

Considering the Potential Benefits of Over-the-Counter Naloxone

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Abstract: Since 1999, annual opioid-related overdose (ORO) mortality has increased more than six-fold. In response to this crisis, the US Department of Health and Human Services outlined a 5-point strategy to reduce ORO mortality which included the widespread distribution of naloxone, an opioid antagonist that can rapidly reverse an opioid overdose. Increased distribution has been facilitated by the implementation of naloxone access laws in each US state aimed at increasing community access to naloxone. While these laws differ from state-to-state, most contain mechanisms to enable pharmacists to dispense naloxone without a patient-specific prescription. These laws have enhanced community naloxone distribution, both from pharmacies and overdose education and naloxone distribution programs, and produced positive effects on ORO mortality. However, a growing body of evidence has revealed that significant barriers to naloxone access from pharmacies remain, and annual ORO deaths have continued to climb. Given these concerns, there has been a push among some clinicians and policymakers for the US Food and Drug Administration to re-classify naloxone as an over-the-counter (OTC) medication as a means to further increase its accessibility. If an OTC transition occurs, educational outreach and funding for clinical innovations will continue to be crucial given the important role of health professionals in recommending naloxone to people at risk for experiencing or witnessing an ORO. Recognizing the severity of the ORO public health crisis, we believe transitioning formulations of naloxone approved for layperson use to OTC status would result in a net benefit through increased access. However, such a change should be combined with measures to ensure affordability.

Keywords: opioid, opioid overdose, naloxone, naloxone access law, over-the-counter

Background

Since 1999, United States (US) drug overdose deaths have surpassed 750,000.¹ Over that timeframe, annual opioid-related overdose (ORO) mortality rates increased more than six-fold. As a result, the US Department of Health and Human Services declared a public health emergency in 2017 and outlined five key measures to mitigate the crisis.^{2,3} One of the five measures delineated was the widespread distribution of naloxone, an opioid antagonist that can rapidly reverse the effects of an overdose resulting from either prescription opioid analgesics (eg, morphine, oxycodone, hydrocodone, among others) or illicit opioids (eg, heroin, illicitly manufactured fentanyl derivatives).³ In the event of a life-threatening ORO, there is a relatively short window of time in which naloxone can be administered to effectively reverse the overdose and prevent long-term morbidity and mortality.⁴ Therefore, increasing naloxone access in the community, particularly among those

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closely associated with persons at elevated overdose risk, is a crucial step to reducing ORO mortality as such measures increase the likelihood of timely naloxone administration.⁵ In 2018, the US Surgeon General released an official advisory highlighting the importance of this measure by recommending that all persons at high risk of ORO and anyone likely to come in contact with them obtain naloxone.⁶

Naloxone was first approved by the US Food and Drug Administration (FDA) in 1971 and has been widely used in acute healthcare settings.⁷ More recently, easier-to-administer intranasal and intramuscular dosage forms have been brought to market to facilitate layperson use in the community setting. While naloxone is not a controlled substance, possesses no abuse potential, and has a relatively benign adverse effect profile, it has traditionally only been available via prescription.⁸

However, prescription-only status presents several potential barriers to access. First, the current level of naloxone prescribing is far from adequate given the number of patients in the country at risk, and despite recommendations, co-prescribing of naloxone to patients at increased risk of overdose remains infrequent.^{9–11} Persons who use drugs (PWUD) may face additional barriers. PWUD are less likely to possess medical insurance and more likely to have a lower socioeconomic status, which may make it more difficult to afford the copays associated with prescriber visits or medication costs.^{12–14} For a variety of reasons, including negative personal experiences and fear of provider stigma, PWUD may also delay or avoid engagement with the conventional healthcare system.^{15,16} These concerns may prevent them from discussing their drug use, requesting a naloxone prescription, or returning to request additional supplies if they use the naloxone.^{17,18} Furthermore, for those who do not have a primary care provider, establishing care may delay access. For similar reasons, stigma at pharmacies may prevent patients from filling naloxone prescriptions.^{16,17} Evidence shows that some PWUD refuse naloxone offered to them due to stigma or self-perception that they are not at-risk while in a period of sobriety.¹⁸ Particularly concerning is evidence that some pharmacists harbor negative thoughts about dispensing naloxone due to concerns regarding “clienteles who would frequent the store” or “providing the person with a ‘free pass’ when they should instead seek professional treatment”.^{19,20}

To help address these barriers, in recent years state legislators have widely implemented naloxone access

laws (NALs) aimed at increasing access to naloxone in the community. While these laws differ significantly from state to state, most contain some or all of the following key features:

(1) criminal or civil liability protection for naloxone prescribers, dispensers, or those administering the medication in good faith, should a negative outcome occur;

(2) permission to prescribe to third-parties (ie, persons who would likely not be the one to whom the medication is ultimately administered);

(3) allowance for laypersons to possess and distribute naloxone without a prescription; and

(4) mechanisms to enable pharmacists to dispense naloxone without a patient-specific prescription (eg, through standing orders with prescribers or state-level protocols directly granting pharmacists the authority to dispense naloxone without a prescription).²¹

While associations between NAL implementation, increased naloxone access, and reduced ORO morbidity and mortality have been observed, overall rates of ORO mortality have unfortunately continued to climb.^{7,22} In 2019, the US experienced a record 50,042 fatal OROs, due in part to a continued increase in the prevalence of ultra-potent synthetic opioids in the illicit market. These distressing statistics indicate that substantial work remains to mitigate ORO mortality. Thus, there has been a push among some clinicians and policymakers to re-classify naloxone as an over-the-counter (OTC) medication as a means to further increase its accessibility. The purpose of this commentary is to describe the successes and shortcomings of the current NAL approach and discuss potential benefits and risks associated with re-classifying naloxone as an OTC medication.

Successes and Shortcomings of Current NALs and Non-OTC Approach

Access

While only four states had passed NALs prior to 2010, today each US state and the District of Columbia have adopted some form of NAL.²³ Evidence shows that these laws have increased naloxone dispensing from pharmacies. According to a study utilizing IQVIA’s National Prescription Audit, naloxone dispensing from US pharmacies increased eight-fold from the fourth quarter of 2015 to the second quarter of 2017.²⁴ Looking more specifically at the impact of individual NAL components, among US

Medicaid patients, implementation of NALs that included provisions for pharmacists to dispense via standing order from a prescriber resulted in an additional 33 naloxone prescriptions per state, per quarter.²⁵ Similarly, two additional studies identified an association between third-party prescribing or standing order provisions and increased naloxone dispensing from community pharmacies, regardless of payer.^{26,27} Finally, though only a limited number of states have mandated naloxone co-prescribing for patients with ORO risk factors, such mandates have been associated with even greater increases in naloxone dispensing.^{26,28}

NALs, along with substantial federal funding to combat the opioid epidemic, have also facilitated the proliferation of community overdose education and naloxone distribution (OEND) programs.^{8,23,29–31} These programs provide education intended to reduce ORO mortality, and free naloxone to at-risk individuals and other laypersons who may find themselves in a position to provide rapid overdose response.^{31,32} In 2019 alone, such programs distributed more than 1 million doses of naloxone,³¹ which represents almost twice as many doses as dispensed from US community pharmacies.^{8,23} OEND and similar training programs have also contributed to a great rise in the number of law enforcement and other first responders trained to respond to an ORO and equipped with naloxone.³³ However, despite their successes, such programs are perpetually underfunded and currently not sufficient to completely address the need for naloxone.^{34,35} Furthermore, logistical barriers such as identifying where, how, and to whom the supply of naloxone should be distributed to provide the greatest impact may limit the effectiveness of such programs to some extent,³⁶ and should a person use the naloxone they obtain from such a program, they may not be immediately able to replenish this supply from another OEND program. Thus, easy accessibility from community pharmacies remains a crucial component of ensuring naloxone is available in the event of an overdose.

Outcomes

Several studies have attempted to quantify the impact of increased naloxone within the community. A recent systematic review analyzed the cumulative body of evidence regarding whether NALs were associated with improved naloxone access and ORO reduction, showing mixed, but generally beneficial, results.²³ While the included studies provided consistent evidence that NALs increase naloxone

access, the evidence regarding their impact on morbidity and mortality was not as uniform across studies. The systematic review also identified increased rates of emergency department utilization, though the authors note this could be explained by more overdose victims surviving to receive hospital care. Looking at the evidence more closely, in one study, NALs were found to reduce ORO deaths by 9–11%.³⁷ In another, NALs were associated with a 14% lower rate of ORO mortality, and greater ORO mortality reductions were observed in African-American and Hispanic populations compared to other groups.⁷ It is also promising that these studies found no evidence of contemporaneous increases in opioid misuse associated with NALs.^{7,37} However, both of the aforementioned studies only included data through 2014. Several studies analyzing more recent data have shown less conclusive evidence regarding the mortality benefits of NALs, with overall mortality benefits not reaching statistical significance.²³ Studies attempting to identify the impact of individual components of NALs on ORO mortality have also been conflicting, leading to uncertainty as to which NAL components have the greatest impact.²³

Studies of the impact of OEND programs additionally point towards positive outcomes associated with increased naloxone access. Naloxone distributed by OEND programs has resulted in tens of thousands of documented overdose reversals and significant reductions in ORO mortality compared to communities without similar programs.^{32,35,38,39} From 1996 to 2014, there were 26,000 reported cases of opioid overdose reversals from laypersons that participated in OEND programs.³² Such models can be particularly effective if the naloxone is distributed to populations more likely to encounter an overdose. In one study, 18% of opioid treatment program patients provided naloxone reported having used it to reverse an overdose.⁴⁰ Increased access to naloxone among law enforcement and other first responders has also been found to reduce opioid overdose mortality.³³

Barriers

While these results reveal progress, a growing body of literature has identified that, despite NALs, there remains a significant opportunity to improve the accessibility of naloxone from community pharmacies.⁴¹ Since 2018, several studies have assessed the accessibility of naloxone without an outside prescription, primarily through telephone audits or surveys of community pharmacists, finding significant variability from state-to-state and identifying that despite the

Table 1 Identified Barriers and Facilitators to Naloxone Access Under Current NAL Approach

Barriers	Facilitators
<ul style="list-style-type: none"> ● Inconsistent stocking of naloxone in community pharmacies ● Lower availability in independent pharmacies vs chain pharmacies ● Lower availability in pharmacies in areas of lower socioeconomic status ● Lower availability in rural vs urban pharmacies ● Misconceptions regarding local NALs or company policies regarding naloxone dispensing ● Lack of clarity regarding insurance billing when dispensing under standing order ● Lack of clarity regarding the use of standing order for dispensing to adolescents ● Less accessibility for PWUD vs third-party customers who do not use prescription or illicit opioids ● Perceived stigma associated with opioid or naloxone use among patients ● Negative beliefs among pharmacists regarding dispensing naloxone ● Need for additional education regarding naloxone or opioid overdose prevention among pharmacists or healthcare providers ● Cost of naloxone ● Significant heterogeneity among NALs from state-to-state 	<ul style="list-style-type: none"> ● Development of easier-to-use naloxone formulations designed for layperson use ● Increased duration of time since the passage of NALs ● Significant funding currently available to support community OEND programs ● Legislative mandates to maintain naloxone supply in community pharmacies ● Educational interventions for pharmacists, managers, and technicians ● Patient-facing signage in pharmacies to promote discussions regarding naloxone ● Naloxone co-prescribing mandates for patients with ORO risk factors

NALs, naloxone is still not immediately available from many community pharmacies.^{19,20,42–58} In fact, studies of pharmacies from Georgia (31%),⁴² New Jersey (31%),⁴⁷ California (23.5%),⁴⁶ Pennsylvania (45%),⁴⁵ Philadelphia, Pennsylvania (34.2%),⁴³ and Ohio (45%)⁴⁴ found naloxone to be in-stock and available via standing order or protocol in less than 50% of pharmacies audited. While several studies showed substantially higher rates in other states, they still identified barriers to naloxone access.^{20,48–57}

Many reasons for barriers to access have been identified, including: inconsistent stocking of the medication in community pharmacies^{19,20,42–58} (which may, in part, be due to low customer demand at some pharmacies),^{20,47} lower availability in independent pharmacies than chain pharmacies,^{42,53,57} in lower socioeconomic locations,⁴⁷ and in rural versus urban settings;⁵³ pharmacist or pharmacy staff misunderstanding of standing order legislation and company procedures regarding their implementation^{44,45,48,50} or age requirements for utilizing standing orders;⁴⁸ less accessibility for PWUD than for third-parties;^{19,51} stigma or negative beliefs regarding dispensing naloxone;^{44,53} and pharmacist time constraints.⁵⁹ Several of these studies also assessed the cash price, finding the mean price of intranasal naloxone, often the only formulation available in community pharmacies,⁵⁰ to be in the range of \$120–150.^{43,45,46,51,52,54–56} While naloxone may be included on many insurance formularies, price remains a major barrier for uninsured or underinsured patients,⁵⁵ and there seems to be a lack of clarity among community pharmacists as to

whether naloxone can be billed to insurance plans when dispensed via standing order.^{44,50} Table 1 summarizes identified naloxone access barriers and potential solutions.

These studies also highlight the great variation in naloxone availability from state-to-state, which may be reflective of the heterogeneous nature of the various state-level NALs and their implementation.^{21,60} One likely contributor to this variability is how each NAL has granted pharmacists increased dispensing authority. Some states provide state-wide protocols or blanket standing orders, enabling all pharmacists within the state to dispense naloxone without a patient-specific prescription, while others allow for the development of standing orders but do not provide a single protocol or standing order for all pharmacists. In the latter case, the legislation may lead to a piecemeal approach in which only certain pharmacies have a standing order in place and there may be significant variation in the standing order protocol from pharmacy-to-pharmacy or chain-to-chain. This can lead to confusion among both patients and pharmacists regarding local NALs or company policies surrounding naloxone dispensing. This was observed among Ohio pharmacists who were found to have an adequate knowledge-base regarding naloxone, but significant misunderstanding regarding state laws pertaining to its distribution.⁴⁴

While these audit studies have identified significant barriers to naloxone access from community pharmacies, several potential strategies to improve the impact of NALs on community pharmacy access can be gleaned as well. In Massachusetts, the Board of Pharmacy mandated that

pharmacies maintain a sufficient supply of naloxone to meet community needs, and subsequently, two separate audit studies of Massachusetts pharmacies observed the naloxone availability to be greater than 80%.⁵¹ Besides mandating that pharmacies stock naloxone, additional pharmacist training also appears to provide benefit in increasing naloxone accessibility. Pharmacist educational interventions have been shown to improve the likelihood to dispense via standing order,⁵⁸ stock naloxone in the pharmacy,^{19,20} and provide SUD counseling,⁶¹ while also increasing the perceived value of patient counseling regarding ORO prevention.⁶² Furthermore, it appears that naloxone accessibility may improve as greater time passes since the initial implementation of the NAL. In a follow-up to an early naloxone availability study, Eldridge et al, found that pharmacy stocking in a small sample of Indiana pharmacies significantly increased from 2016 (57%) to 2018 (92.5%, $P < 0.001$).²⁰ Similarly, it is likely that, over time, increased public access to naloxone may help reduce the stigma associated with opioid use and naloxone obtainment as this practice becomes more commonplace.⁶³ Increased pharmacist experience in dispensing naloxone may also improve pharmacists' understanding of the importance of efforts to improve anonymity and reduce stigma, as well as their comfort level in carrying out such interactions.⁶⁴ However, such interventions will require significant time and resources and are unlikely to be carried out uniformly across the country, perpetuating disparities in naloxone access. Given the continued rise in ORO mortality and persistent gaps in access to naloxone under the current NAL approach, a transition to OTC status warrants serious consideration.

Potential Benefits and Risks of OTC Transition

Feasibility

Davis and Carr previously described the most viable process by which a transition to OTC status could be achieved – federal action by either the Secretary of the Department of Health and Human Services or the Commissioner of the Food and Drug Administration (FDA).⁸ The underlying rationale is that naloxone meets the four FDA criteria for over-the-counter status: (1) the drug's benefits must outweigh its risks; (2) it must treat a condition that can be identified without the assistance of a medical professional; (3) it must have a low potential for misuse; and (4) its label must allow an individual to understand how to use it properly. In particular, the

development of an easy-to-use intranasal naloxone formulation, Narcan[®], has significantly improved layperson ease of use and should facilitate its safe and efficacious use as an OTC product compared to previous intramuscular versions developed for use in healthcare settings.⁶⁵ Furthermore, the FDA Center for Drug Evaluation and Research has already developed and tested a model drug facts label for OTC naloxone.⁶⁶ While the declaration of a public health emergency is not necessary to facilitate this type of unilateral federal action, it provides a compelling backdrop for such a decision regarding this extremely safe medication which the US Surgeon General has recommended for all Americans who might experience or witness an ORO.⁶

Cost

One key concern is that after its transition, some insurance companies may choose not to include OTC naloxone formulations on their insurance formularies. In 2019, Murphy et al estimated that converting naloxone to OTC status would increase pharmacy sales of the drug, though with broad uncertainty regarding the magnitude of this increase (15–179%).⁶⁷ This finding balanced the potential cost increases associated with all naloxone formulations moving OTC, such as the medication potentially no longer being included on insurance formularies, with the increased demand associated with easier access. However, it is unlikely that all formulations of naloxone would transition to OTC status. Instead, formulations of naloxone which have shown substantial ease-of-use advantages and earned FDA approval for use by laypersons (namely Narcan[®] nasal spray) would be the likely candidates for a transition to OTC status.^{8,68} Inflation in the prices of these OTC formulations may be mitigated by continued insurance formulary inclusion of the older, less expensive formulations which are not labeled for layperson use. Additionally, federal- or state-level legislation could compel insurance coverage for OTC naloxone formulations. Several states including Illinois, New York, and Rhode Island mandate insurance coverage for naloxone; such mandates can be extended to cover OTC as well as prescription versions of the medication.^{69–71} Finally, states and localities could use federal grants, legal settlements with opioid manufacturers and distributors, and other funds to subsidize OTC naloxone purchases.

Access

The unique legal status of naloxone under the current NAL approach has led to widespread confusion, particularly

given the variability in state-level NALs and nuances of implementation.⁷² In the experience of the authors, misconceptions regarding the status of naloxone are often present even among healthcare professionals, key stakeholders, and public health decision-makers. These stakeholders often have the authority to make crucial decisions regarding naloxone access processes and to stand in the way of efforts to maximize expedient distribution of naloxone. Converting one or more formulations of naloxone to OTC status may reduce the cloud of confusion that currently surrounds the proper methods for accessing and distributing it, enhancing the impact of community OEND programs.⁸

OTC conversion may also allow naloxone to be sold in locations such as convenience stores and grocery stores that do not have pharmacies and would reduce much of the red tape associated with OEND program acquisition and distribution of the medication. Though little research has been conducted to assess the acceptability or preferability of purchasing naloxone from a non-healthcare setting, this would likely be appealing for some PWUD, the group at highest risk for ORO, who are often wary of engaging with conventional healthcare professionals due to past experiences of discrimination and judgement.^{15,16} However, it may not be realistic to anticipate OTC naloxone formulations would be sold in the gas station aisle alongside inexpensive OTC medications. The closest comparator for OTC naloxone, which would be a relatively high-cost OTC product, may be OTC nicotine replacement therapy (ie, patches, gums, lozenges). These products are typically subject to an extra layer of security to avoid theft, and theft could be even more prevalent for a drug associated with more stigma. Due to this concern, converting naloxone to OTC status may not increase access substantially outside of OEND programs unless efforts are made to subsidize its provision from other locations or promote efforts to reduce the stigma associated with obtaining naloxone from healthcare settings. Educational interventions directed towards pharmacists and healthcare providers, as well as patients, are likely to help mitigate this stigma to some extent.^{64,73} It appears that efforts as simple as placing patient-facing signage around the pharmacy or on dispensed medications recommending the use of naloxone may help reduce stigma and facilitate productive conversations between pharmacists and at-risk patients.⁶⁴

Furthermore, as the Society of Pain and Palliative Care Pharmacists (SPPCP) argued in a position statement opposing conversion of naloxone to OTC status, there may be a downside to selling naloxone in settings that

do not offer access to trained medication experts (ie, pharmacists).⁷⁴ SPPCP notes, and we concur, that a knowledgeable and compassionate pharmacist could provide thorough overdose response education, assist with the selection of an optimal formulation, and facilitate referrals for additional care when indicated. However, we do not agree that pharmacist interaction should be a prerequisite for obtaining naloxone. Unfortunately, the preponderance of evidence regarding pharmacists' current practices related to naloxone dispensing indicates this level of clinical service is increasingly rare in US pharmacies, and that in some cases, a pharmacist may be more likely to hinder naloxone access than to facilitate it.^{41,56} Furthermore, the concern raised by SPPCP could be similarly applied to nearly any OTC medication, including many which possess risks for harm from improper use that exceed that of naloxone. In fact, over a million doses of naloxone are distributed annually from non-pharmacy OEND programs, with no evidence of harmful effects.³¹

Education

Expansion in pharmacists' authority to distribute naloxone has correlated with a surge in the availability of opioid-related continuing education programs.⁷⁵ Several opioid-related practice transformation efforts have also been implemented to expand pharmacists' positive impact on the care of people who use opioids.⁷⁶ Furthermore, colleges of pharmacy have reported expanding their curricular focus on opioid-related topics.⁷⁷ This nationwide focus on opioid-related education for pharmacists and student pharmacists is undoubtedly positive given evidence that pharmacists are more likely to dispense naloxone if they have more knowledge about the drug and local NALs.^{59,78} However, studies continue to document gaps in both pharmacist-reported knowledge regarding naloxone and its actual practice behaviors related to its dispensing, indicating that these educational efforts must remain a high priority.^{51,56,59,78,79} It is possible that converting naloxone to OTC status could remove a powerful incentive for pharmacists to seek, and colleges of pharmacy to provide, opioid-related education. However, this need not and should not be the case, especially since we envision that some formulations would likely remain prescription-only even if more user-friendly versions are moved OTC.

Conclusion

A patchwork of state-level NALs with variable components have contributed to an uncertainty regarding the status of

naloxone. Pharmacists have been slow to embrace expanded authority to dispense naloxone, and community organizations have struggled to navigate complex processes for obtaining and distributing it. However, given the safety profile of naloxone and the availability of easy-to-administer dosage forms, a transition of naloxone formulations designed for layperson use to OTC by the FDA should allow for safe and efficacious use in the community and may promote improved access. If an OTC transition occurs, educational outreach and funding for both health professionals and community OEND programs will continue to be crucial given the important role of both in recommending naloxone to people at risk for experiencing or witnessing an ORO. Recognizing the severity of the public health crisis of ORO, we believe transitioning the formulations of naloxone approved for layperson use to OTC status would result in a net benefit through increased access. However, such a change should be combined with measures to ensure affordability.

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