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Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015

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Because long-term opioid use often begins with treatment of acute pain (*1*), in March 2016, the CDC Guideline for Prescribing Opioids for Chronic Pain included recommendations for the duration of opioid therapy for acute pain and the type of opioid to select when therapy is initiated (*2*). However, data quantifying the transition from acute to chronic opioid use are lacking. Patient records from the IMS Lifelink+ database were analyzed to characterize the first episode of opioid use among commercially insured, opioid-naïve, cancer-free adults and quantify the increase in probability of long-term use of opioids with each additional day supplied, day of therapy, or incremental increase in cumulative dose. The largest increments in probability of continued use were observed after the fifth and thirty-first days on therapy; the second prescription; 700 morphine milligram equivalents cumulative dose; and first prescriptions with 10- and 30-day supplies. By providing quantitative evidence on risk for long-term use based on initial prescribing characteristics, these findings might inform opioid prescribing practices.

A random 10% sample of patient records during 2006–2015 was drawn from the IMS Lifelink+ database, which includes commercial health plan information from a large number of managed care plans and is representative of the U.S. commercially insured population (*3*). The data are provided in a deidentified format and the institutional review board at the authors' institution deemed the study was not human subject research. Records were selected of patients aged ≥18 years who had at least one opioid prescription during June 1, 2006–September 1, 2015, and ≥6 months of continuous enrollment without an opioid prescription before their first opioid prescription. Patients excluded were those who had any cancer (other than nonmelanoma skin cancer) or a substance abuse disorder diagnosis in the 6 months preceding their first opioid prescription, or whose first prescription was for any buprenorphine formulation indicated for treatment of substance abuse.

Patients were followed from the date of their first prescription until loss of enrollment, study end date, or discontinuation of opioids, which was defined as ≥180 days without opioid use. The duration of use and number of prescriptions and cumulative dose (expressed in morphine milligram equivalents*) for the first episode of opioid use (defined as continuous use of opioids with a gap of no greater than 30 days) were calculated. The number of days' supply and average daily dose in morphine milligram equivalents for the first prescription were also calculated. The first opioid prescription was categorized

* Morphine milligram equivalents is a conversion factor to convert different opioids into an equivalent dose of morphine. http://www.pdmpassist.org/pdf/BJA_performance_measure_aid_MME_conversion.pdf.

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into six mutually exclusive categories: long-acting; oxycodone short-acting; hydrocodone short-acting; other Schedule II short-acting; Schedule III–IV and nalbuphine; and tramadol.[†]

The Kaplan-Meier statistic was used to estimate median time to discontinuation of opioid use; probability of continued opioid use at 1 year and 3 years for different treatment duration thresholds (daily for 1–40 days and weekly for 1–26 weeks); number of prescriptions (1–15); and cumulative dose of the first episode of opioid use (50–2000 morphine milligram equivalents). Similarly, the relationship between the number of days' supply, choice of first opioid prescription, and probability of continued opioid use at 1 and 3 years was also examined. Sensitivity analyses were conducted by modifying the discontinuation definition from ≥180 opioid-free days to ≥90 opioid-free days, changing the allowable gap in the first episode of opioid use from 30 days to 7 days, and excluding patients whose average daily dose of the first prescription exceeded 90 morphine milligram equivalents.

A total of 1,294,247 patients met the inclusion criteria, including 33,548 (2.6%) who continued opioid therapy for ≥1 year. Patients who continued opioid therapy for ≥1 year were more likely to be older, female, have a pain diagnosis before opioid initiation, initiated on higher doses of opioids, and publically or self-insured, compared with patients who discontinued opioid use in <365 days (Table). Among persons prescribed at least 1 day of opioids, the probability of continued opioid use at 1 year was 6.0% and at 3 years was 2.9% (supplemental figure 1; https://stacks.cdc.gov/view/cdc/44182) (supplemental figure 2; https://stacks.cdc.gov/view/cdc/44550) with a median time to discontinuation of 7 days (supplemental figure 3; https://stacks.cdc.gov/view/cdc/44551). Approximately 70% of patients have an initial duration of opioids of ≤7 days and 7.3% were initially prescribed opioids for ≥31 days. The largest incremental increases in the probability of continued opioid pain reliever use were observed when the first prescription supply exceeded 10 or 30 days (Figure 1), when a patient received a third prescription (Figure 2), or when the cumulative dose was ≥700 morphine milligram equivalents (supplemental figure 4; https://stacks.cdc.gov/view/cdc/44552). Substantial increases in probabilities of continued opioid use occurred when the initial duration reached 6 and 31 days (supplemental figure 2; https://stacks.cdc.gov/view/cdc/44550); the findings of the sensitivity analyses were similar (supplemental figures 5–10; https://stacks.cdc.gov/view/cdc/44183).

The highest probabilities of continued opioid use at 1 and 3 years were observed among patients who initiated treatment with a long-acting opioid (27.3% at 1 year; 20.5% at 3 years), followed by those whose initial treatment was with tramadol

[†] The six mutually exclusive categories are 1) long-acting: buprenorphine, fentanyl, morphine, oxycodone, oxymorphone, and tapentadol; 2) other Schedule II short-acting: fentanyl, hydromorphone, levorphanol, meperidine, methadone, morphine, oxymorphone and tapentadol; 3) oxycodone short-acting; 4) hydrocodone short-acting; 5) Schedule III–IV and nalbuphine: codeine, dihydrocodeine, butorphanol, nalbuphine, pentazocine and propoxyphene; 6) tramadol.

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TABLE. Characteristics of incident opioid users and patients who continued opioid use for ≥365 days (1 year) and ≥1,095 days (3 years) — United States, 2006–2015

Characteristic	All incident opioid users (N = 1,294,247)		Patients who continued opioid therapy for ≥365 days (n = 33,548)		Patients who continued opioid therapy for ≥1,095 days (n = 6,441)	
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI
Duration of first episode of opioid use	14.81 (65.00)	14.70–14.92	183.28 (343.27)	179.61–186.96	362.40 (593.26)	347.91–376.90
Enrollment duration (yrs)	2.48 (2.04)	2.47–2.48	3.30 (1.83)	2.47–2.48	4.98 (1.48)	4.94–5.02
Age (yrs)	44.52 (14.56)	44.50–44.54	49.58 (13.45)	49.44–49.72	50.52 (12.68)	50.21–50.83
	No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI
Female	698,950 (54.00)	53.92–54.09	18,768 (55.94)	55.41–56.47	3,500 (54.34)	53.12–55.55
Treatment indication						
Back pain	226,681 (17.51)	17.45–17.58	10,396 (30.99)	30.50–31.49	2,137 (33.18)	32.04–34.34
Neck pain	90,352 (6.98)	6.94–7.03	3,824 (11.40)	11.06–11.74	775 (12.03)	11.26–12.85
Head pain	30,123 (2.33)	2.30–2.35	1,495 (4.46)	4.24–4.68	306 (4.75)	4.26–5.30
Joint pain	389,700 (30.11)	30.03–30.19	14,862 (44.30)	43.77–44.83	2,968 (46.08)	44.87–47.30
Patient region						
South	476,565 (36.74)	36.64–36.83	13,437 (40.05)	39.53–40.53	2,449 (38.02)	36.84–39.21
Midwest	376,520 (29.09)	29.01–29.17	9,566 (28.51)	28.03–29.00	1,973 (30.63)	29.52–31.77
East	279,595 (21.60)	21.53–21.67	6,153 (18.34)	17.93–18.76	1,234 (19.16)	18.22–20.14
West	142,698 (11.03)	10.97–11.08	3,640 (10.85)	10.52–11.19	574 (8.91)	8.24–9.63
Missing/Other	19,869 (1.54)	1.51–1.56	752 (2.24)	2.09–2.41	211 (3.28)	2.87–3.74
Payer type						
Commercial	866,815 (66.97)	66.89–67.06	20,920 (62.36)	61.84–62.88	3,910 (60.70)	38.11–40.49
Medicaid/State CHIP	14,855 (1.15)	1.13–1.17	864 (2.58)	2.42–2.76	154 (2.39)	2.05–2.79
Medicare	16,951 (1.31)	1.29–1.33	1,160 (3.46)	3.27–3.66	257 (3.96)	3.52–4.48
Self-insured	387,122 (29.91)	29.83–29.99	10,471 (31.21)	30.72–31.71	2,089 (32.43)	31.30–33.59
RX only/Unknown	8,504 (0.66)	0.64–0.67	130 (0.39)	0.33–0.46	32 (0.50)	0.35–0.70
Prescription characteristic						
First prescription ≥90 MME*	89,438 (6.91)	6.87–6.95	2,613 (7.79)	7.51–8.08	545 (8.46)	7.81–9.17
First prescription ≥120 MME*	22,895 (1.77)	1.75–1.79	1,075 (3.20)	3.02–3.40	244 (3.79)	3.35–4.28
First long-acting opioid prescription†	6,588 (0.51)	0.50–0.52	905 (2.70)	2.53–2.88	226 (3.51)	3.09–3.99

Abbreviations: CHIP = Children's Health Insurance Plan; CI = confidence interval; MME = morphine milligram equivalents; RX = prescription; SD = standard deviation.

* Average daily dose was calculated as total strength of the prescription expressed in MME divided by the days' supply of the first prescription. If a patient had multiple prescriptions on the first day, the daily dose in MME for all the prescriptions on the index date were summed and divided by the days' supply of the longest lasting prescription.

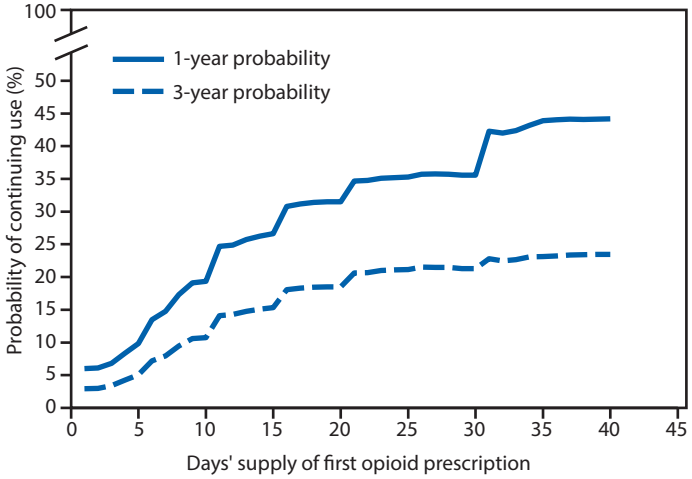
† The first prescription was categorized into six mutually exclusive categories and, in case of multiple prescriptions, on the index date using the following hierarchy to assign category: 1) long-acting; 2) other Schedule II short-acting; 3) Oxycodone short-acting; 4) Hydrocodone short-acting; 5) Schedule III-IV and Nalbuphine; or 6) tramadol.

(13.7% at 1 year; 6.8% at 3 years) or a Schedule II short-acting opioid other than hydrocodone or oxycodone (8.9% at 1 year; 5.3% at 3 years) (supplemental table; https://stacks.cdc.gov/view/cdc/44181). The probabilities of continued opioid use at 1 and 3 years for persons starting on hydrocodone short acting (5.1% at 1 year; 2.4% at 3 years), oxycodone short-acting (4.7% at 1 year; 2.3% at 3 years), or Schedule III–IV (5.0% at 1 year; 2.2% at 3 years) opioids were similar (supplemental table; https://stacks.cdc.gov/view/cdc/44181).

Discussion

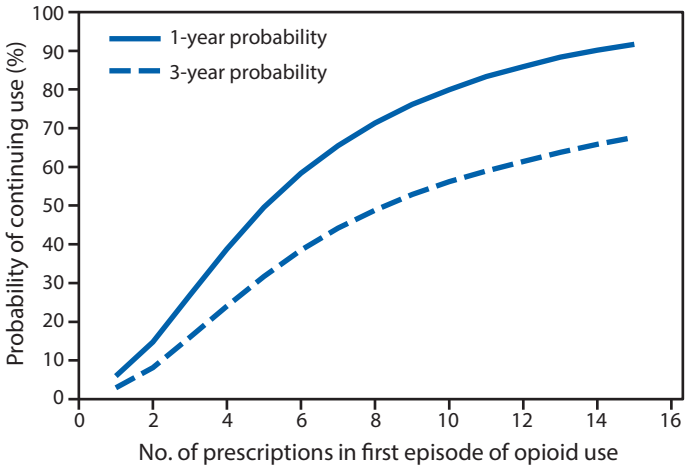
The probability of long-term opioid use increases most sharply in the first days of therapy, particularly after 5 days or 1 month of opioids have been prescribed, and levels off after approximately 12 weeks of therapy. The rate of long-term use was relatively low (6.0% on opioids 1 year later) for persons with at least 1 day of opioid therapy, but increased to 13.5% for persons whose first episode of use was for ≥8 days and to 29.9% when the first episode of use was for ≥31 days. Although ≥31 days of initial opioid prescriptions are not common, approximately 7% do exceed a 1-month supply. Discussions with patients about the long-term use of opioids to manage pain should occur early in the opioid prescribing process, perhaps as early as the first refill, because approximately 1 in 7 persons who received a refill or had a second opioid prescription authorized were on opioids 1 year later. As expected, patients initiated on long-acting opioids had the highest probabilities of long-term use. However, the finding that patients initiated with tramadol had the next highest probability of long-term use was unexpected; because of tramadol's minimal affinity for the μ-opioid receptor, it is deemed a relatively safe opioid agonist with lower abuse potential than other opioids (*4*). However, a report by the Substance Abuse and Mental Health Services Administration determined that emergency department visits associated with tramadol-related adverse events increased by 145% during 2005–2011 (*5*). Long-term

FIGURE 1. One- and 3-year probabilities of continued opioid use among opioid-naïve patients, by number of days' supply* of the first opioid prescription — United States, 2006–2015



* Days' supply of the first prescription is expressed in days (1–40) in 1-day increments. If a patient had multiple prescriptions on the first day, the prescription with the longest days' supply was considered the first prescription.

FIGURE 2. One- and 3-year probabilities of continued opioid use among opioid-naïve patients, by number of prescriptions* in the first episode of opioid use — United States, 2006–2015



* Number of prescriptions is expressed as 1–15, in increments of one prescription.

data on tramadol for pain management are sparse, with only one trial exceeding 12 weeks in duration (*6*). Despite this, among patients initiated with tramadol, >64% of patients who continued opioid use beyond 1 year were still on tramadol, suggesting that tramadol might be prescribed intentionally for chronic pain management. A 2016 study in Oregon (*7*), which did not include tramadol (a predictor of long-term use according to current data), reported similar findings: opioid naïve patients aged <45 years who received two prescription fills (versus one) or a cumulative dose of 400–799 (versus <120) morphine milligram equivalents in their first month of therapy were 2.3 and 3.0 times as likely to be chronic opioid users, respectively. However, that analysis only examined opioid use in the first month after initiation of opioid therapy to characterize risks for long-term use and did not account for the actual duration of therapy.

The findings in this report are subject to at least five limitations. First, although the cumulative dose of the first episode of opioid use is described, the likelihood of long-term use when the prescriber was titrating the dose was not determined. Rather, the total cumulative dose was calculated, which might have been increasing or decreasing over time. Second, the extent to which chronic opioid use was intentional versus the outgrowth of acute use is not known. Less than 1% of patients in this analysis were prescribed Schedule II long-acting opioids at the outset, so intentional chronic opioid prescribing might be uncommon; however, approximately 10% of patients were prescribed tramadol, which might indicate intentional chronic opioid prescribing. Third, information on pain intensity or duration were not available, and the etiology of pain, which might influence the duration of opioid use, was not considered in the analysis. Fourth, the frequency of prescriptions having certain days' supplied (e.g., prescriptions with a 7-day supply would be more frequently observed than those with an 11- or 13-day supply) was not considered. The variability in the relationships between days' supply, the cumulative dose, and duration of first episode and the probability of long-term use could be affected. Finally, prescriptions that were either paid for out-of-pocket or obtained illicitly were not included in the analysis.

Transitions from acute to long-term therapy can begin to occur quickly: the chances of chronic use begin to increase after the third day supplied and rise rapidly thereafter. Consistent with CDC guidelines, treatment of acute pain with opioids should be for the shortest durations possible. Prescribing <7 days (ideally ≤3 days) of medication when initiating opioids could mitigate the chances of unintentional chronic use. When initiating opioids, caution should be exercised when prescribing >1 week of opioids or when authorizing a refill or a second opioid prescription because these actions approximately double the chances of use 1 year later. In addition, prescribers should discuss the long-term plan for pain management with patients for whom they are prescribing either Schedule II long-acting opioids or tramadol.

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Summary

What is already known about this topic?

Based on the CDC Guideline for Prescribing Opioids for Chronic Pain, literature supporting long-term opioid therapy for pain is limited; research suggests an increased risk for harms with long-term opioid use. Early opioid prescribing patterns for opioid-naïve patients have been found to be associated with the likelihood of long-term use.

What is added by this report?

In a representative sample of opioid naïve, cancer-free adults who received a prescription for opioid pain relievers, the likelihood of chronic opioid use increased with each additional day of medication supplied starting with the third day, with the sharpest increases in chronic opioid use observed after the fifth and thirty-first day on therapy, a second prescription or refill, 700 morphine milligram equivalents cumulative dose, and an initial 10- or 30-day supply. The highest probability of continued opioid use at 1 and 3 years was observed among patients who started on a long-acting opioid followed by patients who started on tramadol.

What are the implications for public health practice?

Awareness among prescribers, pharmacists, and persons managing pharmacy benefits that authorization of a second opioid prescription doubles the risk for opioid use 1 year later might deter overprescribing of opioids. Knowledge that the risks for chronic opioid use increase with each additional day supplied might help clinicians evaluate their initial opioid prescribing decisions and potentially reduce the risk for long-term opioid use. Discussions with patients about the long-term use of opioids to manage pain should occur early in the opioid prescribing process.

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Proceedings of a Workshop

IN BRIEF

November 2018

Medication-Assisted Treatment for Opioid Use Disorder

Proceedings of a Workshop—in Brief

On October 30 and 31, 2018, the Committee on Medication-Assisted Treatment (MAT) for Opioid Use Disorder (OUD) held a 1.5-day workshop in Washington, DC. To support the dissemination of accurate patient-focused information about treatments for addiction, and to help provide scientific solutions to the current opioid crisis, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (the National Academies) was created to conduct a study of the evidence base on MAT for OUD. Specifically, the committee was asked to (1) review the current knowledge and gaps in understanding regarding the effectiveness of MAT for treating OUD, (2) examine the available evidence on the range of parameters and circumstances in which MAT can be effectively delivered (e.g., duration of treatment, populations, settings, and interventions to address social determinants of health as a component of MAT), (3) identify challenges in implementation and uptake, and (4) identify additional research needed. The public workshop was designed to assist the committee in gathering evidence, as well as to bring the committee together with a wide range of clinicians, academic experts, policy makers, and representatives of affected individuals and family members for a full discussion of the current initiatives related to MAT, existing evidence and research gaps, and barriers that discourage access to and use of MAT.

This Proceedings of a Workshop—in Brief highlights the presentations and discussions that occurred at the workshop. It should not be seen as reflecting findings, conclusions, or recommendations of the workshop participants or of the committee. Statements, proposals, and opinions expressed are those of individual presenters and participants and have not been endorsed or verified by the National Academies or the committee and they should not be construed as reflecting any group consensus. The committee's Consensus Study Report will be available in spring 2019.

FEDERAL INITIATIVES

The first session focused on the current federal efforts to improve treatment for OUD and access to MAT. Committee members heard the perspectives of two speakers from the agencies sponsoring the study—the National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration (SAMHSA)—as well as from other federal agencies also working in this domain: the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration (HRSA), and the Food and Drug Administration (FDA).

Nora Volkow, director of NIDA, emphasized that OUD is rapidly lethal, killing 2 percent of the 2.1 million people with OUD in the United States each year. Medications are irrefutably the most effective way to treat OUD—reducing the likelihood of overdose death by up to three-fold—but fewer than half of patients receive them due to stigma and structural barriers, and treatment retention is poor, she said. NIDA is focusing on implementation science and service delivery research to expand access to MAT in the health care and criminal justice systems. Priority knowledge gaps include the effectiveness of different MAT modalities across the continuum of OUD severity, optimal duration of MAT, impact of individual factors, and transition off MAT. Volkow maintained that evidence should guide decisions about the type of MAT that is biologically optimal for an individual. She explained that OUD is highly heterogeneous,

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with outcomes shaped by disease severity and the environmental factors, thus patients need support systems to stay in treatment. Volkow remarked that educating all providers about treating OUD is low-hanging fruit. She pointed to insurance and reimbursement problems—as well as the traditional methadone clinic model—as key structural barriers to implementing MAT. She also added that a wider segment of the pharmaceutical industry should be engaged to develop better medications for treating OUD.

Deepa Avula of SAMHSA described how the agency is working to improve MAT service delivery. The State Opioid Response Grants program supports the development of comprehensive care systems for OUD with the flexibility for states to tailor system design to their specific needs and available resources. She noted that SAMHSA strengthened the language around the requirement that programs make MAT available. SAMHSA also engages peers with lived experience to help people with OUD to rebuild their lives and funds public awareness campaigns and extensive OUD-specific training and technical assistance. She said that SAMHSA is rolling out a program to embed buprenorphine-waiver training[1] within medical school curricula to expand access to the medication. She contended, "if every waivered physician were to serve patients even anywhere close to their limit, we would not have an opioid crisis in this country." Avula suggested conducting population-specific research to examine the comparative effectiveness of different care models for people with co-occurring conditions. She also highlighted the importance of community supports to complement medication across the spectrum of care.

Molly Evans outlined CDC's OUD-related activities: conducting surveillance and research; building state, local, and tribal capacity for prevention; supporting providers, health systems, and payers with guidance about opioid prescribing practices; partnering with public safety organizations on prevention strategies in high-intensity drug trafficking areas; and empowering consumers by raising awareness about the risks of prescription opioid misuse. Evans reported that CDC is funding an epidemiologic mixed-methods evaluation of OUD treatment in real-world outpatient settings to better understand the interaction among patients, providers, sites, and treatment type. The study's objectives are to improve treatment outcomes and to inform evidence-based decision making by policy makers, providers, and other stakeholders.

Judith Steinberg explained that HRSA supports health centers in implementing a patient-centered medical home model of care for OUD that integrates behavioral and psychosocial health interventions. The agency also supports workforce development and rural service delivery through telehealth modalities and is working to integrate treatment for OUD into primary care. She said that ongoing challenges include recruiting and retaining providers licensed to prescribe MAT; reimbursing services delivered by support providers; addressing stigma among providers and the community; and coordinating complex, timely, and comprehensive care for OUD. Steinberg said that establishing an evidence base for new models of care, such as MAT delivery in primary care, will be needed to satisfy the stringent requirements of payers. She said evidence is also needed to support the scale up of models that target vulnerable populations that need a customized care approach.

There are currently three FDA-approved medications for treating OUD: methadone, buprenorphine, and naltrexone. According to Rigo Roca, FDA, there are currently 55 active marketing applications related to these three medications, including new drug applications and abbreviated new drug applications (for generic formulations). Recent approvals include buprenorphine depot and another buprenorphine-naloxone film. He explained that they have fast-track and breakthrough therapy designations that can help to expedite regulatory approval for eligible new therapies for MAT. FDA has hosted various meetings to explore ways to expand MAT access and to support patient-focused drug development. Lastly, he noted that FDA also recently published draft guidance on the development of depot buprenorphine products and on endpoints for MAT effectiveness.

CURRENT EVIDENCE AND PRACTICE ON MEDICATION FOR TREATING OPIOID USE DISORDER

The second session surveyed the current evidence and practice on medication for treating OUD. Specifically, the session explored—for each medication—the evidence of effectiveness and evidence gaps related to use (e.g., what is known regarding dosing ranges and optimal duration of treatment); regulations, infrastructure, and care settings required for delivery; and provider and patient preferences and challenges.

Charles O'Brien, University of Pennsylvania, traced the history of opioids as pain treatment from ancient Mesopotamia to the synthesis of heroin in the 19th century to the federal policy restricting or criminalizing opioids for most of the 20th century. Widespread opioid prescribing for non-cancer pain in the 1990s catalyzed the parallel epidemic of street opioids at the core of the current crisis, he explained. Providers remain largely uneducated about addiction and opioids, he said, and he emphasized the need to distinguish between physical dependence, which is a normal physiological process, and addiction, which involves compulsive drug-seeking behavior despite harmful consequences. He also highlighted the need for education and comprehensive approaches for pain management and more extensive use of non-pharmacological pain treatments, which have no risk of addiction.

[1]The Drug Abuse Treatment Act of 2000 (DATA 2000) requires physicians to obtain a waiver to prescribe buprenorphine in office-based settings.

Methadone and buprenorphine are the two FDA-approved opioid agonist medications[2] for OUD. Methadone's effectiveness in treating OUD is indisputable, said Gavin Bart, University of Minnesota. Methadone reduces all-cause mortality, opioid-related mortality, and the risk of acquiring and transmitting HIV (Larochelle et al., 2017; MacArthur et al., 2012; Sordo et al., 2017). He explained that treatment retention improves when people receive higher doses of methadone and with structural advantages such as take-home dosing privileges and nearby treatment settings (Bart et al., 2012; Chutuape et al., 1999; Hser et al., 2011; Simpson et al., 1997; Villafranca et al., 2006). Concerns about methadone's safety persist, he added, despite clear evidence that methadone prescribed at clinics contributes minimally to overdose deaths and that the incidence of cardiac adverse events is not clinically significant (Bart et al., 2017; Johnson and Richert, 2015; Jones et al., 2016; Lofwall and Havens, 2012). Despite the wealth of evidence supporting methadone treatment, it remains stigmatized and excessively regulated; as a result, most people with OUD lack access to long-term methadone treatment (IOM, 1995).

Michelle Lofwall, University of Kentucky, explained that buprenorphine is effective in decreasing mortality (Larochelle et al., 2017; Schwartz et al., 2013). Concerns about diversion and misuse[3] underpin stringent regulatory policies—such as the buprenorphine prescribing waiver and prior authorization criteria—that reduce treatment access, despite evidence that most buprenorphine diversion is actually driven by lack of access to treatment (Lofwall et al., 2014).

Adam Bisaga, Columbia University Medical Center, addressed some common concerns about naltrexone, the only FDA-approved opioid antagonist medication.[4] Starting treatment with naltrexone is challenging, he said, because it requires a period of opioid withdrawal before initiation, unlike agonist medications. He noted that it is important to distinguish between oral naltrexone and the long-acting injectable formulation. A recent study found that treatment retention with injectable naltrexone was better than oral naltrexone (Sullivan et al., 2018). Naltrexone has similar effects on retention, cravings, and opioid use as buprenorphine, he said, with a comparable overdose risk while patients are in treatment. However, he said it is easier to discontinue treatment with naltrexone—because it does not cause dependence—with the risk of overdose increasing after treatment dropout. Naltrexone tends to be a less popular MAT option, he said, but many patients and providers are not aware of its benefits or its superior injectable formulation. He maintained that naltrexone should be seen as among the range of choices for patients, in addition to methadone and buprenorphine.

John Brooklyn, University of Vermont, described how Vermont's hub-and-spoke model integrates OUD treatment into primary care. Spokes, including all buprenorphine-waivered providers, link bi-directionally to one of six regional hubs, which are federally certified opioid treatment programs (OTPs). The model aims to prevent overdoses by providing continuous treatment to everyone with OUD in the state. He reported that as of September 2017, Vermont no longer has a waiting list, OUD treatment is available on demand at any OTP, and most of the state has access to buprenorphine treatment in an office-based setting. He reported that 1.47 percent of the entire population of the state is currently on MAT. In Vermont, the per capita rate of health care expenditures (excluding OUD treatment costs) for people on MAT has declined steadily over the past decade and the expansion of access to MAT has helped stabilize overdose rates.

Maia Szalavitz, American reporter and author, argued that "MAT" is a deeply inappropriate term because medication is the cornerstone of effective OUD care, not an optional add-on. She suggested that "counseling-assisted treatment" would be more apt. As a former patient, she said the treatment she received in methadone clinics was carceral and humiliating. Treating OUD in "ghettoized" methadone clinics is deeply problematic, she said, because it perpetuates stigma and discrimination against people who deserve equitable, respectful, evidence-based care. She said that some people want to come off methadone because the system is so horrible and they perceive it as a "chemical parole," not because of the medication itself. Stipulating that life-saving medications for OUD are contingent on conditions such as counseling, 12-step programs, or abstinence from other drugs would be unthinkable for any other chronic condition, she remarked. Two-thirds of drug courts prohibit MAT entirely and they often mandate participation in Narcotics Anonymous, which does not consider people on medication to be "clean." She added that the demeaning and hostile language used by the health care and judicial systems to describe addiction exacerbates that stigma.

Panelists discussed why treatment programs that discourage or prohibit medications are still so prevalent, given the known effectiveness of MAT. Bart said that such programs will continue to exist as long as they are funded. Several participants noted that many persons on MAT are also denied housing, prevented from participating in sober living environments, taken off medication while incarcerated, and denied other services because of their medication status. Bart emphasized the need to clarify the Americans with Disabilities Act and the Fair Housing Act as including MAT to prevent the ongoing discrimination of persons on MAT. Lofwall commented that the language around addiction must change to better align with the concept of OUD

[2]Opioid agonist medications work by activating the mu-opioid receptor in ways that yield some rewarding effects. Methadone is a full agonist that fully activates the receptor, while buprenorphine is a partial agonist that partially activates the receptor with a ceiling effect that diminishes its potential to cause rewarding effects.

[3]Lofwall defined diversion as the misappropriation of medication prescribed to somebody else, whether or not money is exchanged, and misuse as taking medication in a way other than intended.

[4]An opioid antagonist medication prevents opioids from activating the opioid receptor system, unlike methadone or buprenorphine.

with other chronic medical conditions. In the context of medication choice, Brooklyn and Szalavitz emphasized the importance of patients' preferences and shared decision making. Several participants discussed that the strong public bias toward getting off medications and tapering is largely due to the stigma of addiction and its treatment; for patients with conditions such as diabetes and HIV, the focus primarily is on staying on medications that treat the condition. Lofwall commented that the patient's insurance largely dictates the choice of MAT, while Bisaga noted that many programs only offer a single type of medication.

IMPLEMENTATION AND UPTAKE: EXPLORING OPPORTUNITIES AND BARRIERS

During the third session of the workshop, opportunities and barriers with respect to the implementation and uptake of MAT were explored. The session featured three panels that covered education and training; health care delivery, payment approaches, and economic measures; and social determinants of health. The speakers' presentations are organized here according to the panel in which they spoke, but many touched on a full range of these often interconnected barriers and opportunities.

Education and Training

The first panel focused on the opportunities and barriers related to education and training, including exploring the currently required education and training for providers and potential improvements; identifying the best practices and hurdles to achieving the required workforce to treat OUD; and examining the communication and education needs for patients, families, policy makers, law enforcement, the public, and other stakeholders.

Jeannette Tetrault, Yale University, said that they are developing a thread of addiction content throughout all medical training at the residency, advanced, and fellowship levels of the university. A component of the curriculum is explicitly designed to stop perpetuating the stigmatizing language around addiction in medical training and among faculty educators and mentors. Medical students today tend to be committed to social justice issues and eager to take on the task of ending the OUD epidemic, she said, and making education on addiction care a core requirement would bolster those efforts.

Stephen Patrick, Vanderbilt University, discussed ways to improve outcomes for pregnant women, babies, and adolescents. MAT access is substantially inadequate for vulnerable populations with OUD: only half of pregnant women and one-quarter of youths receive treatment; less than 5 percent of adolescents on Medicaid receive methadone or buprenorphine (Hadland et al., 2017, 2018; Haight et al., 2018; Short et al., 2018). He said that this gap underscores the urgent need for more pediatricians and obstetricians to become buprenorphine-waivered. He reported that both buprenorphine and methadone are recommended for OUD in pregnant women to decrease their risk of overdose and relapse and their infants will have a greater chance of going to term and having a higher birth weight. Infants have an elevated risk of neonatal abstinence syndrome if the mother receives MAT, but new models of trauma-informed, standardized, collaborative care are significantly reducing the length of stay in the hospital and are more inclusive of the mother's needs (Wachman et al., 2018). Patrick noted that the literature on long-term outcomes from neonatal abstinence syndrome is limited, but the long-term effects do not appear profound. He added that early intervention and home nursing visitation services for children born with neonatal abstinence syndrome are effective, but likely underutilized.

Eugenia Oviedo-Joekes, University of British Columbia, described the benefits of short-acting injectable medications for treating patients with the most severe OUD. She said that in addition to methadone, buprenorphine plus naloxone, and slow-release oral morphine, Health Canada offers diacetylmorphine (pharmaceutical-grade heroin) and hydromorphone (dilaudid) short-acting injectable medications as treatment options in controlled settings for people who cannot or will not stop using street drugs. She said that this is a critically important, evidence-based treatment modality for those whom the system failed—for example, people from indigenous communities disproportionately affected by OUD with a history of oppression that discourages care seeking. Offering the option of short-acting injectables engages patients in shared decision making with their provider, reduces the stigma and judgment, and "meets people where they are" to address their full spectrum of needs.

Jules Netherland, Drug Policy Alliance, situated drug use and addiction within a broader public health approach for expanding access to MAT. She called for addressing the social determinants of OUD, decriminalizing drug use, eliminating punitive policies, and integrating harm reduction services. She suggested exploring outcomes other than abstinence within this broader view, such as quality of life, family reunification, stabilization, and employment. People who use drugs should contribute meaningfully to the development of policies and provider training to represent the voices of those directly impacted, she stressed. Netherland described a host of innovative service delivery models to expand access to MAT, including office-based methadone, pharmacy-based methadone and buprenorphine, induction and maintenance in emergency departments (EDs), telemedicine, and mobile delivery. She also said education and training on MAT should be expanded beyond medical providers to individuals that work with hard-to-reach populations, such as street-based medicine, homeless service, and housing providers.

Kathleen Johnson, Advocates for Opioid Recovery, shared her experience of supporting a son with OUD to illustrate its destructive effect on the infrastructure of people's lives. People with OUD often struggle to stay afloat and on treatment in

the face of overwhelming obligations to their families, work, school, finances, and the criminal justice system. She said that broad structural changes are urgently needed so that patients, families, and communities can surmount this multigenerational, decades-long challenge. She remarked that a delicate balance needs to be struck in supporting patients' and families' decision making without overstepping the bounds.

During the panel discussion on mandating or incentivizing provider education on OUD, Tetrault suggested that institutions should be incentivized to have faculty who can model integrated addiction care and that all medical schools should have addiction fellowships. Patrick proposed that medical education at all levels and for all providers, including allied health professionals, should include addiction training and trauma-informed care. He noted that some states require continuing medical education on opioid prescribing for medical licensure, which could be a mechanism to expand provider knowledge on addiction and MAT. He added that patients' and families' experiences in the health system should be integrated into provider education to help mitigate the stigmatizing, mistaken belief that MAT is simply trading one drug for another.

Panelists discussed how to disseminate information about MAT to patients, families, and communities at large. Johnson said that information from grassroots and social media sources is often more helpful than official sources of information that are siloed and difficult to access in a crisis. Oviedo-Joekes explained that when her group publicized the results of a large clinical trial on hydromorphone, an entire team—including patients—collaborated to create a full media communication plan with a clear message that everyone would adhere to, which was vital to preventing the message from being distorted by the media. Netherland suggested partnering with advocacy organizations with experience translating technical findings into lay language for targeted dissemination. She said that crafting the product's format and delivering it in appropriate ways requires working closely with patients and families directly impacted by OUD. Patrick remarked public perception drives policy change and it is incumbent on providers and researchers to frame the narrative carefully using language that reduces stigma and is inclusive of all communities affected by the opioid epidemic since its inception decades ago. Netherland added that efforts to remedy some of the social injustices inflicted on people of color with OUD, for example, might frame the narrative with the same type of humanizing backstories afforded to white victims of the epidemic.

Health Care Delivery, Payment Approaches, and Economics Measures

The second panel explored the opportunities and barriers related to health care delivery, payment approaches, and economics measures to improve the treatment of OUD. The objectives were to discuss how health care access and delivery impact patient access to medications to treat OUD; consider regulations around hospital capacity, administrative burdens, and the tight regulation of medical products; explore the cost, reimbursement, and coverage of medications to treat OUD and discuss measures to help facilitate quality improvement and access; and examine the regulatory differences of for-profit versus nonprofit treatment providers.

Richard Frank, Harvard University, focused on economic issues in improving the treatment for OUD. He began with the demand side: 11–26 percent of people with OUD receive treatment, and among those who do, 34 percent receive MAT (Knudsen et al., 2011); around 50 percent of people are still in treatment after 1 year (Blanco et al., 2013); and people with OUD tend to wait between 4 and 7 years after developing the condition before starting treatment (Wang et al., 2005). On the supply side, he said, around 40 percent of treatment facilities offer MAT—with less than 3 percent offering all three forms (Jones et al., 2015) and less than one-quarter of publicly funded facilities offering MAT (Knudsen, 2015). Wide disparities in Medicaid coverage of OUD treatment across states have serious implications for access, because OUD disproportionately affects people with low income. He explained that MAT has traditionally been highly constrained by insurance regulations, but recent Medicaid expansions have spurred rapid growth in MAT, driven largely by office-based buprenorphine (Maclean and Saloner, 2017). Integrating MAT into general medical practices could substantially increase access, he suggested, but low reimbursement levels disincentivize providers from offering it. He advised that payment models should be better aligned with effective care models and that some of the care management burden should be shifted to non-physician providers—e.g., through bundled payments that link payment to services from outreach to retention. Frank said that the policy levers with the greatest potential payoff to expand MAT access include Medicaid expansion and design, parity implementation, and state regulation of OUD programs and licensure.

Allan Coukell, The Pew Charitable Trusts, remarked that few state-level policy makers have the holistic vision needed to address widespread shortfalls in treatment capacity. Addiction is still not commonly understood as a chronic disease and is compounded by the lingering preference for residential, abstinence-only care among many patients, families, policy makers, and payers. He explained that insurance companies often limit their coverage of MAT; thus discouraging providers while continuing to provide full coverage for non-evidence-based care. He added that administrative burdens arise from low reimbursement levels and lack of uniform prior authorization criteria across payers.

Katrina King, George Mason University, shared her experience as a patient with OUD and as the mother of a child who died by heroin overdose shortly after requesting MAT and being waitlisted. She outlined some of the obstacles that prevent

people from receiving life-saving treatment: lack of insurance coverage, expensive providers, waitlisting, stigma among providers, and the lack of peer recovery support. King has drawn on her firsthand experiences to become a community health navigator. Peer navigators have the shared lived experience to guide and mentor people with OUD who need help in staying on treatment, finding housing and employment, and accessing existing supports in the community. Peer navigation meets people where they are, she explained, and helps them to rebuild connections with their community.

Yngvild Olsen, Institutes for Behavior Resources, Inc., described an alternative payment model that mitigates reimbursement barriers by providing patient-centered opioid addiction treatment in outpatient (non-OTP) settings. The model aims to reimburse appropriately through a one-time initial payment to cover treatment initiation followed by ongoing monthly payments for medical, psychological, and social support services. She explained that some providers offer fully integrated care under one roof, while others join formal collaborative care arrangements. Providers are required to meet quality standards in providing evidence-based services and costs are controlled by eliminating unnecessary spending on ineffective treatments, she said.

During the discussion, panelists explored options for restructuring payments and setting performance measures for MAT. Coukell said that ideally, coverage would attach to the patient and not the facility, so the patient can go to any site and receive the most appropriate care. Frank contended that the performance metrics integrated into current measures used for accountable care organizations are deeply inadequate for mental health and addiction. To create better performance measures that are not as contingent on payment structures, he suggested creating targeted measures to capture access, quality, and retention. Olsen noted that current financial incentives and performance measures based on discharge metrics are not suitable for OUD or other chronic conditions treated by primary care or addiction medicine. She also warned that often bundled payments lack transparency and can incentivize the wrong practices in the absence of targeted performance measures linked to outcomes.

Social Determinants of Health and Special Populations

The third panel focused on the social determinants of health and treatment for OUD. The objectives were to explore the impact of comorbidities on treatment and how this may impact the uptake and overall effectiveness of medications to treat OUD; consider how pregnancy, age, race, gender, genetic variables, mental health, chronic pain, and other factors may influence treatment; and identify further evidence needed to better deliver culturally appropriate care and serve diverse populations.

Mishka Terplan, Virginia Commonwealth University, remarked that women are highly motivated to maximize the health and well-being of their pregnancy, including significant behavior change. Virtually all women with OUD who become pregnant will try to stop using, he said, but their addiction can make it difficult or even impossible to stop without medication to treat withdrawal symptoms. Overdose is one of the leading causes of maternal deaths in the United States and the risk of overdose increases as the postpartum period progresses (Schiff et al., 2018). He explained that the standard of care for pregnant women with OUD is a set of comprehensive collocated services that integrate medication, behavioral counseling, and prenatal care. When women with addiction are treated during pregnancy, birth outcomes are almost identical to women without addiction (Kotelchuck et al., 2017). Even though medications are known to be protective during pregnancy and postpartum, he warned that access to care is extremely limited. Most pregnant women with OUD receive no treatment at all (Terplan et al., 2015) and only half of those who are treated receive MAT (Short et al., 2018). He emphasized that among women who are treated during pregnancy, the postpartum period (the “fourth trimester”) is a critical inflection point when women can easily fall out of treatment due to gaps in insurance coverage and the siloed reproductive health care system.

Anand Kumar, University of Illinois at Chicago, described two vulnerable populations with OUD: people with psychiatric comorbidities and the elderly. He explained that a combination of biological and psychological risk factors plays a role in OUD and given the overlap in the neuronal circuitry underlying OUD and other psychiatric conditions, there is considerable comorbidity of psychiatric disorders. Common comorbidities include major depression, anxiety disorders, posttraumatic stress disorder, other substance use disorders, antisocial personality disorder, and borderline personality disorder. Comorbidities are associated with poorer outcomes in OUD, he said, with some evidence suggesting that treating comorbid conditions may improve the treatment, psychosocial, and functional outcomes of OUD. He added that a range of evidence-based, non-pharmacological psychotherapeutic approaches can also be used to help manage anxiety and depression in the context of addiction treatment. Kumar also noted that older adults present a vulnerable population with regard to opioid use, but receive comparatively little attention. Kumar reported that individuals ages 65 and older represent 25 percent of long-term users of opioids (Mojtabai, 2018), and he emphasized the need for provider education about the special biological and psychosocial vulnerabilities of this population.

Josiah Rich, Brown University, described the process of incorporating MAT into OUD treatment for incarcerated populations in Rhode Island. After implementing a universal screening program, starting everyone with OUD on treatment, and connecting people to continuation treatment upon release, the number of post-release overdose deaths dropped by 60 percent

within 1 year. He found that most people want to be treated when they have access and that people generally have a strong preference for either methadone or buprenorphine; few choose depot naltrexone. He noted that MAT is not offered in most correctional facilities and if it is, only one medication is typically offered—usually depot naltrexone, due to the stigma about agonist therapies. Investing in treatment for incarcerated populations and connecting people to maintenance treatment after release are critically important, he said, but parallel efforts need to work toward diverting people with OUD directly into treatment rather than into the criminal justice system.

Helena B. Hansen, New York University, sketched the history of racial inequalities in addiction treatment to spotlight the biases that continue to permeate U.S. drug policies. She explained that the perceived universality of the opioid crisis today is the product of the specific ethnic marketing of opioids through a separate track of legal, protected narcotics for middle-class whites as well as drug policies that favor white consumers, such as buprenorphine deregulation. During the narcotic epidemic among the black working class decades ago, racial imaging was used to justify the war on drugs, she said. This led to racially disparate law enforcement and mass incarceration, instead of public outcry and efforts to address the social determinants of drug use. The impact of the opioid crisis on whites opens a window of opportunity to address those social determinants, said Hansen. Achieving a population-level public health impact with MAT will require intervening on social structures and inequalities through structural change, she added. To help dispel the historical legacy of suspicion and distrust of health care providers and medication among low-income communities of color, she suggested packaging medication together with social services, community building, and other deliberate social technologies for fostering connections and providing assistance with basic needs. She added that educating providers on the social determinants of addiction would help work against the bias and stereotyping that abounds in clinical practice.

KNOWLEDGE GAPS, FUTURE RESEARCH, AND POTENTIAL POLICY CHANGES

The fourth session focused on knowledge gaps, future research, and next steps. As in previous sessions, speakers addressed a mix of interconnected topics, speaking both of the need to take immediate action to help those now suffering from OUD, as well as the need to advance understanding of how best to deliver and increase access to MAT.

The opioid epidemic has generated unprecedented demand for services, said Sharon Walsh, University of Kentucky, and the most impactful intervention against the rising overdose death toll is expanding treatment for OUD (Pitt et al., 2018). Of the small proportion of people with OUD who get treatment at all, the majority receives treatment that is not evidence-based and potentially harmful, she said. Many people enter prison-like, full-abstinence inpatient facilities where they painfully detoxify without medications that could alleviate their withdrawal symptoms. More affluent people may go to expensive luxury facilities, she added, but regardless of the setting, the end result is usually the same: most people will relapse and then begin the cycle anew. Walsh argued that policy must drive a paradigm shift toward quality, evidence-based, integrated care and against the abstinence-only dogma believed by many patients, communities, providers, and the justice system. She called for an immediate end to federal funding of programs that prohibit evidence-based care. Excessive regulatory barriers to MAT access also need to be lifted, she said, including insurers' fail-first policies and the requirement that both prescriber and implementer must be waivered for the new buprenorphine implant.

Gail D'Onofrio, Yale University, described the role that EDs can play in fighting the opioid crisis. EDs can identify patients, initiate treatment with buprenorphine, distribute naloxone, and link patients to treatment. Only 28 percent of opioid overdose survivors are linked to MAT (Larochelle et al., 2018) despite evidence that people given ED-initiated buprenorphine are twice as likely to be engaged in treatment after 1 month (D'Onofrio et al., 2015). To integrate research into practice, a quality framework for ED treatment of OUD was developed (Samuels et al., 2018). D'Onofrio suggested starting patients on treatment in the ED with high-dose buprenorphine that will last for a few days to sustain them until they can get into treatment, using new longer-acting buprenorphine injectables, and creating referral pathways out of the ED. D'Onofrio said that training on OUD care should be an expectation—not a request—of clinicians that is required by all health systems. The time to act is now, she urged, rather than waiting for research and knowledge gaps to be addressed.

Jonathan Watanabe, University of California, San Diego, discussed the pivotal role pharmacists can play in improving access to MAT. Evidence suggests that having pharmacists directly interface with clinicians to inform them about MAT has the potential to increase access. He suggested that analytics could accelerate efforts to reach more patients by monitoring opioid use and managing the availability of MAT for facilities. Pharmacies and community care clinics can serve as access points and mechanisms for reaching patients in areas hard hit by OUD but underserved by health care systems, he explained. Watanabe reported that there is interest among the pharmacy community about the possibility of allowing pharmacists to obtain waivers to administer buprenorphine, using the rationale that OUD is a public health threat.

Jessica Hulsey Nickel, founder of the Addiction Policy Forum, an OUD patient advocacy group, said that bridging the gap among clinicians, scientists, and the patient community will help to reduce the isolation and stigma that patients and families experience. She shared stories of patients and families to humanize the devastating consequences of the epidemic. Nickel

noted that the current treatment system is built for adults, even though OUD often begins to develop in adolescence. She said that "catch and release" practices in hospitals are far too common: the same person is revived from overdoses on multiple occasions without ever being guided into treatment for OUD. Patients seeking MAT are regularly refused treatment based on insurance companies' fail-first policies and many go on to overdose shortly after. Patients and their families face pervasive stigma about addiction as a decision, not a disease, and must navigate a "troubling constellation of myths and misinformation" about OUD to find effective, evidence-based care for their loved ones. Her organization is working to build awareness and fight against entrenched misconceptions.

During the discussion on research needs, Watanabe suggested more operational research to address logistical and reimbursement challenges related to addiction care. D'Onofrio called for research on starting and retaining patients in treatment, high-risk behaviors in adolescents and how to intervene, harm reduction, reaching young adolescents, and the integration of psychosocial therapies with MAT. Walsh remarked that better medications to treat OUD are needed, but if structural barriers prevent patients from accessing them, then the pharmaceutical industry will not invest in developing them. She added that evidence should be used to eliminate the policies and practices that do *not* work—for example, detoxification without medication and barriers to buprenorphine delivery. Nickel suggested using multidisciplinary approaches to investigate various combinations of medications and psychosocial interventions to treat OUD of different severity levels.

In closing the workshop, Alan Leshner, chair of the Committee on Medication-Assisted Treatment for Opioid Use Disorder, thanked all of the speakers, noting that the presentations and discussions generated a great deal of thought and discussion and will be a valuable supplement to the literature reviews. He reminded attendees that the committee will draft a Consensus Study Report that will undergo the National Academies peer-review process and be released in spring 2019.♦♦♦

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CASE STUDY

Implementation of order sets for opioid alternatives in community hospital emergency departments

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Purpose. The design and implementation of alternatives to opioids (ALTO) order sets for the treatment of acute pain in a community health system's emergency departments are described.

Summary. Healthcare institutions nationwide have incorporated policies and procedures to assist prescribers in the safe and effective management of pain. These adopted approaches may be targeted at mitigating opioid prescribing as well as promoting the optimization of nonopioid analgesics. Institutions that enact innovations and track outcomes may be eligible for reimbursement through the Centers for Medicare and Medicaid Services' Merit-based Incentive Payment System. Emergency departments may monitor implementation progress and outcomes through participation in the American College of Emergency Physician's Emergency Quality Network. Clinical pharmacists were tasked with assisting an institution's emergency departments to create and implement two order sets containing ALTO analgesics and supportive medications for atraumatic headache and general acute pain management. Key steps of order set implementation included collaborative development with emergency department providers, implementation with information services, and the development of provider-focused education by project pharmacists. The implementation of ALTO order sets has set the foundation for expansion of pain control protocols and algorithms within our institution. Furthermore, the approach detailed in this article can be adapted and implemented by other healthcare systems to help reduce opioid prescribing.

Conclusion. The implementation of ALTO order sets within an electronic health record can encourage decreased prescribing of opioids for the treatment of acute pain, promote and optimize dosing of nonopioid analgesics, and may augment reimbursement for services in the emergency department.

Keywords: analgesics; emergency medicine; medication-use technology; non-narcotic

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Between 1999 and 2007, US opioid overdose–related deaths per year rose from 8,048 to 18,515, with an exponential increase to 47,600 in 2017.[1] In October 2017, the United States declared the opioid crisis a national public health emergency.[2] Since 2007, overdose deaths related to use of prescription opioids have gradually increased, whereas deaths associated with street drugs like heroin have escalated rapidly.[1] In a survey of nonprescription opioid abusers, many patients reported that their first abused opioid was a prescription drug.[3]

In light of the opioid crisis, it is especially important for healthcare providers to be judicious in the administration and prescribing of these medications. Pain is commonly encountered in the emergency department (ED) setting, and rapid clinical decision making is required in order to address appropriately. To help assist in this clinical decision making, healthcare institutions nationwide have taken steps to assist prescribers in the efficient and appropriate management of pain through nonopioid modalities by the

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incorporation of alternatives to opioids (ALTO) protocols, pain management algorithms, and order sets. These resources may be used by institutions to facilitate the development of opioid-sparing interventions.

Background

Parkview Health is a community-based health system located in northeastern Indiana. The health system is comprised of a level II trauma center, an urban hospital, and 6 rural community hospitals. In 2018, approximately 206,000 patient visits occurred across all EDs within the health system. The ED provider group is composed of physicians and physician assistants, who routinely rotate among hospital locations for staffing. Decentralized clinical pharmacist coverage is provided at the level II trauma center's ED during the evening shift 7 days a week.

Parkview Health participates in the American College of Emergency Physician (ACEP) Emergency Quality Network (E-QUAL) program.[4] Participation in the E-QUAL program facilitates benchmarking and reporting to the Centers for Medicare and Medicaid Services' Merit-based Incentive Payment System (MIPS).[5] The E-QUAL program offers emergency medicine–focused initiatives to meet the MIPS performance requirements for improvement activities, which mandate that participants actively try to improve the quality and reduce the cost of care. Demonstrating that efforts are made to meet improvement activities requirements helps institutions earn performance-based adjustments of Medicare Part B payments. For the 2018 calendar year, Parkview Health elected to participate in improvement activities related to the opioid management with the goal of reducing opioid-associated harm through safer prescribing and the implementation of evidence-based interventions. Participation in the opioid management improvement activities required that one of the following specific pain indications be selected for evaluation: low back pain, atraumatic headache pain, or dental pain. Atraumatic headache pain was selected by Parkview Health as the measure to be targeted for improvement and assessment.

Problem

ED providers were tasked with implementing opioid optimization strategies that would meet the improvement activities requirements, address the opioid crisis by promoting use of nonopioid modalities, and could be executed across all EDs within the health system. Earlier in 2018, the state's opioid prescription drug monitoring program (PDMP) was integrated into the electronic health record (EHR) to allow providers to consult the database prior to prescribing opioid therapies. Incorporating the PDMP into the EHR earned points for improvement activities in the E-QUAL program; however, additional points were required in order to fully meet the initiative. ED providers requested the development of decision support tools and treatment protocols to aid in analgesic prescribing.

As a result, ED physicians, in collaboration with the project pharmacists, decided to design ALTO order sets that could be integrated into the EHR. Two objectives were deemed necessary by initiative leaders to help guide ALTO order set creation to maximize benefits for patients and the health system: (1) the order sets needed to promote ACEP's policy statement that acutely painful conditions in the emergency department should optimally begin with a nonopioid agent,[6] and (2) an order set was needed to meet the criteria for promoting safe and effective nonopioid analgesia for atraumatic headache. Additionally, providers requested that order sets be user-friendly and that selection of medications for inclusion in order sets be evidence based.

Analysis and resolution

Prototype reveal for provider feedback. Project pharmacists delivered a presentation during monthly ED grand rounds. Objectives of the presentation were to reveal the order set prototype, promote the advantages of ALTO order sets vs opioid prescribing, and encourage provider discussion and feedback. The objectives for the presentations were met by delivering a presentation that briefly described the national and local impact of the opioid crisis, visually demonstrated use of the ALTO order set, and detailed how the project correlated to institutional opioid-reduction strategies. After the presentation, providers were given a written questionnaire designed to assess overall provider support for the order set and, more specifically, the analgesics that were initially proposed for inclusion in the order set project. Space was available for providers to write in additional comments and provide suggestions for other nonopioid analgesics not initially included.

Two major project changes occurred as a result of provider discussion during grand rounds. First, the discussion led to the creation of 2 separate order sets targeting pain; this was done to accommodate 2 areas of provider concern. A majority of providers were concerned that further expansion of the number of analgesics included in the initially proposed order set would create an overly lengthy order set that would hinder order selection. Additionally, some providers were concerned that a single order set might not be enough. Therefore, they proposed creation of a second order set specifically for medications used to treat atraumatic headache would allow for headache-specific analgesics to be included on a second, more concise order set, which would align with and promote E-QUAL initiative goals.

The second major change was to include the order sets as a link on the ED provider Quicklist, a rapid-ordering functionality within the Epic EHR system (Epic Systems Corporation, Verona, WI), rather than requiring a search of available order sets within the order set search bar. Within our EHR, the ED providers have a Quicklist screen that encompasses commonly used medications, laboratory results, consultations, and radiological tools.

The Quicklist facilitates expedited ordering from a single screen as opposed to searching for individual orders. Having the orders sets included as part of the Quicklist was significant as it allowed providers to have easier access to the order sets, and its appearance on the medications tab served as a reminder for provider usage.

Proposed changes to the order set prototype primarily were derived from feedback on the questionnaire distributed to 46 ED providers. The questionnaire response rate was 69.6% (32 of 46 providers). Responses to the questionnaire showed that 29 of 32 providers (90.6%) supported implementation of the ALTO order sets. Survey results showing provider preferences regarding a list of medications originally proposed for inclusion in order sets, as well as write-in suggestions, are presented in Table 1.

Order set analgesic selection. Of the 12 medications originally proposed for order set inclusion, only 2 garnered less than 50% provider support. Despite intravenous (i.v.) lidocaine having less than 50% provider support, it was selected for order set inclusion; but was deemed necessary to build a distinct analgesic i.v. lidocaine order in addition to the existing antiarrhythmic order to reduce dosing and administration errors. Specifically, the i.v. lidocaine for analgesia order included a built-in maximum dose, slower administration rate, and required cardiac monitoring. Due to lack of support, gabapentin was removed from the order set. The lack of support for gabapentin was based on skepticism of its use as an acute analgesic and concern regarding potential adverse effects if the dose were not tapered appropriately. Additionally, our institution routinely serves patients from Ohio, which recently categorized gabapentin as a schedule V controlled substance. Rizatriptan and sumatriptan had a lower provider preference rating, but it was theorized that the approval rating may have reflected the original proposal for one order set and that providers might not have considered that these medications would be limited to the atraumatic headache order set.

With consideration of the 9 provider write-in recommendations, 6 additional agents were added to the order sets. Some analgesics with alternate routes of administration were requested by multiple providers for addition to the order sets, such as intramuscular and oral orphenadrine and intramuscular dicyclomine. Other agents did not have multiple write-in requests for addition to the order sets but were ultimately included, such as i.v. magnesium and i.v. dihydroergotamine. To ensure the atraumatic headache order set had a sufficient breadth of agents available for selection, these medications were reviewed and added despite less than 50% provider support. Intravenous acetaminophen was requested by multiple providers, but due to institutional cost-based formulary restrictions, the medication was not added to the order sets. Due to a concurrent evaluation of ketamine order sets for analgesia in the ED, ketamine was not added to the ALTO order sets to prevent confounding of project results.

After analyzing provider responses regarding analgesic selection, project pharmacists began the process of evaluating route, dose, and frequency for the creation of the 2 order sets. While

Table 1. Results of Survey of Provider Preferences for Medications to be Included in ALTO Order Set

Medication (Route)	No. (%) Supporting Inclusion (n = 32)
Initially proposed for inclusion	
Acetaminophen (oral)	29 (91)
Ibuprofen (oral)	29 (91)
Ketorolac (i.v.)	29 (91)
Lidocaine (transdermal)	26 (81)
Metoclopramide (i.v.)	26 (81)
Dicyclomine (oral)	25 (78)
Orphenadrine (i.v.)	24 (75)
Cyclobenzaprine (oral)	23 (72)
Rizatriptan (oral)	17 (53)
Sumatriptan (subcutaneous)	17 (53)
Lidocaine (i.v.)	14 (44)
Gabapentin (oral)	6 (19)
Proposed by write-in request	
Orphenadrine (i.m.)	13 (41)
Dicyclomine (i.m.)	11 (34)
Acetaminophen (i.v.)	10 (31)
Ketorolac (i.m.)	6 (19)
Haloperidol (i.v.)	5 (16)
Prochlorperazine (i.m.)	5 (16)
Orphenadrine (oral)	2 (6)
Magnesium (i.v.)	1 (3)
Dihydroergotamine (i.v.)	1 (3)

Abbreviations: ALTO, alternatives to opioids; i.m., intramuscular; i.v., intravenous.

many agents selected for the order sets can be administered at different doses and frequencies, the project pharmacists reviewed literature and other institutions' nonopioid analgesic programs to optimize the default dose of each medication specified in the order sets. If providers wanted to change the dose or frequency, they had the option to open the full order and make adjustments via other preselected dose and frequency buttons. For example, the 15-mg dose of ketorolac was selected as the default dose, as recent literature from Motov et al[7] indicated that doses greater than 10 mg were not more effective in pain reduction. As 15-mg ketorolac dose increments are commonly used within our institution, 15 mg was selected as the default option. However, providers have the option to open the full order, where prespecified buttons for 10-, 15-, and 30-mg doses are available. Additionally, some medications on the order sets can be given both intravenously and intramuscularly. Both safety of administration and provider preference of administration route were assessed when selecting a default route. Providers could alter the default parenteral route of administration after selecting the medication on the order sets. Since orphenadrine is supplied in both oral and injectable formulations, a separate entry was created for the oral formulation to prevent errors in dosing, as the i.v.-to-oral conversion ratio is not 1:1.

Although orphenadrine is not referenced frequently in various pain guidelines, provider preference for its inclusion in an order set was strong within our institution. Orphenadrine, like other muscle relaxants, can be used to treat musculoskeletal pain as monotherapy or used in combination with initial pain therapies such as acetaminophen and ibuprofen. Within the order sets, providers can select multiple agents at once to create a multimodal approach to the treatment of acute pain if it is deemed that monotherapy is not clinically appropriate. Additionally, the order sets included several medications as adjuvant therapy for pain that could be combined with first-line options as well as medications with off-label pain indications. Low-dose haloperidol was added to the order set for consideration in the adjuvant treatment of abdominal pain and gastroparesis refractory to other pain control interventions.[8] Intravenous lidocaine was added because recent literature supports its use for the management of pain associated with renal colic.[9] Several other novel pain control approaches, including ultrasound-guided nerve blocks and inhaled nitrous oxide, were discussed during the inaugural meeting; however, these interventions were not included in the final order sets due to cost considerations and complex administration requirements.

Lastly, per provider request, additional medications were selected for their supportive care benefits when used in conjunction with medications on the order set (eg, the treatment of nausea for patients with migraine). Diphenhydramine monotherapy is not commonly used for the treatment of migraine headaches but can be administered with metoclopramide as adjuvant therapy. Additionally, diphenhydramine may reduce the occurrence of undesirable adverse effects associated with metoclopramide (eg, akathisia). Initially, potential inclusion of ondansetron in the order sets was not discussed, as only medications for which there was published data to support use as adjuvant therapies were discussed. Several weeks later, to aid in ordering and reduce provider ordering fatigue, ondansetron was added to the atraumatic headache order set, as it was felt the drug would be ordered at the same time as analgesia for the acute management of migraines. The completed order sets are detailed in Tables 2 and 3.

Order set implementation. Within our institution, the information services (IS) department has a division dedicated to in-house builds and support for the Epic EHR. The pharmacy and ED have dedicated members within the EHR service center who were able to incorporate the order sets into the ED provider Quicklist.

Prior to order set creation, some medications that were incorporated into the order sets were available on the ED Quicklist. To encourage order set usage and congregate similar medications, several medications were removed from the ED Quicklist and transitioned to the order sets. The medications that were removed were nonopioid analgesics not used for alternative therapies (eg, dicyclomine). Medications that have alternative therapies, such as fever reduction, were still included in the order sets and included on the Quicklist for provider accessibility (eg, acetaminophen).

Project pharmacists collaborated with the IS team to set the default dose, route, and frequency for each medication. Pharmacists made additional recommendations regarding prespecified buttons available for each medication when the full order is opened. When deemed necessary, additional order and administration comments were drafted by the pharmacists and incorporated into the order. For example, the i.v. lidocaine included a note that cardiac monitoring was required during the administration period. Additionally, each medication's priority status, as well as the need for pharmacist verification, was evaluated by the pharmacists. Medications deemed appropriate for autoverification did not need a change in dispensing status (ie, emergent vs routine) because they would be readily available for administration after the order is placed. For medications deemed to require pharmacist verification, the priority status was changed to "stat" so that the medications would appear at the top of the pharmacist verification queue to reduce time to medication availability.

Provider education. Education was developed by project pharmacists and targeted to ED providers. The questionnaire distributed to providers during the grand rounds presentation included an assessment of preference of education format and included the options of an emailed handout, a slideshow presentation, or a live in-service. An emailed handout

Table 2. Medications in ALTO Order Set for Generalized Pain, With Default Dose, Route, and Frequency

Medication	Formulation	Dose	Route	Frequency
Acetaminophen	Tablet	1,000 mg	Oral	Every 6 hours
Ibuprofen	Tablet	400 mg	Oral	Every 6 hours
Ketorolac	Injection	15 mg	i.v.	Every 6 hours
Dicyclomine	Capsule	20 mg	Oral	Every 6 hours
Dicyclomine	Injection	20 mg	i.m.	Every 6 hours
Orphenadrine	Tablet	100 mg	Oral	Every 12 hours
Orphenadrine	Injection	60 mg	i.v.	Once
Cyclobenzaprine	Tablet	10 mg	Oral	Every 8 hours
Lidocaine	Infusion	1.5 mg/kg	i.v.	Once
Lidocaine	Patch	4% patch	Transdermal	Every 24 hours
Haloperidol	Injection	2 mg	i.v.	Once

Abbreviations: ALTO, alternatives to opioids; i.m., intramuscular; i.v., intravenous.

Table 3. Medications in ALTO Order Set for Atraumatic Headache, With Default Dose, Route, and Frequency

Medication	Formulation	Dose	Route	Frequency
Acetaminophen	Tablet	1,000 mg	Oral	Every 6 hours
Ibuprofen	Tablet	400 mg	Oral	Every 6 hours
Ketorolac	Injection	15 mg	i.v.	Once
Metoclopramide	Injection	10 mg	i.v.	Once
Diphenhydramine	Injection	25 mg	i.v.	Once
Prochlorperazine	Injection	10 mg	i.m.	Once
Dexamethasone	Injection	8 mg	i.v.	Once
Magnesium	Infusion	1 g	i.v.	Once
Rizatriptan	Tablet	10 mg	Oral	Once, may repeat[a]
Sumatriptan	Injection	6 mg	Subcutaneous	Once
Dihydroergotamine	Injection	1 mg	i.v.	Once, may repeat[b]
Ondansetron	ODT	4 mg	Oral	Once
Ondansetron	Injection	4 mg	i.v.	Once

Abbreviations: ALTO, alternatives to opioids; i.m., intramuscular; i.v., intravenous; ODT, orally disintegrating tablet.
[a]Repeat dose may be given once after 2 hours if significant relief not attained (maximum dose of 20 mg in 24 hours).
[b]Repeat dose may be given once after one hour if significant relief not attained (maximum dose of 2 mg in 24 hours).

was the preferred route of education. The objective of the education was to provide an overview of order set function, information about medications on the order sets, and possible benefits of order set utilization. Overview of the order sets included their location within the Quicklist and functionality of ordering within the order set. Medication-specific information included a summary of the medications on each order set, default settings and available alternative prespecified options, discussion of possible adverse effects and monitoring needs, and clinical pearls for provider consideration. The review of the benefits of order set utilization primarily focused on reduction of opioid prescribing and the functionality of selecting multiple medications in the order set to create a multimodal approach for pain management.

Provider education was conducted 2 weeks prior to the implementation of the order sets. A pharmacist presence in the ED during the implementation period (both clinical pharmacists and

pharmacy residents) helped to promote order set use in addition to serving as an avenue for any provider questions involving order set usage. Pharmacists' activities to promote order set use included reminders of order set availability, recommendations regarding medications included on the order sets, and requests for provider feedback.

Discussion

From the inaugural meeting to completed EHR implementation, the project took place over a 6-month period. Order set usage is trackable within the data analytic center within the EHR. This allows project pharmacists to have the opportunity to complete drug use evaluations for order set analgesics and opioids prescribed in the ED. Areas for possible evaluation include comparison of morphine milligram equivalents administered to patients who receive medications from an ALTO order set and those who did not, comparisons of pain and satisfaction scores, and rates of discharge prescriptions for opioid agents. Participation in the E-QUAL program to improve MIPS reimbursement does not require submission of data to demonstrate that system improvement processes correlate with a reduction of opioid prescribing and adverse effects. Implementation of the order sets meets specific parts of the criteria but not all necessary criteria. Thus, together with fulfillment of other criteria by the health system and medical director, the order set project resulted in an increase in MIPS reimbursement for the next calendar year.

At our institution, as providers become more accustomed to ordering from the ALTO order sets and gain confidence treating pain without the need for opioids, the implementation of further transitional steps can be facilitated. The philosophy of the project was to implement incremental projects one at a time rather than creating large-scale changes in order to maintain provider buy-in and not disrupt other aspects of the current patient care model. One opportunity for further enhancement of this project development could be the removal of opioid medications from the Quicklist and requiring providers to access them via a medication search. The objective of this would be to limit the ease of ordering opioids and encourage further reduction in overall opioid prescribing. During our implementation, opioids were not removed from the Quicklist due to provider pushback, including concerns about increased time to therapy for patients for whom prescribing an opioid would be appropriate and about provider dissatisfaction due to loss of convenience.

When evaluating which type of intervention to make within our institution, we identified institutions that had implemented treatment algorithms or incorporated additional stepwise guidance within order sets to standardize care for specific pain indications. Such interventions were not made within our institution; instead, the implemented order sets allowed providers to select therapy deemed clinically appropriate outside of an algorithm. The education that was provided as part of the order set implementation did not direct providers to select first-, second-, or third-line treatment options but rather provided details of what type of pain or combination of therapy may be appropriate for different types of pain within the clinical pearls section. Depending on data compiled during the initial review of order set implementation, if order set education and availability alone do not result in a trend towards opioid reduction and increased opioid alternative usage, then further prescribing recommendations and algorithm guidance can be built within the order sets.

As previously mentioned, ketamine was not included in the initial ALTO order sets due to concurrent project evaluation. While ketamine usage was not evaluated as part of the project described here, the concurrent project supported a similar goal of opioid reduction through its focus on ketamine as an analgesic. Following completion of the concurrent project evaluation, there may be a future opportunity to include ketamine in the ALTO order sets for convenience and to provide more comprehensive analgesic options. Additionally, as provider preferences change and new information on nonopioid analgesic options emerges, the order sets can be expanded to include therapies not already included. Previously discussed options may also be reviewed, with reconsideration for order set inclusion at a future time. Intravenous acetaminophen was not included in the order sets due to health-system restrictions on use of the medication due to its higher cost relative to alternative formulations. Due to the high level of support for inclusion of i.v. acetaminophen in the order set initiative expressed during grand rounds, future evaluations could lead to expansion of the health system restrictions to include a 1-time dose in the ED; however, this would likely require additional criteria prior to use, as it would not be a preferred first-line formulary option for all pain types.

Conclusion

The implementation of ALTO order sets within our institution's EHR helped to secure increased MIPS reimbursement relating to participation in ACEP's E-QUAL initiative. Additional objectives of order set implementation are to decrease prescribing of opioids for acute pain treatment, promote and optimize dosing of nonopioid analgesics, and further increase pharmacists' ED involvement.

Disclosures

The authors have declared no potential conflicts of interest.

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