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POSITION STATEMENT

American College of Medical Toxicology and the American Academy of Clinical Toxicology Position Statement: Nalmefene Should Not Replace Naloxone as the Primary Opioid Antidote at This Time

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Background

Against the backdrop of a severe opioid crisis that resulted in over 80,000 deaths in the USA in 2021, with synthetic opioids being a primary culprit, researchers are exploring alternative treatment approaches [1]. On May 22, 2023, the US Food and Drug Administration (US FDA) approved nalmefene nasal spray (OPVEE®, Indivior®) for emergency treatment of opioid overdose [2].

Although this is a newly approved route of administration, nalmefene is not a new drug. Nalmefene is an opioid antagonist that was originally US FDA-approved for injection (via the intravenous (IV), intramuscular (IM), or subcutaneous (SC) routes) in 1995 [3]. The original injectable nalmefene product was removed from the market for commercial reasons in 2008 [4, 5]. Clinicians had not found a consistent role for nalmefene, presumably because it did not have a clinically relevant duration of action or ease of use. Naloxone, originally US FDA-approved in 1971 [6], continues to be recognized as the leading opioid antagonist by all routes of administration. Because nalmefene has a high affinity for opioid receptors and long duration of action compared to naloxone, it is marketed as advantageous for use following overdose of synthetic opioids, despite the lack of supporting clinical effectiveness and safety data [7–9].

Because nalmefene was already approved by the US FDA for use via injection, the intranasal (IN) product did not require new clinical data. [9–11]. The IN nalmefene product was submitted to the US FDA as part of an Abbreviated New Drug Application pathway, which required that the sponsor only demonstrate the new administration route is bioequivalent and pharmacokinetically equivalent to the older injectable product [9, 11, 12].

Nalmefene Clinical Trial Data

Nalmefene originally received US FDA approval in 1995 (Revex®) via injection based on data from controlled trials on a total of 1127 patients involving either postoperative opioid reversal or opioid overdose [3]. The original prescribing information and US FDA approval letter provide data on opioid poisoning limited to 284 patients from four trials involving patients presumed to have taken an opioid overdose [3]. While the Revex® product was withdrawn in 2008, the US FDA determined it was not withdrawn for reasons of safety or effectiveness, allowing for future approvals through an Abbreviated New Drug Application [13]. The prescribing information for the newly US FDA-approved generic parenteral formulation of nalmefene contains data from the same 1127 patients (again, 284 of which were presumed to have experienced an opioid overdose), while the prescribing information of the new IN formulation reviews these same 1127 patients solely for adverse events [8, 9]. Neither formulation's prescribing information provides new data gathered from patients with opioid overdose reversed with nalmefene.

Pharmacokinetic data used in the Abbreviated New Drug Application to obtain US FDA approval via the IN route

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were obtained after IN nalmefene was administered to volunteers under controlled conditions and not in patients currently suffering from opioid overdose.

Clinical data on nalmefene used to safely reverse opioid poisoning are sparse [14]. Only one double-blind controlled trial comparing naloxone to nalmefene has been published, and it examined the IV route for both drugs [15]. This trial, which randomized 176 patients to one of three treatments (2 mg naloxone, 1 mg nalmefene, or 2 mg nalmefene), found all three treatments to be effective and safe. While this study found no difference in adverse effects between treatment arms, this study was likely underpowered to detect differences in adverse effects, which were twice as common (31%) with 2 mg nalmefene compared to 1 mg of nalmefene or 2 mg of naloxone (16%). While data from this study are used in support of IN nalmefene in the Abbreviated New Drug Application, it is notable that the authors of this study warn in their manuscript "Clinicians concerned about possible prolonged withdrawal or adverse reactions to nalmefene may want to try naloxone first." Importantly, this trial was conducted in the 1990s, long before fentanyl became the most common cause of opioid overdose in the USA. While parenteral nalmefene, like naloxone, reverses the effects of fentanyl in volunteer studies [16, 17], unlike naloxone, data on nalmefene reversal of fentanyl overdose via the IN route are lacking.

Naloxone and Nalmefene

Naloxone is shorter-acting and is US FDA-approved for administration by IM, IV, IN, and SC routes. Compared to naloxone, nalmefene has fivefold higher binding affinity for opioid receptors (measured by receptor affinity, Ki) than naloxone [6, 18] (See Table 1) [7].

The duration of action of nalmefene compared to naloxone has been promoted as beneficial [7], presumably because it may reduce the use of naloxone infusions or repeat naloxone administration. The primary adverse effect of any opioid antagonist, naloxone included, is to cause acute withdrawal in patients with opioid dependence. Precipitated opioid withdrawal can range in severity from mild dysphoria or gastrointestinal upset to life-threatening conditions including acute respiratory distress syndrome, severe agitation, dysrhythmias, and stress cardiomyopathy. The longer duration of action of nalmefene may predispose to a lengthier period of precipitated opioid withdrawal.

The longer duration of action of nalmefene does not eliminate the need for medical observation after administration. We are concerned that the long duration of action may provide a false sense of comfort that no further care is needed. Compared to naloxone, a long-acting antagonist may result in increased patient emergency department (ED) length of stay and resource utilization. Individuals reversed with nalmefene in the out-of-hospital environment who do not seek formal medical care may attempt to self-treat withdrawal with opioids. The current standard is to observe patients for recurrent sedation and respiratory depression after the opioid antagonist effect dissipates—approximately 90 min following IV naloxone [19]. Patients who receive nalmefene may require longer periods of observation, up to several hours, to observe for resedation and recurrent respiratory depression as the longer-acting antagonist effects wane.

It is not clear that an antagonist with higher affinity for the opioid receptor is desirable or would result in better outcomes, even in patients with synthetic opioid overdose. Increased affinity may contribute to more severe and intractable withdrawal. We do not have clinical data for nalmefene in patients with synthetic opioid overdose.

Moreover, the current standard opioid antidote, naloxone, has a sufficiently high opioid receptor affinity to reverse novel synthetic opioids. In a study of volunteers given the high-affinity synthetic opioid carfentanil, administration of 2 mg of IV naloxone blocked 80.6% of receptors at 5 min [20]. Although 1 mg of IV nalmefene blocked 99% of receptors, the 80% occupancy produced by naloxone is sufficient to restore ventilation, which is the clinical goal. In current clinical practice, much lower doses of naloxone are initially administered to blunt the risk and severity of precipitated opioid withdrawal, highlighting the limited benefit of a higher affinity reversal agent. In published case reports, naloxone successfully reversed dozens of cases of high-dose fentanyl and fentanyl analog overdoses, though on occasion

Table 1 Comparison of naloxone and nalmefene

	Naloxone IN	Naloxone IV	Nalmefene IN
T ½ (h)	2.08	0.5–1.5	7.11
T max (h)	0.25	Nearly instantaneous	0.5
Ki (nM)	5.4	5.4	1.0
Wholesale acquisition Cost ($)	$64.80–75/nasal administration [2-pack]	$5.27–23.72/mL of 0.4 mg/mL solution	$98 [2-pack]

T ½ serum half-life (not a direct measure of duration of action, but may correlate with duration of action), *T max* time of maximum serum concentration, *Ki* inhibitor constant; inversely proportional to receptor affinity, not dependent on route of administration

higher or titrated doses were used [21–23]. A single-center retrospective review found no difference in naloxone dose in patients with fentanyl compared to heroin overdose [24]. We are unable to find clinical evidence that a strategy of repeated or escalating naloxone doses is inferior to a longer-acting antagonist for treatment of opioid overdose.

Position

As physicians, pharmacists, scientists, and specialists in poison information, we are experts in pharmacology, toxicology, and the management of opioid overdose and addiction. We applaud the effort to seek out new therapeutic strategies for management of these patients.

We are concerned that use of a longer-acting reversal agent would not improve on current practice and could potentially cause harm. When withdrawal is precipitated by an opioid antagonist, there are few good management options. In most cases, the best strategy is to address and support the patient's signs and symptoms until the effects of the antagonist wane. In the case of naloxone, which has a relatively short duration of action, severe withdrawal usually lasts less than an hour with effects typically persisting no more than 90 min [25–27]. A longer-acting antagonist is anticipated to cause longer-lasting precipitated withdrawal and may lead to worse patient outcomes. Clinical experience with both naltrexone and nalmefene suggests prolonged withdrawal is a complication of a longer-acting opioid antagonists [28]. Although a longer-acting antagonist may be theoretically beneficial for resuscitation of opioid-naive individuals in an opioid-induced mass casualty incident, this type of event has never been reported in North America and this application is unstudied.

We are also concerned that patients who receive nalmefene may require longer periods of observation, by up to several hours, to observe for recrudescent effects as the antagonist effects wane. Patients who receive nalmefene will still need medical observation to ensure that respiratory depression does not recur after the effects of the medication subside. This will prolong ED visit length and challenge patient and clinician expectations, further burdening a taxed system. Further clinical study is needed to understand whether a reduction in repeat antagonist use justifies a longer length of stay or longer period of withdrawal.

Finally, we are concerned that IN nalmefene has not been adequately studied for effectiveness in the actual setting and patient population: for patients with severe opioid (particularly fentanyl) intoxication in the out-of-hospital environment. Lack of proof of safety and efficacy in real-world use could result in significant harm if widely utilized.

The potential benefits of nalmefene over naloxone (greater opioid receptor affinity, longer duration action) carry risk of causing harm. These benefits, if present, should be demonstrated in the clinical environment, balanced with the risks, and compared to naloxone prior to broad adoption of nalmefene.

Recommendations

We recommend the following actions to inform safe and effective opioid reversal:

1. Continue to recommend naloxone as the preferred first-line agent until, and if, more robust clinical and cost data are available to support the routine use of nalmefene.
2. Conduct additional clinical studies of nalmefene (via the IV, IM, and IN routes) to determine the effectiveness of the drug in its anticipated clinical setting (overdose patients in hospital and out-of-hospital environments).
3. Evaluate important safety endpoints for nalmefene use, particularly related to complications of opioid reversal, such as acute respiratory distress syndrome and prolonged precipitated withdrawal.
4. Perform comparative studies with naloxone to determine differences in effectiveness, adverse outcomes, effect on ED length of stay and other relevant clinical measures, effect on initiation of medications for opioid use disorder, medication and healthcare cost, and overall resource utilization.

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Declarations

Conflicts of Interest None.

Disclaimer While individual practices may differ, this is the position of the American College of Medical Toxicology (ACMT) and American Academy of Clinical Toxicology (AACT) at the time written, after a review of the issue and pertinent literature. This statement does not necessarily represent the official views, nor an endorsement, by the US FDA/US Department of Health and Human Services, or the US Government.

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