



Predictors of availability of long-acting medication for opioid use disorder

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ARTICLE INFO

Keywords:

Opioid use disorder
Naltrexone
Buprenorphine
MOUD
Treatment
Health services

ABSTRACT

Background: The U.S. Food and Drug Administration has approved three long-acting medications for opioid use disorder (MOUD): extended-release naltrexone (XR-NTX) in 2010, a subdermal buprenorphine implant in 2016, and a depot buprenorphine injection in 2017. Long-acting MOUD options may improve adherence while reducing diversion, but their availability compared to daily-dosing MOUD has not been well-characterized. The objective of this analysis was to characterize the availability of long-acting MOUD in substance use disorder treatment settings in the United States.

Methods: Using the 2017 National Survey on Substance Abuse Treatment Services (N-SSATS) and state-level opioid overdose mortality, we examined associations between state- and facility-level factors and offering long-acting MOUD, which included XR-NTX and the buprenorphine implant. We constructed multivariable mixed logistic regression models for both types of long-acting MOUD.

Results: Nationwide, 38% (n = 5141) of substance use treatment facilities provided any kind of MOUD (daily or long-acting). Of these, 62% provided XR-NTX, whereas only 3% offered the buprenorphine implant. Facilities in the East North Central, East South Central, West North Central and Mountain regions had higher odds of offering XR-NTX, as did federally-funded facilities, and facilities in states with the highest opioid overdose mortality rates.

Conclusions: In 2017, XR-NTX was available at most of the minority of facilities offering MOUD, but the buprenorphine implant was not. Increasing the availability of MOUD, including long-acting options, is necessary to address unmet need for opioid use disorder treatment.

1. Introduction

Opioid use disorder (OUD) is a major cause of morbidity and mortality in the United States (Ahmad et al., 2019; Han et al., 2017). Medications for OUD (MOUD) reduce relapse to illicit opioids and overdose deaths, but most OUD patients do not receive treatment or drop out quickly (Goodbar and Hanlon, 2018; Haight et al., 2019; Jones et al., 2015; Knudsen et al., 2011). The U.S. Food and Drug Administration (FDA) approved daily oral buprenorphine and methadone in 2002 and 1974, respectively (Alderks, 2017). Since then, the FDA has approved several long-acting MOUD, but the availability and utilization of long-acting MOUD has not been well-described. We investigated the availability at U.S. substance use disorder (SUD) treatment settings of two long-acting MOUD: extended-release injectable naltrexone (XR-NTX, FDA-approved in 2010) and the six-month subdermal buprenorphine implant (FDA-approved in 2016). Although the FDA approved a monthly depot buprenorphine injection in November of 2017, data on this modality were not available for the current analysis.

There are distinct ways long-acting MOUD could improve treatment for OUD. Among them: 1) stabilize dosing, 2) enhance adherence, 3) reduce diversion, 4) increase patient choice, 5) make treatment more accessible to patients who are far from treatment providers, or have difficulty attending daily or weekly visits, 6) enable MOUD providers to carry larger caseloads (Barnwal et al., 2017). As with any new treatment modality, the extent to which these potential benefits may be realized depends partly on the reach (availability) and adoption (utilization) of long-acting MOUD (Glasgow et al., 1999).

The objectives of this analysis were to characterize the availability of long-acting MOUD and identify geographic, health services, and OUD-related correlates of offering long-acting MOUD among SUD treatment facilities offering any kind of MOUD. We expected that the higher cost of long-acting MOUD relative to methadone or daily buprenorphine would lead it to be offered more often in privately-funded facilities (Barnwal et al., 2017). Medicaid expansion led to an increase in insurance coverage for people with substance use disorders (SUD), increased the proportion of SUD clients covered by Medicaid, and

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<https://doi.org/10.1016/j.drugalcdep.2019.107586>

Received 16 May 2019; Received in revised form 7 August 2019; Accepted 8 August 2019

Available online 25 September 2019

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Table 1

Factors associated with providing long-acting medication for opioid use disorder (MOUD), among sites offering any MOUD in the National Survey of Substance Abuse Treatment Services, 2017 (n = 5, 141).

	Buprenorphine implant ^a			Injectable naltrexone ^a		Total ^b		
	n	%	χ^2	n	%	χ^2	n	%
<i>U.S. Census Division</i>			p = 0.01			p < 0.001		
New England (ME, NH, VT, RI, CT)	21	5%		282	61%		465	9%
Mid Atlantic (NY, PA, NJ)	19	2%		635	62%		1,028	20%
South Atlantic (WV, MD, Wash. DC, DE, VA, NC, SC, GA, FL)	34	3%		560	57%		974	19%
East North Central (WI, MI, IL, IN, OH)	14	2%		520	71%		733	14%
East South Central (KY, TN, MS, AL)	4	2%		159	66%		242	5%
West North Central (ND, SD, MN, IA, NE, KS, MO)	9	3%		221	72%		305	6%
West South Central (TX, OK, AR, LA)	5	2%		114	44%		258	5%
Mountain (MT, ID, WY, NV, UT, CO, AZ, NM)	19	4%		336	74%		452	9%
Pacific (HI, AK, WA, OR, CA)	27	4%		365	56%		653	13%
State expanded Medicaid prior to 2017	111	3%	p = 0.5	2,288	66%	p = 0.1	3,464	68%
<i>State opioid overdose mortality rate, 2017</i>			p = 0.01			p < 0.001		
First quartile (2.6 - 8.5 cases/100,000 population)	54	4%		720	55%		1,309	26%
Second quartile (8.6 - 14.6 cases/100,000 population)	37	3%		842	68%		1,247	24%
Third quartile (14.8 - 18.2 cases/100,000 population)	24	2%		793	60%		1,311	26%
Fourth quartile (18.4 - 43.9 cases/100,000 population)	37	3%		837	67%		1,243	24%
SAMHSA certified Opioid Treatment Program	14	1%	p < 0.001	376	29%	p < 0.001	1,311	26%
Facility serves only OUD clients	17	2%	p = 0.01	184	18%	p < 0.001	1,014	20%
Outpatient treatment offered	115	3%	p = 0.08	2,541	61%	p < 0.001	4,144	81%
Residential treatment offered	55	4%	p = 0.002	972	75%	p = 0.001	1,289	25%
Hospital inpatient treatment offered	8	2%	p = 0.04	336	64%	p = 0.6	528	10%
<i>Funding</i>			p < 0.001			p < 0.001		
Private for-profit	94	4%		1,137	54%		2,109	41%
Private non-profit	54	2%		1,624	67%		2,424	47%
Governmental	4	1%		431	75%		577	11%
Uses sliding scale fee	70	3%	p = 0.1	1,816	67%	p < 0.001	2,722	53%
Methadone offered (oral)	13	1%	p < 0.001	344	27%	p < 0.001	1,265	25%
Buprenorphine with naloxone (oral)	146	4%	p < 0.001	2,286	62%	p = 0.2	3,695	72%
Buprenorphine without naloxone (oral)	140	6%	p < 0.001	1,622	67%	p < 0.001	2,438	48%
Only long-term MAT	4	1%	p < 0.001	791	100%	p < 0.001	792	15%
Total	152	3%		3192	62%		5,110	100%

^a Row percentages.

^b Column percentages. Due to missing values, 32 observations were excluded in the multivariable model.

influenced treatment for psychiatric comorbidities in SUD treatment settings (Abraham et al., 2017; Andrews et al., 2019; Shover et al., 2019); we therefore hypothesized it may also have affected which MOUD options SUD treatment facilities offered. We hypothesized that availability of long-acting MOUD may have regional differences, as have been documented in SUD, Medicaid spending, and healthcare generally (Knudsen, 2015; Kronick and Gilmer, 2012; Wennberg and Gittelsohn, 1973).

2. Materials and methods

The National Survey on Substance Abuse Treatment Services (N-SSATS) is a nationally representative annual survey of U.S. SUD treatment facilities. Using N-SSATS 2017, we measured the availability of long-acting MOUD among sites that provided any MOUD. Covariates of interest included opioid overdose mortality, region, Medicaid expansion, treatment setting, and facility characteristics. Facility-level variables were obtained from survey responses, and facilities were nested within states. State opioid overdose mortality rates for 2017, including overdoses of any intent involving heroin, opium, methadone, other opioids, or other synthetic narcotics (e.g., fentanyl), were obtained from the Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) and grouped by quartile (Centers for Disease Control and Prevention, 2018). States were classified as having expanded Medicaid if the expansion date was before January 1, 2017 (Kaiser Family Foundation, 2019). States were grouped by U.S. Census divisions.

Bivariate associations between the variables of interest and offering XR-NTX, the buprenorphine implant, or any combination thereof, were examined through chi-square tests. Multivariable mixed logistic regression models were constructed to examine associations between

state- and facility-level factors and providing long-acting MOUD. Because this project used only publicly available data, it was exempt from Stanford University's institutional review board review.

3. Results

A minority (38%, n = 5141) of the 13,578 SUD facilities surveyed in N-SSATS 2017 offered any kind of MOUD (Table 1). Nearly two thirds of these (62%, n = 3192) offered XR-NTX, whereas only 3% (n = 152) offered the buprenorphine implant. Availability of the buprenorphine implant differed regionally, with highest proportion of facilities offering it in New England (5%, n = 21). XR-NTX was most likely to be offered in the Mountain (74%, n = 336), West North Central (72%, n = 221), and East North Central (71%, n = 520) regions.

In the multivariable models, offering XR-NTX was associated with geographic and health services factors, whereas offering the buprenorphine implant was significantly associated with factors related to funding and types of treatment offered. Specifically, sites in the East North Central (adjusted odds ratio 1.6, 95% confidence interval 1.1, 2.2), East South Central (AOR 1.7, 95% CI 1.1, 2.6), West North Central (AOR 2.2, 95% CI 1.3, 3.5), and Mountain (AOR 1.9, 95% CI 1.2, 3.0) regions each had higher odds of offering XR-NTX compared to sites in New England (Table 2). States that expanded Medicaid prior to 2017 also had higher odds (AOR 1.3, 95% CI 1.0, 1.6) of offering XR-NTX compared to those that expanded Medicaid later or not at all.

Compared to private, for-profit facilities, both private non-profit and government-funded facilities had lower odds of offering the buprenorphine implant, whereas government-funded facilities had higher odds of offering XR-NTX. The relationship between state opioid overdose mortality and offering XR-NTX was non-linear. The second (8.6–14.6 cases/100,000) and fourth quartile (14.8–18.2 cases/

Table 2

Multivariable mixed logistic regression of factors associated with providing long-acting medication for opioid use disorder (MOUD), among sites offering MOUD in the National Survey of Substance Abuse Treatment Services, 2017 (n = 5, 141).

	Buprenorphine implant	Extended-release naltrexone
<i>U.S. Census Division</i>		
New England (ME, NH, VT, RI, CT)	–	–
Mid Atlantic (NY, PA, NJ)	0.5 (0.2, 1.0)	1.1 (0.8, 1.4)
South Atlantic (WV, MD, Wash. DC, DE, VA, NC, SC, GA, FL)	0.6 (0.2, 1.6)	1.1 (0.7, 1.6)
East North Central (WI, MI, IL, IN, OH)	0.5 (0.2, 1.2)	1.6 (1.1, 2.2)
East South Central (KY, TN, MS, AL)	0.3 (0.1, 1.0)	1.7 (1.1, 2.6)
West North Central (ND, SD, MN, IA, NE, KS, MO)	0.4 (0.1, 2.8)	2.2 (1.3, 3.5)
West South Central (TX, OK, AR, LA)	0.3 (0.1, 1.0)	1.0 (0.6, 1.6)
Mountain (MT, ID, WY, NV, UT, CO, AZ, NM)	0.7 (0.2, 2.0)	1.9 (1.2, 3.0)
Pacific (HI, AK, WA, OR, CA)	0.4 (0.1, 1.3)	1.1 (0.7, 1.7)
State expanded Medicaid prior to 2017	1.1 (0.7, 1.8)	1.3 (1.0, 1.6)
<i>State opioid overdose mortality rate, 2017</i>		
First quartile (2.6 - 8.5 cases/100,000 population)	–	–
Second quartile (8.6 - 14.6 cases/100,000 population)	0.6 (0.3, 1.1)	1.6 (1.2, 2.1)
Third quartile (14.8 - 18.2 cases/100,000 population)	0.4 (0.2, 1.0)	1.2 (0.8, 1.6)
Fourth quartile (18.4 - 43.9 cases/100,000 population)	0.5 (0.2, 1.3)	1.8 (1.3, 2.6)
SAMHSA certified Opioid Treatment Program	0.4 (0.1, 2.8)	0.9 (0.4, 1.7)
Facility serves only OUD clients	1.1 (0.6, 2.3)	0.1 (0.1, 0.2)
Outpatient treatment offered	1.1 (0.6, 1.8)	1.8 (1.4, 2.3)
Residential treatment offered	1.3 (0.8, 2.2)	1.7 (1.4, 2.1)
Hospital inpatient treatment offered	0.4 (0.2, 0.9)	0.8 (0.6, 1.0)
<i>Funding</i>		
Private for-profit	–	–
Private non-profit	0.5 (0.3, 0.7)	0.9 (0.8, 1.1)
Governmental	0.2 (0.1, 0.5)	1.5 (1.2, 1.9)
Uses sliding scale fee	1.0 (0.7, 1.4)	1.0 (0.9, 1.3)
Methadone offered (oral)	0.6 (0.1, 5.4)	0.4 (0.2, 0.8)
Buprenorphine with naloxone (oral)	2.7 (1.2, 6.5)	0.4 (0.3, 0.4)
Buprenorphine without naloxone (oral)	8.7 (4.7, 16.1)	2.0 (1.7, 2.3)
Only long-term MOUD		
Total		

100,000) had higher odds of offering XR-NTX than the lowest quartile (2.6–8.5 cases/100,000), but the third quartile (14.8–18.2 cases/100,000) had odds statistically indistinguishable from the lowest quartile. Other MOUD offered at the facility was also significantly associated with offering either of the long-acting MOUDs. Offering daily buprenorphine without naloxone was associated with higher odds of offering the buprenorphine implant (AOR = 8.7, 95% CI 4.7, 16.1) and XR-NTX (AOR = 2.0, 95% CI 1.7, 2.3), whereas offering buprenorphine with naloxone was associated with lower odds of offering XR-NTX (AOR = 0.4, 95% CI 0.3, 0.4) and higher odds of offering the buprenorphine implant (AOR = 2.7, 95% CI 1.2, 6.5).

4. Discussion

Consistent with findings from earlier years, in 2017 most U.S. SUD treatment facilities did not offer any MOUD (Mojtabai et al., 2019). Of the 38% of facilities that offered any MOUD, most offered XR-NTX, whereas the buprenorphine implant was rarely offered. Low availability of the buprenorphine implant in the 1.5 years post-FDA approval likely indicates low levels of early adoption. That XR-NTX was more commonly offered in the central U.S. (specifically, East North Central, East South Central, West North Central and Mountain regions), after accounting for higher odds in states with Medicaid expansion, demonstrates regional differences in MOUD choices.

One of the most promising aspects of long-acting MOUD is how it allows individuals to take an action on one day that can support recovery for a month or longer. This contrasts with regimens that may require a person to attend a methadone clinic daily for supervised dosing or take oral buprenorphine at least once a day. Aspects of stabilized dosing may appeal to some patients whereas others will prefer the daily regimen; having options can thus facilitate recovery (U.S. Department of Health and Human Services (HHS) Office of the Surgeon General, HHS, 2018). Choice between treatment options is highly

valued in other medical domains, such as HIV treatment and prevention, contraception, and healthcare generally (Elwyn and Edwards, 2016; Kowal et al., 2018; Shacklett et al., 2019).

Despite these promising aspects, the roll-out of XR-NTX has had challenges. Data collected in 2011 through 2013, prior to the implementation of the Affordable Care Act and Medicaid expansion, showed that 19 states excluded XR-NTX from the Medicaid preferred drug list and 12 required prior authorization (Mark et al., 2015). More recently, a nationwide study comparing time to discontinuation for different MOUD found that about half of people prescribed XR-NTX discontinued after the first 30 day prescription, compared to about 30% of those prescribed oral buprenorphine with naloxone (Morgan et al., 2018). However, 30-day discontinuation was worse for oral naltrexone (70%), suggesting that XR-NTX offers some advantage in retaining patients who prefer an opioid antagonist treatment, despite its higher cost per dose. Wider availability of XR-NTX may also improve retention in programs that bar patients from receiving partial opioid agonist (buprenorphine) or full agonist (methadone) treatment (e.g., some SUD treatment in criminal justice settings). Although real-world retention data for the buprenorphine implant are not yet available, clinical trials have found retention outcomes comparable to those of sublingual buprenorphine (Rosenthal et al., 2016, 2013). If the pragmatic results are similar, long-acting buprenorphine may address shortcomings of XR-NTX observed outside of clinical trials. Regardless, both will be needed because people with SUD have diverse preferences for care.

Several factors may explain the low availability of the buprenorphine implant. Currently, the buprenorphine implant is approved for use in patients who have been stable on oral buprenorphine for six months or more. It is only approved to be used for two six-month periods for a single individual, which limits its utility as a long-term maintenance strategy. Some of the limited availability may be due to these restrictions, and the narrower range of patients who fit the prescribing guidelines. If future studies establish the safety of recurring

implants, these guidelines may be relaxed. High initial cost to treatment providers to stock the buprenorphine implant, as well as high cost to patients once prescribed, may contribute to low availability of this modality. Some of these barriers should be less severe for the depot buprenorphine injection. Notably, the data used in this analysis were collected before the State Targeted Response (STR) grants were awarded to states with high opioid overdose mortality to address the opioid crisis. They thus provide a baseline for future research to examine the impact of STR grants on expanding capacity to deliver MOUD generally and specifically newer MOUD modalities.

4.1. Limitations

Because N-SSATS does not report prescribing numbers or patterns at clinics where long-acting MOUD was offered, we could not assess the degree to which availability reflects utilization. N-SSATS does not include independent clinics or primary care offices unaffiliated with a substance use treatment program, which may have led this study to underestimate the availability of the buprenorphine implant, which like oral buprenorphine can be provided in such settings. A final limitation of the study is that XR-NTX is also FDA-approved for treatment of alcohol use disorder, but N-SSATS does not report whether a facility offers the medication only for this indication or for OUD as well. If facilities restrict XR-NTX to alcohol use disorder the data reported here would overestimate availability of long-acting MOUD.

4.2. Conclusions

In 2017, most U.S. substance use disorder treatment programs did not offer MOUD. Among those that did provide MOUD, the finding that two-thirds offered XR-NTX is encouraging for patients who may benefit from long-acting MOUD. Low availability of the buprenorphine implant highlights the need for studies examining how both patient interest and provider capacity may influence the effectiveness of this and other new modalities outside clinical trials.

Role of funding source

The funding sources had no role in design, conduct, or interpretation of the research.

Contributors

CLS conceptualized, designed and conducted the analysis, and drafted the manuscript. KH contributed to interpreting results and critically revised the manuscript.

Declaration of Competing Interest

No conflicts of interest to declare.

Acknowledgements

CLS was supported by the National Institute on Drug Abuse of the National Institutes of Health under award number T32DA035165. KH was supported by a Senior Career Research Scientist Award from the Veterans Health Administration and the Esther Ting Memorial Professorship at Stanford University. CLS and KH were supported by the Wu Tsai Neurosciences Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the authors' employers. We thank Noel Vest, PhD for reviewing a draft of the manuscript. The authors have no conflicts of interest to declare.

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