

**Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the
Drug Safety and Risk Management Advisory Committee on October 5, 2016**

**FDA Advisory Committee on the Most Appropriate Dose or
Doses of Naloxone to Reverse the Effects of Life-threatening
Opioid Overdose in the Community Settings**

2 September 2016

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RECOMMENDATION

In this document and associated materials, the Sponsor provides supporting rationale for the following recommendation to the Advisory Committee:

1. To be confident a consistently adequate naloxone exposure is achieved in a community based setting and use by non-medical professionals, the Sponsor recommends one common threshold for naloxone onset and exposure apply for all formulations and routes of administration that approximates 2mg naloxone administered by injection (the high end of the established safe and effective initial dose range), rather than 0.4mg (the low end of the initial dose range).
2. That devices intended for lay use in the community use demonstrate they can support safe, ready and rapid administration of a fixed dose of naloxone, and are supplied with a back-up/additional device.

1. CURRENT LANDSCAPE

a. **The Opioid Overdose Epidemic in the United States:**

Opioid overdose is a major public health problem in the United States (US) and other countries. In the US, opioid overdose contributes to a significant number of accidental deaths. Centers for Disease Control and Prevention (CDC) data indicate that in 2014 drug overdose deaths from prescription opioids and heroin reached almost 29,000 – or an average of 78 fatalities daily. CDC data for 2014 indicate the rates of increase in opioid overdose fatalities over the prior year were highest for synthetic opioids, such as fentanyl, and heroin (1).

Opioids include illegal drugs, such as heroin and illicitly manufactured synthetic opioids such as fentanyl, as well as prescription opioid medications, such as morphine, codeine, methadone, oxycodone, hydrocodone, hydromorphone, fentanyl and buprenorphine. The CDC data suggests that in 2014, heroin was implicated in approximately 30% of all fatalities and prescription opioids implicated in approximately 70% of cases. The majority of fatalities arise in non-medical facilities, most frequently at the deceased's home (1).

Various federal agencies including Substance Abuse and Mental Health Services Administration (SAMHSA) and CDC have identified heightened risk factors for opioid overdose. These include, but are not limited to, the chronic use of higher dose opioids, a current or past opioid use disorder diagnosis or opioid overdose event, or illicit opioid use.

The public health response to the epidemic involves (i) increasing education about opioid overdose risks and changing prescriber opioid prescribing practices, (ii) expanding access to naloxone and (iii) increasing access to opioid dependency treatments.

b. Expanding Access to Naloxone

As a narcotic antagonist, naloxone displaces opiates from receptor sites in the brain and can reverse respiratory depression that is usually the cause of overdose deaths. Naloxone has been approved in injectable form for over 40 years. It can be an effective treatment for suspected opioid overdose if an adequate dose is administered in time.

CDC data indicate that most opioid overdose deaths happen in the community (rather than medical facilities), and so many stakeholders have called for the development and Food and Drug Administration (FDA) approval of easy-to-use naloxone formulations intended for emergency administration by individuals (including non-medically trained individuals), at the site of a suspected opioid overdose.

c. Naloxone Products in Use in Community Settings

There are multiple naloxone products used to treat opioid overdoses in the community today, each with differing pharmacokinetic profiles.

The FDA granted fast track designation and approved, under priority review, two new formulations of naloxone intended for community use. Specifically:

- **Narcan[®] Nasal Spray**, 4mg/0.1ml naloxone hydrochloride nasal spray. Narcan Nasal Spray is a single-use, drug-device combination product. It is intended for use as an emergency treatment in all settings by individuals to treat those suspected of experiencing the potentially life threatening effects of an opioid overdose while awaiting emergency medical attention. In pharmacokinetic studies, the dose adjusted bioavailability of a single 4 mg dose of Narcan Nasal Spray is approximately 47% as compared to naloxone administered by intramuscular (IM) injection. Narcan Nasal Spray is supplied in packs of two doses (2).
- **Evzio[®] Injection**, 0.4 mg/0.4mL naloxone hydrochloride auto-injector. Evzio is a single-use, drug-device combination product approved for the same indication as Narcan. It is an auto-injector with a trainer and speaking instructions. In pharmacokinetic studies, each Evzio achieved equivalent exposure to 0.4 mg naloxone administered by subcutaneous or IM injection. It is supplied in packs of two doses plus one trainer device (3).

Non-FDA approved Improvised Nasal Naloxone Kit. The non-FDA approved nasal route using naloxone hydrochloride injection, 2 mg/2 mL vials combined with a mucosal atomizer device for an improvised nasal naloxone kit has existed for many years, and is still widely used in EMS programs and by communities who seek to address the public health problem of opioid overdose. The pharmacokinetic properties of the improvised nasal kit is not published. In particular, the impact of the formulation and large volume sprayed (2 mL) on bioavailability is not known and thus the exposure cannot be estimated. The FDA has stated in the Summary

Review for Regulatory Action for Narcan[®] Nasal Spray: *“There is evidence that the off-label use of naloxone by the intranasal route has been effective in reversing opioid overdose in many cases. However, there are no data that specifically quantitate the success rate, leaving the question of whether there are situations that could have benefited from a higher dose of naloxone. Unpublished pharmacokinetic data suggest that naloxone levels following off-label use by the intranasal route are lower than by the approved routes of administration. The lowest effective dose of naloxone is unclear, and is likely dependent on a number of factors, including dose, route of administration, and the amount and type of opioid involved in the overdose.”*(4).

Intramuscular injections. Some community based harm reduction organizations dispense 0.4mg/mL naloxone hydrochloride intramuscular injections.

In summary, there are multiple naloxone products in use in the community. Differences in the dose, routes of administration and formulations of these products expose patients, perhaps unwittingly, to different pharmacokinetic naloxone profiles and potentially sub-optimal clinical outcomes.

d. No Single Effective Naloxone Dose.

There is no single effective dose for all opioid overdoses. Many, often unknown, factors determine an adequate dose. These factors include opioid related factors such as the specific opioid(s) consumed, the opioid dose/formulation, administration mode, and concurrent medications taken (e.g. benzodiazepines); patient related factors, such as underlying diseases (e.g. respiratory illnesses), opioid tolerance, genetic make-up of the patient, and exogenous stimulatory factors; and naloxone related factors (dose and formulation) (5-7).

e. Dose Considerations for Naloxone Products Intended for Community Use

Injectable formulations of naloxone have been used for many years in clinical settings and the FDA approved labeling recommends an initial doses of 0.4mg to 2mg naloxone by the IM or intravenous (IV) route of administration, followed by repeat doses up to a total dose of 10mg (8). Inherent in the dosing instructions in the FDA approved labeling for injectable naloxone formulations are the assumptions that (i) a clinician is immediately available to determine a patient specific appropriate initial dose between 0.4 mg and 2 mg naloxone by injection and a rate of titration for repeat doses, if required; (ii) additional doses of naloxone, as may be required, are available to achieve an adequate dose; (iii) medical monitoring expertise and equipment to assess respiratory depression necessary to support clinical decision-making, are available.

In contrast, an opioid overdose witness, equipped with a naloxone formulation in a community setting may be solely reliant on that product as an initial emergency treatment to bridge to the arrival of medical help. As previously stated, there are many unknown factors that determine the appropriate dose. In addition, the witness may not have access to medical training to inform initial emergency dose or titration decisions, access to medical monitoring equipment, alternative

resuscitative techniques, or additional doses of naloxone. Further, non-medically trained individuals, in particular, may be at increased risk of needle-stick injury.

The FDA has advised that to support FDA approval of naloxone intended for community use, using the 505B(2) regulatory pathway, a sponsor's proposed product should achieve exposure at least comparable to the lowest FDA approved dose (0.4mg intramuscular injection) (9).

2. COMMUNITY USE NALOXONE RECOMMENDATIONS

As treatment with naloxone is expanded beyond the hospital setting into the community setting it is critical that the available naloxone dose is consistently adequate for the emergency treatment of an opioid overdose and can be readily and rapidly administered by the witness without exposure to needle-stick injury.

As it is impossible to select an appropriate dose in advance of an overdose event, to be confident a consistently adequate dose will be available, the sponsor recommends that all naloxone products dispensed for community use in the event of an opioid overdose, rapidly meet a single threshold for exposure and onset that approximates 2mg naloxone administered by injection (the high end of the established safe and effective initial dose range), rather than 0.4mg (the low end of the initial dose range).

Any naloxone product intended for use in non-medical settings should be administered as a fixed efficacious dose to ensure that the optimal initial dose is administered as quickly as possible.

Further, the ease of use, accuracy and reliability of any manually operated device must be adequately demonstrated per FDA guidelines. The product should also be supplied with a back-up or additional device, in the event of misadministration or device failure. [Appendix \[1\]](#) includes further information on device considerations in respect of Narcan Nasal Spray 4mg.

These recommendations are underpinned by the relatively favorable risk/benefit profile of naloxone, particularly for non-opioid dependent persons; the urgent need to rapidly achieve higher naloxone exposure to counter the dramatic rise in rapid onset, high potency synthetic opioids (e.g. fentanyl); and the criticality of ensuring that as access is expanded to new lay users in the community setting, that naloxone products intended for community use allow anyone to safely, rapidly and readily administer a dose that achieves a consistently adequate initial exposure to bridge to medical care.

3. FACTORS SUPPORTING SPONSOR RECOMMENDATIONS

a. Naloxone Favorable Risk/Benefit Profile

Injectable formulations of naloxone have been FDA approved for the treatment of opioid overdose symptoms for many years at initial doses of 0.4mg to 2mg naloxone by the IM or

IV route of administration, followed by repeat doses up to a total dose of 10mg (8). Naloxone is well established as an effective treatment for the symptoms of opioid overdose, if an adequate dose is administered in time. A key risk of administering too little naloxone too late in opioid overdose, is potential morbidity and mortality.

Naloxone is an essentially pure opioid antagonist, i.e., it does not possess the “agonistic” or morphine-like properties characteristic of other opioid antagonists. While the mechanism of action of naloxone is not fully understood, *in vitro* evidence suggests that naloxone antagonizes opioid effects by competing for the mu, kappa, and sigma opiate receptor sites in the Central Nervous System (CNS), with the greatest affinity for the mu receptor. When naloxone hydrochloride is administered by IV injection, the onset of action is generally apparent within 2 minutes; the onset of action is slightly less rapid when it is administered by subcutaneous injection (SC) or IM injection (8). Appendix [2] and [2a] includes further information on naloxone pharmacokinetic and pharmacodynamics profile.

When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity. Naloxone has not been shown to produce tolerance or cause physical or psychological dependence (8). Naloxone bolus doses of up to 90 mg daily and 5.4mg/kg have been administered to non-opioid dependent persons without any reported adverse events (6, 10).

The known effective target plasma level varies and depends on multiple, often unknown, factors. These factors include opioid related factors such as the specific opioid(s) consumed, the opioid dose/formulation, administration mode, and concurrent medications taken (e.g. benzodiazepines); patient related factors, such as underlying diseases (e.g. respiratory illnesses), opioid tolerance, genetic make-up of the patient, and exogenous stimulatory factors; and naloxone related factors (dose and formulation) (5, 7).

The complexity is compounded in situations involving the adulteration of ‘known’ illicit opioids, such as heroin, with unknown, numerous, synthetic and cheaper fentanyl analogues of differing potencies (11). A review of the FDA AERS database, by Adapt Pharma revealed that in the past 18 years there has been 5,114 cases that mention naloxone alone or in combination with another agent as the primary or secondary suspect product. No identifiable signal or trend was observed. Similarly, albeit in a much smaller time period, Adapt has identified no signal or trend in the 7 months since launch of Narcan Nasal Spray.

The key warnings related to naloxone include:

- Risk of Recurrent Respiratory and CNS Depression as the duration of effect of naloxone may be shorter than the opioids been antagonized. This is thought to be a result of naloxone's more rapid dissociation from opioid receptors. It is recommended that medical care is sought, surveillance maintained and additional naloxone doses administered, if needed (2).
- Risk of Limited Efficacy with Partial Agonists or Mixed Agonists/Antagonists. Naloxone may have incomplete reversal of opioid overdose symptoms caused by partial agonists or mixed against/antagonists and higher or repeat doses are recommended, if required (2).
- Abrupt postoperative reversal of opioid depression may result in adverse cardiovascular effects. These events have primarily occurred in patients who had preexisting cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects. It is recommended these patients be monitored closely in an appropriate healthcare setting (2).
- Precipitation of Severe Opioid Withdrawal: Use in patients who are opioid dependent may precipitate opioid withdrawal. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. It is recommended these patients be monitored for the development of opioid withdrawal (2). Withdrawal symptoms, may appear within minutes of administration and subside in about 2 hours. The severity and duration of the withdrawal syndrome are related to the dose of naloxone and to the degree and type of opioid dependence (8). While unpleasant, symptoms are generally not life-threatening (6, 12, 13). In non-opioid dependent individuals (e.g. children that accidentally ingest opioids or elderly persons that mix up opioid dose), no withdrawal symptoms present. Appendix [3] includes further information on Acute Withdrawal Symptoms.

In summary, the majority of opioid overdose deaths involve prescription opioids and happen in the community, most frequently at home (14). Naloxone's risk/benefit profile strongly favors rapidly achieving naloxone exposure approximating the high end of the established safe and effective initial dose range (2mg parenterally), because the consequences of under dosing or delayed dosing are life threatening or may lead to permanent disabilities. No withdrawal symptoms present in non-opioid dependent patients.

In respect of opioid dependent persons, while it is possible to induce a rapid opioid withdrawal, these side effects are rarely life threatening and must be viewed in the context of the risk of mortality or morbidity from achieving too little naloxone exposure too late.

b. Dramatic Rise in Opioid Overdoses From Rapid Onset High Potency Opioids (e.g. fentanyl)

In 2014, CDC data indicate total opioid overdose deaths increased 14% over the prior year. While the majority of opioid overdose deaths reportedly involved prescription opioids, very significant increases in opioid overdose deaths from heroin (+26%) and synthetic opioids such as fentanyl (+80%) were recorded in 2014 compared to the prior year (15).

State level data highlight the dramatic increase in opioid overdose deaths involving highly potent rapid onset fentanyl. Examples include Massachusetts, which reports that fentanyl was implicated in 2 of every 3 opioid overdose deaths in the first six-months of 2016. Likewise, New Hampshire reported that fentanyl was implicated in almost half of opioid overdose deaths in 2014, up from 11% in 2013, while Ohio reported fentanyl was implicated in 24% of opioid overdose deaths in 2014, up from just 6% in 2013 (11, 16, 17).

The increase in reports of opioid overdose deaths involving fentanyl mirrors data from the Drug Enforcement Agency (DEA) that reports a 400% increase in seizures of fentanyl by its officers in 2014 versus 2013 (18).

Federal agencies such as CDC, DEA have rapidly increased warnings about fentanyl to the public and indeed to law enforcement officials. CDC issued fentanyl reports in June 2013 and August 2013, and a Health Alert in October 2015 (11). In March 2015, the Drug Enforcement Agency (DEA) issued a nationwide alert on fentanyl as a threat to health and public safety. DEA Administrator Michele Leonhart commented, “Drug incidents and overdoses related to fentanyl are occurring at an alarming rate throughout the United States and represent a significant threat to public health and safety” (19). Original media reports concerning opioid overdose involving fentanyl reached 1,000 in the past six-months alone. Many of these federal agency warnings and media pieces focused on reports that prescription opioids and heroin are being ‘adulterated’ with highly potent, rapid onset illicitly manufactured fentanyl which may require additional multiple naloxone doses to effect a reversal. Law enforcement officials are reportedly at-risk in the course of undertaking their duties as they may be inadvertently exposed to fentanyl through transdermal absorption or inhalation (20).

Fentanyl, is estimated to have 100 times the analgesic effect of morphine (21) so a very small dose can be dangerous. It is highly lipophilic (22) and prescription fentanyl’s respiratory depressive effects peak in 5-15 minutes and, depending on dose, these effects may last for many hours (21). This compares to an estimated 30 minutes for morphine to reach peak respiratory depressive effects (23). In-vitro models confirm that naloxone, which is also highly lipophilic, can potently displace fentanyl from opioid receptors (24).

Effective dose of naloxone

It has been estimated that 50% opioid receptor occupancy by naloxone is required to treat the effects of an opioid overdose (25). Two studies in health volunteers assessed the naloxone dose required to block 50% of opioid receptors. These studies concluded that a 2mg dose administered by IV injection achieved 80% opioid receptor occupancy, while a 1mg dose administered by IV injection achieved 50% opioid receptor occupancy. The effectiveness of naloxone, and thus the exposure required, will depend on the opioid dose, the potency of the opioid in binding receptors, the lipophilicity of the opioid in crossing into the CNS system and the elimination half-life of the opioid, together with patient factors (7, 26). Appendix [2] and [2a] includes further information on naloxone pharmacology.

The complex pharmacology of appropriate dosing is further compounded as often the fentanyl involved is illicitly manufactured without normal procedures or controls and may be introduced surreptitiously into heroin or prescription painkillers. Reports from the field confirm the need for additional naloxone doses to reverse opioid overdoses including those involving more potent fast onset synthetic opioids. For example, Massachusetts EMS report that in 2005 naloxone (per protocol either 0.4mg-2mg injection or 2mg improvised nasal atomizer) was administered more than once in 33% of incidents, an increase of 40% rise compared to 2013 (27). An October 2015 CDC Health Advisory states "...a higher dose or multiple number of does per overdose event may be required to revive a patient due to the high potency of [fentanyl]." (11). Finally, case studies in the literature report the need for higher and prolonged naloxone administration in treating opioid toxicity from adulterated fentanyl tablets. For example, Sutter et al. report on 18 patients that were admitted to hospital having taken adulterated fentanyl tablets who required higher and prolonged naloxone treatment than is typical (28). Appendix [2a] and [4] include further information on fentanyl pharmacology and pharmacokinetics.

In summary, the dramatic rise across the nation in opioid overdose deaths involving high potency and rapid onset synthetic opioids such as fentanyl, emphasize the need to rapidly achieve a consistently adequate initial naloxone exposure as a bridge to medical care. While overdoses from fentanyl can be reversed with naloxone, because of fentanyl's potency, rapid onset and long lasting respiratory depressive effects, the window of intervention may be narrower and rapid attainment of a higher target plasma level of naloxone may be needed.

The consequences of administering too little naloxone too late can be life-threatening and could undermine the effectiveness of the public health response to the crisis if a naloxone product intended for community use achieves too low a naloxone exposure, too slowly. This reinforces the urgent need to ensure all naloxone products intended for community use can be safely, rapidly and readily administered to rapidly achieve exposure approximating that achieved by a total 2 mg dose of naloxone hydrochloride administered by IM injection.

c. Expanded Naloxone Access to New Users in Non-Clinical Settings

CDC data indicate the majority of opioid overdose deaths happen in non-medical facilities, most frequently in the decedent's home (14). Expanding access to naloxone is a key element of the public policy response to the opioid overdose epidemic. While naloxone hydrochloride, administered by injection, has been approved by FDA and used for more than 40 years to treat opioid overdose symptoms, its use has historically been intended for clinicians and other medically trained personnel, such as EMS.

Many states have enacted laws to both support expanded access and administration of naloxone, and to encourage opioid overdose witnesses to seek medical care. Federal agencies and states have also contributed funds to purchase naloxone. A growing list of first responders including law enforcement, firefighters, EMS, and harm reduction organizations are now equipped with naloxone. Though naloxone remains prescription status, more recently, states have supported naloxone pharmacy access to new user groups to include patients and their caregivers without requiring an individual prescription (under various standing order, local protocols or collaborative practice agreements). Leading retail pharmacies are rolling out these programs, which have the effect of providing naloxone access to patients and/or their caregivers without a physician prescription specific to the recipient. For example, CVS Health has announced that it offers naloxone without a patient specific prescription in 31 states (29).

In summary, as the group of potential naloxone administrators expands from clinicians, EMS and those already familiar with naloxone administration, to any potential witness (including non-medically trained individuals), it is even more critical that naloxone products intended for community use can be safely, readily and rapidly administered and rapidly achieve a consistently adequate fixed initial naloxone exposure a bridge to emergency medical care.

As previously highlighted, there are many unknowns that determine appropriate exposure in an opioid overdose situation. However, titrating to an efficacious dose in a community setting is not viable as witnesses may lack the medical expertise, multiple doses and equipment to dose select, monitor and titrate. In addition, these individuals may not understand the different naloxone exposures achieved (and related treatment consequences) with multiple different naloxone products intended for community use.

CDC data indicate that prescription opioids account for the majority of opioid overdose fatalities and the majority of all opioid overdose fatalities occur in the community most frequently at home (14). Many of these incidents may involve non-opioid dependent patients that do not present with withdrawal symptoms. In these cases, there is little downside to naloxone products that achieve exposure approximating the high end of the established safe and effective initial dose range.

Narcan Nasal Spray

FDA approved an intranasal (IN) form of naloxone, Narcan Nasal Spray, which delivers a 4 mg initial dose of naloxone hydrochloride in a single spray. Narcan Nasal Spray is indicated for the emergency treatment of known or suspected opioid overdose. It is not a substitute for medical care which should always be sought (2).

The bioavailability of a single 4 mg dose of Narcan Nasal Spray is approximately 47% of that achieved by IM injection (2). Thus, a single administration of Narcan Nasal Spray 4 mg rapidly achieves plasma exposure to naloxone approximately 5 times greater than that achieved by a single 0.4 mg naloxone by IM injection. Narcan Nasal Spray is supplied as a carton containing two devices (2).

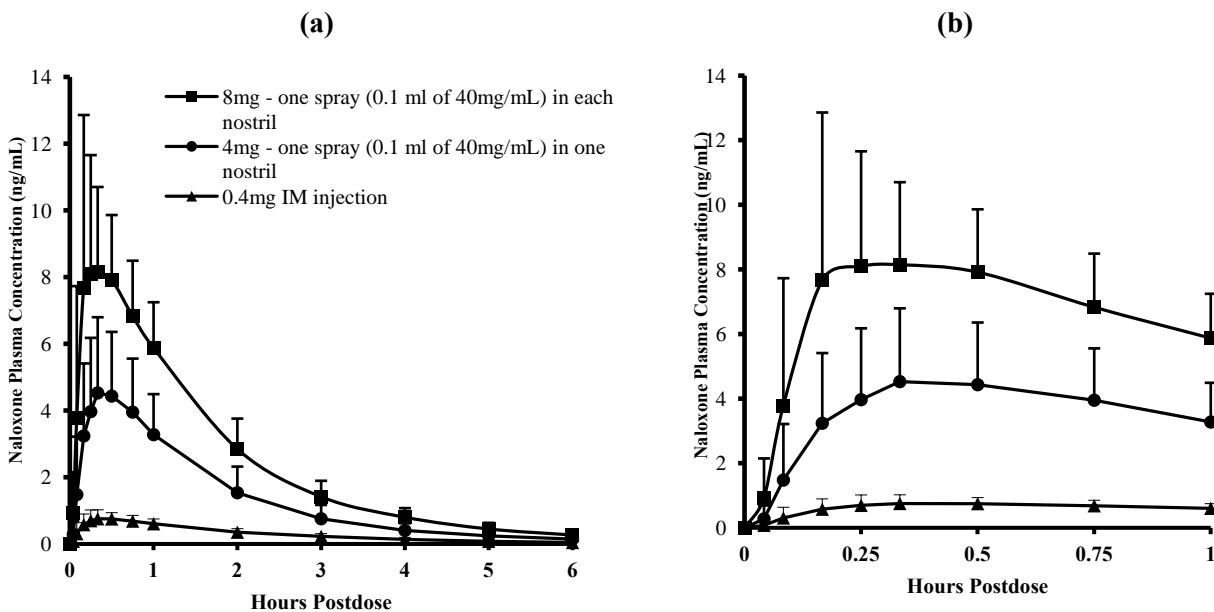
The rate of absorption and time to reach efficacious levels of Narcan Nasal Spray is as fast as naloxone administered by IM. The labeling of Narcan Nasal Spray highlights the rapid absorption of both a single and two-dose administration as compared to IM naloxone dosed at 0.4 mg. Thus, the approval of Narcan Nasal Spray was supported by the fact that the rate of absorption more than met, and the exposure and duration of plasma concentrations were higher and longer, respectively, than the 0.4 mg IM injection (30).

Table–1. Pharmacokinetic Parameters (CV%) of Naloxone Following Single Intranasal Administration and Intramuscular Injection of Naloxone to Healthy Subjects

Parameter	4 mg – One Spray 40 mg/mL IN	8 mg – Two Sprays 40 mg/mL IN	0.4 mg IM
t _{max} (h) [†]	0.50 (0.17,1.00)	0.33 (0.17,1.00)	0.38 (0.08,2.05)
C _{max} (ng/mL)	4.83 (43.1)	9.70 (36.0)	0.877 (30.5)
C _{max} /Dose (ng/mL/mg)	1.21 (43.1)	1.21 (36.0)	2.19 (30.5)
AUC _{0-t} /Dose (h*ng/mL/mg)	1.97 (37.4)	1.91 (23.0)	4.29 (22.9)
AUC _{0-inf} (h*ng/mL)	7.95 (37.3)	15.5 (22.7)	1.76 (22.6)
AUC _{0-inf} /Dose (h*ng/mL/mg)	1.99 (37.3)	1.93 (22.7)	4.40 (22.6)
Relative BA (%) vs. IM	46.7 (31.4)	43.9 (23.8)	100
C _{max} /Dose Ratio (IN vs. IM) (%)	56.6 (47.5)	55.3 (41.4)	100
t _{1/2} (h)	2.08 (29.5)	2.10 (32.4)	1.24 (25.9)

[†] t_{max} reported as median (minimum, maximum)

Figure 1 Mean \pm SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intranasal Administration and Intramuscular Injection



The Narcan Nasal Spray device delivers its drug load with a single activation and does not allow for partial dosing. Narcan Nasal Spray administration is needle-free and the device is ready-to-use, without assembly, which both support expanded access to naloxone and are important features for safety and efficacy. [Appendix \[1\]](#) provides additional information on the device features of Narcan Nasal Spray.

In approving Narcan (naloxone hydrochloride) Nasal Spray at a fixed initial 4 mg intranasal dose (which achieves plasma exposure to naloxone as rapidly and in a range approximating that achieved by a total 2 mg dose of naloxone hydrochloride administered by intramuscular injection), the FDA has already considered the criticality of dose/target plasma levels, accuracy and reliability of the device and time to onset. These three factors are critical in rapidly and consistently achieving an effective initial naloxone exposure when administered for the emergency treatment of suspected opioid overdose in a community setting.

Narcan Nasal Spray Field Experience

Narcan Nasal Spray 4 mg has been on the market for 6 months. In excess of 125,000 cartons have been dispensed (or 250,000 doses). In August it became the most frequently prescribed form of naloxone, according to IMS Health. The adverse events reported to the Sponsor or solicited as part of a Narcan Nasal Spray use survey (detailed below) are consistent with the known naloxone profile and there has been no trend in safety signal.

In an effort to understand the initial experiences with Narcan Nasal Spray in the community setting, Adapt Pharma recently commissioned a survey of community organizations that have implemented use of the product. 40 interviews were conducted with organizations that acquired 18,637 cartons of Narcan Nasal Spray. Estimates of the total number of opioid overdose reversals specifically using NARCAN Nasal Spray were provided by 15 organizations (accounting for 7,669 units distributed by Adapt Pharma); estimates from these individuals totaled more than 1,400 overdose reversals.

Eight organizations provided various levels of case report summary data on 261 attempted reversals, accounting for 350 total doses of NARCAN Nasal Spray administered; 1 dose was used in 165 (63%) of these reversals, **while 2 doses were used in 83 (32%) reversals.**

Narcan Nasal Spray was reported to be effective in all but 3 attempted overdose reversals. In 2 unsuccessful reversals, the product was reported to be not administered in time. No additional information was available for the third unsuccessful reversal. Doses ranging from 4-16 mg were reportedly administered. The vast majority of reported events were consistent with opioid withdrawal and non-serious. The events are consistent with the known naloxone profile and there has been no trend in safety signal.

In [Appendix \[5\]](#) we provide more information on the Field Experience Survey conducted by Synchrony Medical on behalf of the Sponsor.

Discussion

Adapt has previously discussed, in general terms, the need for higher doses of naloxone. Indeed, a Citizen Petition was previously submitted, [Appendix \[6\]](#), to the Commissioner requesting the establishment of appropriate guidance for all naloxone products intended for the emergency treatment of suspected opioid overdose in all settings (including non-medical settings) by individuals (including non-medically trained individuals), that include the optimal fixed initial dose for each route of administration as well as the required exposure levels to achieve an efficacious onset of action and duration of effect.

Conclusion

- a. There are a wide range of naloxone products achieving different naloxone exposures being used in the community today.
- b. While titration to a patient specific adequate dose is possible in a clinical setting, in the community setting (out-of-hospital) the sponsor believes the goal for ALL community use naloxone products should be to safely, rapidly and readily achieve a consistently adequate initial naloxone exposure to bridge to the arrival of medical care.
- c. To avoid confusion in the community setting and recognizing the multiple unknown factors that impact an adequate dose, the Sponsor believes that one common threshold of onset and exposure should apply to all naloxone products intended for community use.
- d. In selecting an appropriate threshold, the safety profile of naloxone doses in the established effective range were reviewed, together with naloxone post marketing surveillance reports and field experience with Narcan Nasal Spray. Naloxone has been used for many years and has a relatively favourable risk/benefit profile. In particular, naloxone has been administered safely at very high doses to patients that are not-opioid dependent and do not present with withdrawal symptoms. Naloxone may precipitate opioid withdrawal symptoms in opioid dependent patients, which while unpleasant, subside after about 2 hours and are rarely life-threatening. The risk/benefit must be viewed not only in the light of naloxone's potential to reduce opioid overdose related morbidity and mortality but also the key risk of dispensing community use naloxone formulations that achieve too low exposure to naloxone too late. The Sponsor believes the risk/benefit profile supports a threshold onset and exposure of naloxone that approximates that achieved at the high end (2mg injection) of the established safe and effective initial dose range.
- e. Secondly, high potency, fast onset and longer acting opioids (such as fentanyl) are implicated in a rapidly growing proportion of opioid overdose fatalities. Fentanyl is highly lipophilic and 100 fold more potent than morphine. While naloxone potently displaces fentanyl at opioid receptors, the literature and in-field reports suggest stronger/additional naloxone doses than have been typically used are required. Compounding a complex pharmacological picture, much of the fentanyl is reportedly illicitly manufactured and used to adulterate heroin or prescription opioid pills. The Sponsor believes the risk to public and law enforcement health from highly potent rapid onset opioids urgently requires a threshold onset and exposure of naloxone that approximates that achieved at the high end (2mg injection) of the established safe and effective initial dose range. The risk is clear that the public policy response of expanded naloxone access may be sub-optimal if the exposure achieved by naloxone products used in the community is inadequate or insufficient quantities are on-hand to reverse respiratory depression induced by synthetic opioids such as fentanyl. Naloxone access is being expanded to new groups of users via novel distribution channels, such as pharmacy

naloxone access programs without individual prescriptions, for example under standing orders. These new users and settings lack the medical expertise or equipment to titrate to an individualized naloxone dose. In light of these new paradigms, it is recommended:

- That the optimal effective initial target plasma levels for naloxone products intended for emergency treatment in the community should achieve exposure and onset that approximates 2mg naloxone administered by injection (the high end of the established safe and effective initial dose range).
- FDA's traditional pharmacokinetic parameters (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) should be maintained but alone are NOT sufficient to account for the early clinical exposure needed to achieve efficacy with naloxone containing products intended to treat opioid overdose. Critical pharmacokinetic issues regarding naloxone administration are the rate of absorption and the time to reach plasma concentrations that correlate with efficacy, in this case, the reversal of respiratory depression. Thus, the standard criteria for AUC and C_{max} would not be adequate to cover the time period of the onset of action.
- FDA should also consider the duration of exposure such that naloxone plasma levels are maintained above a threshold for period (for example, at least 2 hours) to allow for subjects to recover from the opioid overdose and for rescue medical personnel to provide assistance.
- FDA should only approve a formulation, which cannot be inadvertently or purposefully partially administered. The formulation should require that the dose is actuated in a simple movement that cannot be stopped once started. This ensures the intended dose is administered and eliminates critical delays in administering divided doses.
- Human factor and label comprehension studies should be completed in representative study population including teenagers and low literacy adults. These studies should ensure that the formulation is intuitive to use and recognizable to the individual (including non-medically trained individuals), as a device that is for the intended route of administration only. The human factor and label comprehension studies should support the use of the proposed formulation by the intended population (including pediatrics), with or without device training.
- Since speed to delivery is critical, FDA should establish standards for the rate at which the device can be removed from packaging and administered in an emergency situation.

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COMMUNITY USE NALOXONE DOSE

ADAPT PHARMA

OCTOBER 5 2016

AGENDA

- 1. Current Practice**
- 2. Recommendations**
- 3. Rationale for Recommendations**
- 4. Narcan Nasal Spray**
- 5. Conclusion**

CURRENT PRACTICE FOR COMMUNITY USE NALOXONE

Multiple Naloxone Products with Differing PK Profiles are in Community Use

- FDA approved
- Improvised nasal atomizers
- Injections

Effective Dose Depends on Often Unknown Factors Specific to OD Event

- Opioid [1]
- Patient [1]
- Naloxone

Clinical Select Dose and Titrate Approach Not Viable in Community Setting

- Clinical Setting: Select Dose (0.4-2 mg injection) and Titrate (up to 10mg injection) [2]
- Community Setting: Lack medical equipment/expertise, multiple doses to Select Dose and Titrate

PK-Pharmacokinetics, OD-Overdose,

[1] Dahan A et al. *Anesthesiology*. 2010; [2] *Naloxone Hydrochloride Prescribing Information*; [3] *Role of Naloxone in Opioid Overdose Fatality Prevention*

RECOMMENDATIONS FOR COMMUNITY USE NALOXONE

Goal for Community Use Naloxone as a bridge to medical care

- Safely, readily and rapidly administration
- Consistently adequate exposure to naloxone

Single PK/PD Threshold for All Community Use Naloxone Products

- Onset and Exposure Approximating 2mg Injection (the High End) not 0.4mg Injection (the Low End) of the Established Safe and Effective Recommended Initial Dose Range for Injection
- Supplied with a back-up or additional dose/device

Community Use Naloxone Device Attributes are as Critical as Dose

RATIONALE FOR RECOMMENDATIONS

Favourable Risk/Benefit Profile

Dramatic Rise in Opioid Overdoses from Rapid Onset High Potency Opioids

Expanded Access to New Users in Non-Clinical Settings

Favourable Risk/Benefit Profile

EFFICACY LINKED TO ADEQUATE EXPOSURE AND TIME

Naloxone has been FDA Approved for About 45 Years[1]

- Reverses symptoms of Opioid OD (prescription narcotics, heroin, fentanyl and its analogues)
- Effective if an adequate exposure is achieved in time (including time to administration and onset)
- Binds to opioid receptors temporarily displacing opioids [1]

Receptor Occupancy Data Support Recommended 2mg IV Exposure

- At least 50% opioid receptor occupancy by naloxone required to reverse respiratory depression [3]
- 1mg naloxone injection achieves 50% coverage and 2mg achieves 80% coverage in healthy subjects [3,4]
- Adequate naloxone exposure depends on often unknown factors: [2]
 - > Opioid (amount, type, concurrent substances taken, time)
 - > Patient (respiratory illnesses, tolerance, receptor condition in opioid dependents)

[1] Naloxone Hydrochloride Prescribing Information [2] Dahan A et al. *Anesthesiology*. 2010 [3] Melichar et al 2003 *EurJPharmacol*. 459:217-219; [4] Kim S et al. *J Nucl Med*. 1997;38:1726-1731

NALOXONE SAFETY

Naloxone Warnings [1]

- Duration of effect
- Limited Efficacy in partial agonists; mixed agonist/antagonists
- Possible CV effects in those with pre-existing condition
- Withdrawal in opioid dependent persons

Naloxone Profile

- No reported AEs in non-opioid dependents at high naloxone doses (up to 90mg per day) [2]
- Does not produce tolerance or dependence [1]

CV- cardiovascular AEs Adverse events,

[1] *Naloxone Hydrochloride Prescribing Information* [2] *Janinski et al Journal of Pharmacology 1967*

WITHDRAWAL IN OPIOID DEPENDENTS

Withdrawal May be Induced in Chronic Opioid Users [1,2,3,4]

- Severity and duration depend on naloxone dose and patient opioid dependency [5]
- Wide range of estimated incidence (7-46%) in those receiving 1-2mg IV injection [1]
- Possible adverse effects (including pulmonary edema, arrhythmias and seizure) thought to be linked to underlying disease process, opioids, hypoxia, other drugs used or underlying conditions [1,3]

Withdrawal Symptoms Generally Not Life-Threatening and Subside in 30-60 Minutes [1,2,3,4]

No Withdrawal in Non-Opioid Dependent

- Majority of opioid overdose deaths involve prescription opioids including for example, accidental or mistaken consumption by child or a senior

Acute Withdrawal Symptoms [1,4]

- Agitation
- Yawning
- Diaphoresis
- Rhinorrhoea
- Lacrimation
- Piloerection
- Myalgias
- Nausea
- Vomiting
- Diarrhea

[1] Clarke SF, et al EMJ. Sep 2005;22(9):612-616 [2] Wermeling DP. Therapeutic Advances in Drug Safety. 2015;6(1):20-31 [3] Buajordet I et al. Euro J Emerg Med. 2004; 11(1):19-23 [4] Boyer EW. N. Engl. J. Med. Jul 12 2012;367(2):146-155. [5] Naloxone Hydrochloride Prescribing Information

In Community Setting:

**Risk/Benefit Profile Strongly Favours Achieving Onset and Exposure
Approximating the High End of Initial Dose Range (2mg IV)**

The Consequences of Under Dosing or Delayed Dosing are Life Threatening

RATIONALE FOR RECOMMENDATIONS

Dramatic Rise in Opioid Overdoses from Rapid Onset High Potency Opioids (e.g. fentanyl)

FENTANYL IMPLICATED IN GROWING % OF OVERDOSES

Synthetic opioid OD deaths (e.g. fentanyl) +80% in 2014 versus 2013 [1]

Recent State Data Highlight Alarming Fentanyl Trend

- **Massachusetts** fentanyl implicated in 66% of deaths in 1H16 [2]
- **New Hampshire** fentanyl implicated in 49% of deaths in 2014 (2013:11%) [3]
- **Ohio** fentanyl implicated in 24% of deaths in 2014 (2013: 6%) [4]

Multiple Warnings by DEA and CDC [5]

- Risks to opioid users but also law enforcement and crime lab staff

1. CDC Wonder Database; [2] opioid related overdose deaths among ma residents august 2016;[3] New Hampshire Office of the Chief Medical Examiner [4] CDC Health Advisory Note October 2016; [5] CDC, DEA

FENTANYL REQUIRES HIGH AND RAPID NALOXONE EXPOSURE

Rapid Exposure and Higher Naloxone Dose Needed for Fentanyl ODs [4,5]

- Estimated to be 100 times more potent than morphine [1]
- Highly lipophilic [2] so peak respiratory depressive effects from 5 mins [1] v c.30 mins for morphine [3]
- Much of the fentanyl is illicitly manufactured and surreptitiously introduced to heroin /illicit narcotic pills

Lower Dose Naloxone Products May Deliver Too Little Too Late for Fentanyl

- Massachusetts EMS multiple naloxone administration incidents increased 40% (2015-v-2013) [6]
- CDC Health Advisory "...a higher dose or multiple number of doses per overdose event may be required to revive a patient due to the high potency of [fentanyl]". [7]
- Published case studies highlight need for higher and longer naloxone treatment [8]
- Hardest hit cities reporting need for 5-9 administrations of the improvised nasal naloxone product

[1] Fentanyl Citrate Prescribing Information; [2] Volpe DA, McMahon Tobin GA, Mellon RD, et al. *Regul. Toxicol. Pharmacol.* Apr 2011;59(3):385-390.

[3] Olofsen E, van Dorp E, Teppena L, et al. *Anesthesiology.* Jun 2010;112(6):1417-1427. [4] Melichar et al 2003 *EurJPharmacol.* 459:217-219; [5] Kim HK, Nelson LS. *Exp Opin Drug Saf.* 2015;14(7):1137-1146. [6]. Opioid-related EMS Transports Massachusetts Residents: 2013-2015; [7] CDC HAN 00384 October 2015; [8] Sutter et al *Acad Emer Med* 2016 Jun 20

RAPID ONSET HIGH POTENCY OPIOIDS CONCLUSION

Community Use Naloxone Products that Rapidly Achieve High Naloxone Exposure are Now Needed to Treat Overdoses from Tidal Wave of High Potency:Rapid Onset Opioids

EXPANDED ACCESS TO NEW USERS IN NON-CLINICAL SETTINGS

EXPANDED ACCESS LAY USE IN COMMUNITY SETTINGS

Naloxone Access Expanding to New Users in Community Settings

- Most opioid overdose deaths happen in the community most frequently at home
- Legal framework (naloxone access and good Samaritan laws)
- Pharmacy access programs

Need easy-to-use naloxone presentations that achieve consistently adequate initial exposure in a simple step

- Lay persons lack medical expertise, equipment, or stock of multiple doses to dose select and titrate
- Many unknowns determine an adequate dose

Allow Anyone Safely, Rapidly And Readily Administer A Single Metered Dose

NARCAN NASAL SPRAY

NARCAN NASAL SPRAY

NARCAN NASAL SPRAY

Narcan Nasal Spray 4mg/0.1ml

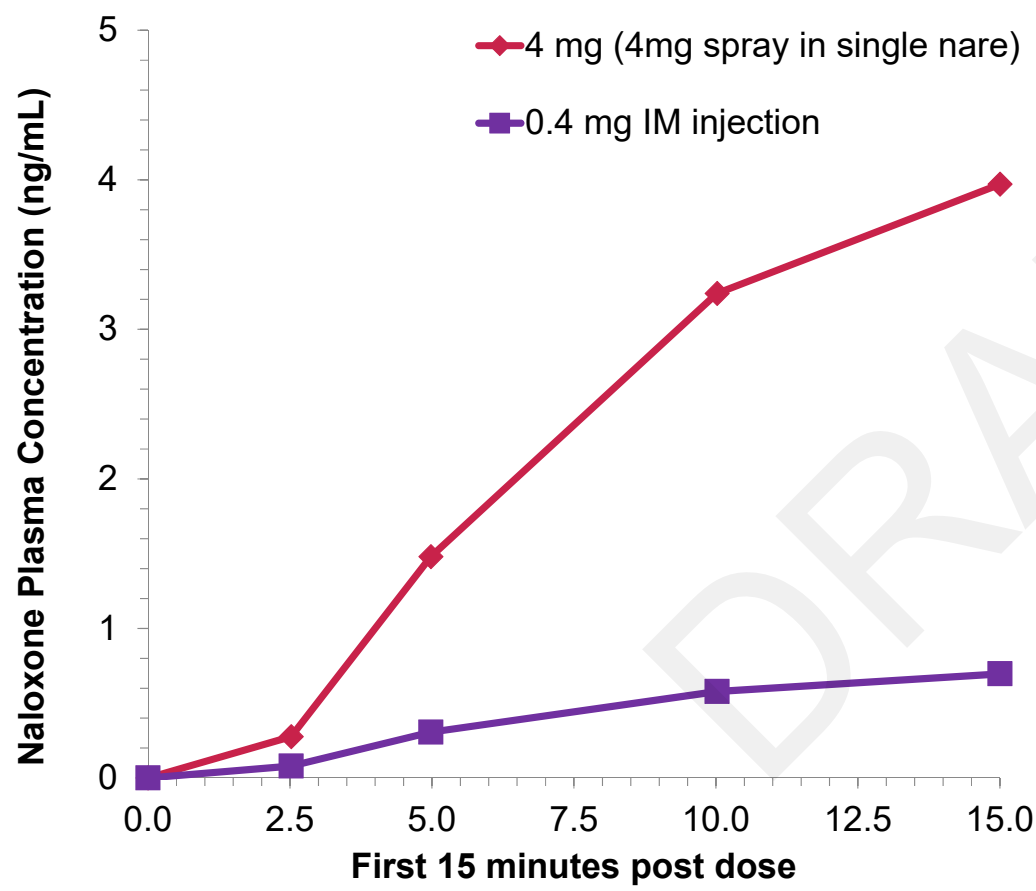
- First FDA approved nasal naloxone – launched in 2016
- For emergency naloxone treatment until medical care arrives
- Needle-free, ready-to-go, lay use
- Supplied as a carton containing 2 devices (total of 8mg available)

Each device achieves 5X the exposure of a 0.4mg IM injection

- Relative bioavailability 47% compared to IM injection
- Onset comparable



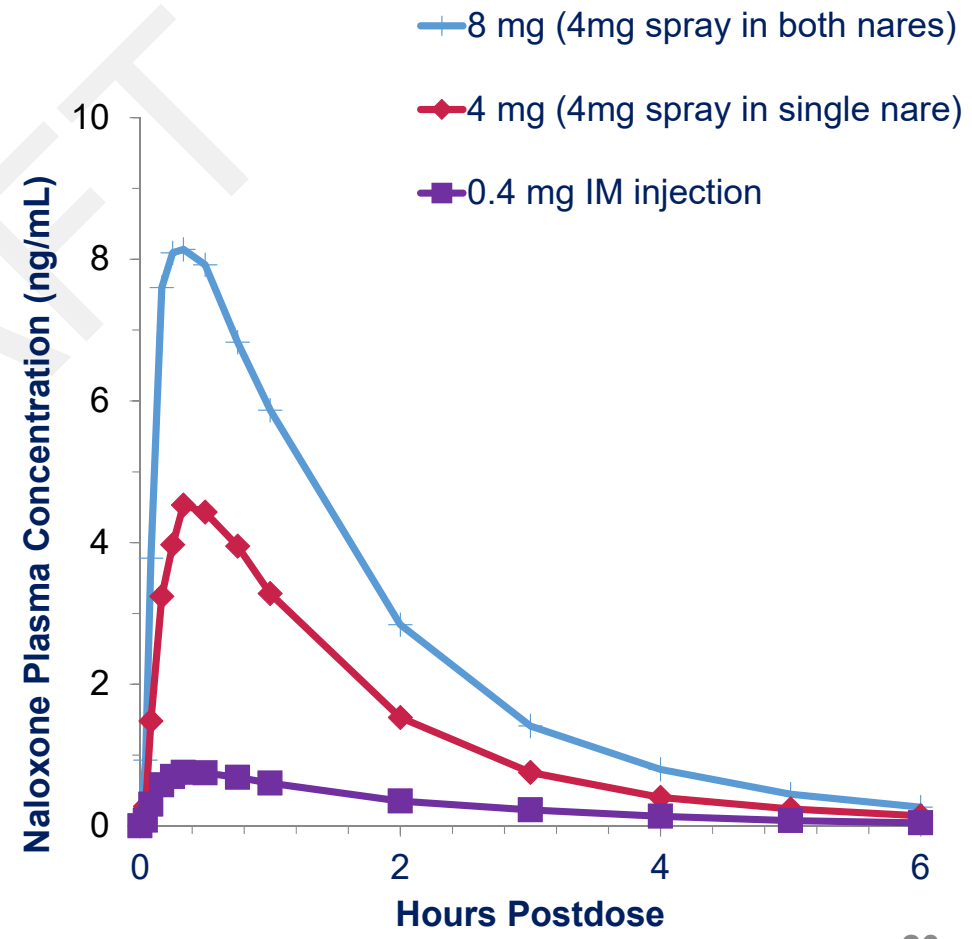
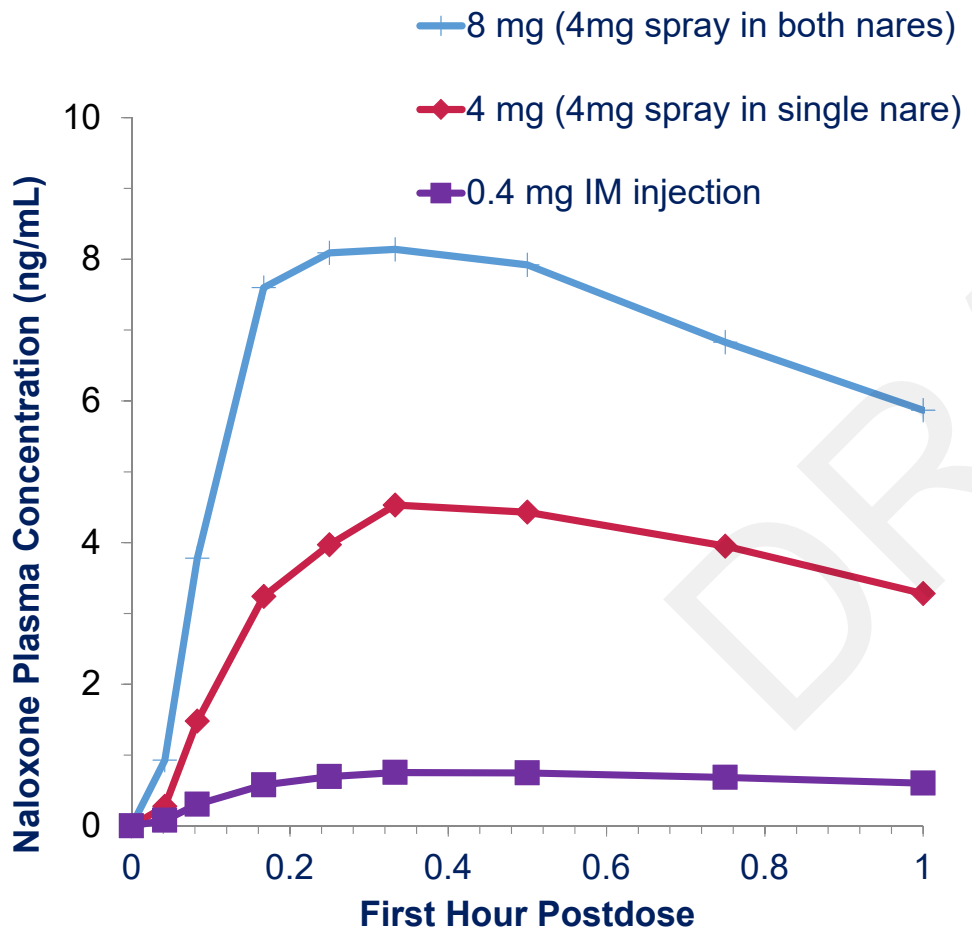
NARCAN EXPOSURE IN CRITICAL FIRST FEW MINUTES



Parameter	4 mg – One Spray	8 mg – Two Sprays	0.4 mg IM
tmax (h)	0.50	0.33	0.38
Cmax (ng/mL)	4.83	9.70	0.877
AUC _{0-inf} (h*ng/mL)	7.95	15.5	1.76
Relative BA (%) vs.IM	46.7	43.9	----

The relative bioavailability of IN-administered naloxone is based on the dose-normalized values of AUC_{0-inf} compared to the IM treatment

NARCAN NASAL RAPIDLY ACHIEVES HIGH NALOXONE EXPOSURE



FIELD EXPERIENCE WITH NARCAN NASAL SPRAY

- 125,000 cartons (250,000 doses) dispensed in first 6 months
- Conducted survey to understand field experience of Narcan Nasal Spray Users
 - > Conducted interviews with 40 organizations that acquired 18,637 Narcan Nasal Spray cartons
 - > 15 organizations (that acquired 7,669 cartons) reported over 1,400 reversals with Narcan Nasal Spray
 - > A subset of 8 organizations provided case report summary data on 261 attempted reversals
 - > 1 dose was used 63% of cases and 2 doses in 30% of cases. Doses ranged from 4-16 mg.
 - > All but 3 attempts were successful, (in 2 cases product not administered in time, one event no information)
- Review of observations/adverse events conducted and no new safety concerns
- The vast majority of reported events were consistent with opioid withdrawal

CONCLUSION

Community Use Naloxone Dosing

- Favourable risk/benefit at recommended initial dose
- Treating overdose from high potency fast acting opioids require high and rapid exposure to naloxone
- Clinical dosing not viable with lay users in community setting

A Key Safety Risk Is Achieving Too Little Naloxone Exposure Too Late

RECOMMENDATIONS FOR COMMUNITY USE NALOXONE

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Community Use Naloxone Device Attributes are as Critical as Dose

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DEVICE SECTION

Narcan nasal spray is supplied as a single 4 mg dose of naloxone hydrochloride in a 0.1 mL intranasal spray. Each Narcan 4 mg dose delivered by intranasal administration is approximately equivalent to a 2 mg dose of naloxone hydrochloride delivered by intramuscular injection. One single dose of Narcan Nasal Spray delivers 4 mg naloxone hydrochloride, it is packed in a carton of two doses. This allows for timely administration of a second dose if necessary, and an initial dose if the first dose was wasted, e.g. in panic situation, misfired into air. The simplicity of use, and therefore expedited administration to the nares cannot be underestimated, especially in those situations, where the witness is unfamiliar with dose administration, where the opioid is highly potent, or is not known, and witness must act rapidly.

Approval of Narcan Nasal Spray is supported by two pharmacokinetic (PK) bioequivalence studies in healthy adult subjects. Additional clinical studies with naloxone hydrochloride via nasal administration have not been conducted. A human factor usability study was also conducted.

Narcan Nasal Spray is for intranasal administration only. It may be used for treatment of suspected opioid overdose and frequently must be performed by someone other than the patient. This requires a simple, robust and easy to understand administration device.



Alternative Devices

The simplicity of the nasal spray was critical in device selection. There are many possible devices and most could not be used reliably in a respiratory depression reversal event. Some examples are Nasal Spray bottle (already used in nasal administration) but not considered useable for multiple patients even using anti-microbial preservative; dip tube operation are not suitable for horizontal use in supine subjects, there would also be too many doses. Nasal adapter on conventional Metered dose inhaler (MDI), pressurized MDI requires “vertical” MDI to ensure refilling of valve for next dose so more impacted by patient position. MDI requires correct priming before use. Nebulizers are similar to previous but also need battery pack and are less portable, with of course, the risk of power loss. Single use systems were not considered, such as prefilled syringes “jerry-rigged” with atomizers, as used in some unapproved drug administration use, including intranasal administration of naloxone. There are other unidose systems, for instance those used for flu vaccines but these have a graduated syringe barrel and potential for titration, or mistake with volume drawn and insufficient dose being administered.

Selection Criteria

Selection of the chosen device for Narcan Nasal Spray was based on the small volume of liquid sprayed which remained in the nostril, 100 μL (microliters), regarded as the optimal for nasal administration (50-250 μL). The fill volume, set at manufacture, does not require priming before use. No electronics or requirement for power packs which “age” with time or need replacement. The orientation independent fine spray, with controlled spray geometry/shape, and amount of droplets capable of being sprayed and adhering to the nasal cavity wall, without the patient being conscious or need to inhale. No sharp or penetrating parts to harm subject or user before or after use. Simple operation by applying force between thumb and fingers, the action causes an O-ring to be broken and force delivers a complete dose, not a partial dose. Extremely difficult therefore to titrate a partial dose. Simple and unlikely to harm subject when inserted nasally and can be operated by inexperienced users. Simple quick action to remove device from pack and immediately use. Product is also stable without outer packaging, making it even more readily useable. Simple mechanics which offer high reliability. Easy to dispose of with no product residual concern about re-use or misuse.

The spray is formed by the liquid exiting the device spray orifice and is characterized by a number of approved laboratory techniques such as spray pattern and droplet size. These techniques are critical for not only routine quality control, batch to batch consistence, but link back to the original clinical batches and registrations batches, the bases of FDA approval.

The singular most disastrous event that could occur during an overdose occurrence, is the failure not only of one Adapt Narcan Nasal Spray, but as the product is supplied and potentially used and presented as two doses, that two devices would fail. The probability of

such as event is 1 in 250 000 000, and only one of two failing is 1 in 50 000. This probability is quite conservation, based on a series of component defect, such as dimensional or visual defects (cracks), not actual, “no spray” or no fire failures.

Features or Device Target Profile

Each paragraph below identifies a unique **attribute** and a **rationale** for that attribute. A description of the **risk** if the product was defective and how it is **migrated** in the Adapt product, and lastly the **selected attribute** features achieved.

Narcan Nasal Spray Product is easily portable as it must be available for immediate use. Any delay in treatment may be harmful or fatal. The packaging is small and discreet, which again is easily portable. Commercial package presentation; two units of , single use spray inside light weight foil/plastic blister pack, inside cardboard carton, approximately 9 x 7 x 3 cm. Weight of single device in blister pack is approximately 5 gram.

Product is easy to open and make ready for use as must be available for immediate use. Delay in treatment may be harmful or fatal. Easily opened secondary packaging (still providing adequate protection). Device ready for immediate use, without priming or attaching needles or other preparation steps. Blister pack is designed for easy opening with peel tab for quick opening. Nasal spray is then ready for immediate use without priming or other actions. Human factors studies show time to use is much shorter than injection devices which require more preparation steps.

Product must be easily non-tamper evident. Must be available for immediate use and be correct quality product. Administration of incorrect/counterfeit product may be harmful or fatal. Tamper evident features easily recognized as is quality product easily recognized. Product name is on device and on blister. Easy to check blister is intact and not interfered with. Also the device actuator plunger is held firm, by welded plastic O-ring, when not fired.

Product must be easy to administer to a stranger without medical or significant user training. Must be administered properly. Incorrect administration may be harmful or fatal. Ready to use with no priming or attaching of needles. Avoiding injection via needles and need for needle protection or aseptic practices. Obvious to use correct way up and to administer by correct route. The unaccustomed users administering will intuitively recognize the product as a nasal type product. Blister pack has peel tab for quick opening. Nasal spray is then ready for immediate use without priming or other actions. Human factors studies show time to use is much shorter than injection devices which require more preparation steps. Human Factors validation study confirmed over 90% of users inserted device nozzle into nostril and actuated the unit.

Product must be not be harmful to unconscious patient. Must not administer potentially allergenic materials. Unconscious patient condition adversely affected and unable to communicate. Avoid use of potentially allergenic or irritating materials e.g. latex rubber. Nasal spray device made from commonly used plastics.

Product must not be harmful to stranger administering to subject. Must be easy to administer without risk to administering person. Incorrect administration may be harmful to administering person. May result in refusal to administer to subject. Ready to use with no priming or attaching of needles. Avoiding injection via needles and need for needle protection. Avoid use of pressurized or mechanical systems where incorrect e.g. upside down use could cause harm. Avoid use of e.g. latex. Nasal spray requires blister pack to be opened and then ready for use. Human factors studies show time to use is much shorter than injections. Human Factors validation study confirmed over 90% of users inserted device nozzle into nostril and actuated the unit.

Product must deliver full required dose. Target 4 mg based on approximately 50% relative bioavailability. Insufficient dose would require another dose to be given at shorter time than 60-90 minutes. Single dose with high accuracy of fill. Action delivers full dose and cannot deliver partial dose. High reliability of dose delivered evident in specification and routine testing.

Product must deliver full dose to conscious or unconscious patient upright or supine intranasal administration requires device which operates vertically and below horizontal. Different and potentially defective dose vs orientation of device. Device which does not rely on gravity or valve filling orientation. Device delivers dose via spray orifice base on simple pressure applied by user pressing between fingers and thumb. Device works at all orientations with dose independent of gravity.

Product formulation must be delivered in volume which remains in nostril. Avoids excessive solution from being swallowed which has much lower oral bioavailability. Avoids excessive solution being inhaled and coughing/choking in unconscious patient. Concentration and volume of spray to be optimized and including supine use. Variation in dose could result in shorter times to re-administer. Dose delivered controlled to very tight limits. Volume of 100 µL per spray remains within nostril.

Product formulation must be well tolerated in nasal cavity. Avoids sneezing and local effects on swallowing/ coughing/choking in unconscious patient. Formulation to be optimized for tonicity, choice of ingredients and drug concentration avoids local irritation causing sneeze/cough/swallow/vomit in unconscious patients. Formulation uses commonly used nasal components and materials. No significant irritation of local mucosa noted in clinical.

Product must be robust and reliable when carried around in normal use. Police and first responders to emergency calls or use by members of public would require device to be carried by patient or person administering. Stable at room temperature with excursions above to cover

winter and summer use. Not affected by defects from walking, driving, normal work. Avoids defects developing while carried around before use. Needs to work or obvious failure after e.g. being dropped in stressful situations. Simple design of container-closure system of standard glass vial and stopper held within plastic nasal adapter with holder encasing glass vial ensures separation cannot occur. Damage from e.g. drop testing is minimized by plastic device construction. Low product weight, approximately 5 g and fully plastic enclosed vial is sufficient to prevent damage if dropped accidentally.

Product should not be potentially harmful after use and require specialized disposal. Avoids potential harm to administering person and public if discarded after use. Avoid sharps and potential “needle stick injury” Avoid source of viral contamination. Intranasal solution in small glass vial with plastic parts. Avoids injection. No sharps disposal required. No sharp parts or parts having penetrated human skin after use. Glass encased in plastic device. Solution is fully used by full dose expelled.

Human Factors Studies and Experience in Product Use

A number of studies were completed. Firstly, qualitative studies were carried to refine the product label to a point where quantitative studies were initiated. Two validation studies were completed and described below; the first study tested the product as a two dose (two devices) packaged configuration and the second validation study which tested and evaluated a single device packaged configuration.

Qualitative Study

An Accelerated and Compressed Evaluation (ACE), which consisted of 3 consecutive and iterative Human Factors/ Label Comprehension Pre-Tests, was conducted over a 5-day period to assess the ability of subjects to understand the labelling [Patient Insert and Quick Start Guide (QSG)] and to demonstrate simulated use of a naloxone nasal prototype device.

The purpose of this testing schedule was to learn and adjust the labelling and materials in an iterative and accelerated manner. The objectives of the study included evaluation of the subject’s ability to demonstrate administration the drug product and monitor patients; comprehend the key messages in the label; and also evaluate a number of labels.

In-person interviews and observations were conducted. In total, 61 interviews were completed. Of the 61 subjects who completed the interviews, 24.6% (n=15) tested as low literate and gender was nearly equally split between female (50.8%; n= 31) and male (49.2%; n=30). The study population included adults (18+) from all age groups – approximately half (45.9%, n=28) were under 45 years of age. Overall, more than 94% of the 58 subjects were able to successfully administer the naloxone nasal spray in a simulated situation of opioid overdose. The key steps of the first administration of Narcan Nasal Spray were well understood and

accurately followed. Subjects were less likely to wait the full 2-3 minutes prior to the second dose (77.2%) with only 80% checking for a response in the opioid overdose patient.

Administration of the second dose was accurately accomplished in 92.9% of the simulations. Over 94% of subjects called for emergency assistance both initially and after the second dose. These results confirm that the subjects in this study clearly understood the instructions in assessing the situation and dosing naloxone nasal spray for the first administration. Subjects were less likely to wait for the appropriate time period after the first dose and to check for a response prior to the second dose. Thus, in more than 20% of the cases it is likely the patient would receive two doses regardless of the response to the first dose. The results of this study provide further support that a single 4 mg naloxone intranasal dose is the most appropriate to ensure rescue and simplify the dosing.

Human Factors and Usability Studies Validation Studies

The validation studies were carried out using the proposed commercial label and packaging. Both studies were carried out in accordance with the Draft Guidance for Industry and Food and Drug Administration Staff: Applying Human Factors and Usability Engineering to Optimize Medical Device Design, June 22, 2011¹⁸ and the Guidance for Industry—Label Comprehension Studies for Nonprescription Drug Products, August 2010.

Adolescents aged 12 to 17 years and adults 18 years of age or older participated in the 2 human use studies. The REALM test²⁰ and REALM-Teen test²¹ were administered to the adults and adolescents, respectively, in order to screen literacy levels for information only in analyzing the population.. The subjects needed to be able to read, speak, and understand the nature of the study procedures.

The study was conducted in rooms equipped with 1-way mirrors for observation. To simulate a real-life emergency, study participants were challenged with administering the medication to an unconscious victim, simulated by a full-sized mannequin. **No training on the use of the device was provided prior** to the usability assessment. Intranasal devices were filled with 0.1 mL of water and packed into a blister card. The blister card, along with a Quick Study Guide (QSG) and patient information section of the package insert were packed into a carton. Study A (2 devices) was slightly more complex and was conducted prior to study B (1 device) in order to determine if individuals were able to perform critical tasks without reviewing the QSG. The objective of the QSG was to provide clear and concise instructions (combined with pictures) for use in a crisis situation with limited time to interpret the directions.

Subjects in study A were randomized to 1 of 2 arms: subjects in arm 1 were given an opportunity to read the QSG in advance of the simulation, whereas subjects in arm 2 did not review the QSG in advance. Subjects in study B (1 device) did not review the QSG in advance of the simulation. Subjects were presented with a scenario of an unconscious overdose victim simulated by a life-sized mannequin similar to those used for cardiopulmonary resuscitation training. Subjects were given the product with labeling and asked to proceed as they would in

a real-life emergency; **no training or coaching was provided either prior to or during the simulation.** Background noise, in the form of TV and radio, was introduced into the scenario to simulate voices and noise from onlookers. A trained observer (located behind a 1-way mirror) documented the steps that the subject took during the simulation. Once the subject completed the simulation, an interview was conducted in a separate room to evaluate comprehension of key concepts in the patient information section of the package insert.

Data Analyses

The primary endpoints for the critical tasks were (1) inserting the device nozzle into a nostril and (2) pressing the plunger to release a dose into the nose. Secondary endpoints included (3) checking for response, (4) calling 911, and (5) moving to a recovery position after administering dose. Study A also included (6) waiting 2 to 3 minutes to assess the effectiveness of the first dose and (7) re-administration using a new unit (if needed). For study A; 90.6%, (n=29 of 32) subjects of Arm1 and 90.3% (n=28 of 31) subjects in Arm 2 were able to complete both critical tasks in a manner which would have resulted in a successful administration of one dose of Narcan Nasal Spray to an overdose patient in an emergency situation. In Study B; 90.6% (n=48 of 53) of subjects were able to complete both critical tasks correctly.

Validation Summary

Both validation studies were very comparable giving consistent results with just over 90% success rate. As part of the evaluation of the device by FMEA; the two most important potential risk were “No dose” delivered by device” and “Non insertion into nasal cavity” , both of these risks are impacted by incorrect spraying once inserted or not correctly inserted intranasally. Based on these Human Factor studies and improved labelling and QSG, these risks are considered As Low as Reasonably Possible. Nevertheless, a second device dose is packaged in the commercial product thereby lower the failure rate even lower.

PHARMACOLOGY OF NALOXONE - GENERAL

Opioid antagonist

- Naloxone is a potent mu-receptor antagonist (Wermeling DP 2010)
- Antagonizes opioid effects by competing for the same receptor sites reversing the effect of opioids, including respiratory distress, sedation, and hypotension. (Narcan® Nasal Spray P.I.)
- Binds to opioid receptors in the body more strongly or with a higher affinity than agonists, blocking opiate receptors and weakening the effects of the opiate (opiate.com/antagonist)

PHARMACOLOGY OF NALOXONE - GENERAL

Rescue or reversal of opioid overdose (ie, respiratory depression)

- Provides antagonist effects when bound to the mu-opioid receptors
(must occupy 50% of receptors to do this)
(Melichar JK et al. Eur J Pharmacol. 2003) (Clarke SFJ et al. Emerg Med J. 2005)
- Naloxone reverses opiate-induced respiratory depression
(Dahan A et al. Anesthesiology. 2010)

PHARMACOLOGY OF NALOXONE - IN VITRO RAT

In vitro Rat

- Study: Postsynaptic opioid sensitivity of periaqueductal gray neurons (PAG) in rat brain

(Chieng and Christie J Neuroscience, November 15, 1996, 16(22):7128-7136)

- Intracellular recordings from brain slices of morphine-dependent rats were used to study opioid dependence in ventrolateral PAG neurons
- Brain slices obtained from rats were maintained in morphine in vitro.
- Naloxone (100 nM or 1mM) depolarized 25 of 51 PAG neurons from morphine-dependent rats.
- 19 of the PAG neurons were previously classified as opioid-sensitive.
- In the presence of naloxone, action potential frequencies were greater than in control neurons in the absence of opioids, and in control neurons in the presence of both morphine and naloxone, demonstrating opioid withdrawal.

PHARMACOLOGY OF NALOXONE - IN VITRO RAT

In vitro Rat, (cont'd)

- Results:
 - Development of both tolerance and withdrawal in PAG neurons was demonstrated.
 - Results suggest induction of a novel opioid-sensitive current that could be involved in withdrawal behavior.

PHARMACOLOGY OF NALOXONE - IN VIVO MOUSE

In vivo Mouse

- Study: In vivo activation of a mutant mu-opioid receptor by antagonist in mice
(Law et al 2003 PNAS February 18, 2003, 100(4):2117-2121)
 - Opioid antagonists have the in vitro ability to activate the mu-opioid receptor mutant (S196A)
 - To test this ability in vivo, this study utilized mice with the S196A mutation (by a knock-in strategy) and wild-type littermates

PHARMACOLOGY OF NALOXONE - IN VIVO MOUSE

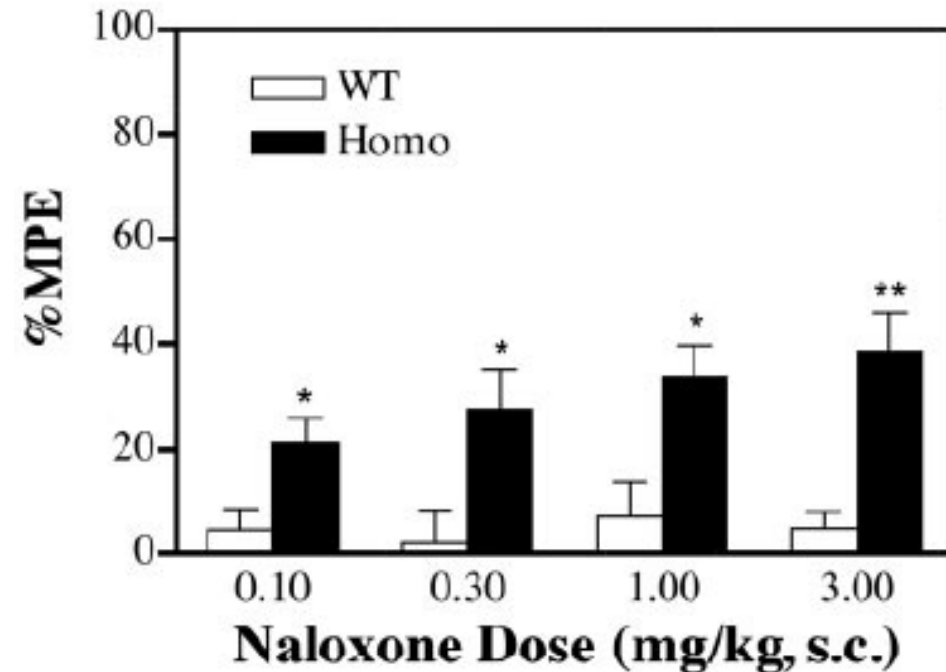
In vivo Mouse, (cont'd)

- To assess the ability of opioid antagonists (eg, naloxone) to produce analgesic effects the following set of testing (2 tests) was performed:
 1. Antinociceptive testing (tail-withdrawal testing)
 - Withdrawal responses were recorded 12-minutes post administration by subcutaneous (s.c.) injection of various doses
 - Percent of maximum possible effect was calculated
 2. Attenuation of opiate dependence

PHARMACOLOGY OF NALOXONE - IN VIVO MOUSE

In vivo activation Mouse, (cont'd)

- Antinociceptive testing: Results of the tail-withdrawal latencies for wild-type mice (WT) and homozygous mutant mice (homo) are noted in the following figure:



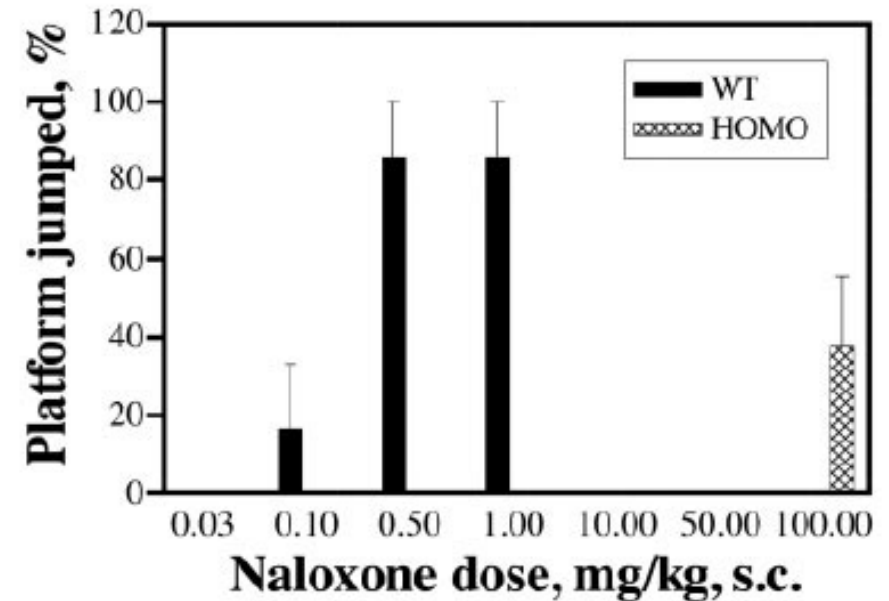
- The ED₅₀ value for homozygous mutant mice = 1.32 ± 0.08 mg/kg (source: radiant heat). It was noted that similar results were observed using warm water (53°C) as the heat source.

PHARMACOLOGY OF NALOXONE - IN VIVO MOUSE

In vivo activation Mouse, (cont'd)

Attenuation testing of the opiate dependence in the homozygous mice: Results are shown in the following figure:

- 72-hours post treatment, naloxone was administered (0.03 to 100.0 mg/kg i.p.); platform jumping was counted over a 10-minute period
- For the wild-type mice, a maximal naloxone dose of 1 mg/kg s.c. was used. For the homozygous mice, a maximal dose of 100 mg/kg s.c. was used.



PHARMACOLOGY OF NALOXONE - IN VIVO MOUSE

In vivo activation Mouse, (cont'd)

- Per the authors, with a constant dose of morphine during chronic treatment, the frequency of jumping is directly related to the dose of naloxone administered.
- As shown in the figure on the previous slide, the amount of naloxone needed to precipitate the platform-jumping behavior in the homozygous mice was >200-fold higher than that required in the wild-type animals.
- Results: Naloxone exhibited antinociceptive effects similar to that of partial agonists.

PHARMACOLOGY OF NALOXONE - IN VIVO RAT

In vivo Rat

- Study: Rat In Vivo Receptor Occupancy

(Rorick-Kehn et al. Int J Neuropsychopharmacol. 2015; 1-11)

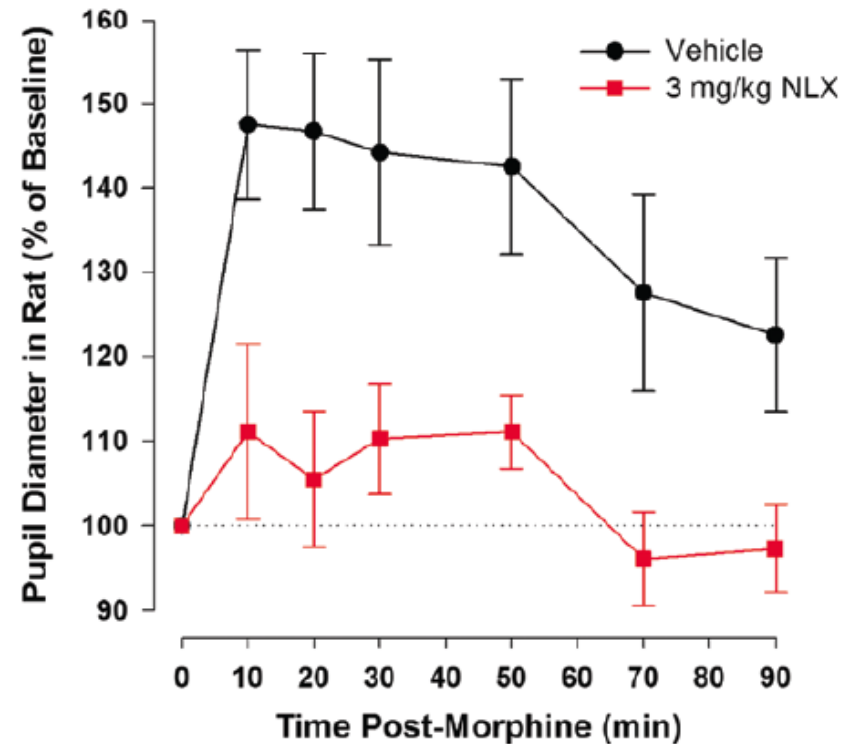
- Naloxone was used to establish the mu-associated effects, or mu activity, on morphine-induced mydriasis.
- Assessment of mu-opioid receptor antagonism by naloxone was measured using translational pupillometry in rats.
- Naloxone showed dose- and concentration-dependent occupancy of putative opioid receptors.
- The ED₅₀, or doses at which 50% receptor occupancy was observed at mu, kappa, and delta opioid receptors, were 0.49, 0.75, and 3.45 mg/kg, respectively.

(Refer to figure on next page)

PHARMACOLOGY OF NALOXONE - IN VIVO RAT

Rat In Vivo Receptor Occupancy, (cont'd)

- Results: Naloxone completely blocked morphine-induced mydriasis (ie, 3 mg/kg naloxone, which produced 90% mu-opioid receptor occupancy).



PHARMACOLOGY OF NALOXONE - IN VIVO RAT

Rat In vivo Receptor Occupancy (cont'd)

- Naloxone showed dose-dependent in vivo receptor occupancy at putative mu, kappa, and delta opioid receptors 60 minutes after administration.

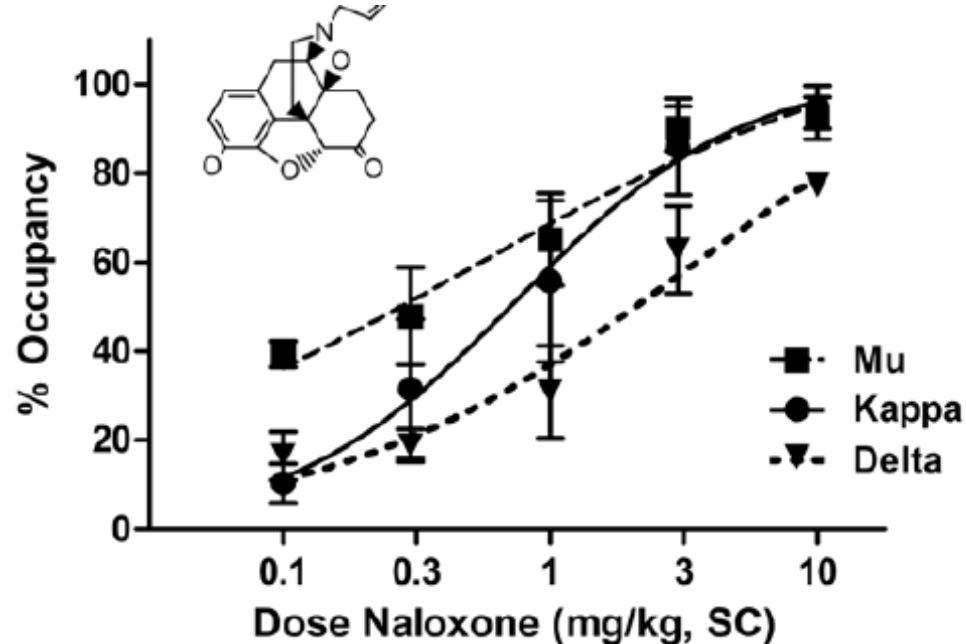


Fig 1a., Rorick-Kehn et al. Int J Neuropsychopharmacol. 2015; 1-11

PHARMACOLOGY OF NALOXONE - IN VIVO HUMAN

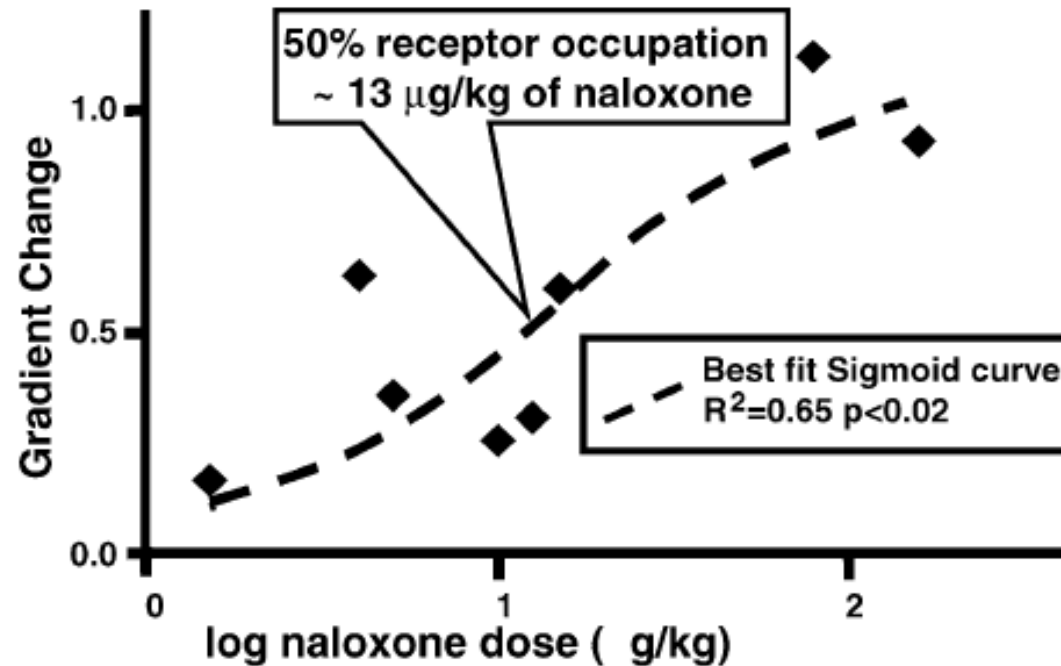
In vivo Human

- Human In vivo Receptor Occupancy (Melichar et al 2003 EurJPharmacol. 459:217-219)
 - In Vivo receptor occupancy and binding was assessed using a non-tomographic alternative to PET scan (Multiple Organs Coincidences Counter, MOCC).
 - MOCC is a whole body gamma-ray counter modified to detect coincident counts from whole regions of the body and is very sensitive, detecting radiolabelled tracers given at <1% of the dose used in PET.
 - Reproducible time activity curves of exactly the same temporal profile to those from conventional PET can be obtained from whole body areas, exposing patients to less radiation as with conventional PET.
 - This study used the pulse chase, or displacement, in the MOCC to measure naloxone occupancy in the human brain and to assess the relationship between naloxone occupancy and the doses required in clinical use.

PHARMACOLOGY OF NALOXONE - IN VIVO HUMAN

Human In Vivo Receptor Occupancy, (cont'd)

- It is estimated that 50% of opioid receptors in the brain are occupied by naloxone at a dose of approximately 13 $\mu\text{g}/\text{kg}$, as shown in the following figure:



PHARMACOLOGY OF NALOXONE - IN VIVO HUMAN

Human In Vivo Receptor Occupancy, (cont'd)

- Results: It was shown that the dose needed to occupy 50% of available receptors in the adult human brain was approximately 13 $\mu\text{g}/\text{kg}$, which corresponds to 1.04 mg in an 80-kg man or 0.910 mg in a 70-kg man.
 - Dose needed may vary in an opioid-dependent individual due to changes in the number of opioid receptors caused by chronic misuse.

PHARMACOLOGY OF NALOXONE - IN VIVO HUMAN

In vivo Human

- **Review Article: Naloxone reversal of respiratory depression**
(Dahan A et al. Anesthesiology. 2010)
 - Discussion of reversal of opioid respiratory depression by use of IV naloxone.
 - Side effects of postoperative analgesic doses of opioids include nausea, vomiting, sedation, and respiratory depression.
 - Of these side effects, respiratory depression remains the main hazard of opioid use because of the obvious risk of fatal outcome.

PHARMACOLOGY OF NALOXONE - IN VIVO HUMAN

In vivo Human, (cont'd)

- Per the authors, opioid ligands exert their biologic effects in vivo through interactions with multiple opioid receptors, namely mu-, delta-, and kappa-opioid receptors; has been recognized that opioid-induced respiratory depression is mediated largely by the mu-opioid receptor (s).
- Clinically, naloxone has been shown in many studies to effectively and rapidly reverse respiratory depression induced by opioid full agonists, such as morphine and fentanyl.

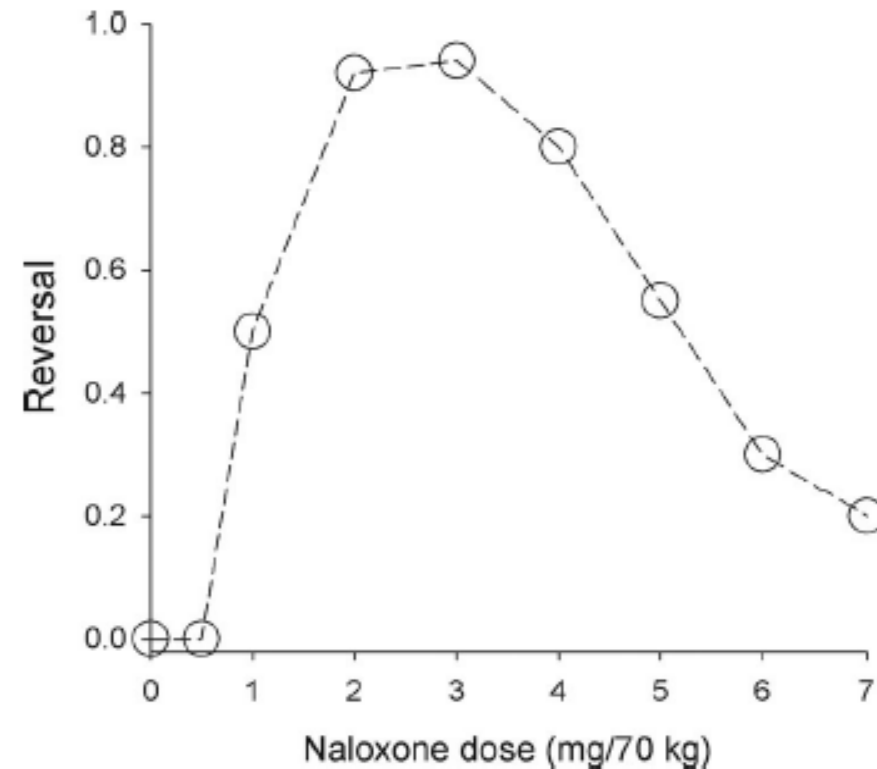
PHARMACOLOGY OF NALOXONE - IN VIVO HUMAN

In vivo Human, (cont'd)

Naloxone reversal of respiratory depression

- The figure shows a bell-shaped naloxone reversal of opioid-induced respiratory depression.
- Per the authors, naloxone inhibits all pharmacological effects of opioids and produces a parallel right shift in the dose-response curves of opioids.

(Not presented in paper)



PHARMACOKINETICS OF NALOXONE – IN VIVO RAT

Pharmacokinetics

- Rat Study (Misra et al. JPET February 1976. 196 (2):257-268)
 - ¹⁴C naloxone was administered SC to male Wistar rats at 1 mg/kg and 10 mg/kg
 - After 1 mg/kg dose: mean peak levels of drug in brain and plasma were 506 ng/g and 119 ng/mL, respectively.
 - After 10 mg/kg dose: peak levels in brain and plasma were 4.31 mug/g and 1.27 mug/mL, respectively.
 - Half-life with 1 mg/kg and 10 mg/kg was 0.4 hour.

PHARMACOKINETICS OF NALOXONE – IN VIVO RAT

Pharmacokinetics

- Major metabolite – naloxone-3-glucuronide
- Within tissue, findings from a 10 mg/kg dose resulted in significant amounts of radioactivity that persisted in tissues, but not in plasma 96 hours post dose.
- Excretion was recorded as a percentage of dose in urine and feces 96 hours post 10 mg/kg dose:
 - Free naloxone were 4.1 and 3.9, respectively
 - Conjugated drug; 15.4 and 1.2, respectively
 - Total radioactivity; 43.3 and 20.9, respectively

NARCAN NASAL SPRAY 4MG HUMAN PHARMACOKINETICS

Geometric Mean Pharmacokinetic Parameters (CV%) of Naloxone Following Single Intranasal (IN) Administration and Intramuscular (IM) Injection of Naloxone to Healthy Subjects, Study Naloxone-Ph1a-002 (N=29)

Parameter	2mg IN Dose One Spray 20 mg/mL	4mg IN Dose Two Sprays 20 mg/mL	4mg IN Dose One Spray 40 mg/mL	8mg IN Dose Two Sprays 40 mg/mL	0.4mg IM Injection
$t_{1/2}$ (h)	1.81 (34.9)	2.23 (34.5)	2.08 (29.5)	2.10 (32.4)	1.24 (25.9)
t_{max} (h) †	0.33 (0.25, 1.00)	0.33 (0.17, 0.57)	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
C_{max} (ng/mL)	2.92 (34.3)	6.20 (31.9)	4.83 (43.1)	9.70 (36.0)	0.877 (30.5)
$C_{max}/Dose$ (ng/mL/mg)	1.46 (34.3)	1.55 (31.9)	1.21 (43.1)	1.21 (36.0)	2.19 (30.5)
AUC_{0-t} (h*ng/mL)	4.51 (27.2)	9.32 (24.0)	7.87 (37.4)	15.3 (23.0)	1.72 (22.9)
$AUC_{0-t}/Dose$ (h*ng/mL/mg)	2.25 (27.2)	2.33 (24.0)	1.97 (37.4)	1.91 (23.0)	4.29 (22.9)
AUC_{0-inf} (h*ng/mL)	4.56 (26.9)	9.43 (24.0)	7.95 (37.3)	15.5 (22.7)	1.76 (22.6)
$AUC_{0-inf}/Dose$ (h*ng/mL/mg)	2.28 (26.9)	2.36 (24.0)	1.99 (37.3)	1.93 (22.7)	4.40 (22.6)
Relative BA (%) vs. IM	51.9 (21.7)	53.6 (22.5)	46.7 (31.4)	43.9 (23.8)	100

†: Median (minimum, maximum)

The relative bioavailability of IN-administered naloxone is based on the dose-normalized values of AUC_{0-inf} compared to the IM treatment

PHARMACOKINETICS OF NALOXONE – HUMAN PK

The pharmacokinetics of naloxone are shown in the table below:

Parameter	2mg IN Dose One Spray 20 mg/mL	4mg IN Dose Two Sprays 20 mg/mL	4mg IN Dose One Spray 40 mg/mL	8mg IN Dose Two Sprays 40 mg/mL	0.4mg IM Injection
	2 mg - One Spray 20 mg/mL IN (N = 29)	4 mg - Two Sprays 20 mg/mL IN (N = 29)	4 mg - One Spray 40 mg/mL IN (N = 29)	8 mg - Two Sprays 40 mg/mL IN (N = 29)	0.4 mg IM (N = 29)
λ_z (1/h)	0.382 (34.9)	0.310 (34.5)	0.334 (29.5)	0.330 (32.4)	0.557 (25.9)
$t_{1/2}$ (h)	1.81 (34.9)	2.23 (34.5)	2.08 (29.5)	2.10 (32.4)	1.24 (25.9)
t_{max} (h) †	0.33 (0.25, 1.00)	0.33 (0.17,0.57)	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
C_{max} (ng/mL)	2.92 (34.3)	6.20 (31.9)	4.83 (43.1)	9.70 (36.0)	0.877 (30.5)
$C_{max}/Dose$ (ng/mL/mg)	1.46 (34.3)	1.55 (31.9)	1.21 (43.1)	1.21 (36.0)	2.19 (30.5)
AUC_{0-t} (h*ng/mL)	4.51 (27.2)	9.32 (24.0)	7.87 (37.4)	15.3 (23.0)	1.72 (22.9)
$AUC_{0-t}/Dose$ (h*ng/mL/mg)	2.25 (27.2)	2.33 (24.0)	1.97 (37.4)	1.91 (23.0)	4.29 (22.9)
AUC_{0-inf} (h*ng/mL)	4.56 (26.9)	9.43 (24.0)	7.95 (37.3)	15.5 (22.7)	1.76 (22.6)
$AUC_{0-inf}/Dose$ (h*ng/mL/mg)	2.28 (26.9)	2.36 (24.0)	1.99 (37.3)	1.93 (22.7)	4.40 (22.6)
AUC% Extrapolated (%)	1.06 (56.5)	0.935 (60.1)	0.965 (53.5)	0.963 (69.3)	2.18 (57.5)
CL/F (L/h)	438 (26.9)	424 (24.0)	503 (37.3)	518 (22.7)	227 (22.6)
Relative BA (%) vs. IM	51.9 (21.7)	53.6 (22.5)	46.7 (31.4) ^{††}	43.9 (23.8)	100
$C_{max}/Dose$ Ratio (IN vs. IM) (%)	66.6 (41.4)	70.7 (37.7)	56.6 (47.5) ^{††}	55.3 (41.4)	100

Study Naloxone-Ph1a-002; Phase 1, Pharmacokinetic Evaluation of Intranasal and Intramuscular Naloxone in Healthy Volunteers (Table 4.2)

PHARMACOKINETICS OF NALOXONE – RAT ADME

Naloxone Rat ADME

- Results from absorption studies with ligated intestinal loops indicated that poor absorption of naloxone is not the cause of its relatively low oral potency.
- In vitro metabolic studies with rat liver slices confirmed rapid naloxone metabolism, suggesting that the lower potency of oral naloxone compared to parenteral naloxone is due to rapid first-pass liver metabolism.

PHARMACOKINETICS OF NALOXONE – HUMAN ADME

Naloxone Human ADME

- Absorption: rapidly absorbed from the nasal cavity; as effective as IV administration at reversing the effects of opioid overdose.
- Distribution after IV administration is rapid with response often described as dramatic, with recipients feeling clearheaded and unaware of any residual effects of the opioid.
- Primarily metabolized in the liver via glucuronide conjugation; major metabolite - naloxone-3-glucuronide.

PHARMACOKINETICS OF NALOXONE – HUMAN ADME

Naloxone Human ADME

Per the article, findings from a comparative study of IN, IV, and intraduodenal administration of naloxone in rats included the following:

- Naloxone was completely absorbed from the nasal cavity; peak plasma levels obtained within 3 minutes.
- Demonstrated that the relative systemic availability of IN administration was similar to that of IV delivery.

Naloxone Human ADME

- Excretion

After an oral or IV administration

- About 25-40% of the drug is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours
(<http://www.rxlist.com/narcan-drug/clinical-pharmacology.htm>)
 - 7,8-dihydro-14-hydroxynormorphinone, and N-allyl-7,8-dihydro-14-hydroxynormorphine have been identified as metabolites in a human urine specimen
(<http://www.sciencedirect.com/science/article/pii/S0022354915381296>)

HUMAN PK/PD DATA

- Morphine at a dose of 0.15 mg/kg IV was administered to healthy volunteers to induce non-life threatening respiratory depression.
- Maximal respiratory depression occurred at 30 minutes post-dose.
- A single dose of naloxone (0.4 mg IV) rapidly reversed the respiratory depression back to baseline levels.

HUMAN PK/PD DATA

- The duration of blockade of cerebral mu-opioid receptors by naloxone was studied in 8 healthy volunteers.
- Subjects received naloxone by IV administration at a dose of 2 mg or 2 mcg/kg.
- At a dose of 2 mg, naloxone provided 80.6% blockade of cerebral mu-opioid receptors at the 5 minute postdose timepoint.

CLINICAL DOSE-RESPONSE DATA

- Surgical patients were premedicated with morphine sulfate 5 mg to 10 mg IM and their respiratory rate was measured.
- Three groups of patients received the following doses of naloxone:
 - 5mcg/kg IV
 - 10 mcg/kg IV
 - 5 mcg/kg IV plus 10 mcg/kg IM
- All doses of naloxone reversed respiratory depression caused by morphine administration back to baseline levels
- The duration of effect of the reversal of respiratory depression increased with increasing doses of naloxone

CLINICAL DOSE-RESPONSE DATA

- Per the article, current management recommendations for the use of naloxone to reverse opioid intoxication is 0.04 mg (initial dose) up to 2 mg.
- Additionally, 2 mg of naloxone is recommended in patients with apnea or near-apnea with cyanosis, irrespective of drug use history.



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**Background White Paper: Pharmacology and Pharmacokinetics of Naloxone
and Fentanyl in Support of the Adapt Pharma Advisory Committee Meeting
(October 5, 2016)**

Study Drug: NARCAN[®] Nasal Spray
Sponsor: Adapt Pharma, Inc.
100 Matsonford Rd, Suite 201
Radnor, PA 19087

Report Prepared By: DUCK FLATS Pharma
Date: August 31, 2016
Version: Final

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
CNS	Central nervous system
HEK	Human embryonic kidney
IC ₅₀	Mean inhibitory concentration
IM	Intramuscular(ly)
IN	Intranasal(ly)
IV	Intravenous(ly)
K _i (s)	Binding affinity(ies)
MOCC	Multiple Organs Coincidences Counter
PAG	Periaqueductal gray
PET	Positron emission tomography
PK(s)	Pharmacokinetic(s)
rCBF	Regional cerebral blood flow
SC	Subcutaneous(ly)
SL	Sublingual
V _{dss}	Volume of distribution at steady-state
WT	Wild type

INTRODUCTION

This section provides detailed summaries and references of the published literature presented in the primary and backup slides for the advisory committee meeting on October 5, 2016.

Naloxone is a potent mu-receptor antagonist.¹ This drug antagonizes opioid effects by competing for the same receptor sites reversing the effects of opioids, including respiratory depression, sedation, and hypotension.² Naloxone binds to opioid receptors more strongly, or has a higher affinity, than agonists blocking opiate receptors, weakening the effects of the opiate. In addition, naloxone has high lipophilicity compared with some opioids, which allows naloxone to reach higher central nervous system (CNS) concentrations and achieve competitive mu-receptor antagonism.³ Overall, the pharmacological activity of naloxone is described as its strong binding affinity to opioid receptors over opiate agonists.

One such opiate agonist, fentanyl, is used primarily in surgical anesthesia or to treat moderate to severe pain. As the use of fentanyl has increased in recent years, relevant scientific and medical information is also presented for this drug.

1. PHARMACOLOGY OF NALOXONE

1.1. In Vitro Opioid Receptor Binding Studies

1.1.1. Rat

Postsynaptic opioid sensitivity of periaqueductal gray neurons (PAG) was studied in rat brain.⁴ Intracellular recordings from brain slices of morphine-dependent rats were used to study opioid dependence in ventrolateral PAG neurons. Naloxone (100 nM or 1 mM) depolarized 25 of 51 PAG neurons from morphine-dependent rats, 19 of which were previously classified as opioid-sensitive. In the presence of naloxone, action potential frequencies were greater than in control neurons in the absence of opioids, and in control neurons in the presence of both morphine and naloxone, demonstrating opioid withdrawal.

1.1.2. In Vitro Studies – Human

No published in vitro human opioid receptor binding data for naloxone was found.

1.2. In Vivo Opioid Receptor Binding Studies

1.2.1. Mouse – Activation of the mu-opioid Receptor

In vivo activation of the mu-opioid receptor by naloxone and its ability to produce analgesic effects was assessed in mice with a mutant mu-opioid receptor. In this study, naloxone exhibited antinociceptive effects similar to that of partial agonists.⁵

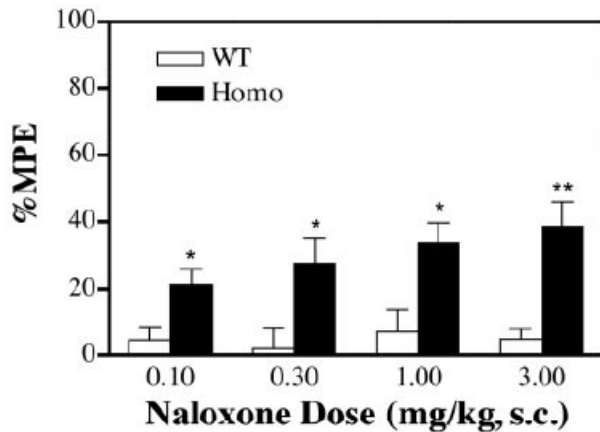
Naloxone was administered at various doses (0.10, 0.30, 1.00, and 3.00 mg/kg subcutaneous [SC]) to mice with a genetic mutation of the mu-opioid receptor (designated as S196A mutation) and their wild-type (WT) littermates to assess its effect on antinociceptive responses and on morphine-dependence. The following test methods were utilized for the assessment:

- Antinociceptive responses in homozygous mutant mice and their WT littermates via tail-withdrawal latency testing.
- Platform jumping behavior elicited by naloxone in mice chronically treated with morphine.

Naloxone produced a dose-dependent antinociceptive response in the homozygous mutant mice in tail-withdrawal testing which was not observed in WT littermates. The effective dose (ED₅₀), or dose of drug that produced a therapeutic response or desired effect in 50% of the animals tested, for homozygous mice was 1.32±0.08 mg/kg with similar results observed using warm water (53°C) as the heat source.

Tail-withdrawal latencies were recorded as percent maximum possible effect versus naloxone dose administered. Results of the assessment for WT and homozygous mutant mice (homo) are shown in [Figure 1](#).

Figure 1: Naloxone Dose Versus Percent Maximum Possible Effect

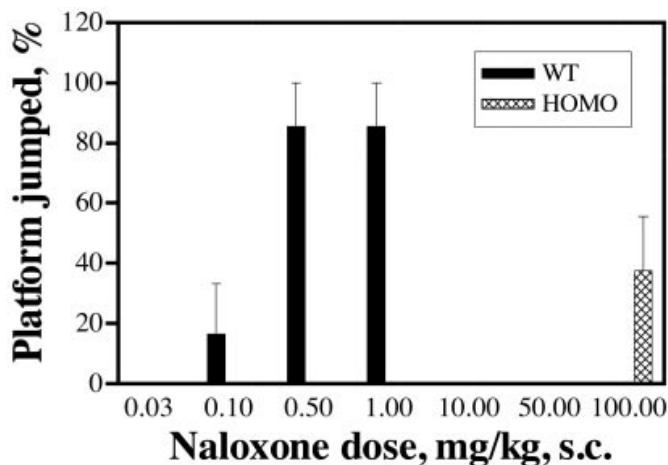


Source: Law et al⁵; figure 3.

Abbreviations: HOMO = homozygous; MPE = maximum possible effect; s.c. = subcutaneous; WT = wild-type.

Attenuation of the opioid dependence was observed post treatment with naloxone in mice chronically treated with morphine as determined by platform-jumping behavior. In the morphine-treated mice, a maximal naloxone dose of 100 mg/kg SC was administered. In the WT mice, a maximal naloxone dose of 1 mg/kg SC was used. The frequency of jumping was directly related to the dose of naloxone administered. In the homozygous mice, the amount of naloxone needed to precipitate platform-jumping behavior was >200-fold higher than that required for the WT animals; only at 100 mg/kg did naloxone induce <40% of mice platform jumping (refer to Figure 2).

Figure 2: Naloxone Dose Versus Percent Platform Jumped



Source: Law et al⁵; figure 5.

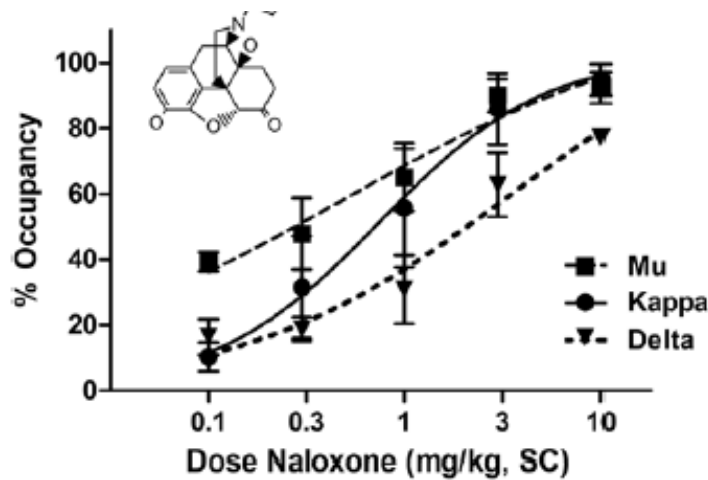
Abbreviations: HOMO = homozygous; s.c. = subcutaneous; WT = wild type.

1.2.1.1. Rat – Antagonism of the mu-opioid Receptor

Assessment of mu-opioid receptor antagonism by naloxone was measured using translational pupillometry in rats.⁶ This noninvasive research technique is useful in studying the centrally mediated effects of opioid and other drugs in both preclinical and clinical paradigms, and is a translational biomarker for evaluating the potency, efficacy, and duration of action of opioid receptor agonists and antagonists.

Naloxone was administered at doses of 0.1 to 10 mg/kg SC resulting in a dose-dependent in vivo receptor occupancy at the putative opioid receptors (mu, kappa, and delta), as shown in [Figure 3](#).

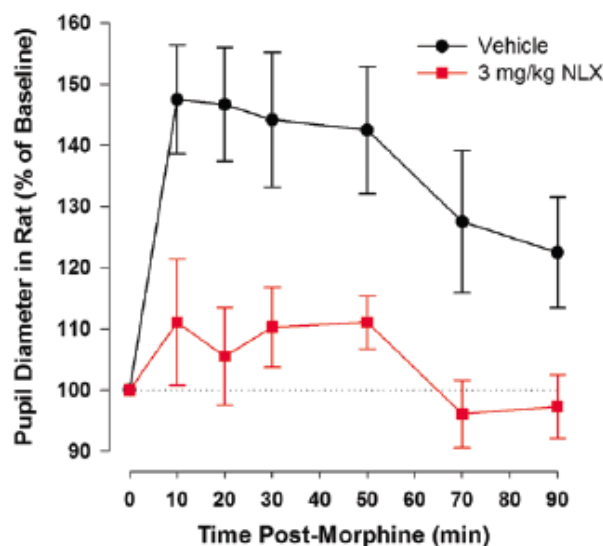
Figure 3: Naloxone Dose (mg/kg, SC) Versus % Occupancy



Source: Rorick-Kehn et al⁶; figure 1a.
Abbreviations: SC = subcutaneous.

The effect of naloxone at a dose of 3 mg/kg on morphine-induced mydriasis (pupil dilation) is shown in [Figure 4](#).

Figure 4: Effect of Naloxone (3 mg/kg) on Pupil Diameter Versus Time Post-Morphine



Source: Rorick-Kehn et al⁶; figure 2a.
Abbreviations: NLX = naloxone.

This study demonstrated a dose-dependent occupancy of putative opioid receptors post naloxone administration. Findings of the study indicated that naloxone at a dose of 3 mg/kg completely blocked morphine-induced mydriasis by producing 90% mu-opioid receptor occupancy.

1.2.2. In Vivo Studies – Human

1.2.2.1. Opioid Receptor Site Displacement by Naloxone

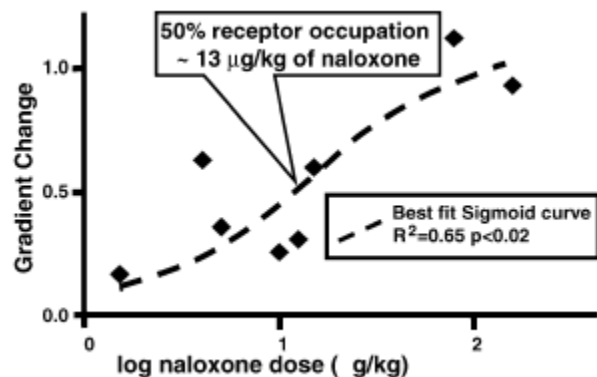
In vivo receptor occupancy and binding of naloxone was assessed in the human brain to evaluate the relationship between naloxone occupancy and the dose required in clinical use.⁷

A sensitive non-tomographic positron detecting system was used to measure the dose-response curve. The Multiple Organs Coincidences Counter (MOCC), an alternative to positron emission tomography (PET), is a whole body gamma-ray counter modified to detect coincident counts from whole regions of the body which is very sensitive, detecting radiolabeled tracers given at <1% of the dose used in PET scans. Reproducible time activity curves of exactly the same temporal profile of conventional PET can be obtained from whole body areas. This study used a pulse chase in the MOCC, or displacement paradigm, to measure naloxone occupancy in the human brain and to assess the relationship between naloxone occupancy and the doses required in clinical use.

A total of 5 healthy volunteers received an initial injection of [¹¹C]diprenorphine; the activity was recorded for 1 hour post injection. Thirty minutes after the initial injection, study subjects received a bolus intravenous (IV) injection of naloxone at various doses (to include 1.5, 4, 5, 10, 12.5, 15, 80 and 160 µg/kg corresponding to 0.12, 0.32, 0.4, 0.8, 1, 1.2, 6.4 and 12.8 mg in total, respectively, for an 80-kg adult). The change in gradient of the washout curve was measured before and after administration of naloxone. Finding indicated that approximately 50% of

available opioid receptors must be occupied by naloxone to block/reverse the effects of opioid overdose, as shown in Figure 5.

Figure 5: Log Dose: Naloxone Versus Gradient Change



Source: Melichar et al⁷; figure 2.

In this study it was shown that the dose of naloxone needed to occupy 50% of available receptors in the adult human brain was approximately 13 µg/kg, corresponding to 1.04 mg (in an 80-kg adult). For an opioid-dependent individual, the dose needed may vary due to changes in the number of opioid receptors caused by chronic misuse.

1.2.2.2. Reversal of Respiratory Depression

It has been recognized that opioid ligands exert their biologic effects in vivo through interactions with multiple opioid receptors (ie, mu, delta, and kappa) and that opioid-induced respiratory depression is mediated largely by the mu-opioid receptor(s). Naloxone has a strong binding affinity to the mu-opioid receptors and clinically has been shown in many studies to effectively and rapidly reverse respiratory depression induced by opioid full agonists, such as morphine and fentanyl.⁸

The most commonly used drugs to treat moderate to severe postoperative pain are the opioid analgesics (eg, morphine, methadone, and fentanyl) which have been used for decades. These opioids have become accepted treatment and, as standard protocol, are administered to patients by anesthesiologists. The side effects of postoperative analgesic doses of opioids include nausea, vomiting, sedation, and respiratory depression. Of these side effects, respiratory depression remains the main hazard of opioid use because of the obvious risk of fatal outcome.

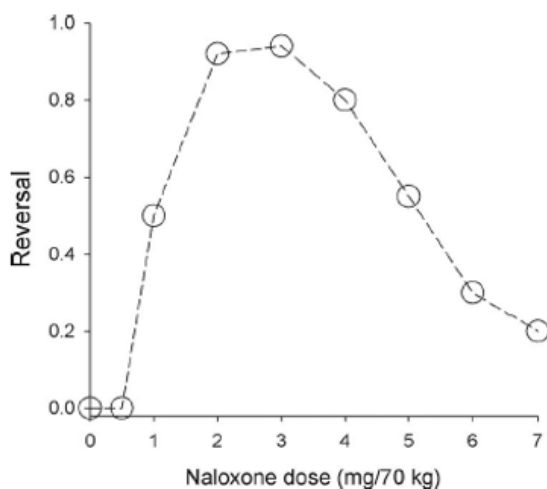
An example of the reversal effects of naloxone on opioid-induced respiratory depression was observed in a study of healthy volunteers without pain. The subjects experienced respiratory changes induced by IV administration of morphine (0.15 mg/kg) which were reversed completely by administration of IV naloxone at a dose of 0.4 mg. However, the reversal was short lived with a rapid return to full respiratory depression (or re-narcotization after 30 minutes).

A naloxone dose-response relationship with buprenorphine, a partial opioid receptor agonist, has been shown in a healthy volunteer study. Naloxone reversal effects were recorded in subjects

given IV buprenorphine at a dose of 0.2 mg who were then treated with IV naloxone at various doses. Results of the study are listed below, and are presented in [Figure 6](#):

- No reversal effect at standard doses of IV naloxone (up to 0.8 mg).
- Full reversal effect at increased doses of naloxone (2 to 4 mg).
- Decline in reversal activity seen at increasing doses of naloxone (5 to 7 mg).

Figure 6: Naloxone Dose (mg/70kg) Versus Reversal Effects



Source: Dahan et al⁸; figure 4.

Reversal of high-affinity opioids may require greater naloxone concentrations and/or continuous infusion to exhibit reversal in comparison with an opioid with lower receptor affinity. For an effective and safe reversal of opioid-induced respiratory depression, it is important to understand the pharmacokinetics (PKs) and pharmacodynamics of the opioid agonist and antagonist, and their interactions.

Naloxone has been shown to inhibit all pharmacological effects of opioids and produces a parallel right shift in the dose-response curves of opioids. (Results are not presented in this paper)

1.3. Clinical Dose-response, Concentration-response Related to Opioid-induced Respiratory Depression

1.3.1. Clinical Dose-response

1.3.1.1. Antagonism of Morphine-induced Respiratory Depression

Reversal of morphine anesthesia with naloxone shows a greater tendency for postoperative respiratory depression.⁹

Naloxone was used to reverse postoperative respiratory depression in 21 healthy patients who had received morphine-nitrous oxide-oxygen anesthesia for nonthoracic surgical procedures. Surgical patients were premedicated with morphine sulfate 5 mg to 10 mg intramuscular (IM) and their respiratory rate was measured. Three groups of patients received the following doses of naloxone:

- 5mcg/kg IV
- 10 mcg/kg IV
- 5 mcg/kg IV plus 10 mcg/kg IM

All doses of naloxone reversed respiratory depression caused by morphine administration back to baseline levels. The duration of effect of the reversal of respiratory depression increased with increasing doses of naloxone.

1.3.1.2. Reversal of Morphine-induced Respiratory Depression

Morphine-induced respiratory depression was rapidly reversed by a single 0.4 mg IV dose of naloxone.¹⁰

A clinical study in healthy volunteers assessed the respiratory-depressive effects of morphine and its reversal by naloxone. Morphine at a dose of 0.15 mg/kg IV was administered to healthy volunteers to induce non-life threatening respiratory depression. Maximal respiratory depression occurred at 30-minutes postdose. A single dose of naloxone (0.4 mg IV) rapidly reversed the respiratory depression back to baseline levels.

1.3.1.3. Opioid Receptor Occupancy

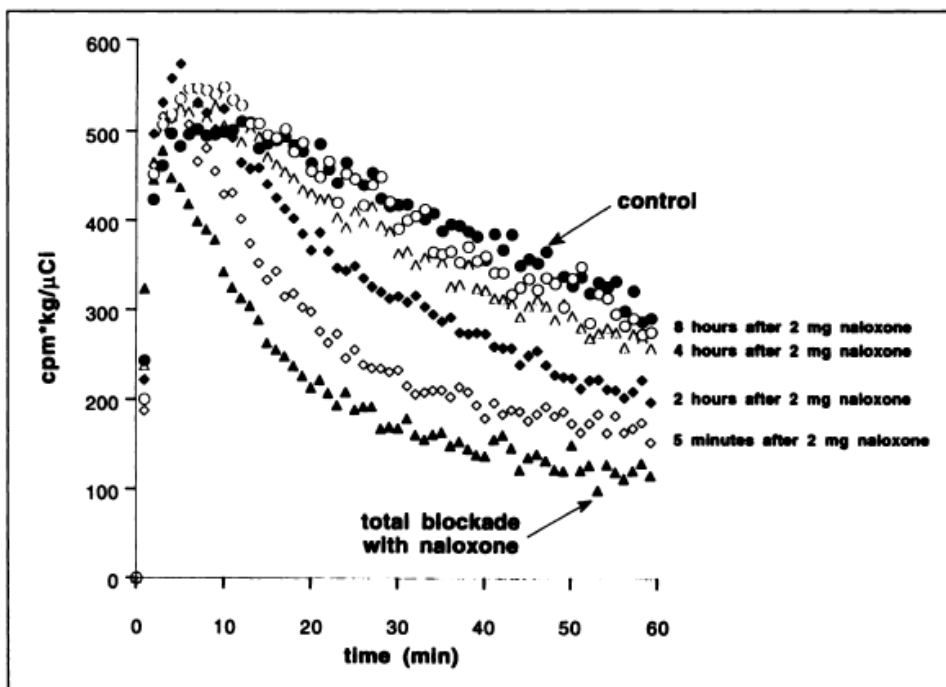
Naloxone, at a dose of 2 mg IV, provided 80.6% blockade of cerebral mu-opioid receptors.¹¹

A randomized, crossover study compared the duration of blockade of cerebral mu-opioid receptors by naloxone and nalmefene, a long-acting opioid antagonist, in 8 healthy volunteers. The use of a simple dual-detector positron radiation detector system and the radiotracer [¹¹C]carfentanil allowed for monitoring of brain kinetics for 5 minutes, 2, 4, 8, and 24 hours post administration of each study drug. Blood samples were obtained at the same time for plasma concentration determinations.

Subjects were randomly assigned to receive either naloxone at a dose of 2 mg or 2 mcg/kg or nalmefene at a dose of 1 mg or 1 mcg/kg by IV administration. All subjects were injected with [¹¹C]carfentanil on the first study day and brain kinetics were monitored at 5 minutes, and 2, 4, 8, and 24 hours post administration. Time-activity curves were generated for 60 minutes to obtain a baseline estimate of the total binding of [¹¹C]carfentanil. After the baseline was obtained, total blockade of the subject's opioid receptors was achieved by use of a dosage regimen of naloxone known to block more than 90% of the available opioid receptors in the human brain. This was used to estimate nonspecific binding.

During subsequent study days, each subject received a bolus IV injection of either naloxone or nalmefene. [¹¹C]carfentanil was injected at 5 minutes and 2, 4, 8, and 24 hours post administration of each drug and time-activity curves were generated. The time-activity curve associated with naloxone at a dose of 2 mg is presented in [Figure 7](#).

Figure 7: Time-activity Curves Post Administration of Naloxone: 2 mg Dose



Source: Kim et al¹¹; figure 3.

Abbreviations: \diamond = 5 minutes; \blacklozenge = 2 hours; Δ = 4 hours; \circ = 8 hours.

One of the criterion used to estimate the degree of receptor occupancy included percent specific blockade of mu-opioid receptors. Additional criteria were clearance half-time (or disappearance of the blockade) and the washout rate of [¹¹C]carfentanil. The percent specific blockade of mu-opioid receptors attributed to naloxone post treatment is presented in [Table 1](#).

Table 1: Percent Specific Blockade of Naloxone at 2 mg and 2 mcg/kg

Naloxone Treatment	Time Post-drug Injection				
	5 min	2 hr	4 hr	8 hr	24 hr
2 mg	80.6±2.6	47.2±4.0	43.8±7.3	7.1±5.4	NA
2 mcg/kg	42.6±8.9	6.2±6.3	33.1±10.0	10.0±11.4	NA

Source: Kim et al¹¹; table 2.

Abbreviations: hr = hours; min = minutes; NA = not applicable.

At 5 minutes, the degree of receptor occupancy by naloxone was 80.6% at a dose of 2 mg.

1.3.1.4. Reversal of Opioid-induced Respiratory Depression

The current naloxone dose recommended for management of the reversal of opioid intoxication is 0.04 mg (initial dose) up to a dose of 2 mg.³

In an article by Kim and Nelson³, it was noted that naloxone is well-absorbed when administered by parenteral routes (ie, IV, IM, SC, and inhalation [nebulized]) and readily crosses the

blood-brain barrier due to its high lipophilicity. In addition, naloxone achieves a brain-serum ratio that is 15-fold greater than that of morphine.

The standard recommended dose of naloxone (0.4 mg) has its origin from the anesthesiology literature of the 1960s when excessive postoperative opioid anesthesia was reversed with naloxone in non-opioid surgical patients. To manage the reversal of opioid intoxication, the current recommended naloxone dose ranges from 0.04 mg (initial dose) up to a dose of 2 mg.

Limited empirical evidence exists to support use of the lower dose of naloxone. In a review of medical textbooks and internet medical resources, the maximum naloxone dose ranged widely from 2 to 20 mg IV. Additionally, a 2 mg dose of naloxone is recommended for use in patients with apnea or near-apnea with cyanosis, irrespective of drug use history.

One of the concerns raised about the use of naloxone and its public health role in the opioid abuse epidemic is that of recurrence of opioid intoxication after prehospital administration, particularly in cases where further care is refused. After a single dose of naloxone, the risk of recurrence of opioid intoxication is higher with exposure to long-acting prescription opioids (eg, methadone and extended-release formulations) as compared to heroin.

1.3.2. Clinical Concentration-response

No in vivo human concentration-response data for naloxone were found in published literature.

1.4. Pharmacokinetics and ADME of Naloxone

1.4.1. In Vitro Studies – Animal

1.4.2. Rat - Absorption and Distribution

Results from absorption studies with ligated intestinal loops indicate that poor absorption of naloxone is not the cause of its relatively low oral potency.¹²

In vitro metabolic studies with rat liver slices confirmed rapid naloxone metabolism, suggesting that the lower potency of oral naloxone compared to parenteral naloxone is due to rapid first-pass liver metabolism.

1.4.3. In Vitro Studies – Human

No human in vitro studies of PKs or ADME were found in published literature.

1.4.4. In Vivo Studies – Animal

1.4.4.1. Rat - Physiological Disposition and Biotransformation

The PK properties of naloxone were determined after SC administration of radiolabeled naloxone (C¹⁴) to male Wistar rats at doses of 1 and 10 mg/kg.¹³

Peak levels of drug in brain and plasma were:

- 1 mg/kg dose: 506 ng/g and 119 ng/mL, respectively.
- 10 mg/kg dose: 4.31 mug/g and 1.27 mug/mL, respectively.

Half-life with 1 and 10 mg/kg: 0.4 hour.

Major metabolite: naloxone-3-glucuronide.

Distribution: A 10 mg/kg dose results in significant amounts of radioactivity that persisted in tissues, but not in plasma 96 hours post dose.

Excretion: (96 hours post 10 mg/kg dose) recorded as a percentage in urine and feces:

- Free naloxone: 4.1 and 3.9, respectively.
- Conjugated drug: 15.4 and 1.2, respectively.
- Total radioactivity: 43.3 and 20.9, respectively.

1.4.4.2. Rat - Systemic Availability

In a review of naloxone studies conducted in animals, a comparative study of intranasal (IN) and IV administration of naloxone in rats demonstrated the following:¹⁴

- The relative systemic availability of IN administration was similar to that of IV delivery.
- Post administration of IN naloxone found that it was completely absorbed from the nasal cavity; peak plasma levels obtained within 3 minutes.

1.4.5. In Vivo Studies – Human

1.4.5.1. Pharmacokinetic Parameters of Naloxone

A summary of the PK parameters of naloxone in healthy human volunteers following single IN administration and IM administration is presented in [Table 2](#).¹⁵

Table 2: Pharmacokinetic Evaluation of IN and IM Naloxone in Healthy Volunteers

Parameter	2mg IN Dose One Spray 20 mg/mL	4mg IN Dose Two Sprays 20 mg/mL	4mg IN Dose One Spray 40 mg/mL	8mg IN Dose Two Sprays 40 mg/mL	0.4mg IM Injection
	2 mg - One Spray 20 mg/mL IN (N = 29)	4 mg - Two Sprays 20 mg/mL IN (N = 29)	4 mg - One Spray 40 mg/mL IN (N = 29)	8 mg - Two Sprays 40 mg/mL IN (N = 29)	0.4 mg IM (N = 29)
λ_z (1/h)	0.382 (34.9)	0.310 (34.5)	0.334 (29.5)	0.330 (32.4)	0.557 (25.9)
$t_{1/2}$ (h)	1.81 (34.9)	2.23 (34.5)	2.08 (29.5)	2.10 (32.4)	1.24 (25.9)
t_{max} (h) †	0.33 (0.25, 1.00)	0.33 (0.17, 0.57)	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
C_{max} (ng/mL)	2.92 (34.3)	6.20 (31.9)	4.83 (43.1)	9.70 (36.0)	0.877 (30.5)
$C_{max}/Dose$ (ng/mL/mg)	1.46 (34.3)	1.55 (31.9)	1.21 (43.1)	1.21 (36.0)	2.19 (30.5)
AUC_{0-t} (h*ng/mL)	4.51 (27.2)	9.32 (24.0)	7.87 (37.4)	15.3 (23.0)	1.72 (22.9)
$AUC_{0-t}/Dose$ (h*ng/mL/mg)	2.25 (27.2)	2.33 (24.0)	1.97 (37.4)	1.91 (23.0)	4.29 (22.9)
AUC_{0-inf} (h*ng/mL)	4.56 (26.9)	9.43 (24.0)	7.95 (37.3)	15.5 (22.7)	1.76 (22.6)
$AUC_{0-inf}/Dose$ (h*ng/mL/mg)	2.28 (26.9)	2.36 (24.0)	1.99 (37.3)	1.93 (22.7)	4.40 (22.6)
AUC% Extrapolated (%)	1.06 (56.5)	0.935 (60.1)	0.965 (53.5)	0.963 (69.3)	2.18 (57.5)
CL/F (L/h)	438 (26.9)	424 (24.0)	503 (37.3)	518 (22.7)	227 (22.6)
Relative BA (%) vs. IM	51.9 (21.7)	53.6 (22.5)	46.7 (31.4) ^{††}	43.9 (23.8)	100
$C_{max}/Dose$ Ratio (IN vs. IM) (%)	66.6 (41.4)	70.7 (37.7)	56.6 (47.5) ^{††}	55.3 (41.4)	100

Source: Study Naloxone-Ph1a-002¹⁵; table 4-2.
Abbreviations: IM = intramuscular; IN = intranasal.

1.4.5.2. Absorption, Distribution, and Metabolism of IN Naloxone in Humans

A review of several studies investigated the use of IN naloxone in humans for the treatment of opioid overdose and reported the absorption, distribution, and metabolism characteristics as follows:¹⁴

- Absorption: rapidly absorbed from the nasal cavity; as effective as IV administration at reversing the effects of opioid overdose.
- Distribution after IV administration: rapid with response after described by recipients as dramatic.
- Metabolism: primarily metabolized in the liver via glucuronide conjugation; major metabolite - naloxone-3-glucuronide.

1.4.5.3. Elimination of Oral or IV Naloxone in Humans

After an oral or IV administration about 25% to 40% of the drug is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60% to 70% in 72 hours.¹⁶

2. PHARMACOLOGY OF FENTANYL

Fentanyl is a synthetic, lipophilic phenylpiperidine opioid agonist with a rapid onset and short duration of action. The principal actions of therapeutic value are analgesia and sedation.

Although chemically unrelated to morphine, fentanyl produces pharmacologic effects and degree of analgesia similar to morphine. On a weight basis, fentanyl is 50 to 100 times more potent than morphine; a parenteral dose of 100 mcg of fentanyl is approximately equivalent in analgesic activity to 10 mg of morphine. Fentanyl differs from morphine by its short duration of analgesic activity, lack of emetic activity, and minimal hypotensive activity.¹⁷

The action of fentanyl is qualitatively similar to that of morphine, ie, analgesia, euphoria, miosis, bradycardia, respiratory depression, bronchoconstriction, muscle rigidity, and suppression of cough reflexes. These effects can be reversed by specific narcotic antagonists, eg naloxone. As with morphine, fentanyl-induced bradycardia from vagal stimulation is blocked or reversed by atropine. Alterations in respiratory rate and alveolar ventilation associated with opioid analgesics may last longer than the analgesic effect. As the dose of the opioid is increased, the decrease in pulmonary exchange becomes greater. Larger doses may produce apnea.¹⁸

Following parenteral administration, the action of fentanyl is faster and less prolonged than that of morphine.¹⁹ The onset of action of fentanyl is almost immediate when the drug is given IV, but the maximal analgesic and respiratory depressant effects may not be noted for several minutes. The usual duration of action of analgesic effect is 30 to 60 minutes after a single IV dose of up to 100 mcg.¹⁸

Following IM administration, onset of action is from 7 to 8 minutes, and the duration of action is 1 to 2 hours.

Following epidural administration, onset of analgesia occurs between 5 and 10 minutes and the duration of action is generally 2 to 5 hours.

Receptor Binding

The action of opioid compounds is mediated through activation of specific opioid receptors. Three major opioid receptors (mu, kappa, and delta) have been cloned in many species, and each is functionally sub-classified into several pharmacological subtypes. Opioid receptors exist in the nervous system as well as in peripheral organs, such as heart, lungs, liver, gastrointestinal and reproductive tracts. The expression and distribution of these receptors vary significantly among different organs as well as among different animal species.²⁰

Fentanyl selectively binds predominantly to the mu-receptor in the CNS thereby mimicking the effects of endogenous opiates. Stimulation of the mu-subtype opioid receptor stimulates the exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) on the G-protein complex, and subsequently inhibits adenylate cyclase. This results in a decrease in intracellular cyclic adenosine monophosphate (cAMP) and leads to a reduction in the release of neurotransmitters such as substance P, gamma-aminobutyric acid (GABA), dopamine, acetylcholine and noradrenaline. The analgesic effect of fentanyl is likely due to its metabolite morphine, which induces opening of G-protein-coupled inwardly rectifying potassium (GIRK)

channels and blocks the opening of N-type voltage-gated calcium channels, thereby resulting in hyperpolarization and reduced neuronal excitability.¹⁹

Two types of mu receptors have been established: the very high affinity, low density, mu₁ receptor subtype appears to mediate supraspinal analgesia, and the lower affinity, high density, mu₂ receptor subtype appears to mediate respiratory depression, physical dependence, and inhibition of gastrointestinal motility.²¹

2.1. In Vitro Opioid Receptor Binding

2.1.1. In Vitro Studies – Animal

2.1.1.1. Rat – Binding Characteristics

Studies of the binding characteristics of [3H]fentanyl in rats demonstrated that fentanyl has selective affinity for the morphine mu-receptor. In a study by Villiger et al²², using homogenates of the rat CNS, association of [3H]fentanyl with its binding site was rapid ($t_{1/2} = 2.5$ min), and stereospecific. Dissociation was biphasic ($t_{1/2} = 4.0$ and 100 min) suggesting the existence of high and low affinity binding sites. Opiate agonists, antagonists and mixed agonist-antagonists all displaced [3H]fentanyl with median inhibitory concentration (IC₅₀) values in the low nanomolar range. The mu- and delta-selective peptides, morphiceptin and [D-Ala²,D-Leu⁵]enkephalin displaced [3H]fentanyl with IC₅₀ values of 87 and 9.2 nM, respectively.

The regional distribution of [3H]fentanyl binding was in the rank order: striatum \approx midbrain >hypothalamus >cortex >hippocampus >brainstem >spinal cord >cerebellum. Comparison of [3H]fentanyl, [3H]naloxone and [D-Ala²,D-Leu⁵]enkephalin binding in the (mu-enriched) hypothalamus-thalamus compared with the frontal cortex-striatum (delta enriched) indicated that the pattern of [3H]fentanyl labelling was similar to that obtained with [3H]naloxone, but differed from that obtained with [D-Ala²,D-Leu⁵]enkephalin, suggesting that [3H]fentanyl binds to the mu-opiate receptor.

The finding that [3H]fentanyl and [3H]dihydromorphine bound with similar affinities to the opiate receptor suggested that the difference between these opiates in analgesic potency was not due to a difference in opiate receptor affinity, but rather to the greater penetration of fentanyl into the brain as compared with morphine.

2.1.1.2. Rat, Guinea Pig – Binding Selectivity

The binding selectivity profiles of a series of opioid analgesics (morphine, fentanyl, dezocine, butorphanol, and nalbuphine) were evaluated in rat and guinea pig brain preparations. The ability of these drugs to compete with radiolabeled ligands for binding at the mu₁, mu₂, kappa₁, and delta opioid receptors was characterized.²¹ Fentanyl exhibited the highest affinity for the mu₁ site of all the drugs tested, consistent with its clinical actions as a potent opioid analgesic. The similar binding affinities (K_i's) for morphine (8.6 nM) and fentanyl (6.5 nM) at the mu₂ receptor, thought to mediate respiratory depression, were inconsistent, with the observation that 2 to 5 mcg/kg doses of fentanyl have been shown to induce both analgesia and respiratory depression in humans. The divergence of affinity and potency in this study might be attributable to differences in the binding characteristics of rat brain mu₂ receptors compared to human mu₂ receptors.

The K_i 's for the various drugs at each opiate receptor site were determined from the IC_{50} value, and results are summarized in [Table 3](#).

Table 3: Competitive Binding of Selected Opioid Analgesics to μ_1 , μ_2 , κ_1 , and delta Receptors

Drug	K_i (nM)			
	μ_1	μ_2	κ_1	delta
Morphine	0.26 ± 0.03	8.6 ± 1.2	52 ± 12	358 ± 47
Fentanyl	0.007 ± 0.0005	6.5 ± 0.5	242 ± 11	1140 ± 31
Butorphanol	0.13 ± 0.01	0.7 ± 0.16	0.5 ± 0.1	5.1 ± 1
Nalbuphine	0.49 ± 0.12	3.2 ± 0.35	5.1 ± 1.4	102 ± 11
Dezocine	0.42 ± 0.10	9.0 ± 1.7	72 ± 21	144 ± 50

Source: Chen et al²¹; table 1 and table 2.

2.1.2. In Vitro Studies - Human

2.1.2.1. Select Opioid Drugs and mu-opioid Receptor Binding

A compendium of uniformly derived binding constants using commercially available cell membranes expressing human mu-opioid receptors was developed by Volpe et al.²³ The results are presented in [Table 4](#).

Table 4: Ranking of mu-opioid Receptor Binding Constants for Selected Opioid Drugs

Drug	K_i (nM)	Drug	K_i (nM)
Tramadol	12,486	Nalbuphine	2.118
Codeine	734.2	Fentanyl	1.346
Meperidine	450.1	Morphine	1.168
Propoxyphene	120.2	Butorphanol	0.7622
Pentazocine	117.8	Levorphanol	0.4194
Hydrocodone	41.58	Oxymorphone	0.4055
Oxycodone	25.87	Hydromorphone	0.3654
Diphenoxylate	12.37	Buprenorphine	0.2157
Alfentanil	7.391	Sufentanil	0.1380
Methadone	3.378		

Source: Volpe et al²³; table 2.

In this study, the authors noted that although binding affinities, measured as K_i values, are a widely used measure of relative potency, other factors contribute to the potencies of opioid drugs when used clinically, including secondary pharmacology, the ability to act as full or partial agonists, and the relative ability to partition into the brain. For example, based on the binding data alone, the affinity of fentanyl and morphine are similar. However, a typical IM dose of fentanyl is 50 to 100 mcg compared to 10 mg of IM morphine; that is, fentanyl is approximately 100 times more potent than morphine. The difference in potency can in part be attributed to the

differential lipophilicity of these drugs. Thus, when compared to phenanthrene drugs (eg, morphine, oxycodone), the phenylpiperidine drugs (eg, alfentanil, fentanyl, sufentanil) have greater lipophilicity and rapidly cross the blood brain barrier resulting in greater analgesic potency.

2.1.2.2. Delta-opioid Receptor Binding

Delta-opioid receptors play a modulatory role in analgesia, hibernation, autonomic nervous system function, neuroendocrine system function, mood driven behaviors and olfaction. The activation profiles of a series of opioid ligands in transfected human embryonic kidney (HEK) cells expressing only delta-opioid receptors were developed by Gharagozlou et al²⁴ to define the relative potencies of a set of opioid ligands compared to one another and differentiate between full and partial agonists at delta-opioid receptors. Results are summarized in [Table 5](#).

Table 5: Binding Profile of Opioid Ligands in HEK-delta Cells

Ligand	Affinity K _i (nM)
Xorphanol	1.0 ± 0.2
WIN 44,441	2.6 ± 0.9
Nalorphine	38.5 ± 4.0
Morphine	68.5 ± 19.5
Nalbuphine	77 ± 8
Fentanyl	242.5 ± 102.5

Source: Gharagozlou et al²⁴; table 2.

Based on receptor binding assays, fentanyl has low affinity and low potency at delta-opioid receptors; its affinity for mu-opioid receptors is 100- to 1000-fold higher than that for delta-opioid receptors.

2.1.3. In Vivo Studies – Animal

2.1.3.1. Mouse – Efficacy, Tolerance, and mu-Opioid Receptor Regulation

The relationship between efficacy, tolerance and mu-opioid receptor regulation was examined by Sirohi et al²⁵ in mice. In this study, the efficacy of fentanyl in the mouse tailflick assay was found to be relatively high compared to oxycodone and morphine.

To examine the effect of fentanyl on mu-opioid receptor density in spinal cord, mice were infused with fentanyl (1, 2, or 4 mg/kg/day) for 7 days or injected once/day for 7 days (200 mcg/kg/day).

Chronic infusion with fentanyl at the highest dose (4 mg/kg/day) significantly reduced mu-opioid receptor density by 28% without altering affinity, whereas the lower dose infusions (1 or 2 mg/kg/day), and intermittent injections (200 mcg/kg/day) had no significant effect.

Fentanyl infusions (1, 2, or 4 mg/kg) for 7 days dose-dependently decreased morphine potency with the highest fentanyl dose reducing morphine potency by approximately 6 fold. Neither acute nor 7 days of intermittent fentanyl (100 or 200 mcg/kg) injections had any significant effect on morphine potency.

The following conclusions were reached from this study:

- Fentanyl is a higher efficacy opioid analgesic in a model of analgesia in the mouse.
- Fentanyl infusion produced spinal mu-opioid receptor downregulation consistent with the direct relationship between efficacy and mu-opioid receptor downregulation in vivo.
- Fentanyl infusions dose-dependently produced substantial tolerance while acute or intermittent fentanyl injections produced minimal tolerance in all dosing groups, irrespective of duration of treatment confirming the inverse relationship between efficacy and tolerance.
- Opioid analgesic efficacy is predictive of mu-opioid receptor regulation and tolerance.

2.1.4. In Vivo Studies – Human

There were 2 in vivo studies from published literature that demonstrated the analgesic mechanisms of fentanyl as measured by PET imaging. Most PET imaging studies of opioid receptors in humans have been conducted with the fentanyl analog [¹¹C]carfentanil²⁶, and there is very little data available on the use of PET imaging to study receptor binding of fentanyl in humans.

2.1.4.1. Brain Activity Responses to Fentanyl Analgesia

Brain activity responses to fentanyl analgesia as measured by PET was studied by Firestone et al.²⁷ In this study, PET scanning in 6 volunteers examined the effects of a small IV bolus (1.5 mcg/kg) of fentanyl on regional cerebral activity as reflected by regional cerebral blood flow (rCBF). Comparison of rCBF during fentanyl infusion with that during placebo revealed significant increases consistent with regional neuronal activation in both cortical and subcortical areas, and in both hemispheres. These areas included bilateral cingulates, prefrontal cortices, and caudate nuclei. No statistically significant fentanyl-related activation was detected in the somatosensory cortical areas. These data indicated that fentanyl's effects are highly localized, and specifically affect cerebral regions associated with descending pain modulation, as well as vocalization and visceromotor responses to pain. The presence of attentional, learning, and reward networks in fentanyl-activated areas suggested other means by which opioids may modulate pain behavior.

2.1.4.2. Elucidation of the Supraspinal Analgesic Mechanisms of Opioids

The potential of PET in elucidating the supraspinal analgesic mechanisms of opioids in humans was reviewed by Kurata et al.²⁸ The effects of low-dose fentanyl on the regional blood flow of the brain in 6 normal subjects with no pain demonstrated that fentanyl administration (1.5 mcg/kg IV bolus) was associated with a significant increase of rCBF in bilateral anterior cingulate, prefrontal cortices, and caudate nuclei, but not in the somatosensory cortical areas. A significant decrease of rCBF in the left prefrontal, right temporal cortices, and cerebellum was also observed. Postmortem autoradiographic studies in humans have demonstrated high opioid receptor concentrations in all the brain regions found to be activated by fentanyl in this study, but

also in many others. It was thus concluded that the results with fentanyl in this study could not be a simple consequence of stimulating action at all opioid receptor-containing neurons.

In 9 healthy subjects with painful stimulus, fentanyl significantly increased rCBF in the anterior cingulate and contralateral motor cortices, and significantly decreased rCBF in the bilateral thalamus and ipsilateral posterior cingulate cortex. This particular subregion in the anterior cingulate cortex did not overlap with the pain-activated subregion. Fentanyl augmented the pain-related increase of rCBF in the supplementary area and ipsilateral inferior frontal cortex significantly, but not in the anterior cingulate and thalamus. This phenomenon was associated with a significant decrease in visual analogue scale scores indicating that these areas are most likely the neuroanatomic substrates of fentanyl analgesia. These data indicated that fentanyl analgesia involves augmentation of pain-evoked cerebral responses in certain areas, as well as both activation and inhibition in other brain regions unresponsive to pain stimulation alone.

2.2. Pharmacokinetics and ADME of Fentanyl

2.2.1. In Vivo Studies – Human

2.2.1.1. Pharmacokinetic Parameters of IV Fentanyl

The PKs of fentanyl, sufentanil, and alfentanil were compared and reviewed by Halliburton²⁹ and the descriptive data is summarized in Table 6. All data were obtained from studies performed on adult surgical patients, ASA classification I or II.

Table 6: Pharmacokinetic Parameters of Intravenous Fentanyl, Sufentanil, and Alfentanil Using a 3-Compartment Model

Mean Parameter	Fentanyl (6.4 mcg/kg)	Sufentanil (5 mcg/kg)	Alfentanil (125 mcg/kg)
V _{dc} (L/kg)	0.356	0.10	0.0806
V _{dss} (L/kg)	3.99	1.74	0.708
Cl (mL/min/kg)	12.6	11.8	5.06
k ₁₂ (min ⁻¹)	0.185	0.670	1301.4
k ₂₁ (min ⁻¹)	0.103	0.279	973.8
k ₁₃ (min ⁻¹)	0.141	0.194	170.4
k ₃₁ (min ⁻¹)	0.020	0.013	65.4
k ₁₀ (min ⁻¹)	0.041	0.145	225.6
t _{1/2B} (min)	219	164	94

Source: Halliburton²⁹; table 1.

Abbreviations: Cl = clearance; k₁₀ = elimination rate constant from central compartment; k₁₂₋₁₃ = rate constants representing drug transfer from central to peripheral compartments; k₂₁₋₃₁ = rate constants representing drug transfer from peripheral to central compartment; t_{1/2B} = terminal elimination half-life (the time in which 50% of the available drug is eliminated from the central compartment); V_{dc} = volume of distribution central compartment; V_{dss} = volume of distribution at steady-state.

After injection, fentanyl underwent an initial rapid distribution phase, followed by a second slower distribution phase and a terminal elimination phase, best described by a 3-compartment

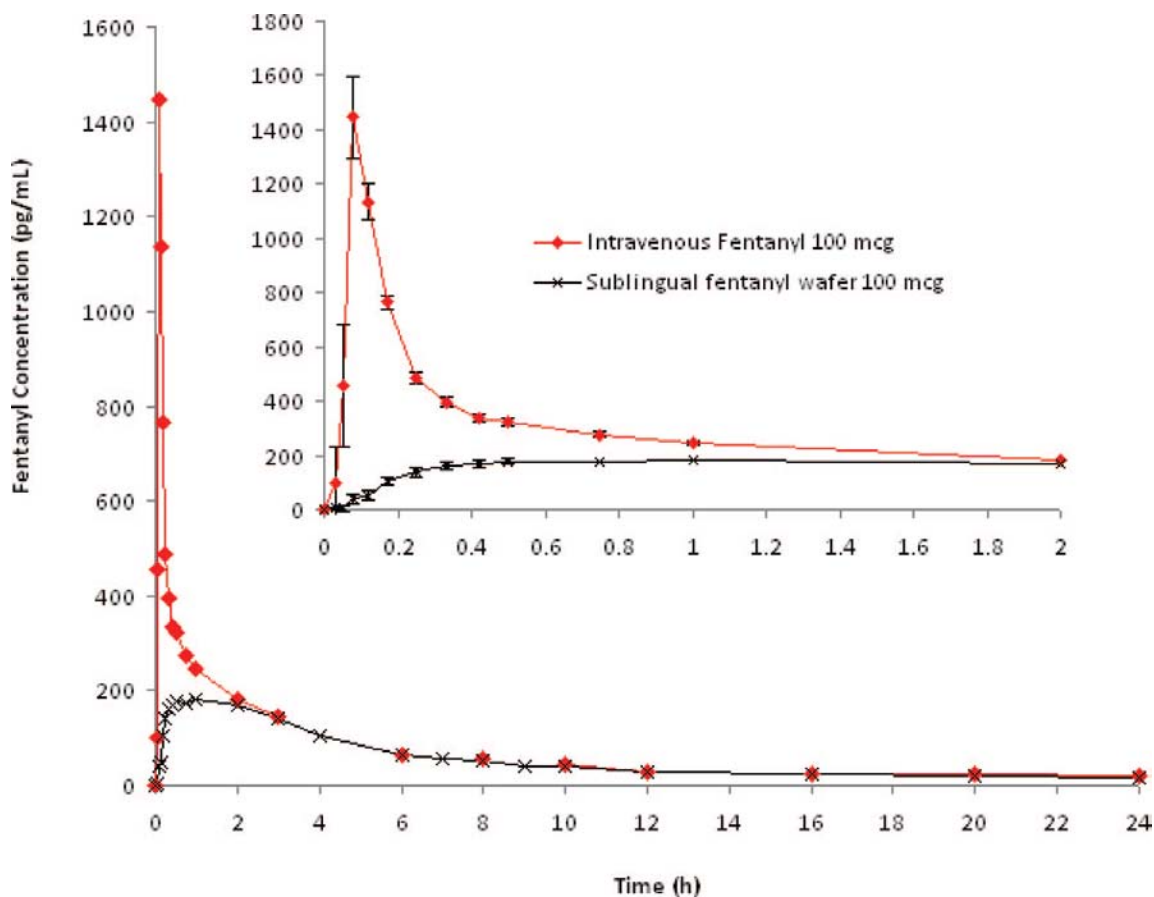
model. Fentanyl had the longest $t_{1/2B}$ of 219 minutes, attributed to its relatively large volume of distribution at steady-state (V_{dss}) of 4 L/kg.

2.2.1.2. Pharmacokinetic Parameters of IV and Sublingual Fentanyl

In a Phase 1 PK and bioavailability study³⁰ of a sublingual (SL) fentanyl wafer in healthy volunteers, the PK parameters were compared to those of IV fentanyl. This was a single-center, randomized, open-label, single-dose, 2-treatment, 2-period, 2-way crossover study. Subjects received either IV fentanyl citrate or an SL fentanyl citrate wafer (equivalent to 100 mcg of fentanyl). After a 7-day washout period, each subject received drug via the alternative administration route.

The mean plasma (\pm SEM) fentanyl concentration versus time curves for the IV and SL routes are shown in Figure 8, and the mean (SD) values for the plasma PK parameters are summarized in Table 7. The C_{max} of SL fentanyl was 18.8% (CI, 14.4% to 24.6%) of the IV administration value, with the average time to maximum concentration being 0.9 hour. For IV administration, C_{max} generally occurred at the end of the infusion with a rapid reduction over the half hour immediately postdose. From approximately 2 hours postdose, the mean concentration–time profiles were similar for the 2 modes of administration.

Figure 8: Mean (\pm SEM) Plasma Concentration Over Time Profiles for Sublingual and Intravenous Fentanyl



Source: Lim et al³⁰; figure 1.

Note: Inset figure is an expanded profile for the initial 2-hour period.

Table 7: Mean (SD) Plasma Pharmacokinetic Parameters for Intravenous and Sublingual Fentanyl

Treatment	t _{max} (h)	C _{max} (pg/mL)	AUC ₀₋₁₂ (h·pg/mL)	AUC _{0-t} (h·pg/mL)	AUC _{0-∞} (h·pg/mL)
IV Fentanyl (100 mcg) n=22	0.12 (±0.05)	1451.0 (±970.1)	1404.8 (±285.5)	1703.7 (±375.9)	1952.9 (±378.8)
SL Fentanyl (100 mcg) n=22	0.91 (±0.73)	219.3 (±70.5)	1046.1 (±388.4)	1299.8 (±517.1)	1739.9 (±815.2)

Source: Lim et al³⁰; table 2.

Note: IV fentanyl was administered as a 5-minute infusion.

2.2.1.3. Absorption of Fentanyl in Humans

According to the product information for Sublimaze[®] injection¹⁸ (fentanyl citrate), the onset of action of fentanyl is almost immediate when the drug is given IV; however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of analgesic effect is 30 to 60 minutes after a single IV dose of up to 100 mcg. Following IM administration, the onset of action is from 7 to 8 minutes and the duration of action is 1 to 2 hours.

2.2.1.4. Distribution of Fentanyl in Humans

From the Product Monograph for Fentanyl Citrate Injection USP¹⁷, with doses of approximately 3 to 30 mcg/kg IV in humans, the serum curves could be described in terms of a 3-compartment open model.

At all doses, plasma levels have been reported to fall rapidly in the first 5 minutes to approximately 20% of the peak value.

The elimination half-life is approximately:

- from 0.73 to 1.63 minutes for the first distribution phase;
- from 5.1 to 21 minutes for the second phase;
- from 86.6 to 346.5 minutes for the third phase.
- Urinary excretion was very low during the first two hours.

Fentanyl has a V_c (volume of distribution of the central compartment) of 13 L, and a total V_{dss} of 339 L. The total blood binding of fentanyl is about 83%, comprised of plasma protein binding about 43% (principally to alpha1-acid glycoprotein but also to albumin, and lipoproteins), and red blood cell binding about 40%.¹⁸

Fentanyl is highly lipophilic and distributes rapidly from blood into the brain, heart, lungs, kidneys, and spleen in animals. It then redistributes more slowly into skeletal muscle and fat compartments, and redistributes slowly from these tissues into systemic circulation. Fentanyl crosses the placenta and is distributed into breast milk. Alterations in blood pH may alter ionization of fentanyl and therefore its distribution between plasma and the CNS. Large single or repeated doses can result in substantial accumulation, potentially resulting in an extended duration of effect.³¹

2.2.1.5. Metabolism of Fentanyl in Humans

Fentanyl is extensively metabolized by the liver and it has a high hepatic extraction ratio (0.8 to 1.0). Consequently, the hepatic clearance of fentanyl approaches hepatic blood flow. The liver is the most important metabolizing organ, whereas extrahepatic metabolism occurs only to a very minor degree in the kidney. The metabolites of fentanyl are reported to be: phenylacetic acid, norfentanyl (4-N-[N-propionyl-3H-anilino]piperidine), propionic acid, and despropiofentanyl (1-2 [phenethyl]-4-N-anilino- piperidine). In vitro experiments in humans have demonstrated that fentanyl is metabolized mainly by cytochrome P450 3A4 (CYP 3A4) to norfentanyl via oxidative N-dealkylation.^{17,18}

2.2.1.6. Elimination of Fentanyl in Humans

Approximately 75% of the administered dose is excreted in the urine within 72 hours and only 8.4% of the dose recovered in urine is present as unchanged drug.¹⁸

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ACUTE OPIOID WITHDRAWAL SYMPTOMS

Unlike in alcohol or benzodiazepine withdrawal, acute opiate withdrawal is not associated with life-threatening effects such as seizures or coma.

Smithedajkul PY, Cullen MW. Managing acute opiate withdrawal in hospitalized patients. *ACP Hospitalist*. Oct 2009. <http://www.acphospitalist.org/archives/2009/10/residents.htm> (accessed Aug 11, 2016).

ACUTE OPIOID WITHDRAWAL SYMPTOMS

Acute withdrawal symptoms (AWS) in opioid tolerant individuals can include:

- Agitation
- Yawning
- Diaphoresis
- Rhinorrhoea
- Lacrimation
- Piloerection
- Myalgias
- Nausea
- Vomiting
- Diarrhea

Naloxone could potentially cause withdrawal symptoms in opioid dependent individuals however, these symptoms, while unpleasant, are generally not life-threatening.

Clarke SF, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope. *Emergency medicine journal : EMJ*. Sep 2005;22(9):612-616.

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ACUTE OPIOID WITHDRAWAL SYMPTOMS

In one study (Oslo, Norway) designed to investigate the safety of treating heroin overdoses in an out-of-hospital setting, a high incidence (45%) of adverse events may have been related to naloxone use or could have been related to hypoxia and extensive use of heroin in combination with other agents.

- Most common AEs (33%) were related to opioid withdrawal: GI disorders, aggressiveness, tachycardia, shivering, sweating and tremor.
- Cases of confusion/restlessness (32%) might be related either to opioid withdrawal or to the effect of heroin in combination with other drugs.
- Headache and seizures (25%) were probably related to hypoxia.
- Most events were non-serious. In three episodes (0.3%) the patients were hospitalized because of adverse events.

Buajordet I, Naess AC, Jacobsen D, Brors O. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. *Eur. J. Emerg. Med.* Feb 2004;11(1):19-23.

ACUTE OPIOID WITHDRAWAL SYMPTOMS

Although a number of possible adverse effects of naloxone have been published, in many of these reports it can be difficult to differentiate between the effect of naloxone and the effect of the underlying disease process or other drugs that have been ingested or administered.

- **Pulmonary edema:** most instances have occurred in the postoperative period or in the presence of pre-existing cardiorespiratory disease. Instances of pulmonary edema secondary to opioid toxicity have been published and it has been suggested that naloxone simply reveals the opioid-induced pulmonary edema that had been masked by the respiratory depression.
- **Seizures and arrhythmias:** have also been noted, but could have been caused by hypoxia, the opioids themselves, their coingestants (most notably cocaine), or pre-existing disease.

In contrast with the above concerns, high doses (up to 5.4 mg/kg boluses and 4 mg/kg/h infusions) of naloxone have been given to non-opioid dependent subjects without any reported adverse effects.

Clarke SF, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope. *Emergency medicine journal : EMJ*. Sep 2005;22(9):612-616.

PHARMACOLOGY OF FENTANYL: GENERAL

- Synthetic, lipophilic phenylpiperidine opioid agonist with analgesic and anesthetic properties.
- Exerts its principal pharmacologic effects on the central nervous system.
- Alterations in mood, euphoria and dysphoria, and drowsiness commonly occur.
- Depresses the respiratory centers, depresses the cough reflex, and constricts the pupils.
- May increase the patient's tolerance for pain and decrease the perception of suffering.
- Selectively binds predominately to the mu-receptors distributed in the human central nervous system (CNS), thereby mimicking the effects of endogenous opiates.
- Also binds to kappa and delta-type opioid receptors.

National Center for Biotechnology Information. PubChem Compound Database; CID=3345, <https://pubchem.ncbi.nlm.nih.gov/compound/3345> (accessed Aug. 11, 2016).

PHARMACOLOGY OF FENTANYL: GENERAL

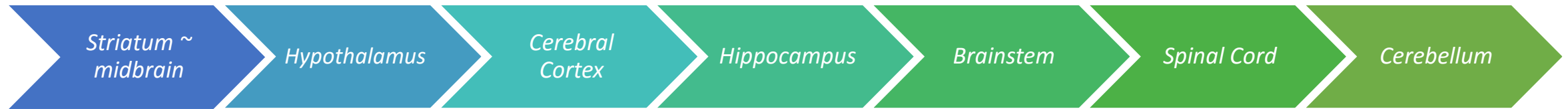
- Fentanyl is up to 100 times more powerful than morphine and 50 times more powerful than heroin.
- Stimulation of the mu-subtype opioid receptor stimulates the exchange of GTP for GDP on the G-protein complex and subsequently inhibits adenylate cyclase.
 - Results in a decrease in intracellular cAMP and leads to a reduction in the release of neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline.
 - The analgesic effect of fentanyl is likely due to its metabolite morphine, which induces opening of G-protein-coupled inwardly rectifying potassium (GIRK) channels and blocks the opening of N-type voltage-gated calcium channels, thereby resulting in hyperpolarization and reduced neuronal excitability.

U.S. Department of Justice, Drug Enforcement Administration. (2015, March 18). *DEA issues nationwide alert on fentanyl as threat to health and public safety.* Retrieved from <http://www.dea.gov/divisions/hq/2015/hq031815.shtml>

PHARMACOLOGY OF FENTANYL: RAT IN VITRO (CNS)

Receptor Binding

- [^3H]fentanyl binds to homogenates of the rat central nervous system with the regional distribution rank order:



Villiger JW, Ray LJ, Taylor KM. Characteristics of [^3H]fentanyl binding to the opiate receptor. *Neuropharmacology*. Apr 1983;22(4):447-452.

PHARMACOLOGY OF FENTANYL: RAT IN VITRO (CNS)

Receptor Binding

- Selective affinity for morphine (μ) receptors.
- Rapid association ($t_{1/2} = 2.5$ min).
- Biphasic dissociation ($t_{1/2} = 4.0$ and 100 min) suggesting existence of high affinity ($K_D = 0.35$ nM) and low affinity ($K_D = 8.65$ nM) binding sites, both μ receptors.

Villiger JW, Ray LJ, Taylor KM. Characteristics of [3 H]fentanyl binding to the opiate receptor. *Neuropharmacology*. Apr 1983;22(4):447-452.

PHARMACOLOGY OF FENTANYL: RAT IN VITRO (CNS)

Receptor Binding

- Similar binding capacities were obtained in mu- and delta-rich homogenates for [³H]fentanyl and [³H]naloxone
 - The amount of [³H-D-Ala²,D-Leu⁵]enkephalin binding was 4 times greater in the delta-rich homogenate.
- Opiate antagonist naloxone potently displaced [³H]fentanyl, with IC₅₀=2.5 nM.

Villiger JW, Ray LJ, Taylor KM. Characteristics of [³H]fentanyl binding to the opiate receptor. *Neuropharmacology*. Apr 1983;22(4):447-452.

PHARMACOLOGY OF FENTANYL: RAT IN VITRO (BRAIN)

Receptor Binding

Two types of mu receptors have been established:

- **mu₁ receptor subtype:** high affinity, low density - appears to mediate supraspinal analgesia.
- **mu₂ receptor subtype:** lower affinity, high density - appears to mediate respiratory depression, physical dependence, and inhibition of gastrointestinal motility.

Chen JC, Smith ER, Cahill M, Cohen R, Fishman JB. The opioid receptor binding of dezocine, morphine, fentanyl, butorphanol and nalbuphine. *Life Sci.* 1993;52(4):389-396.

PHARMACOLOGY OF FENTANYL: RAT IN VITRO (BRAIN)

Receptor Binding

- Fentanyl had the highest affinity for the μ_1 site, consistent with its clinical actions as a potent opioid analgesic.
- Affinity for the μ_2 receptor was similar to morphine. Differences in the binding characteristics of μ_2 receptors in humans vs rat brain may explain divergence of affinity and potency for fentanyl in this study.

Chen JC, Smith ER, Cahill M, Cohen R, Fishman JB. The opioid receptor binding of dezocine, morphine, fentanyl, butorphanol and nalbuphine. *Life Sci.* 1993;52(4):389-396.

PHARMACOLOGY OF FENTANYL: RAT IN VITRO (BRAIN)

Receptor Binding

- Low affinity for kappa₁ and delta receptors.

Competitive binding of morphine and fentanyl to mu₁, mu₂, kappa₁, and delta receptors

Drug	K _i (nM)			
	mu ₁	mu ₂	kappa ₁	delta
Morphine	0.26	8.6	52	358
Fentanyl	0.007	6.5	242	1140

Chen JC, Smith ER, Cahill M, Cohen R, Fishman JB. The opioid receptor binding of dezocine, morphine, fentanyl, butorphanol and nalbuphine. *Life Sci.* 1993;52(4):389-396.

PHARMACOLOGY OF FENTANYL: HUMAN IN VITRO

Receptor Binding

- A single competitive receptor binding assay in a cell membrane preparation expressing recombinant human mu-opioid receptors (MOR).
- Binding affinity (K_i) values correlate with in vitro measurements of potency and efficacy.

Ranking of mu-opioid receptor binding constants for selected opioid drugs

Drug	K_i (nM)	Drug	K_i (nM)
Tramadol	12,486	Nalbuphine	2.118
Codeine	734.2	Fentanyl	1.346
Meperidine	450.1	Morphine	1.168
Propoxyphene	120.2	Butorphanol	0.7622
Pentazocine	117.8	Levorphanol	0.4194
Hydrocodone	41.58	Oxymorphone	0.4055
Oxycodone	25.87	Hydromorphone	0.3654
Diphenoxylate	12.37	Buprenorphine	0.2157
Alfentanil	7.391	Sufentanil	0.1380
Methadone	3.378		

Volpe DA, McMahon Tobin GA, Mellon RD, et al. Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. *Regul. Toxicol. Pharmacol.* Apr 2011;59(3):385-390.

PHARMACOLOGY OF FENTANYL: RECEPTOR BINDING AFFINITY

In addition to receptor-binding affinity, other factors contribute to the potencies of opioid drugs when used clinically, such as:

- ability to act as full or partial agonists
- secondary pharmacology
- relative ability to partition into the brain.
- Although the affinity of fentanyl and morphine are similar, fentanyl is ~100 times more potent than morphine.

Volpe DA, McMahon Tobin GA, Mellon RD, et al. Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. *Regul. Toxicol. Pharmacol.* Apr 2011;59(3):385-390.

PHARMACOLOGY OF FENTANYL: RECEPTOR BINDING AFFINITY

- The difference in potency can, in part, be attributed to the differential lipophilicity of these drugs.
- Compared to phenanthrene drugs (eg, morphine, oxycodone), phenypiperidine drugs (eg, alfentanil, fentanyl, sufentanil) have greater lipophilicity and rapidly cross the blood brain barrier, resulting in greater analgesic potency.

Volpe DA, McMahon Tobin GA, Mellon RD, et al. Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. *Regul. Toxicol. Pharmacol.* Apr 2011;59(3):385-390.

PHARMACOLOGY OF FENTANYL: IN VITRO – HEK CELLS (RECEPTORS)

Receptor Binding

- Delta opioid receptors play a modulatory role in analgesia, hibernation, autonomic nervous system function, neuroendocrine system function, mood driven behaviors and olfaction.
- Based on receptor binding assays, fentanyl has an affinity for mu-opioid receptors that is 100 – 1000 fold higher than that for delta-opioid receptors.

Gharagozlou P, Demirci H, Clark JD, Lamah J. Activation profiles of opioid ligands in HEK cells expressing delta opioid receptors. *BMC neuroscience*. Nov 18 2002;3:19.

PHARMACOLOGY OF FENTANYL: IN VITRO – HEK CELLS (RECEPTORS)

Receptor Binding

Fentanyl has low affinity and low potency at delta-opioid receptors.

Binding Profile of Opioid ligands in HEK- δ cells

Ligand	Affinity K_i (nM)
Xorphanol	1.0
WIN 44,441	2.6
Nalorphine	38.5
Morphine	68.5
Nalbuphine	77
Fentanyl	242.5

Gharagozlou P, Demirci H, Clark JD, Lameh J. Activation profiles of opioid ligands in HEK cells expressing delta opioid receptors. *BMC neuroscience*. Nov 18 2002;3:19.

PHARMACOLOGY OF FENTANYL: MOUSE IN VIVO

Relationship between Efficacy, Tolerance and mu-Opioid Receptor Regulation

- Fentanyl infusion downregulated spinal mu-opioid receptors.
- The efficacy of fentanyl in the mouse > oxycodone and morphine.
- Chronic infusion with fentanyl (4 mg/kg/day) significantly reduced mu-opioid receptor density by 28% in mouse spinal cord without altering affinity, whereas 1 or 2 mg/kg/day fentanyl infusions had no significant effect.

Sirohi S, Dighe SV, Walker EA, Yoburn BC. The analgesic efficacy of fentanyl: relationship to tolerance and mu-opioid receptor regulation. *Pharmacol. Biochem. Behav.* Nov 2008;91(1):115-120.

PHARMACOLOGY OF FENTANYL: MOUSE IN VIVO

Relationship between Efficacy, Tolerance and mu-Opioid Receptor Regulation

- Fentanyl infusions (1, 2 or 4 mg/kg) for 7 days dose-dependently decreased morphine potency with the highest fentanyl dose reducing morphine potency by ~6 fold.
- Neither acute nor 7 days of intermittent fentanyl (100 or 200 μ g/kg) injections had any significant effect on morphine potency.
- **These results are consistent with the inverse relationship between efficacy and tolerance; and the direct relationship between efficacy and mu-opioid receptor downregulation in vivo.**

Sirohi S, Dighe SV, Walker EA, Yoburn BC. The analgesic efficacy of fentanyl: relationship to tolerance and mu-opioid receptor regulation. *Pharmacol. Biochem. Behav.* Nov 2008;91(1):115-120.

PHARMACOLOGY OF FENTANYL: HUMAN IN VIVO

- Positron Emission Tomography (PET) has been used to measure brain activity responses to fentanyl analgesia.
- Data indicate that fentanyl's effects are highly localized and specifically affect cerebral regions associated with a range of pain-related behaviors. as well as both activation and inhibition in other brain regions unresponsive to pain stimulation alone.

Kurata J, Gyulai FE, Firestone LL. Use of Positron Emission Tomography to Measure Brain Activity Responses to Fentanyl Analgesia. *Current review of pain*. 1999;3(5):359-366.

PHARMACOLOGY OF FENTANYL: HUMAN IN VIVO

- Positron Emission Tomography (PET) has been used to measure brain activity responses to fentanyl analgesia.
- Data indicate that fentanyl's effects are highly localized and specifically affect cerebral regions associated with a range of pain-related behaviors.
- Fentanyl affects activation and inhibition in other brain regions unresponsive to pain stimulation alone.

Kurata J, Gyulai FE, Firestone LL. Use of Positron Emission Tomography to Measure Brain Activity Responses to Fentanyl Analgesia. *Current review of pain*. 1999;3(5):359-366.

- Most PET imaging studies of opioid receptors in humans have been conducted with the fentanyl analog [¹¹C]carfentanil.

Hirvonen J, Aalto S, Hagelberg N, et al. Measurement of central mu-opioid receptor binding in vivo with PET and [¹¹C]carfentanil: a test-retest study in healthy subjects. *European journal of nuclear medicine and molecular imaging*. Feb 2009;36(2):275-286.

PHARMACOKINETICS OF FENTANYL

After IV fentanyl administration:

- Initial rapid distribution phase
- Second slower distribution phase / terminal elimination phase
- Described by a 3-compartment model.

Halliburton JR. The pharmacokinetics of fentanyl, sufentanil and alfentanil: a comparative review. *AANA J.* Jun 1988;56(3):229-233.

PHARMACOKINETICS OF FENTANYL

Pharmacokinetic Parameters of Intravenous Fentanyl, Sufentanil and Alfentanil Using a 3-Compartment Model

Mean Parameter	Fentanyl (6.4 mg/kg)	Sufentanil (5 mg/kg)	Alfentanil (125 mg/kg)
V_{dc} (L/kg)	0.356	0.10	0.0806
V_{dss} (L/kg)	3.99	1.74	0.708
Cl (mL/min/kg)	12.6	11.8	5.06
k_{12} (min^{-1})	0.185	0.670	1301.4
k_{21} (min^{-1})	0.103	0.279	973.8
k_{13} (min^{-1})	0.141	0.194	170.4
k_{31} (min^{-1})	0.020	0.013	65.4
k_{10} (min^{-1})	0.041	0.145	225.6
$t_{1/2}$ (min)	219	164	94

Cl, clearance; k_{10} , elimination rate constant from central compartment; k_{12-13} , rate constants representing drug transfer from central to peripheral compartments; k_{21-31} , rate constants representing drug transfer from peripheral to central compartment; $t_{1/2}$, terminal elimination half-life (the time in which 50% of the available drug is eliminated from the central compartment); V_{dc} , volume of distribution central compartment; V_{dss} , volume of distribution at steady-state.

Halliburton JR. The pharmacokinetics of fentanyl, sufentanil and alfentanil: a comparative review. *AANA J.* Jun 1988;56(3):229-233.

Fentanyl Citrate Injection USP

Pharmacokinetics:

- With doses of approximately 3 to 30 mcg/kg IV in humans, the serum curves could be described in terms of a three-compartment open model.
- At all doses, plasma levels have been reported to fall rapidly in the first 5 minutes to approximately 20% of the peak value.

Sandoz Canada Inc. (July 29, 2014). *Fentanyl Citrate Injection USP: Product Monograph*. Boucherville, QC, Canada.

Fentanyl Citrate Injection USP

Pharmacokinetics: (cont'd)

- The elimination half-life is approximately:
 - from 0.73 to 1.63 minutes for the first distribution phase;
 - from 5.1 to 21 minutes for the second phase;
 - from 86.6 to 346.5 minutes for the third phase.
- Urinary excretion was very low during the first two hours.

Sandoz Canada Inc. (July 29, 2014). *Fentanyl Citrate Injection USP: Product Monograph*. Boucherville, QC, Canada.

Fentanyl Citrate Injection USP

Metabolism and Excretion:

- The concentration of fentanyl excreted unchanged in the urine is usually about 8 to 10%.
- The liver is the most important metabolizing organ, whereas extrahepatic metabolism occurs only to a very minor degree in the kidney.

Sandoz Canada Inc. (July 29, 2014). *Fentanyl Citrate Injection USP: Product Monograph*. Boucherville, QC, Canada.

Fentanyl Citrate Injection USP

Metabolism and Excretion: (cont'd)

- The metabolites of fentanyl are reported to be: phenylacetic acid, norfentanyl (4-N-(propionyl- 3H-anilino)piperidine), propionic acid and despropiofentanyl (1-2 (phenethyl)-4-N-anilino- piperidine).

Sandoz Canada Inc. (July29, 2014). *Fentanyl Citrate Injection USP: Product Monograph*. Boucherville, QC, Canada.

SUBLIMAZE[®] Injection (Fentanyl Citrate)

Pharmacokinetics

- Onset of action is almost immediate when administered IV.
- Maximal analgesic and respiratory depressant effect may not be noted for several minutes.
- Usual duration of action of analgesic effect is 30 to 60 minutes after a single IV dose of up to 100 mcg.

SUBLIMAZE[®] Injection (Fentanyl Citrate)

Pharmacokinetics: (cont'd)

- Following intramuscular administration, the onset of action is from 7 to 8 minutes and the duration of action is 1 to 2 hours.
- Peak respiratory depressant effect of a single IV dose is noted 5 to 15 minutes following injection.

JANSSEN-CILAG Pty Ltd. (July 3, 2015). SUBLIMAZE[®] Injection for Intramuscular use: Product Information. Australia.

SUBLIMAZE[®] Injection (Fentanyl Citrate)

Distribution

- After IV injection, fentanyl plasma concentrations fall rapidly, with sequential distribution half-lives of 1 minute and 18 minutes.
- Terminal elimination half-life is 475 minutes.
- V_c (volume of distribution of the central compartment) is 13 L.

SUBLIMAZE[®] Injection (Fentanyl Citrate)

Distribution: (cont'd)

- Total V_{dss} (distribution volume at steady-state) is 339 L.
- Total blood binding of fentanyl is about 83% (comprised of plasma protein binding about 43% and red blood cell binding about 40%).

JANSSEN-CILAG Pty Ltd. (July 3, 2015). SUBLIMAZE[®] Injection for Intramuscular use: Product Information. Australia.

SUBLIMAZE[®] Injection (Fentanyl Citrate)

Metabolism

- Fentanyl is extensively metabolized by the liver.
- Has a high hepatic extraction ratio (0.8 – 1.0). Consequently, the hepatic clearance of fentanyl approaches hepatic blood flow.
- Human in vitro experiments have demonstrated that fentanyl is metabolized mainly by cytochrome P450 3A4 (CYP 3A4) to norfentanyl via oxidative N-dealkylation.

SUBLIMAZE[®] Injection (Fentanyl Citrate)

Elimination

- Approximately 75% of the administered dose is excreted in the urine within 72 hours.
- 8.4% of the dose recovered in urine is present as unchanged drug.

PHARMACOKINETICS OF FENTANYL

Mean (SD) Plasma Pharmacokinetic Parameters for Intravenous (IV) and Sublingual (SL) Fentanyl

Treatment	t_{\max} (h)	C_{\max} (pg/mL)	AUC_{0-12} (h·pg/mL)	AUC_{0-t} (h·pg/mL)	$AUC_{0-\infty}$ (h·pg/mL)
IV Fentanyl (100 mg) n=22	0.12 (±0.05)	1451.0 (±970.1)	1404.8 (±285.5)	1703.7 (±375.9)	1952.9 (±378.8)
SL Fentanyl (100 mg) n=22	0.91 (±0.73)	219.3 (±70.5)	1046.1 (±388.4)	1299.8 (±517.1)	1739.9 (±815.2)

Lim CB, Schug SA, Sunderland VB, Paech MJ, Liu Y. A phase I pharmacokinetic and bioavailability study of a sublingual fentanyl wafer in healthy volunteers. *Anesth. Analg.* Sep 2012;115(3):554-559.

**Use of NARCAN® Nasal Spray in the Community Setting:
A Survey of Use in Community Organizations**

An Interim Report of Methodology and Preliminary Results

SMC-AP-082116

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August 23, 2016

Use of NARCAN[®] Nasal Spray in the Community Setting: A Survey of Use in Community Organizations

Introduction

The United States is experiencing an ongoing epidemic of deaths due to overdose from opioid substances, including a 200% increase in the rate of overdose deaths involving opioids.¹ The Centers for Disease Control and Prevention (CDC) reported a total of 47,055 drug overdose deaths in the United States in 2014, representing a significant 1-year increase of 6.5% in overdose deaths overall and a significant increase in overdose deaths specifically related to opioids of 14%.¹ Between 2013 and 2014, the age-adjusted rate of death involving natural and semisynthetic opioid pain relievers, heroin, and synthetic opioids other than methadone (eg, fentanyl) increased 9%, 26%, and 80%, respectively.¹ The increase in deaths involving synthetic opioids (other than methadone) indicates a worsening of the opioid epidemic, necessitating continued action to not only prevent opioid abuse and dependence, but also to prevent death in individuals who overdose.¹

An increasing number of community-based programs have offered opioid overdose prevention services to persons who use drugs, their families and friends, and service providers.² Over the past 20 years, programs have increasingly provided laypersons with training and kits containing naloxone hydrochloride (naloxone), an opioid antagonist used to reverse the potentially fatal respiratory depression caused by heroin and other opioids.² A recent study conducted by the Harm Reduction Coalition found that providing opioid overdose training and naloxone kits to laypersons who might witness an opioid overdose can help reduce opioid overdose mortality.²

NARCAN[®] (naloxone hydrochloride) Nasal Spray is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.³ Until the approval of NARCAN Nasal Spray (supplied as a single 4-mg dose of naloxone hydrochloride in a 0.1-mL intranasal spray)³ in November 2015, naloxone was available only in injectable formulations.⁴ In response to the growing concerns about the opioid epidemic in the United States, NARCAN Nasal Spray was approved through fast-track review by the US Food and Drug Administration (FDA) to provide increased access to easy-to-administer naloxone for use by nonmedical personnel in the community setting.⁴

In an effort to understand the initial experiences with NARCAN Nasal Spray in the community setting, Synchrony Medical Communications, LLC, conducted a survey of community organizations that have implemented use of the product.

Methods

Organization Contact

Contact information was available for 216 community organizations to which Adapt Pharma has distributed a total of 57,882 units of NARCAN Nasal Spray. The organizations to which NARCAN Nasal Spray has been distributed represent a wide spectrum of community service groups, including:

- Law enforcement
- County government
- Health departments
- Emergency medical services
- Advocacy groups
- Community outreach and harm reduction organizations, volunteers, and shelters
- Pharmacy service centers

In general, the objectives were to obtain answers to qualitative questions concerning the organizations' overall experiences as well as to obtain any data the organization may have for purposes of quantitative analysis.

During the time period of August 1-19, 2016, each organization was contacted via email and/or telephone, with several rounds of follow-up completed for non-responders. Contacts were prioritized by the number of NARCAN Nasal Spray units that had been distributed to the organization, beginning with higher numbers. During initial communications, the contact was queried regarding willingness to answer questions about use of NARCAN Nasal Spray by his or her organization and availability for a telephone interview (to last approximately 30-60 minutes). Telephone interviews were scheduled and conducted through August 19.

The purpose of the qualitative interview was to obtain background on the organization, insight into the community the organization serves, information regarding use of NARCAN Nasal Spray by the organization, including total number of reversals, and overall impressions of NARCAN Nasal Spray by the organization contact. Each contact was queried regarding whether his or her organization collected any form of data regarding NARCAN Nasal Spray use and whether the organization was willing to share these data.

Data Collection and Analysis

For organizations with available data and in agreement to provide these data, the level/type of data collected as well as the format in which these data were provided varied. In general, data were sought that included number of attempted reversals, the presumed substance involved in the attempted reversal, the number of doses of NARCAN Nasal Spray administered, and the outcome of the reversal, including any observed events. Provided data included submission of individual case report forms, Microsoft Excel summary data, individual patient data in Microsoft Excel, tables provided via email, and qualitative email summary reports. Data were compiled into single spreadsheet for evaluation using summary statistics.

Results

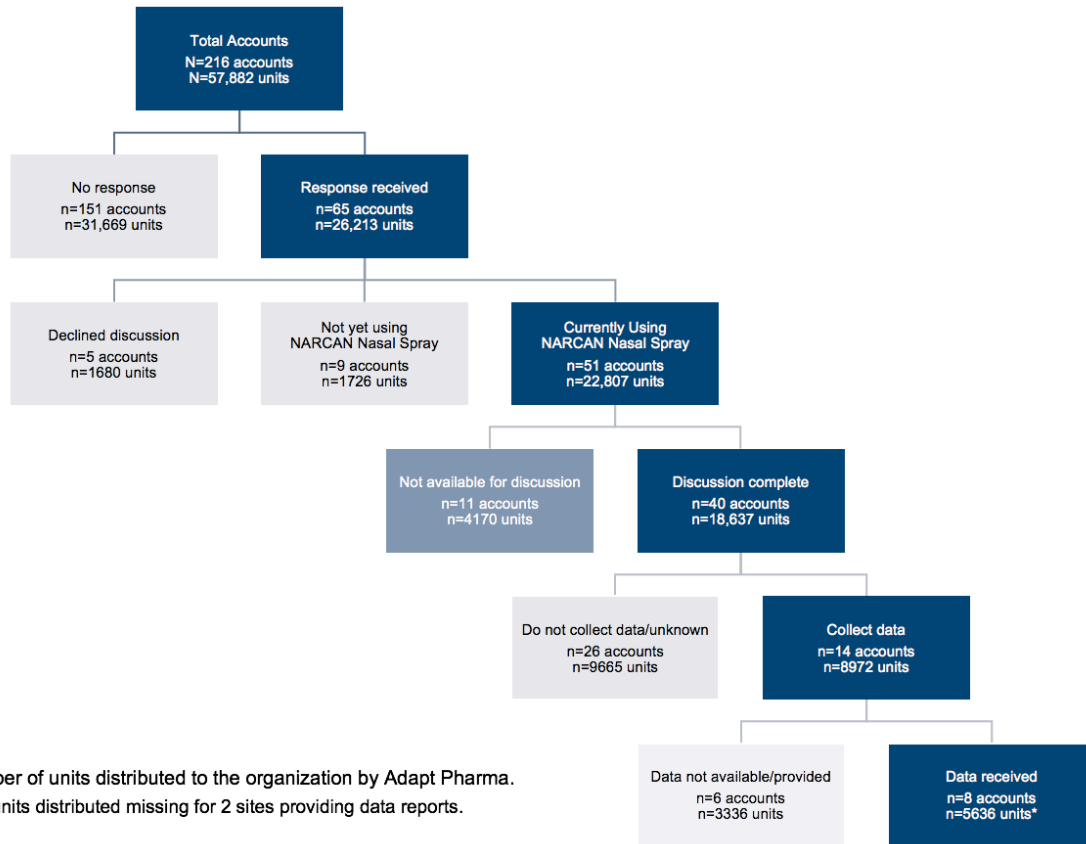
Qualitative Interviews

Details regarding the results of attempted contacts for telephone interviews are provided in **Figure 1**. Of the 216 organizations with whom contact was attempted, an initial response was received from 65 contacts, of whom 51 have been using NARCAN Nasal Spray in the community. A total of 40/216 (19%) organization contacts (accounting for 18,637 units of NARCAN Nasal Spray distributed by Adapt Pharma to the organizations) participated in a telephone interview (see *Appendix A, Table 1*). During the qualitative discussions, 23 of the organization contacts indicated an estimated length of time for which NARCAN Nasal Spray has been in use, which ranged from 3 weeks to 6 months, with 13 of the 23 organizations reporting use for 5-6 months (beginning in February or March 2016). Estimates of the total number of opioid overdose reversals specifically using NARCAN Nasal Spray were provided by 15 organizations (accounting for 7669 units distributed by Adapt Pharma); estimates from these individuals totaled more than 1400 overdose reversals. A total of 14 of the 40 organizations contacted indicated that the organization collects some form of data on attempted reversals. For these organizations, attempts were made to obtain these data for use in the quantitative analysis portion of the survey.

Quantitative Data Collection

Case report summary data on attempted opioid overdose reversals using NARCAN Nasal Spray were received from 8/216 (4%) organizations, accounting for 5636 units distributed by Adapt Pharma to 6 of the 8 organizations (data missing regarding number of distributed units for 2 organizations) (**Figure 1**). These organizations included county government (n=1), behavioral health system (n=1), drug and alcohol commission (n=1), overdose prevention organization (n=1), and community outreach and harm reduction organizations/volunteers (n=4) (see *Appendix A, Table 2*). Patient information was de-identified on all reports received.

Figure 1. Results of Attempted Contact With Organizations Using NARCAN Nasal Spray



Units indicate number of units distributed to the organization by Adapt Pharma.
 *Data on number of units distributed missing for 2 sites providing data reports.

Doses Administered

The 8 organizations provided case report data on a total of 261 attempted overdose reversals using NARCAN Nasal Spray, accounting for 350 known total doses administered. A single dose was administered in 165 (63%) of the 261 attempted reversals, 2 doses were administered in 83 (32%), and 3 or more doses in 6 (2%). The administered dose was unknown in 7 (3%) cases (**Table 1**).

Table 1. NARCAN Nasal Spray Doses Administered in Attempted Overdose Reversals

No. of NARCAN Nasal Spray Doses Administered	Reversal Attempts, no. (%) N=261
1 dose	165 (63)
2 doses	83 (32)
3 or more doses	6 (2)
Dose unknown	7 (3)

Agents Involved in Overdose

The substance presumed to be involved in the opioid overdose was reported for 173 (66%) of 261 attempted reversals. The majority of overdoses (165/173; 95%) were thought to involve heroin, and 49/173 (28%) were thought to involve other CNS depressants, such as benzodiazepines and alcohol. A total of 9/173 (5%) of cases were thought to involve some form of fentanyl, either alone (n=1), or combined with heroin (n=8). Of the 173 attempted reversals reporting a presumed substance, 65 (38%) of the overdoses were thought to involve multiple substances (**Table 2**).

Table 2. Presumed Substance Involved in Opioid Overdose

Presumed Substance	Overdoses, no. (%)* n=173
Opioid	
Heroin	165 (95)
Fentanyl	9 (5)
Morphine	2 (1)
Oxycodone (IV)	2 (1)
Buprenorphine	1 (0.5)
Codeine	1 (0.5)
Opioid/pain medication, unspec.	4 (2)
Other CNS depressant	
Alcohol	27 (16)
Benzodiazepines	22 (13)
Multiple involved substances	65 (38)
Other/unknown	25 (14)

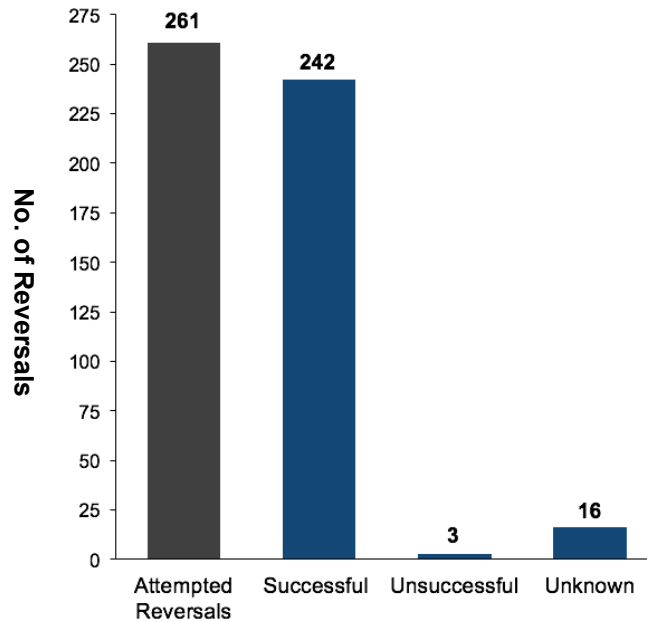
*Percentages may total >100%; agents reported separately for overdoses involving multiple substances.

Reversal Outcomes

The majority of attempted reversals (242/261; 93%) were reported as successful, with unsuccessful reversal reported for 3 (1%) attempted reversals. Reversal outcome was reported as unknown in 16 (6%) cases (**Figure 2**).

Additional details were available for 2 of the 3 unsuccessful reversals; in both cases, the individual who overdosed was thought to be deceased prior to administration of NARCAN Nasal Spray. One attempt was for a female (age unknown), in whom heroin combined with alcohol was presumed to precipitate the overdose. A friend administered 1 dose of NARCAN Nasal Spray and called emergency medical services; rescue breathing was also performed. The friend stated that he or she “tried too late”. The other attempt was on an individual (sex and age unknown) in whom overdose was presumed to be caused by a combination of “pills,” heroin, alcohol, and Xanax® (alprazolam). The person administering the NARCAN Nasal Spray (1 dose administered) called 911, but stated that he “knew it was already too late.”

Figure 2. Reported Reversal Outcomes Using NARCAN Nasal Spray



Observed Events

Six of the 8 organizations providing case report summaries included information on observed events. Information regarding observed events was provided for 196 (75%) of the 261 total reversals. Of these 196 attempted reversals for which information on observed events was provided, 122 (62%) cases were specifically noted as “none” or “N/A”. Observed events were reported in 74/196 (38%) cases (**Table 3**). The most commonly reported events (included in ≥10% of reports) cases were withdrawal, nausea/vomiting, and anger. The vast majority of reported events were consistent with opioid withdrawal. No unexpected or life-threatening events were reported.³

Table 3. Observed Events

Events	No. of Events (%) n=196
None	122 (62)
Cases with any event*	74 (38)
Withdrawal	28 (14)
Nausea/vomiting	20 (10)
Anger	19 (10)
Aggression	4 (2)
No memory of event	4 (2)
Seizure	3 (2)
Sweating	3 (2)
Dizziness	2 (1)
Headache	2 (1)
Confusion	1 (<1)
Trembling (shaking)	1 (<1)
Miscellaneous	10 (5)

*More than one event may have occurred in a single case.

“Withdrawal” was specifically reported in a total of 28/196 (14%) attempted reversals, 2 (1%) of which were reported as “severe” or “strong” withdrawal, and 6 (3%) of which were reported as “mild” or “minor” withdrawal. No severity qualifier was provided for the remaining 20 instances of “withdrawal.” A total of 5 additional events were reported with specific qualifiers suggesting potential significant events. Four of these (2%) related to vomiting, including “severe withdrawal/vomiting” in 1 case (<1%), “heavy vomiting” in 2 cases (1%), and “vomiting everywhere” in 1 case (<1%). “Extreme anger” was reported in 1 case (<1%). Seizure was reported in 3 cases (2%).

Based on qualitative reports of an apparent association of fentanyl overdose with vomiting when the overdose is reversed, observed events for overdoses presumed to involve fentanyl were summarized separately. Of the 9 overdoses thought to involve fentanyl, information regarding observed events was available for 8 cases. Vomiting was reported in 4 (50%) of these 8 cases, 2 instances of which were the reports of “heavy vomiting” noted above.

Dose of NARCAN Nasal Spray was known for 192 (98%) of the 196 cases for which information on observed events was available. Of these, 117 cases were administered 1 dose, 71 cases received 2 doses, and 4 cases received 3 doses. Observed events were reported in 54 (46%) of 117 cases in which 1 dose was administered and in 36 (51%) of 71 cases in which 2 doses were administered (**Table 4**). Nausea/vomiting was the only observed event that that may have been associated with with a dose response relationship.

Table 4. Observed Events by Dose of NARCAN Nasal Spray

Events	1 Dose NARCAN n=117	2 Doses NARCAN n=71	3 Doses NARCAN n=4	NARCAN Dose Unknown n=4	Total, n (%) n=196
None	63 (54)	35 (49)	3 (75)	2 (50)	122 (62)
Cases with any event*	54 (46)	36 (51)	1 (25)	2 (50)	74 (38)
Withdrawal	17 (15)	11 (15)	-	-	28 (14)
Nausea/vomiting	7 (6)	10 (14)	1 (25)	2 (50)	20 (10)
Anger	12 (10)	6 (8)	-	1 (25)	19 (10)
Aggression	2 (2)	2 (3)	-	-	4 (2)
No memory of event	3 (3)	1 (1)	-	-	4 (2)
Seizure	1 (<1)	2 (3)	-	-	3 (2)
Sweating	2 (2)	-	-	1 (25)	3 (2)
Dizziness	2 (2)	-	-	-	2 (1)
Headache	2 (2)	-	-	-	2 (1)
Confusion	-	1 (1)	-	-	1 (<1)
Trembling (shaking)	-	-	-	1 (25)	1 (<1)
Miscellaneous	6 (5)	3 (4)	-	1 (25)	10 (5)

*More than one event may have occurred in a single case.

Summary

In an effort to understand the initial experiences with NARCAN Nasal Spray in the community setting, Adapt Pharma recently commissioned a survey of community organizations that have implemented use of the product. Eight organizations provided various levels of case report summary data on 261 attempted reversals, accounting for 350 total doses of NARCAN Nasal Spray administered; 1 dose was used in 165 (63%) of these reversals, while 2 doses were used in 83 (32%) reversals.

NARCAN Nasal Spray was reported to be effective in all but 3 attempted overdose reversals. In 2 unsuccessful reversals, the product was reported to be not administered in time. No additional information was available for the third unsuccessful reversal. No unexpected or life-threatening events were reported with doses ranging from 4-16 mg.³ The vast majority of reported events were consistent with opioid withdrawal.

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2. Wheeler E, Jones TS, Gilbert MK, Davidson PJ. Opioid overdose prevention programs providing naloxone to laypersons – United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2015;64(23):631-635.
3. Narcan (naloxone hydrochloride) Nasal Spray [package insert]. Radnor, PA: Adapt Pharma, Inc.; 2015.
4. US Food and Drug Administration. FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473505.htm>. Accessed August 22, 2016.



11 July 2016

**Janet Woodcock M.D., Director,
Center for Drug Evaluation and Research (CDER),**

Division of Dockets Management,
Food and Drug Administration,
Department of Health and Human Services,
5630 Fishers Lane, rm. 1061,
Rockville, MD 20852

RE: CITIZEN PETITION - Petition Requesting FDA Guidelines for the Optimal Dose and Pharmacokinetics for any Naloxone Containing Product Intended for the Emergency Treatment of Suspected Opioid Overdose in All Settings (Including Non-Medical Settings) by Individuals (Including Non-Medically Trained Individuals)

Dear Dr. Woodcock,

Opioid overdose is a major public health problem in the United States (US) and other countries. In the US, opioid overdose contributes to a significant number of accidental deaths. Centers for Disease Control and Prevention (CDC) data indicate that in 2014 drug overdose deaths from prescription opioids and heroin reached almost 29,000 – or an average of 78 fatalities daily.

Opioids include illegal drugs, such as heroin, as well as prescription opioid medications, such as morphine, codeine, methadone, oxycodone, hydrocodone, hydromorphone, fentanyl and buprenorphine. The CDC data suggests that in 2014, heroin was implicated in approximately 30% of all fatalities and prescription opioids implicated in approximately 70% of cases. The majority of fatalities arise in non-medical facilities, most frequently at the deceased's home.

Various federal agencies including Substance Abuse and Mental Health Services Administration (SAMHSA) and CDC have identified heightened risk factors for opioid overdose. These include, but are not limited to, the chronic use of higher dose opioids, a current or past opioid use disorder diagnosis or opioid overdose event, or illicit opioid use.



The public health response to the epidemic involves (i) increasing education about opioid overdose risks and changing prescriber opioid prescribing practices, (ii) expanding access to naloxone and (iii) increasing access to opioid dependency treatments.

Adapt is the manufacturer of Narcan Nasal Spray, 4 mg, which is the first intranasal product containing naloxone that has been approved by the Food and Drug Administration for the treatment of opioid overdose. In approving Narcan Nasal Spray at a fixed initial 4 mg intranasal dose (which achieves plasma exposure to naloxone as rapidly and in a range comparable to that achieved by a total 2 mg dose of naloxone hydrochloride administered by intramuscular injection), the FDA has already considered the criticality of dose/target plasma levels, accuracy and reliability of the device and time to onset. These three factors are critical in rapidly and consistently achieving an effective exposure when administered for the emergency treatment of suspected opioid overdose by individuals (including non-medically trained individuals), including in non-medical settings.

As treatment with naloxone has expanded beyond use by clinicians in the hospital setting it is critical that the available naloxone dose is consistently adequate for the emergency treatment of an opioid overdose and can be readily and rapidly administered by the witness without exposure to needle-stick injury. Any naloxone product intended for use in non-medical settings should be administered as a fixed efficacious dose to ensure that the optimal initial dose is administered as quickly as possible. Further, the ease of use, accuracy and reliability of any manually operated device must be adequately demonstrated per FDA guidelines.

What has changed recently is an acceleration of expanded naloxone access to new potential witnesses and more potent and faster onset opioids being implicated in a growing proportion of opioid overdose deaths. These provide an urgent need to ensure that new naloxone formulations intended for emergency treatment in all settings, (including non-medical settings), by anyone (including non-medically trained individuals), deliver a consistently efficacious fixed initial dose that achieves optimal exposures to naloxone (i.e. plasma levels) and can be easily and rapidly administered.

The purpose of this submission is to request the Commissioner to establish appropriate guidance for all naloxone products intended for the emergency treatment of suspected opioid overdose in all settings (including non-medical settings) by individuals (including non-medically trained individuals), that include the optimal fixed initial dose for each route of administration as well as the required exposure levels to achieve an efficacious onset of action and duration of effect.

The undersigned submits this petition under the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. 10.30 to request the Commissioner of Food and Drugs to:

- 1. Higher potency, faster onset and longer acting opioids (such as fentanyl) are implicated in a rapidly growing proportion of opioid overdose fatalities. At the same time, naloxone access is being expanded to new groups of users via novel distribution channels, such as pharmacy naloxone access programs without personal prescriptions. In light of these new paradigms, the Petitioner requests that before approving new naloxone treatments intended for use by individuals, including non-medically trained individuals, in settings including non-medical settings, FDA evaluate the optimal initial fixed dose of naloxone appropriate for treating a suspected opioid overdose.**
- 2. Before approving new naloxone treatments intended for use by individuals (including non-medically trained individuals) in all settings (including non-medical settings), the petitioner is requesting the Agency to publish an FDA Guideline for Naloxone that defines the required pharmacokinetic exposure levels for naloxone that are required to be achieved from the recommended optimal dose of naloxone, including time to onset and duration of effect;**
- 3. The petitioner is requesting the FDA to require naloxone products from an applicant to utilize a product formulation and device that allows for an individual, (including a non-medically trained individual) in all settings, (including non-medical settings), to readily and rapidly administer a fixed initial dose.**

Please feel free to contact me directly at 858-335-1300 or e-mail at Richard@PacificLinkConsulting.com if there are any questions with respect to this correspondence.

Yours sincerely,



Richard E. Lowenthal, MS, MBA
Adapt Pharma Limited Regulatory Representative

**Petition Requesting FDA Guidelines for the Optimal Dose
and Pharmacokinetics for any Naloxone Containing Product
Intended for the Emergency Treatment of Suspected Opioid
Overdose in All Settings (Including Non-Medical Settings)
by Individuals (Including Non-Medically Trained
Individuals)**

11 July 2016

CITIZEN PETITION

11 July 2016

The undersigned submits this Petition under the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. 10.30 to request the Commissioner of Food and Drugs to issue a requirement for naloxone products from an applicant to utilize a product formulation and device that allows for an individual, (including a non-medically trained individual) in all settings, (including non-medical settings), to readily and rapidly administer a fixed initial dose.



11 July 2016

Richard E. Lowenthal
Adapt Regulatory Representative

Date

A. Actions Requested

The undersigned submits this petition under the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. 10.30 to request the Commissioner of Food and Drugs to:

1. **Higher potency, faster onset and longer acting opioids (such as fentanyl) are implicated in a rapidly growing proportion of opioid overdose fatalities. At the same time, naloxone access is being expanded to new groups of users via novel distribution channels, such as pharmacy naloxone access programs without personal prescriptions. In light of these new paradigms, the Petitioner requests that before approving new naloxone treatments intended for use by individuals, including non-medically trained individuals, in settings including non-medical settings, FDA evaluate the optimal initial fixed dose of naloxone appropriate for treating a suspected opioid overdose.**
 - FDA should convene an Advisory Committee to determine the optimal effective initial dose and corresponding target plasma levels for each route of administration for naloxone products intended for emergency treatment of suspected opioid overdose administration as emergency therapy in settings where opioids may be present.

2. **Before approving new naloxone treatments intended for use by individuals (including non-medically trained individuals) in all settings (including non-medical settings), the Petitioner is requesting the Agency to publish an FDA Guideline for Naloxone that defines the required pharmacokinetic exposure levels for naloxone that are required to be achieved from the recommended optimal dose of naloxone, including time to onset and duration of effect.**
 - FDA's traditional pharmacokinetic parameters (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) should be maintained but alone are NOT sufficient to account for the early clinical exposure needed to achieve efficacy with naloxone containing products intended to treat opioid overdose. Critical pharmacokinetic issues regarding naloxone administration are the rate of absorption and the time to reach plasma concentrations that correlate with efficacy, in this case, the reversal of respiratory depression. Thus, the standard criteria for AUC and C_{max} would not be adequate to cover the time period of the onset of action.
 - FDA should also consider the duration of exposure such that naloxone plasma levels are maintained above a threshold for period (for example, at least 2 hours) to allow for subjects to recover from the opioid overdose and for rescue medical personnel to provide assistance.

3. The Petitioner is requesting the FDA to require naloxone products from an applicant to utilize a product formulation and device that allows for an individual, (including a non-medically trained individual) in all settings, (including non-medical settings), to readily and rapidly administer a fixed initial dose.

- FDA should only approve a formulation, which cannot be inadvertently or purposefully partially administered. The formulation should require that the dose is actuated in a simple movement that cannot be stopped once started. This ensures the intended dose is administered and eliminates critical delays in administering divided doses.
- Human factor and label comprehension studies should be completed in representative study population including teenagers and low literacy adults. These studies should ensure that the formulation is intuitive to use and recognizable to the individual (including non-medically trained individuals), as a device that is for the intended route of administration only. The human factor and label comprehension studies should support the use of the proposed formulation by the intended population (including pediatrics), with or without device training.
- Since speed to delivery is critical, FDA should establish standards for the rate at which the device can be removed from packaging and administered in an emergency situation.

B. Statement of Grounds

1. Key Strategy Considerations for Petition

a. The Opioid Overdose Epidemic in the United States:

Opioid overdose is a major public health problem in the United States (US) and other countries. In the US, opioid overdose contributes to a significant number of accidental deaths. Centers for Disease Control and Prevention (CDC) data indicate that in 2014 drug overdose deaths from prescription opioids and heroin reached almost 29,000 – or an average of 78 fatalities daily (1).

Opioids include illegal drugs, such as heroin, as well as prescription opioid medications, such as morphine, codeine, methadone, oxycodone, hydrocodone, hydromorphone, fentanyl and buprenorphine. The CDC data suggests that in 2014, heroin was implicated in approximately 30% of all fatalities and prescription opioids implicated in approximately 70% of cases. The majority of fatalities arise in non-medical facilities, most frequently at the deceased's home (1).

Various federal agencies including Substance Abuse and Mental Health Services Administration (SAMHSA) and CDC have identified heightened risk factors for opioid overdose. These include, but are not limited to, the chronic use of higher dose opioids, a current or past opioid use disorder diagnosis or opioid overdose event, or illicit opioid use.

The public health response to the epidemic involves (i) increasing education about opioid overdose risks and changing prescriber opioid prescribing practices, (ii) expanding access to naloxone and (iii) increasing access to opioid dependency treatments.

Expanding Access to Naloxone

As a narcotic antagonist, naloxone displaces opiates from receptor sites in the brain and can reverse respiratory depression that is usually the cause of overdose deaths. Naloxone has been approved in an injectable form for over 40 years. It can be an effective treatment for suspected opioid overdose if an adequate dose is administered in time.

Because most opioid overdose deaths happen in the community, many stakeholders have called for the development and FDA approval of easy-to-use naloxone formulations intended for emergency administration by individuals (including non-medically trained individuals), at the site of a suspected opioid overdose.

The Food and Drug Administration (FDA) responded to such calls by granting fast track designation and approving, under priority review, two new formulations of naloxone (an auto-injector in April 2014 and nasal spray in November 2015).

b. Need to consider optimal initial effective dose for new naloxone formulations to reflect recent changes in potency of opioids implicated in overdoses, potential naloxone users and use settings

Expanding access to naloxone is a key element of the public policy response to the opioid overdose epidemic. While naloxone hydrochloride, administered by injection, has been approved by FDA and used for more than 40 years to treat opioid overdose symptoms, its use has historically been intended for clinicians and other medically trained personnel, such as EMS.

Naloxone Properties

Naloxone is an essentially pure opioid antagonist, i.e., it does not possess the “agonistic” or morphine-like properties characteristic of other opioid antagonists. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity. Naloxone has not been shown to produce tolerance or cause physical or psychological dependence. In the presence of physical dependence on opioids, naloxone will produce withdrawal symptoms, which may appear within minutes of administration and subside in about 2 hours. The severity and duration of the withdrawal syndrome are related to the dose of naloxone and to the degree and type of opioid dependence. While the mechanism of action of naloxone is not fully understood, *in vitro* evidence suggests that naloxone antagonizes opioid effects by competing for the mu, kappa, and sigma opiate receptor sites in the Central Nervous System (CNS), with the greatest affinity for the mu receptor. When naloxone hydrochloride is administered by intravenous injection (IV), the onset of action is generally apparent within 2 minutes; the onset of action is slightly less rapid when it is administered by subcutaneous injection (SC) or intramuscular injection (IM).

Naloxone Dosing Instructions

Injectable formulations of naloxone have been FDA approved for the treatment of opioid overdose symptoms for many years at initial doses of 0.4mg to 2mg naloxone by the IM or IV route of administration, followed by repeat doses up to a total dose of 10mg. Inherent in the dosing instructions in the FDA approved labeling for injectable naloxone formulations are the assumptions that (i) a clinician is immediately available to determine a patient specific appropriate initial dose between 0.4 mg and 2 mg naloxone by injection and a rate of titration for repeat doses, if required; (ii) additional doses of naloxone, as may be required, are available to achieve an adequate dose; and (iii) medical monitoring expertise and equipment to assess respiratory depression necessary to support clinical decision-making, are available.

In contrast, opioid overdose witnesses, including non-medically trained individuals, equipped with a naloxone formulation in non-medical settings may be solely reliant on that product as an initial emergency treatment to bridge to the arrival of medical help. The witness may not have access to medical training to inform initial emergency dose or titration decisions, access to medical monitoring equipment, alternative resuscitative techniques, or additional doses of

naloxone. Further, non-medically trained individuals, in particular, may be at increased risk of needle-stick injury.

As treatment with naloxone is expanded beyond the hospital setting it is critical that the available naloxone dose is consistently adequate for the emergency treatment of an opioid overdose and can be readily and rapidly administered by the witness without exposure to needle-stick injury. Any naloxone product intended for use in non-medical settings should be administered as a fixed efficacious dose to ensure that the optimal initial dose is administered as quickly as possible. Further, the ease of use, accuracy and reliability of any manually operated device must be adequately demonstrated per FDA guidelines.

In approving Narcan (naloxone hydrochloride) Nasal Spray at a fixed initial 4 mg intranasal dose (which achieves plasma exposure to naloxone as rapidly and in a range comparable to that achieved by a total 2 mg dose of naloxone hydrochloride administered by intramuscular injection), the FDA has already considered the criticality of dose/target plasma levels, accuracy and reliability of the device and time to onset. These three factors are critical in rapidly and consistently achieving an effective naloxone exposure when administered for the emergency treatment of suspected opioid overdose by individuals (including non-medically trained individuals), in settings including non-medical settings.

What has changed recently is (i) an acceleration of expanded naloxone access to new potential witnesses and (ii) more potent and faster onset opioids being implicated in a growing proportion of opioid overdose deaths. These factors provide an urgent need to ensure that new naloxone formulations intended for emergency treatment in all settings, (including non-medical settings), by anyone (including non-medically trained individuals), deliver a consistently efficacious fixed initial dose that achieves optimal exposures to naloxone (i.e. plasma levels) and can be easily and rapidly administered.

Expanded Naloxone Access to New Potential Witnesses

Many states have enacted laws to both support expanded access and administration of naloxone, and to encourage opioid overdose witnesses to seek medical care. Federal agencies and states have also contributed funds to purchase naloxone. A growing list of first responders including EMS, law enforcement and harm reduction organizations are now equipped with naloxone. More recently, states have supported naloxone pharmacy access to new user groups to include patients and their caregivers without requiring a personal prescription (under various standing order, local protocols or collaborative practice agreements). Leading retail pharmacies are rolling out these programs which have the effect of providing naloxone access to patients and/or their caregivers without a recipient specific physician prescription.

As the group of potential naloxone administrators expands from clinicians, EMS and those already familiar with naloxone administration, to any potential witness (including non-medically trained individuals), the criticality of distributing a naloxone formulation that delivers a consistently adequate fixed initial naloxone dose and target plasma level that can

be easily and rapidly administered for the emergency treatment of suspected opioid overdose by these new users, increases.

Emerging Problem of More Potent and Faster Onset Opioids

Emphasizing the need for a consistently efficacious dose, over the last two years, fentanyl, a synthetic opioid estimated to be 30 to 50 times more potent than heroin, has emerged as a significant factor in opioid overdose fatalities. CDC issued fentanyl reports in June 2013 and August 2013, and a Health Alert in October 2015 (2). In March 2015, the Drug Enforcement Agency (DEA) issued a nationwide alert on fentanyl as a threat to health and public safety. DEA Administrator Michele Leonhart commented, “Drug incidents and overdoses related to fentanyl are occurring at an alarming rate throughout the United States and represent a significant threat to public health and safety” (3). While overdoses from fentanyl can be reversed with naloxone, because of fentanyl’s potency, rapid onset and long lasting respiratory depressive effects, the window of intervention may be narrower and a higher dose/target plasma level of naloxone may be needed. Prescription fentanyl’s respiratory depressive effects peak in 5-15 minutes and, depending on dose, these effects may last for many hours (4).

As more potent and faster onset opioids are implicated in a growing proportion of opioid overdose deaths, the criticality and urgency of distributing a naloxone formulation for use by individuals (including non-medically trained individuals) in settings (including non-medical settings), that delivers a consistently efficacious fixed initial naloxone dose and target plasma levels that can be easily and rapidly administered for the emergency treatment of the effects of more potent opioids, increases.

In the context of expanding naloxone access to individuals (including non-medically trained individuals), for use in all settings (including non-medical settings), for the emergency treatment of suspected opioid overdose including those involving more potent and faster onset opioids, we believe that any naloxone formulation should support rapid and easy use by all individuals. **Therefore, we suggest an expert review of the most optimal effective initial dose and target plasma levels in these settings and by these users is necessary. Put another way, the FDA should determine the optimal threshold bioavailability or exposure levels for any new naloxone product intended for use in all settings by any witness.**

Absent this step there is a risk that the public health response is sub-optimal because the naloxone dispensed to individuals (including non-medically trained and naloxone inexperienced individuals), may deliver too low an initial naloxone dose, too slowly for the effective emergency treatment of a suspected opioid overdose event.

c. Key Pharmacokinetic Considerations for Achieving the Optimal Naloxone Dose in an Emergency Opioid Overdose Treatment Situation

During a suspected emergency opioid overdose situation the most critical effect is respiratory depression and arrest. Most opioid overdose victims die from respiratory arrest, or if they

survive may have brain damage from lack of oxygen due to respiratory depression. Thus, the time it takes to administer a rescue medication and for that medication to take effect is most critical in avoiding death or serious co-morbidities from an incident of opioid overdose.

In evaluating naloxone products intended for use in all settings (including non-medical settings) by individuals (including non-medically trained individuals) there are two critical pharmacokinetic issues related to the dose/exposure required to achieve efficacy:

1. The rate of absorption and the time to reach plasma concentrations, which correlate with efficacy, in this case the reversal of respiratory depression.
2. The overall absorption and duration of effect, which is critical given that the effect of naloxone may wear off prior to that of the opioid, and the victim may relapse into respiratory depression if the overall bioavailability and duration of exposure to naloxone from a formulation is not adequate.

The standard FDA bioavailability criteria for Area Under the Curve (AUC) and Maximum Concentration (C_{max}) would not be adequate to evaluate exposure in the time period to onset of action or the duration of effect. Therefore, proposed new naloxone formulations intended for use in all settings (including non-medically settings) by individuals (including non-medically trained individuals) should demonstrate bioavailability performance based on criteria that appropriately address these two critical points.

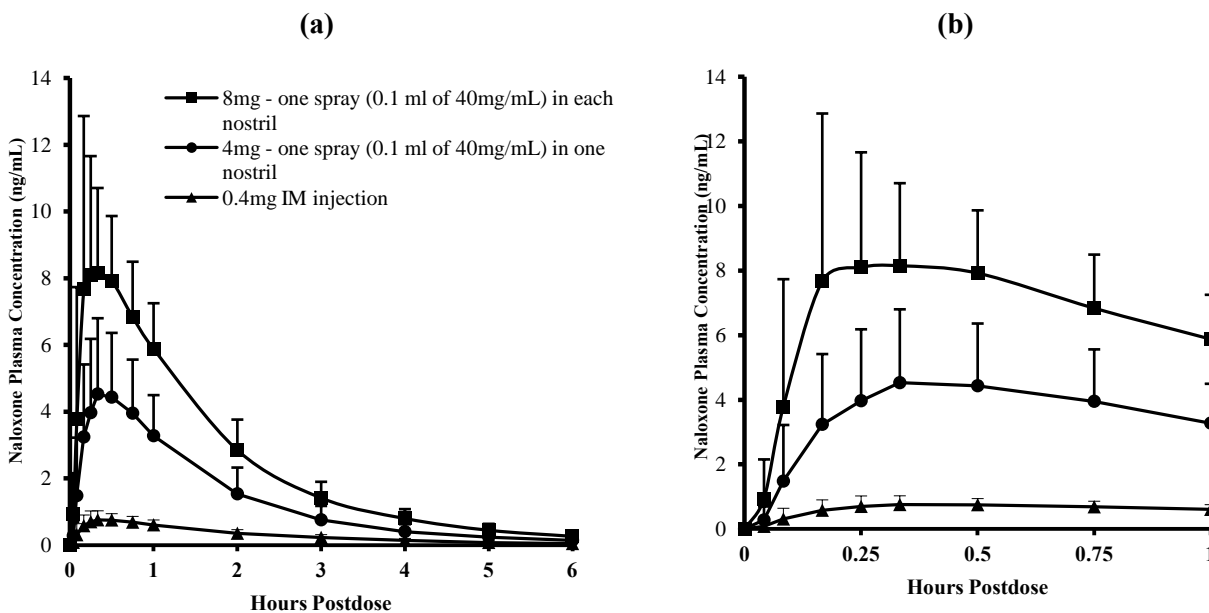
Dosing recommendations from the naloxone prescribing information are to administer an initial dose of naloxone of between 0.4 mg and up to 2 mg by the IM or IV route for any person that is suspected to be experiencing an opioid overdose. The safety of this dose is considered to be well established and the duration of effect is expected to be 30 to 90 minutes by IM administration. While it is possible to induce a rapid opioid withdrawal in opioid dependent patients, this side effect must be viewed in the context of the benefit of naloxone use to arrest the life-threatening symptoms of overdose.

Recently, FDA approved an intranasal (IN) form of naloxone, Narcan Nasal Spray, which delivers a 4 mg initial dose of naloxone hydrochloride in a single spray. Narcan Nasal Spray administration is needle-free and the device is easy-to-use, without assembly, which both support expanded access to naloxone. The bioavailability of a single 4 mg dose of Narcan Nasal Spray is approximately 47% of that achieved by IM injection. Thus, a single administration of Narcan Nasal Spray 4 mg rapidly achieves plasma exposure to naloxone in a range comparable to that achieved by a total 2 mg IM dose, or approximately equivalent to 5 repeat administrations of 0.4 mg naloxone by IM injection. The device delivers its drug load in with a single activation and does not allow for partial dosing, which is an important feature for safety and efficacy.

The rate of absorption and time to reach efficacious levels of Narcan Nasal Spray is as fast as naloxone administered by IM. The only other naloxone product approved by FDA for use as an emergency treatment for suspected opioid overdose in settings where opioids may be present is

Evzio (0.4 mg IM naloxone auto-injector). The labeling of Narcan Nasal Spray highlights the rapid absorption of both a single and two-dose administration as compared to IM naloxone dosed at 0.4 mg. Thus, the approval of Narcan Nasal Spray was supported by the fact that the rate of absorption more than met, and the exposure and duration of plasma concentrations were higher and longer, respectively, than the 0.4 mg IM injection.

Figure 1 Mean ± SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intranasal Administration and Intramuscular Injection



Thus, the Petitioner strongly believes that FDA needs to establish guidelines for the approval of any naloxone product for use in all settings (including non-medical settings) under 505(b) of the Act that ensures that the pharmacokinetics and exposure of the product will be adequate to address (i) the short term onset of action that is critical in an opioid overdose situation, (ii) the achievement of adequate blood levels, especially in the context of recent changes expanding naloxone access to new users in new settings and the recent trends in higher potency/faster onset opioids, such as fentanyl, and (iii) maintains efficacious exposure for a period sufficient to ensure emergency medical attention can be accessed.

As such the Petitioner believes that the Agency cannot just consider the dose of a naloxone containing product that is administered to treat suspected opioid overdose, but also must consider the overall exposure of that product to ensure that the onset of action and duration of effect is adequate to achieve optimal efficacy in an emergency treatment situation.

d. Human Factor Studies to Ensure Label Comprehension and Accuracy of Use for the Device to Deliver Naloxone

Human use factor and label comprehension studies that support the use of any proposed naloxone formulation by individuals (including non-medically trained individuals) in all settings (including non-medical settings) is necessary to ensure a consistently adequate fixed dose of naloxone can be readily and rapidly administered. In addition, time to dose administration must be considered as this impacts the overall time to achieve efficacious exposures to treat respiratory depression. Thus evaluating absorption and pharmacokinetics alone are not enough, and any applicant should be required to demonstrate that the formulation used to deliver naloxone is both reliable and allows individuals, whether medically trained or not, to rapidly administer a fixed, consistently adequate, dose.

e. Improvised Nasal Naloxone Kits

There are two FDA approved products intended for the emergency treatment of opioid overdose by individuals in settings where opioids may be present. Specifically:

- Narcan Nasal Spray, 4 mg naloxone, is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Narcan Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present. Narcan Nasal Spray is not a substitute for emergency medical care. It is presented in packs containing two doses.
- Evzio, 0.4 mg naloxone, is also approved for the same indication and available as a 0.4 mg strength by IM route of administration. It is an auto-injector with a trainer and speaking instructions, in packs of two doses.

Narcan Nasal Spray is a single-use, drug-device combination product. It is designed for use in all settings (including non-medical settings) by individuals to treat those suspected of experiencing the potentially life threatening effects of an opioid overdose while awaiting emergency medical attention. It is available in a 4 mg strength by intranasal route of administration, in packs of two. In pharmacokinetic studies, the dose adjusted bioavailability of a single 4 mg dose of Narcan Nasal Spray is approximately 47% as compared to IM injection. The current labeling of Naloxone injection, IV, IM, SC, recommends an initial dose of 0.4 mg to 2 mg, followed by repeated doses up to a total dose of 10 mg.

The non-FDA approved use of naloxone hydrochloride, injection, 2 mg/2 mL vials combined with a mucosal atomizer device for an improvised nasal naloxone kit has existed for many years, and is still widely used in EMS programs and by communities who seek to address the public health problem of opioid overdose.

The FDA has stated in the Summary Review for Regulatory Action for Narcan Nasal Spray:

There is evidence that the off-label use of naloxone by the intranasal route has been effective in reversing opioid overdose in many cases. However, there are no data that specifically quantitate the success rate, leaving the question of whether there are situations that could have benefited from a higher dose of naloxone. Unpublished pharmacokinetic data suggest that naloxone levels following off-label use by the intranasal route are lower than by the approved routes of administration. The lowest effective dose of naloxone is unclear, and is likely dependent on a number of factors, including dose, route of administration, and the amount and type of opioid involved in the overdose (5).

As suggested, larger doses/higher target plasma levels of naloxone may be necessary to treat suspected opioid overdoses events. These events could require multiple doses of the 0.4 mg naloxone by IM injection or non-FDA approved improvised nasal naloxone kits, as the opioid overdose may not be reversed with a single administration before severe injury or death occurs.

The known effective dose/target plasma level varies and depends on multiple factors including but not limited to, opioid dose consumed, opioid formulation, concomitant use of alcohol or benzodiazepines, adulteration of 'known' illicit opioids such as heroin with unknown, numerous, synthetic and cheaper fentanyl analogues of differing potencies.

In these situations, a larger initial dose of naloxone makes sense such as Narcan Nasal Spray 4 mg. IM doses of 0.4 mg may have to be available in multiple packs to achieve comparable exposure. In addition, there may be a heightened risk of needle-stick injury.

When arriving at an effective minimum initial dose and target plasma level there is the advantage with naloxone that there are well characterized adverse events and minimal risks from administration of a dose of up to 10 mg IM in those that are not opioid dependent. In those that are opioid dependent – acute withdrawal is a known side effect – which has to be considered in the context of the benefit of administering an adequate dose.

Narcan Nasal Spray 4 mg has been on the market for 4 four months without any trend in safety signal. It is needle free, which is important in this setting. Its simplicity of use should not result in substantial delay in administering a fixed- dose and seeking emergency care.

2. Conclusion

We submit this Citizen's Petition because there are special dose and, where applicable, device considerations for any naloxone product intended for use in settings including non-clinical settings by individuals (including non-medically trained individuals). These special considerations are necessary to ensure a consistently optimal efficacious fixed initial dose of naloxone can be easily and readily administered for the emergency treatment of suspected opioid overdose.

These special considerations reflect the recent expansion of naloxone access (for example, via pharmacy distribution without individual prescriptions) and the dramatic increase in high potency, rapid onset opioids (such as fentanyl) implicated in overdose fatalities.

The success of the public health response of expanding naloxone access and distribution depends, in part, on ensuring witnesses, who may not have prior naloxone administration experience, immediate recourse to additional naloxone doses, or other medical interventions/equipment, have an appropriate naloxone formulation to rapidly and consistently administer a consistently adequate fixed initial dose to rapidly achieve adequate target plasma levels of this potentially life-saving medication.

To bridge the safety and efficacy of a 505(b) application for a naloxone containing product, intended for emergency treatment of suspected opioid overdose in all settings (including non-medical settings) and by all individuals (including non-medical trained individuals), the Petitioner suggests that the Agency issue guidelines to ensure that adequate criteria are set to address (i) the optimal fixed initial dose for each route of administration; (ii) the overall time to reach an efficacious naloxone exposure (i.e. plasma level, including both ease of use of the device and rate of absorption; and (iii) the overall exposure and plasma levels to achieve an adequate duration of effect. Further, the speed of delivery from the device is a significant factor in rescuing an opioid overdose victim. Finally, the duration of exposure is critical to ensure that the effect will be maintained long enough for emergency rescue personnel to arrive or the victim to be taken to a medical facility for further treatment.

As such, the Petitioner is requesting FDA to establish guidance for all naloxone products intended for the emergency treatment of suspected opioid overdose in all settings (including non-medical settings) by individuals (including non-medically trained individuals), that include the optimal fixed initial dose for each route of administration as well as the required exposure levels to achieve an efficacious onset of action and duration of effect.

C. Environmental Impact

We claim categorical exclusion under 25.30, 25.31, 25.32, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter.

D. Economic Impact

Economic impact information will be submitted upon request of the commissioner.

E. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date of May 2015. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Adapt Pharma Operations Ltd. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.



11 July 2016

Richard E. Lowenthal
Adapt Regulatory Representative

Date

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