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Update on Barriers to Pharmacotherapy for Opioid Use Disorders

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Abstract
Purpose of Review The recent heroin and prescription opioid misuse epidemic has led to a sharp increase in the number of opioid overdose deaths in the USA. Notwithstanding the availability of three FDA-approved medications (methadone, buprenorphine, and naltrexone) to treat opioid use disorder, these medications are underutilized. This paper provides an update from the recent peer-reviewed literature on barriers to the use of these medications.
Findings These barriers are interrelated and can be categorized as financial, regulatory, geographic, attitudinal, and logistic. While financial barriers are common to all three medications, other barriers are medication-specific.
Summary The adverse impact of the current opioid epidemic on public health can be reduced by increasing access to effective pharmacotherapy for opioid use disorder.

Keywords Methadone · Buprenorphine · Naltrexone · Pharmacotherapy for opioid use disorder · Barriers to drug abuse treatment

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Introduction

Beginning at the turn of the twenty-first century, the prevalence of heroin use and non-medical use of prescription opioids in the USA increased and has spread to largely non-urban, white populations [1, 2]. The epidemic has been associated with a 200% increase in opioid overdose deaths between 2000 and 2014, with 28,647 such deaths in 2014 alone [3]. The increase in opioid injection has also raised concerns about the spread of HIV and HCV infection [4].

Three FDA-approved medications can be employed to treat patients with what is now termed opioid use disorder (OUD) [5]. The opioid agonist methadone is available for the treatment of OUD solely through specially regulated Opioid Treatment Programs (OTPs). It is the most studied of the three medications and has been found in clinical trials to be more effective than non-medication approaches in retaining patients in treatment and in reducing heroin use [6]. Buprenorphine is a partial opioid agonist that can be provided through OTPs as well as through physicians who have completed an approved 8-h training or have specialty addiction board certification and have obtained a federal "waiver" [7]. Clinical trials have shown that buprenorphine treatment is superior to placebo in retaining patients in treatment and in reducing illicit opioid use [8]. There is also evidence that treatment with either of these two agonist medications is associated with reduced risk of overdose from illicit opioids [9–14]. The opioid antagonist naltrexone is available in both oral and extended-release injectable form (XR-NTX) with an effective duration of approximately 30 days. XR-NTX was shown in a clinical trial in Russia to be superior to placebo injection in reducing illicit heroin use [15] and in an open-label trial in the USA to be superior to treatment-as-usual (without medication) in reducing illicit opioid use

among adults with criminal justice involvement [16]. The use of naltrexone, unlike methadone and buprenorphine, has no special regulatory constraints.

Expanding access to pharmacotherapy for OUD is an important part of the multipronged effort currently underway in the USA to address the nation's opioid epidemic [17]. There is a substantial gap between the number of individuals in need of OUD treatment and the capacity to provide agonist medications [18••]. Indeed, the majority of the nation's OTPs is at 80% or greater of their full capacity, and if all buprenorphine-waivered physicians in the USA were at full capacity, there would remain a treatment gap in excess of 1 million out-of-treatment individuals [18••]. In terms of the specialty substance use treatment sector of the 14,152 treatment facilities operating in the USA in 2014, only 9% were OTPs, 23% provided buprenorphine, and 14% offered XR-NTX [19]. While clearly not everyone with an opioid use disorder will seek treatment and not all will seek treatment with medications, there are waiting lists for treatment at some OTPs [20]. There is a need to expand access to pharmacotherapy, yet barriers exist to treatment expansion. This paper provides an update on the barriers to the use of these medications based on recent peer-reviewed literature. These barriers, although interrelated, can be categorized as financial, regulatory, geographic, attitudinal, and logistical.

Financial Barriers

In the USA, the treatment of OUD with medications is available in a robust private for-profit sector fee-for-service delivery system. For example, about half of the nation's OTPs are for-profit organizations [21]. Generally, treatment is available in these programs if they are within driving distance and the patient can pay out-of-pocket or has insurance that the programs accept. For those who cannot pay out-of-pocket, there are a number of government-subsidized grants and insurance programs. However, coverage under these programs varies widely from state to state. Financial barriers to delivering pharmacotherapy for OUD exist [22, 23] and can cut across both opioid agonist and antagonist treatment.

Medicaid, a federal health insurance program for the disabled and for low-income individuals, is an important funder of treatment [24–26]. States have a great deal of latitude in determining Medicaid eligibility, as well as whether their Program will pay for substance use treatment, which treatments it will pay for, and which medications will be covered at what rates and under what restrictions. In 2006, the fourth year following buprenorphine's approval for the treatment of OUD, it was found that states' Medicaid Program coverage of buprenorphine was significantly associated with its use in outpatient treatment programs [22]. From 2004 through 2013, the number of states whose Medicaid Programs covered both methadone and buprenorphine rose from 21 to 32. However, by 2013, five states covered neither medication, and eight states did not cover methadone treatment [27••].

The lack of Medicaid coverage for opioid agonist treatment could make this treatment out of reach for low-income individuals unless such treatment can be provided through the federal Substance Abuse Prevention and Treatment (SAPT) block grant [28, 29] or local funding [23]. Saloner and colleagues [30••] examined the impact of state Medicaid and SAPT block grant funding for methadone on the utilization of methadone treatment among Medicaid enrollees. They found that, adjusting for demographic and substance use history variables, the rates of OUD-diagnosed patients with Medicaid receiving methadone treatment were 17% in states with neither block grant nor Medicaid coverage for methadone, 30% in states with only block grant coverage, and 45% in states with Medicaid coverage. These findings have important implications for reducing barriers to treatment because a number of states with grave opioid problems have not expanded Medicaid under the Affordable Care and Patient Protection Act, and some states that did expand Medicaid did not include methadone treatment in their benefits package [30••].

While Medicaid expansion and coverage for OUD pharmacotherapy can reduce barriers to access, they are not sufficient. Medicaid managed care companies' policies can create barriers to access. For example, Burns and coworkers [27••] documented a threefold increase in requiring pre-authorization for buprenorphine treatment. Other policy changes included implementing copayments and requiring counseling beyond that provided by the physician. Requiring pre-authorization can deter physicians from providing treatment because of the delays and administrative burdens of dealing with bureaucracy. Copayments can make treatment beyond the reach of some patients. Finally, requiring additional counseling increases patient burden because they must obtain services that they may not want or may not be able to access. Indeed, a recent study by Hutchinson and coworkers [31•] among family practitioners in rural Washington State who completed buprenorphine training found that the most frequently endorsed barrier to providing buprenorphine was the lack of counseling availability in the state, whose Medicaid Program required counseling to accompany buprenorphine treatment. Importantly, such policies do not appear to be supported by the extant research evidence that, to date, has found no apparent clinical benefit to adding counseling to buprenorphine treatment beyond that provided by the treating physician through medical management [32–34].

In the context of an intervention to increase the use of opioid treatment medications within a health plan and their associated treatment programs in three Mid-Atlantic states, Alanis-Hirsh and colleagues [35•] gathered qualitative data

from key treatment center personnel, health plan managers, employees of the manufacturer of XR-NTX, and their technical assistance contractor. As with the findings regarding buprenorphine described above, this study found several payer policy barriers to providing XR-NTX. Some payers required prior authorization for XR-NTX and some required patients to "fail" non-medication treatment prior to authorizing the medication. Some insured patients who had high copayments or deductibles may have found the medication cost prohibitive, and at retail cost of about US$1200 per monthly dose (not counting provider charges), it was out of reach for the uninsured.

Surprisingly, providing XR-NTX can also be cost prohibitive to providers if the health plan requires that the provider buys the medication for a particular patient prior to its administration. Such plans permit the provider to invoice the health plan only after the medication is administered to the patient. This arrangement puts the provider at risk for the cost of the medication should it go unused or should the plan refuse to reimburse the provider.

Regulatory Restrictions

In the USA, in contrast to those in other countries, physicians who wish to treat OUD (but not pain) with buprenorphine must meet several special requirements. First, there is a training requirement such that only physicians with addiction specialty board certification or who have completed an 8-h course in the treatment of OUD, and now nurse practitioners and physician's assistants who have completed an extended course, are eligible to apply for a waiver to prescribe this medication. However, even after receiving the waiver, there are limits placed on the number of patients that can be treated by the waivered prescribers based on how long they have had the waiver. This policy is, for example, in contrast to France, where any licensed physician can prescribe buprenorphine and where it was reported that an increase in buprenorphine treatment was associated with a drop in overdose deaths [9].

The study in Ohio by Molfenter and colleagues [23] described above found that the federal cap on the number of patients that could be treated with buprenorphine per physician was a barrier to expanding treatment access. At the time of that study, waivered physicians were limited to 30 buprenorphine patients at any one time during their first year with the waiver and up to 100 patients thereafter [7]. Since publication of that paper, a final rule was published in August 2016 to permit waivered physicians, under certain conditions, to treat up to 275 patients [36]. This may alleviate capacity shortfalls in some situations.

OTPs are highly regulated and must abide by federal and state regulations. Additionally, local regulations such as those pertaining to zoning can interact with attitudes held by politicians and local communities to restrict the opening of programs or how many patients they can treat. Some zoning restrictions have been determined to be discriminatory under the Americans with Disabilities Act [37]. Federal and state regulations requiring counseling to accompany opioid agonist treatment can be a barrier and lead to waiting lists when there are an inadequate number of counselors. Interim methadone treatment, providing methadone without counseling to individuals on OTP waiting lists, is permitted under federal regulations and has been shown to be superior to waiting list in terms of treatment entry and suppressing illicit opioid use [38, 39]. Sigmon and colleagues [20] piloted interim buprenorphine through self-administration via a computerized device that released one dose per day in the patient's home, permitting clinic visits every other week (rather than daily). In addition, patients were asked to report daily through an interactive voice response program. This pilot study found high levels of adherence, acceptability, and negative urine drug screening tests and is undergoing further testing.

Geographic Barriers

There is geographic variation in access to OTPs in the USA [40]. There have recently been several studies examining the relationship between geographic location and availability of buprenorphine-waivered physicians [41–42, 43••]. In a nationwide study, Knudsen [41] examined the supply of waivered physicians as a function of the state's macro environment, health-related resources, and demand for OUD treatment. At the end of 2013, there were 23,629 US physicians who had the waiver to prescribe buprenorphine, of whom 29% were approved to treat up to 100 patients. There were 8.0 (SD = 5.2) waivered physicians per 100,000 people with significantly higher rates in the northeast compared to those in other regions. A multivariate regression analysis found that state-level availability of Medicaid coverage and the number of OTPs and other drug treatment programs were associated with higher rates of waivered physicians. Furthermore, states with higher rates of illicit opioid overdose deaths appeared to have higher rates of waivered physicians, indicating that the medical profession may be responding to the public health need in their community, although there may be other interacting factors at play involving financing and other issues.

Stein and colleagues [43••] used SAMHSA and US census data from 2008 to 2011 to examine the number of waivered physicians per county population as part of a study examining the influence of state policies on the availability of buprenorphine prescribers. Although the mean number of physicians per county increased from 4.8 (SD = 19.5) in 2008 to 7.0 (SD = 27.7) in 2011, these increases were not evenly distributed across the counties. Just over half of the

counties had no waivered physicians in 2008, although that percentage had decreased to 43.4% by 2011. Furthermore, the distribution of waivered physicians was skewed. Thus, there is substantial room to increase the number of waivered physicians in many counties throughout the USA. Importantly, this study found that counties located in states with either Medicaid or other state funding for buprenorphine treatment had the highest rates of waivered physicians, highlighting the importance of funding.

Geographic Barriers Cited by Physicians in Rural Areas

Physicians have indicated that barriers to prescribing buprenorphine include a lack of institutional support, fear of being overwhelmed by the number of patients, and concerns that their patients would be unable to afford the medication [44, 45]. Given the uneven geographic distribution of buprenorphine-waivered physicians and the lack of OTPs in less populated areas of the country, it is of some importance to understand the barriers perceived by family physicians in rural states to prescribing this medication. Two studies shed some light in this area.

In the paper mentioned above by Hutchinson and coworkers [31•], family practitioners in rural Washington State who did not prescribe buprenorphine after completing waiver training or did not apply for the waiver indicated a lack of office support, time constraints, a lack of confidence in their ability of treat OUD, and resistance from practice partners as barriers to prescribing. In addition, DeFlavio and colleagues [46] conducted an anonymous Web-based survey among 108 family physicians in New Hampshire and Vermont, the majority of whom (97) were buprenorphine non-prescribers. The most important barriers noted by these physicians were inadequately trained staff (88%), lack of time (80%), and inadequate payment (52%).

Attitudinal Barriers

People in all walks of life, including physicians, criminal justice professionals, individuals with OUD in and out of treatment, recovering people, and even treatment providers, can have philosophical opposition to or negative attitudes toward pharmacotherapy [35•, 47–53]. A qualitative study in Ohio of county board leadership and addiction treatment providers found that negative attitudes toward opioid agonist treatment, even in counties with additional funding for such treatment, were associated with lower buprenorphine use rates compared to those counties in which respondents had more positive attitudes [23]. Negative attitudes toward XR-NTX for "philosophical" reasons on the part of some substance abuse treatment programs in Washington State were also found to be a barrier [35•].

Attitudinal Barriers in Criminal Justice Settings

There are many individuals with OUD in the criminal justice system [54] where pharmacotherapy has been underutilized [47]. Jails in the USA commonly discontinue opioid agonist treatment for detained individuals who are enrolled in treatment at the time of arrest, exposing them to high risk of relapse and overdose death upon release [55]. Interrupting methadone treatment was found in a randomized trial to result in lower rates of returning to treatment after release compared to maintaining methadone during detention [55]. Opioid-addicted individuals report that fear of having their methadone interrupted during detention is a reason not to enter treatment [56, 57].

Drug courts have played an increasing role in the USA since their founding in 1989. By 2012, there were 2734 such courts operating in every state [58]. In a representative survey of primarily drug court coordinators and administrators (84%), the majority of whom were non-physician clinicians, half the respondents indicated that opioid agonist medications are not available under any circumstances. Only 40% reported that participants already receiving opioid agonist treatment were permitted to continue treatment [59••].

The reasons that drug courts did not permit the use of these medications varied to some extent by medication. For buprenorphine, the most common barriers cited were the following: cost (43%), clients were withdrawn from illicit opioids prior to entering the court (42%), inadequate supply of providers (41%), and court policies (40%). For methadone, the most common barriers were the following: court policies (52%), not being recommended by the local provider (49%), the client being withdrawn prior to entry into the court (45%), and a perceived risk of medication diversion (36%).

These findings are surprising for several reasons. Drug courts were created as a therapeutic alternative within the criminal justice system, yet many report barring FDA-approved medications with proven effectiveness [6, 8]. In that regard, it is unfortunate that a key barrier to their use stems from treatment providers' recommendations. This situation could reflect the general lack of support for pharmacotherapy among some providers, or it could reflect a selection bias in which drug courts prefer to work with providers who do not support the use of medications.

Drilling down, Matusow et al. [59••] examined attitudes and knowledge among non-physician drug court staff survey respondents regarding the use of these medications. Overall, more than 40% of respondents agreed that buprenorphine and methadone reduce relapse and a similar percentage reported being uncertain of this. This finding potentially shows room for educating drug court staff regarding the effectiveness of medications.

Logistical Barriers

Logistical barriers to receiving pharmacotherapy often stem from an interaction between regulatory restrictions described above, financial restrictions, lack of information about where to seek care, and those related to the formulation of the medication (e.g., XR-NTX).

Intravenous heroin users are an important population to attract into treatment. Previous research has examined approaches to engage needle exchange participants in methadone treatment [60–62]. Fox and colleagues [63] interviewed 93 needle exchange participants in New York who had heard of buprenorphine to determine their perceived barriers to receiving buprenorphine treatment. Half of the participants (51%) reported not knowing where they could enter treatment. Less frequently mentioned barriers included lack of money (33%) and transportation (28%). The subset of participants who had versus who had not used illicit buprenorphine was significantly more likely to not know where to get treatment, and 83% of the former group indicated that they would be very likely to enroll in buprenorphine treatment if it was offered through the needle exchange.

XR-NTX has been much less frequently used than opioid agonists [24], and barriers to its use have been less studied. In the qualitative study by Alanis-Hirsh and coworkers [35•] described above with treatment staff, health plan managers, employees of the manufacturer of XR-NTX, and their technical assistance contractor, barriers to the use of XR-NTX appeared to exceed those of buprenorphine, despite the lack of regulatory barriers for XR-NTX. Several formulation-related barriers included the need to ship XR-NTX from specialty pharmacies under refrigerated conditions and to be refrigerated at the treatment site. The dose must be assembled after 45 min of warming at room temperature by mixing the diluent and medication powder and drawn up in a syringe provided with the medication. Providers noted that this requires a special ordering process that must be managed and choreographed to warm the mixture to room temperature and deliver the intramuscular injection shortly thereafter. These logistics were reported to sometimes lead patients to leave prior to receiving their dose. An additional barrier was the recommended 7–10 days of opioid abstinence prior to administration to avoid precipitated withdrawal. This period of opioid abstinence was reported to be difficult to achieve on an outpatient basis and challenging to achieve as an inpatient because the payer may be reluctant to approve such a long residential treatment stay. Promising new approaches to decreasing the time between opioid use and initiation of XR-NTX have recently been tested [64, 65]. Sullivan and coworkers found that outpatients could be started on XR-NTX 7 days sooner using a rapid induction process compared to patients following a standard buprenorphine dose taper with a 7-day abstinence period. The more rapid approach entailed providing one dose of buprenorphine, followed by daily oral doses of naltrexone starting at only 1 mg and gradually increasing each day to 25 mg on the seventh day. Such rapid induction approaches could be used by specialty providers to reduce an important logistical barrier to the use of XR-NTX.

Conclusions

The current epidemic of opioid use and overdose death in the USA highlights the importance of reducing the regulatory, geographical, attitudinal, and logistical barriers to prompt access to proven pharmacotherapies including methadone, buprenorphine, and naltrexone. In some cases, there are multiple barriers and overcoming one is not sufficient to improve access. For example, providing block grant funding may not necessarily reduce the geographic barrier to opening an OTP when the number of potential patients is too small to make such a program economically feasible.

Funding for pharmacotherapies is uneven from state to state. States that did not expand Medicaid through the Affordable Care Act or do not cover methadone treatment through Medicaid or their block grant have limited access to care for low-income populations [30••]. As private for-profit OTPs expand in states with poor coverage for the indigent, such care is available for individuals with means but not for those who cannot afford it [66]. Even in states with Medicaid coverage for treatment, restrictive managed care policies, such as preauthorization and copayments, can serve as barriers to pharmacotherapy access [27••]. In some states, constraints not grounded in research evidence, such as requiring counseling to receive buprenorphine beyond that provided by a physician, can also serve as a barrier [27••]. Financial barriers can be overcome if states are willing to take action by expanding their Medicaid Program, covering all three medications for OUD, discouraging managed care organizations to erect further administrative barriers, and using federal block grant dollars to fill the gaps.

Unlike naltrexone, which can be prescribed by any licensed medical practitioner, methadone and buprenorphine have regulatory constraints. As described above, methadone treatment for OUD (unlike for pain) can only be provided through specially licensed OTPs which must deliver counseling, urine testing, and directly observed administration of methadone. When lack of OTP counselors leads to waiting lists, interim methadone treatment may be useful to provide effective treatment during the wait for admission to the full bundle of services [38]. Because of cost, economies of scale, and challenges for patients to travel long distances, there are limited numbers of OTPs in rural areas. In many countries outside the USA, primary care physicians can prescribe methadone and patients receive their medication through pharmacies [67]. Such arrangements could increase access to methadone treatment and are permissible under the federal OTP regulations

through the use of "medication units" in existing pharmacies or physician offices attached administratively to an OTP [68].

Buprenorphine has its own distinct regulatory constraints, but they are far less burdensome than those for methadone treatment. Its additional federal training requirements and a cap on the number of patients a physician may treat at any given time are unusual in the practice of medicine in the USA. There are no such restrictions on prescribing opioids with greater potential lethality for analgesia. The recent expansion of the cap to 275 patients under certain conditions and new regulations permitting nurse practitioners and physician's assistants to obtain a waiver may help to reduce barriers to care.

New medication formulations such as implantable buprenorphine, which was recently approved by the FDA for use in patients stabilized on sublingual buprenorphine, may be helpful in overcoming some geographical and logistical barriers. Rural physicians who did not prescribe buprenorphine following training reported not feeling confident in their ability to treat OUD [31•]. The availability of mentorship through the American Academy of Addiction Psychiatrists Providers' Clinical Support System might help to alleviate these concerns [69]. Geographic barriers to OTPs can be overcome by providing treatment through mobile methadone programs as those in NJ [70], but the provision of buprenorphine by waivered physicians and dispensed at pharmacies is more practical, although it is accompanied by a greater risk of medication diversion that treatment in an OTP. XR-NTX requires only monthly physician visits, but its logistics and funding challenges remain as barriers.

Negative attitudes toward medications for OUD are deep-seated and long-standing [71]. Some proponents of 12-step recovery have so-called philosophical objections to such medications, believing that only a recovery without medications is genuine. Other critics may not be aware of the extensive evidence to support the use of medications and might change their views in response to training and education. Addressing these negative attitudes is important because they may suppress the use of medications even in circumstances in which funding for them is available [23]. This is particularly true in the criminal justice arena, given the large number of individuals with OUDs that are under its supervision.

The preponderance of data suggests that the adverse impact of the current opioid epidemic on public health can be reduced by increasing access to the three FDA-approved medications that effectively treat OUD. Given the scope of the opioid epidemic in the USA, the challenge is to overcome the barriers to the use of medications and increase access to these evidence-based treatments.

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Compliance with Ethical Standards

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