Pharmacokinetic properties of intranasal and injectable formulations of naloxone for community use: a systematic review

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Practice points

• The US FDA has approved two naloxone products for use by laypersons in community settings for emergency treatment of known or suspected opioid overdose: an intranasal spray with a concentrated naloxone dose of 2 or 4 mg in 0.1 ml and an auto-injector for intramuscular (im.) or subcutaneous (sc.) use with a naloxone dose of 0.4 or 2 mg.
• In the absence of head-to-head, comparative efficacy studies, which are not feasible for ethical and logistical reasons, pharmacokinetic data provide important information about effective doses and routes of administration of naloxone for opioid overdose reversal.
• In pharmacokinetic studies, both the approved intranasal spray and the im./sc. auto-injector demonstrated bioequivalence with a previously approved formulation, indicating that naloxone exposure was adequate to reverse an opioid overdose.
• Both the approved intranasal spray and the im./sc. auto-injector demonstrated sufficient plasma exposure within the first 15–20 min after administration.
• Usability studies with laypersons in simulated overdose conditions have found that more than 90% of participants were able to successfully administer naloxone using the approved intranasal spray or im./sc. auto-injector without prior training; however, these studies have identified critical errors with the proper assembly and use of unapproved intranasal kits, even when training had been provided.
• Approved intranasal naloxone is appropriate for most patients, with the exception of those with known nasal pathology (e.g., polyps and chronic intranasal drug use).
• Providing prescriptions for community-use naloxone may reduce future risk in patients who are receiving chronic opioid therapy for pain control or who have histories of illicit opioid use.

Aim: To assess the pharmacokinetic properties of community-use formulations of naloxone for emergency treatment of opioid overdose. Methods: Systematic literature review based on searches of established databases and congress archives. Results: Seven studies met inclusion criteria: two of US FDA-approved intramuscular (im.)/subcutaneous (sc.) auto-injectors, one of an FDA-approved intranasal spray, two of unapproved intranasal kits (syringe with atomizer attachment) and two of intranasal products in development. Conclusion: The pharmacokinetics of im./sc. auto-injector 2 mg and approved intranasal spray (2 and 4 mg) demonstrated rapid uptake and naloxone exposure exceeding that of the historic benchmark (0.4 mg im.), indicating that naloxone exposure was adequate for reversal of opioid overdose.

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Keywords: auto-injector ● bioavailability ● community use ● drug overdose ● intramuscular ● intranasal ● naloxone ● nasal spray ● pharmacokinetics ● reversal

Background

Drug poisoning is the leading cause of accidental death in the USA and is driven largely by overdose of prescription or illicit opioids [1–3]. From 2000 to 2014, the rate of opioid-related (e.g., prescription analgesics and heroin) overdose deaths tripled [2], with a further increase of 16% observed from 2014 to 2015 [3]. A sharp increase was noted in overdose deaths related to fentanyl and fentanyl derivatives, potent synthetic opioid analgesics that can be...
manufactured or purchased illicitly [4–6]. Of 52,404 deaths caused by drug overdose in the USA in 2015, 63.1% (33,091 deaths) involved an opioid [3].

Each year, there are more than one million emergency department visits for drug poisoning in the USA [7]. From 2008 through 2011, 14% of emergency department visits for unintentional overdose were opioid related [7]. An analysis of the 2010 Nationwide Emergency Department Sample found that 67.8% of emergency department visits for opioid overdose involved prescription opioids, and 16.1% involved heroin (13.4% were unspecified and 2.7% involved multiple opioid types) [8].

Importance
Since its introduction more than 40 years ago, the opioid antagonist naloxone has been used to reverse respiratory and central nervous system depression resulting from opioid overdose [9]. Until 2014, naloxone was approved by the US FDA only in injectable formulations for use by trained healthcare professionals [10]. In response to the increase in fatalities caused by opioid overdose, government agencies and community organizations have worked to establish wider access to naloxone [11–13]. Unapproved intranasal kits contain an injectable formulation of naloxone (e.g., prefilled syringe); to enable intranasal administration, the user must first attach an atomizer (manufactured by another company but provided in the kit) to the syringe [14]. Such kits have been increasingly available for public use [14] and have been employed successfully by first responders (e.g., emergency medical service personnel, police officers and bystanders) to reverse opioid overdose [15–20]. Although these products are FDA approved as injectables, they are not FDA approved for intranasal administration when included in a kit with an atomizer. Furthermore, little data have been collected on the bioavailability of naloxone when administered using these unapproved intranasal kits [14]. Importantly, human factors studies have found that many laypersons (i.e., individuals with no medical training) were unable to employ unapproved intranasal kits correctly, even after training [21,22]. For example, a prospective usability study of 42 healthy adults found that no participants (0%) could successfully administer a dose of naloxone using an unapproved intranasal kit before training, and fewer than 60% of participants were able to successfully administer a dose of naloxone using this kit after receiving training [21].

The FDA has approved two naloxone products for use by laypersons in community settings for emergency treatment of known or suspected opioid overdose: an auto-injector for intramuscular (im.) or subcutaneous (sc.) use with a naloxone dose of 0.4 or 2 mg (EVZIO®; Kaléo, Inc., VA, USA) [23,24] and an intranasal spray with a concentrated naloxone dose of 2 or 4 mg in 0.1 ml (NARCAN®; Adapt Pharma, Inc., PA, USA) [25]. The efficacy of naloxone for reversing opioid overdose is well established; therefore, FDA approval of these products was based on other data, including: compliance with good manufacturing practice requirements for combination products (drug + device) [26], human factors studies demonstrating label comprehension and ease of use [27,28] and pharmacokinetic studies demonstrating adequate bioavailability [27].

Goals of this investigation
The purpose of this systematic review is to summarize the pharmacokinetic properties of formulations of naloxone for community use (i.e., formulations currently available or in commercial development for use by laypersons for opioid overdose reversal) as a means for understanding the speed of onset, adequacy and duration of the clinical effects. With the increasing availability of highly potent synthetic opioids, the naloxone dose required to reverse opioid overdose has increased, and multiple dosing has also become common [29,30]. Consequently, the approved naloxone products and products in development offer larger naloxone doses in the devices. Therefore, it is important to evaluate the pharmacokinetic properties of these new formulations to understand their potential role in highly potent opioid overdose reversal. A secondary aim is to establish selection of optimal naloxone product based on patient-specific and product-specific factors such as route of administration, formulation and dosing considerations for community use. Community-use formulations include the im./sc. auto-injector, approved intranasal spray, unapproved intranasal kits and intranasal in-development products.

Methods
Searches of the MEDLINE and Embase® databases were conducted on 9 November 2017. Search terms included ‘naloxone’ and ‘pharmacokinetic’ OR ‘pharmacokinetics’, with the dates of publication set as 2000 to present. Congress programs and abstract archives from January 2012 through October 2017 were accessed online for scientific meetings of pain medicine (American Academy of Pain Medicine and PAINWeek), addiction medicine (American Society of Addiction Medicine and Society for the Study of Addiction) and emergency medicine
Pharmacokinetic properties of intranasal & injectable formulations of naloxone for community use: a systematic review

Results

The literature search and study selection are described in Figure 1 [24,31–37]. Seven studies were included in this review [24,31–36]. Three studies with naloxone pharmacokinetic data [38–40] were excluded because they used study-specific, investigator-compounded agents that did not represent formulations or doses currently available for community use (or in development for community use). Table 1 provides a summary of the study designs and formulations/doses used. Naloxone pharmacokinetic data were obtained from two studies of im./sc. auto-injector, one study of the approved intranasal product, two studies of unapproved intranasal kits and two studies of intranasal products in development. Results for the prespecified pharmacokinetic variables (C<sub>max</sub>, t<sub>max</sub>, AUC, t<sub>1/2</sub> and bioavailability) from each study are shown in Table 2 [24,31–36].

FDA-approved products for community use

Naloxone pharmacokinetics for the im./sc. auto-injector were evaluated in two studies that varied with regard to the naloxone doses included. A study of 30 healthy volunteers assessed 0.4 mg of naloxone via im./sc. auto-injector, with 0.4 mg of naloxone im. via standard syringe and needle as the reference product [31]. Pharmacokinetic parameters of the im./sc. auto-injector and im. syringe and needle were similar for mean C<sub>max</sub> (1.2 and 1.1 ng/ml, respectively), median t<sub>max</sub> (0.25 and 0.33 h, respectively), mean AUC<sub>0-∞</sub> (1.9 and 2.0 ng·h/ml, respectively) and mean t<sub>1/2</sub> (1.3 and 1.4 h, respectively). The relative bioavailability of naloxone for the im./sc. auto-injector compared with im. syringe and needle was 98.3% (Table 2).

A separate study of 24 healthy volunteers evaluated im./sc. auto-injector doses of 0.4, 0.8 mg (administered as two injections of 0.4 mg) and 2 mg [24]. Mean C<sub>max</sub> and AUC<sub>0-∞</sub> were dose proportional (Table 2) [24]. Median t<sub>max</sub> and mean t<sub>1/2</sub> were similar across doses.

Naloxone pharmacokinetics for the approved intranasal spray were evaluated at various doses (2 mg [1 spray], 4 mg [as 1 or 2 sprays] and 8 mg [2 sprays]) in a study of 30 healthy volunteers, with 0.4 mg of naloxone im. via standard syringe and needle as the reference product [32]. Mean C<sub>max</sub> and AUC<sub>0-∞</sub> were dose proportional for the approved intranasal spray (Table 2). Mean C<sub>max</sub>, AUC<sub>0-∞</sub> and t<sub>1/2</sub> were greater for all doses of the approved intranasal spray compared with the im. reference. Mean C<sub>max</sub> was 3.1 and 5.3 ng/ml, respectively, for the approved intranasal (single spray) 2 and 4 mg, compared with 0.9 ng/ml for the im. reference (Figure 2) [32]. Mean AUC<sub>0-∞</sub> was 4.7 and 8.5 ng·h/ml, respectively, for the approved intranasal (single spray) 2 and 4 mg, compared with 1.8 ng·h/ml for the im. reference. In addition, the mean t<sub>1/2</sub> was 1.9 and 2.2 h, respectively, for the approved intranasal (single spray) 2 and 4 mg, compared with 1.3 h for the im. reference. Median t<sub>max</sub> was generally similar for the approved intranasal spray (0.3–0.5 h) and im. reference (0.4 h). Early-stage plasma concentrations for the 4-mg dose of the approved intranasal spray relative to the im. reference are shown in Figure 3 [25]. Compared with
im. administration, the relative bioavailability of naloxone for the approved intranasal spray was 51.9% for 2 mg, 46.2% for 4 mg administered in one spray, 53.5% for 4 mg administered in two sprays of 2 mg and 43.9% for 8 mg (administered in two sprays of 4 mg).

Unapproved intranasal kits

A study of 36 adults with chronic rhinitis assessed a commercially available, unapproved intranasal kit (2-mg naloxone as 1 mg/ml in each nostril) compared with 2-mg im. (1 mg/ml in each thigh via standard needle and syringe) [33]. C_max and AUC_0-∞ were lower for the unapproved intranasal kit compared with the 2-mg im. (mean C_max of 1.3 vs 4.5 ng/ml, respectively; mean AUC_0-∞ of 1.5 vs 9.8 ng•h/ml, respectively) (Table 2) [33]; however, the im. reference dose was five-times greater than that used in other pharmacokinetic studies [31,32,35]. For both formulations, median t_max (0.25 h) and mean t_1/2 (1.5 h) were similar. Relative bioavailability (which takes dose into account) was 14.6% for the unapproved intranasal compared with im. naloxone. The use of an intranasal vasoconstrictor (30 min prior) reduced the naloxone exposure obtained using the unapproved intranasal kit (Table 2).

A study of six volunteers used a population-pharmacokinetic modeling and simulation approach to evaluate unapproved intranasal, im. and intravenous (iv.) delivery of naloxone (commercially available, 0.4 mg/ml) [34].
### Table 1. Summary of included studies.

<table>
<thead>
<tr>
<th>Naloxone formulation</th>
<th>Study (year)</th>
<th>Naloxone dose(s)</th>
<th>Comparator product(s)</th>
<th>Study design</th>
<th>N</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>US FDA-approved formulations for community use</td>
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<tr>
<td>im./sc. auto-injector (EVZIO&lt;sup&gt;⃝&lt;/sup&gt;)</td>
<td>Edwards et al. (2015)</td>
<td>0.4 mg (midanterolateral thigh)</td>
<td>0.4-mg im. standard syringe and needle (midanterolateral thigh)</td>
<td>R, single-blind, single-dose, 2-period, 2-sequence, crossover</td>
<td>30 healthy adult volunteers</td>
<td>[31]</td>
</tr>
<tr>
<td>im./sc. auto-injector (EVZIO&lt;sup&gt;⃝&lt;/sup&gt;)</td>
<td>Product PI</td>
<td>0.4 mg (1 injection) 0.8 mg (2 injections of 0.4 mg administered 2 min apart) 2 mg (1 injection)</td>
<td>–</td>
<td>Crossover (other design details not specified)</td>
<td>24 healthy volunteers (age not specified)</td>
<td>[24]</td>
</tr>
<tr>
<td>Approved intranasal (NARCAN&lt;sup&gt;⃝&lt;/sup&gt;)</td>
<td>Krieter et al. (2016)</td>
<td>2 mg (1 spray of 2 mg/0.1 ml) 4 mg (1 spray of 4 mg/0.1 ml) 4 mg (1 spray of 2 mg/0.1 ml in each nostril) 8 mg (1 spray of 4 mg/0.1 ml in each nostril)</td>
<td>0.4-mg im. standard syringe and needle (0.4 mg/1 ml, gluteus maximus)</td>
<td>R, OL, 5-period, 5-treatment, 5-sequence, crossover</td>
<td>30 healthy adult volunteers</td>
<td>[32]</td>
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<tr>
<td>Unapproved intranasal kits</td>
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<td>Unapproved intranasal (LMA&lt;sup&gt;⃝&lt;/sup&gt; MAD Nasal&lt;sup&gt;™&lt;/sup&gt;)†</td>
<td>Edwards et al. (2016)</td>
<td>2 mg (1 mg/ml in each nostril)</td>
<td>2-mg im. standard syringe and needle (1 mg/1 ml in each thigh)</td>
<td>R, OL, single-dose, 3-period, crossover</td>
<td>36 adults with chronic rhinitis but no significant nasal abnormalities, surgery, polyps or trauma</td>
<td>[33]</td>
</tr>
<tr>
<td>Unapproved intranasal (MAD)‡</td>
<td>Dowling et al. (2008)</td>
<td>0.8 mg (1 spray of 0.4 mg/1 ml in each nostril) 2 mg (1 spray of 1 mg/2.5 ml in each nostril)</td>
<td>0.8-mg iv. 2-mg iv. 0.8-mg im. standard syringe and needle (gluteus maximus)</td>
<td>OL, crossover</td>
<td>6 healthy adult volunteers</td>
<td>[34]</td>
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<tr>
<td>Community-use formulations in development</td>
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<tr>
<td>Intranasal in development (Mundipharma)</td>
<td>McDonald et al. (2017)</td>
<td>1 mg (1 spray of 1 mg/0.1 ml) 2 mg (1 spray of 2 mg/0.1 ml) 4 mg (2 sprays of 2 mg/0.1 ml)</td>
<td>0.4-mg im. standard syringe and needle (primary reference; deltoid muscle) 0.4-mg iv.</td>
<td>R, OL, 5-way, crossover</td>
<td>38 healthy adult volunteers</td>
<td>[35]</td>
</tr>
<tr>
<td>Intranasal in development (dne pharma)</td>
<td>Tylleskar et al. (2017)</td>
<td>0.8 mg (1 spray of 0.8 mg/0.1 ml) 1.6 mg (2 sprays of 0.8 mg/0.1 ml)</td>
<td>1.0-mg iv.</td>
<td>R, OL, 3-way crossover</td>
<td>12 healthy adult volunteers</td>
<td>[36]</td>
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</table>

†Teleflex, Inc. NC, USA. ‡Wolf-Tory Medical, UT, USA.
im.: Intramuscular; iv.: Intravenous; LMA: Laryngeal mask airway; MAD: Mucosal atomizer device; OL: Open label; PI: Prescribing information; R: Randomized; sc.: Subcutaneous.

Pharmacokinetic parameters were not reported separately for each formulation, with the exception of relative bioavailability (derived from the modeling/simulation), which was 4% for unapproved intranasal compared with iv. administration. The relative bioavailability of im. versus iv. administration was 36%.

### Community-use formulations in development

Naloxone pharmacokinetics for the two intranasal products in development were evaluated in one study each. A study of 38 healthy volunteers assessed an intranasal spray (Mundipharma) at doses of 1, 2 and 4 mg, with 0.4 mg of naloxone im. via standard syringe and needle as the primary reference product (and also 0.4-mg iv. naloxone) [35]. Geometric mean C<sub>max</sub> was 2.9 ng/ml for the 2-mg intranasal in-development product compared with 1.3 ng/ml for 0.4-mg im. (standard needle and syringe) and 5.9 ng/ml for 0.4-mg iv. (Figure 4) [35]. Also, geometric mean AUC<sub>0-∞</sub> was 5.0 ng•h/ml for the 2-mg intranasal in-development product compared with 2.1 ng•h/ml for both the 0.4-mg im. (standard needle and syringe) and the 0.4-mg iv. product. Median t<sub>max</sub> was somewhat longer for the 2-mg intranasal in-development product (0.5 h) compared with 0.4-mg im. (0.2 h) naloxone; whereas, mean t<sub>1/2</sub> was similar (1.4 h for both). Early-stage plasma concentrations for the intranasal in-development product relative...
to the iv. and im. reference products are shown in Figure 5. Compared with im. administration, the bioavailability for intranasal in-development naloxone was 50.8% for 1 mg, 47.1% for 2 mg and 48.3% for 4 mg (administered as two sprays of 2 mg).

A different intranasal in-development product (manufactured by dne pharma) was assessed in 12 healthy volunteers; naloxone doses were 0.8 and 1.6 mg (2 sprays of 0.8 mg), with 1.0-mg iv. naloxone as the reference product [36]. Mean C\text{max} was 2.6 ng/ml for the 1.6-mg intranasal in-development product compared with 14.2 ng/ml for iv. administration (Figure 6) [36]. Mean AUC\text{0-t} was 3.1 ng\cdot h/ml for intranasal in-development product 1.6 mg compared with 4.0 ng/ml for 1.0 mg iv. Mean t\text{max} was longer for intranasal in-development product 1.6 mg (0.3 h) compared with iv. (0.04 h) naloxone; whereas, mean t\text{1/2} was similar (1.3 and 1.2 h, respectively). Compared with iv. administration, the bioavailability for the intranasal in-development naloxone was 54% for the 0.8-mg dose and 52% for the 1.6-mg dose.

**Discussion**

Two naloxone products for community use have been approved by the FDA for emergency treatment of known or suspected opioid overdose, based on pharmacokinetic and human factors studies: an im./sc. auto-injector and a concentrated naloxone dose via an intranasal spray (no device assembly required) [23–25]. In the absence of head-to-head, comparative efficacy studies in the community-use setting, which are not feasible for ethical and logistical limitations, the following considerations are essential:

<table>
<thead>
<tr>
<th>Community-use formulations in development</th>
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<tbody>
<tr>
<td>Intranasal in development (Mundipharma) [35]</td>
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<tr>
<td>1 mg (1 spray of 1 mg/0.1 ml)</td>
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<tr>
<td>2 mg (1 spray of 2 mg/0.1 ml)</td>
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<tr>
<td>4 mg (2 sprays of 2 mg/0.1 ml)</td>
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<tr>
<td>Intranasal in development (dne pharma) [36]</td>
</tr>
<tr>
<td>0.8 mg (1 spray of 0.8 mg/ml)</td>
</tr>
<tr>
<td>1.6 mg (2 sprays of 0.8 mg/ml)</td>
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</table>

\(^{††}\) Relative to 1.0-mg iv., based on AUC\text{0-t}.
\(^{‡‡‡}\) Data shown as mean (95% CI).
\(^{ linebacker}\) Relative to 0.4-mg im. standard syringe/needle.
\(^{§§}\) Oxymetazoline HCl 0.05% nasal solution (Afrin\textsuperscript{TM}) atomizer.
\(^{¶¶}\) Mean C\text{max} was 2.6 ng/ml for the 1.6-mg intranasal in-development product compared with 14.2 ng/ml for iv. administration (Figure 6) [36]. Mean AUC\text{0-t} was 3.1 ng\cdot h/ml for intranasal in-development product 1.6 mg compared with 4.0 ng/ml for 1.0 mg iv. Mean t\text{max} was longer for intranasal in-development product 1.6 mg (0.3 h) compared with iv. (0.04 h) naloxone; whereas, mean t\text{1/2} was similar (1.3 and 1.2 h, respectively). Compared with iv. administration, the bioavailability for the intranasal in-development naloxone was 54% for the 0.8-mg dose and 52% for the 1.6-mg dose.

**Discussion**

Two naloxone products for community use have been approved by the FDA for emergency treatment of known or suspected opioid overdose, based on pharmacokinetic and human factors studies: an im./sc. auto-injector and a concentrated naloxone dose via an intranasal spray (no device assembly required) [23–25]. In the absence of head-to-head, comparative efficacy studies in the community-use setting, which are not feasible for ethical and logistical limitations, the following considerations are essential:
reasons, pharmacokinetic data provide important information about effective doses and routes of administration of naloxone for opioid overdose reversal.

In pharmacokinetic studies, both the im./sc. auto-injector and the approved intranasal spray demonstrated bioequivalence with a previously approved formulation, indicating that naloxone exposure was adequate to reverse an opioid overdose [31,32]. By contrast, unapproved intranasal kits (syringe with atomizer attachment) using a commercially available naloxone solution intended for iv. use (0.4 mg/ml, 2 mg/2 ml [predominantly used]) have shown low bioavailability of naloxone relative to iv. (4%) [34] or im. (15%) [33] administration; additionally, the unapproved kits lack the label comprehension or human-use study data needed for FDA approval of a combination drug/device product. The poor bioavailability for the unapproved intranasal kits is likely related to the large volume of the solution that has to be atomized and absorbed in the nasal cavity, which may result in a loss of naloxone from the site of absorption (via drainage, either into the nasopharynx or externally) [41,42]. As a consequence of nasopharyngeal drainage, intranasal administration of a large volume of solution fails to bypass the extensive first-pass metabolism associated with oral administration of naloxone [43]. The approved intranasal spray addresses this issue by using a highly concentrated solution of naloxone such that the volume of each spray is only 0.1 ml [25]. Consistently, an explorative review integrating patent application data for noninjectable naloxone for opioid overdose and scientific publications reported that bioavailability of intranasal naloxone products has a positive association with dose and negative association with volume [44]. Although there are concerns of overantagonism with higher doses of naloxone resulting in severe withdrawal symptoms [45,46], the risk of inadequate reversal, especially with overdose of potent opioids such as fentanyl, is far greater than the risk of unpleasant opioid withdrawal reactions [46]. No studies have yet assessed the initial dose of naloxone required to reverse a fentanyl-related overdose.

Rapid uptake of naloxone is critically important because opioid overdose may result in respiratory depression with hypoxia, which leads to cardiopulmonary arrest and long-term damage to the central nervous system or
The need for both rapid onset and adequate duration of the naloxone effect is especially significant in light of the increase in overdose deaths involving high-potency, synthetic opioids [2–4]. Both the im./sc. auto-injector and the approved intranasal spray demonstrated sufficient plasma exposure within the first 15–20 min after administration to garner FDA approval. By contrast, a different intranasal spray was denied approval, potentially because of inadequate early-stage uptake of naloxone [48]. The duration of action is shorter for naloxone compared with most opioids; additional dose(s) may be required if the initial response is inadequate or if signs of overdose (e.g., respiratory depression) recur [23,25,27,49].

The optimal naloxone dose is one that successfully reverses opioid overdose without precipitating acute withdrawal symptoms [50]. However, most of the information necessary to make a precise dose determination (e.g., mu receptor affinity of the opioid taken and dose taken) is unavailable at the time that naloxone is administered, and varying naloxone dosing algorithms have been suggested [43,49,50]. The recent increase in overdose deaths related to potent opioids such as fentanyl [4] has tipped the balance toward the need for adequately high naloxone doses to prevent overdose fatalities. The FDA stance on naloxone dosing is evident in the approval of a new, higher dose (2 mg) for the im./sc. naloxone injector and a limited indication for the lower dose (2 mg) of intranasal naloxone (only for opioid-dependent patients expected to be at risk for severe opioid withdrawal [assuming this information is known at the time of naloxone administration]). The higher dose of the im./sc. auto-injector was developed to ensure that adequate naloxone would be provided for reversing overdose of various types of opioids, including potent opioids such as fentanyl [24]. In fact, an FDA advisory committee voted in 2016 to increase the current pharmacokinetic benchmark (0.4-mg im.) for approval of naloxone products for community use [51,52]. The makers of the im./sc. auto-injector intend to discontinue manufacturing the lower (0.4-mg) dose [53].
Approved intranasal spray initially received FDA approval in 2015 at a dose of 4 mg. A concentrated solution (4 mg/0.1 ml) is used for optimal absorption in the nasal cavity, with repeat dosing available if necessary [25]. The recently approved 2-mg dose of approved intranasal spray has a restriction in the ‘Indications for Use’ section of the label that limits its use to a specific patient population under particular circumstances. Specifically, use of the 2-mg dose is restricted to “opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts” [25]. In practice, the lower (2-mg) dose of the approved intranasal spray provides a dosing alternative for patients in whom there are concerns about precipitating severe opioid withdrawal living in situations where the lower dose of naloxone will not put other members of the household at risk for opioid overdose [54]. The intranasal products in development appear highly similar in both formulation (high concentration and low volume) and device to the approved intranasal spray [32,35–36].

Although comparative efficacy studies of naloxone formulations in the community-use setting are not feasible, the use of unapproved intranasal naloxone spray in a prehospital setting has been shown to be effective in reversing opioid overdose in retrospective studies [17,19], prospective nonrandomized studies [15,18,20] and in a randomized controlled study with im. naloxone as a comparator treatment arm [16]. A recent survey of first responders and community-based organizations assessing the initial real-world experience of the approved 4 mg intranasal naloxone spray reported successful reversal of opioid overdose in 98.8% of the cases [55].

In addition to efficacy, usability is a vital characteristic for community-use formulations of naloxone, which are expected to be used by laypersons in highly stressful situations. Studies have identified critical errors with the proper assembly and use of unapproved intranasal kits by laypersons in simulated overdose conditions, even when training had been provided [21,22]. However, human factors studies have found that more than 90% of participants were
able to successfully administer naloxone using the im./sc. auto-injector [21,22] or the approved intranasal spray [32] without prior training.

A study conducted at an urban hospital in Canada evaluated an emergency-department-based take-home naloxone program for patients at the risk of opioid overdose [56]. Of 201 participants, 68.2% accepted an unapproved intranasal kit and training. Since 92% of participants believed that take-home naloxone was “a good idea”, acceptance would likely be greater for an FDA-approved product that can be used successfully without training (instead, a brief explanation should be provided and recipients of the product should be encouraged to read the instructions for use thoroughly). Prescription of approved naloxone products also may reduce the training burden on pharmacists, since the counseling required by standing naloxone protocols in effect at pharmacies in many states is simpler for approved products than for unapproved intranasal kits [57–59].

Clinical implications
Providing prescriptions for community-use naloxone to patients at risk of opioid overdose (prescribed opioids or illicit use) may help reduce the number of opioid-related fatalities [56]. A prescription for community-use naloxone may be particularly appropriate for patients receiving daily opioid therapy for chronic pain and for patients who are known (or suspected) users of illicit opioids, based on self-report or observed signs and symptoms. For patients on daily opioid therapy, guidelines from the Centers for Disease Control and Prevention suggest a dose threshold of concern at 50 morphine milligram equivalents (MME) per day [60]. Specifically, the guidelines state “Clinicians should use caution when prescribing opioids at any dosage, should carefully reassign evidence of individual benefits and risks when considering increasing dosage to 50 MME or more per day and should avoid increasing dosage to 90 MME or more per day or carefully justify a decision to titrate dosage to 90 MME or more per day” [60].
Figure 6. Time course of plasma concentrations (mean [error bars 95% confidence interval]) of naloxone after intravenous (1.0 mg) and intranasal (0.8 and 1.6 mg) administration in healthy human volunteers (n = 12 for intravenous and intranasal 0.8 mg, n = 11 for intranasal 1.6 mg). Squares are the 0.8 mg intranasal, dots are the 1.6 mg intranasal and triangles are the 1.0 mg iv. [36]. CI: Confidence interval; iv.: Intravenous. Adapted with permission from [36] © Springer (2017).

Healthcare providers may consider giving a naloxone prescription to patients with chronic pain with a daily opioid dose $\geq 50$ MME and to all patients who are known or suspected users of illicit opioids.

Selection of the optimal community-use naloxone product depends on patient-specific and product-specific factors. Approved intranasal naloxone is appropriate for most patients, with the exception of those with known nasal pathology (e.g., polyps and chronic intranasal drug use [e.g., heroin and cocaine]). Auto-injector delivery of naloxone is im. or sc., based on the depth of the needle relative to the patient’s clothing and adipose tissue. Because information about sc. absorption of naloxone is limited, we suggest that use of approved intranasal naloxone is preferred in patients who are overweight (BMI of 25–30 kg/m²) or obese (BMI > 30 kg/m²).

When selecting the dose of a community-use product, the need for the maximum available safe dose of naloxone (that does not harm the patient) is paramount. For high-concentration, low-volume intranasal spray formulations (both approved and in development), bioavailability relative to im. administration was approximately 50% (Table 2), indicating that similar overall naloxone exposure would be achieved with a 4-mg intranasal dose (using a high-concentration product) and a 2-mg im. dose. For the approved intranasal spray, 4 mg is the first dose of the product approved by the FDA and is considered the standard dose for this product; the 2-mg dose is indicated only for patients considered at risk of severe opioid withdrawal [54]. If members of the patient’s household are at risk for accidental or intentional exposure to opioids, the 4-mg dose of the approved intranasal spray is indicated. Because the 0.4-mg dose will be discontinued, the im./sc. auto-injector should be prescribed at the 2-mg dose [53].

As with any medication, cost and availability are relevant concerns for patients and their families and caregivers. Prescribers should take into consideration potential socioeconomic barriers to obtaining naloxone products (e.g., insurance coverage and out-of-pocket costs). Although cost is one of the most relevant barriers to gaining
access to naloxone, standard metrics for comparing medication costs (e.g., wholesaler acquisition cost) do not reflect the actual costs of these products to patients. FDA-approved naloxone products are covered by most insurers (commercial and public), often with low (or no) copays. For patients without insurance coverage, clinicians can identify community organizations that may provide naloxone at no cost.

For community-use naloxone, ease of use under stressful conditions is also of critical importance. Consideration should be given to providing the community-use naloxone product directly to patients, since overdose may occur before a naloxone prescription is filled if dispensing pharmacy resources are not easily available. Education of patients, family members and companions in the use of the naloxone product selected may be provided by nursing staff, as is typical for other newly prescribed medications such as inhalers, epinephrine auto-injectors or glucometers, although naloxone products will universally be administered by bystanders in a community-use setting. The integration of public health resources into emergency departments may serve to reach at-risk and underserved populations [61]. Similarly, public health programs for opioid overdose prevention may target patients who are at-risk users of opioids (via either legitimate prescriptions or illicit sources).

**Limitations**

Despite a search of recent congress presentations, as well as MEDLINE and Embase, relatively few studies were identified. Methodology varied across studies, including differences in the reference products used, injection sites for the reference im. products, AUC parameters reported and statistical analyses performed. In addition, study participants were primarily healthy volunteers rather than the intended population for naloxone prescription (i.e., patients at risk for opioid overdose). Because of copyright restrictions, it was not possible to show AUC curves for all naloxone products available for community use.

**Conclusion**

The US opioid epidemic continues to worsen; unintentional overdose of prescription and illicit opioids remain all too common. Two naloxone products for community use have been approved by the FDA (based on compliance with good manufacturing practice requirements for combination [i.e., drug plus device] products, human use/label comprehension studies and pharmacokinetic studies) and have been used successfully by laypersons to reverse opioid overdose. Prescriptions for community-use naloxone may reduce future risk in patients who are receiving chronic opioid therapy for pain control or who have histories of illicit opioid use. Selection of community-use naloxone formulation and dose is based on product- and patient-specific characteristics. It is imperative that providers take into account the need for the maximum available safe dose of naloxone (especially in areas where synthetic opioids such as fentanyl are prevalent). It is also important to prescribe community-use formulations that are simple to use and appropriate for the individual patient.

**Future perspective**

Turning the tide on the epidemic of opioid overdose deaths will require a multifaceted approach that includes safer opioid prescribing, increased access to treatment programs for opioid abuse (e.g., medication-assisted treatment with behavioral therapies) and increased access to naloxone for opioid overdose reversal [2]. Recent US data indicate that opioid prescribing decreased from 2010 through 2015 but remained three-times greater than 1999 levels [62]. Wider access to community-use naloxone (in adequate dosages and easy-to-use formulations) is important for reducing the number of opioid-related deaths in the coming years.

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Pharmacokinetic properties of intranasal & injectable formulations of naloxone for community use: a systematic review

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Papers of special note have been highlighted as: ● of interest; ●● of considerable interest


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Pharmacokinetic study of approved intranasal naloxone compared with intramuscular naloxone injection, and human factors study on the usability of approved intranasal naloxone.
** CDC prescribing guideline with a focus on the benefits and risks of opioids for chronic pain.