Conflict of interest

Drs. Tami Mark and Will Parish have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jsat.2019.05.001>.

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