Naloxone for Treatement of Opioide Overdose

Advisory Committee of October 5, 2016

Insys Development Company, Inc.

.

ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE

TABLE OF CONTENTS

TABLE OF CONTENTS....2
1. ALTERNATIVE ROUTES OF ADMINISTRATION....3
2. DOSE....7
3. TIMING....8
4. PEDIATRICS....9
5. CONCLUSION....10
6. REFERENCES....11

1. ALTERNATIVE ROUTES OF ADMINISTRATION

Fatalities from opioid overdose have been increasing steadily over recent years, with the rate of opioid overdoses tripling since 2000 and more deaths reported in the United States in 2014 than in any previous year on record. In 2014, a total of 47,055 drug overdose deaths occurred in the United States. Of these, prescription opioid analgesics and heroin, accounted for 28,647 deaths, or 61% of all drug overdose fatalities. Over 1,000 people are treated in emergency departments for misusing prescription opioids daily. Unfortunately, the epidemic is not limited to adults. As reported by Bond et al. and Bailey et al., there is a significant and concerning rise in opioid overdose-related deaths in children and adolescents as well [Bond et al. 2012; Bailey et al. 2009].

The majority of drug-overdose deaths are unintentional or accidental (74.3%). Suicidal drug poisoning accounts for approximately 13.1%, mental and behavioral disorders from drug use 5.1%, and homicide <1%. The highest drug-induced mortality is associated with the following factors: 40–49 years of age, male gender, non-Hispanic whites, and living in the South, which account for approximately 38.2% of drug-induced deaths in the US (CDC, 2012; Volkow et al., 2014).

The pathophysiology and acute medical management of an opioid overdose is similar irrespective of whether the opioid that was taken was legally prescribed or illegally bought on the street. Heroin and prescription opioids such as oxycodone, hydrocodone, codeine, fentanyl, and morphine are opioid receptor agonists. They can effectively modify the perception of pain by binding to opioid receptors in pain pathways within the brain and spinal cord (NIDA 2015). With larger doses, respiratory depression can occur, limiting adequate oxygenation of blood, which reduces oxygen availability to the brain and heart, leading to unresponsiveness, anoxia, cyanosis, and death (Boyer 2012). This respiratory depression, which is reversible until death occurs, can take 1 or 3 hours and can be reversed with the pharmacological antidote naloxone, which displaces opioids from the opioid receptor and blocks the binding of additional opioids for 20 to 90 minutes (Hawk et al., 2015).

Drug overdose is the leading cause of accidental death in the United States and is a global public health issue (Wermeling, 2013). Overdose is defined as the accidental or intentional administration of a drug at a quantity substantially greater than normally used or recommended resulting in serious harmful symptoms or death. The most frequent drug overdose is due to opioid misuse (CDC, 2014).

Administration of an opioid antagonist has become an accepted part of the out-of-hospital management of opioid overdose. Acute opioid intoxication is characterized by drowsiness, euphoria, miosis, and respiratory depression. In overdose, respiratory depression becomes profound enough to cause anoxia, leading to death (Wanger et al., 1998). Naloxone has been used for in-hospital opioid reversal for more than 40 years, and although rare side effects have been reported, is has an excellent safety profile (Burris et al., 2001; Davis et al., 2014). Naloxone requires a prescription but is not a controlled substance and has no abuse potential.

Naloxone is readily transported across the blood-brain barrier and has a fast onset of action in reversing opioid effects (Ngai et al., 1976). However, the ability of naloxone to reverse opioid effects is mainly determined by the pharmacologic characteristics of the interacting opioid agonist (i.e., the opioid that requires antagonism) (van Dorp et al., 2007). As naloxone is devoid of agonistic activity at the μ-opioid receptor, it is regarded as a safe drug to use (ibid).

Naloxone is absorbed not only through intravenous (IV), but also by intramuscular (IM), subcutaneous (SC), endotracheal, sublingual, intralingual, submental, and nasal routes. Via the IV route, onset of action is within 1-2 minutes.

However, venous access can be difficult or impossible to achieve in the chronic IV drug user. The difficulty in obtaining venous access in chronic IV drug users under emergency conditions in the field and the enhanced risk of occupation blood contact with patients who have high risk factors for HIV and hepatitis B suggest the need for an alternative to the IV route of administration (Wanger et al., 1998).

Naloxone was first approved in the USA in 1971 (Narcan® injection) as a sterile solution for intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration with IV being the recommended route. Narcan injection has been discontinued and is no longer marketed. However, generic naloxone HCl injection solution products are commercially available in pre-filled syringes and vials. The injection is available in two strengths, 0.4 mg/mL and 1.0 mg/mL. The initial adult dose of naloxone in known or suspected narcotic overdose is 0.4 to 2 mg, which may be repeated to a total dose of 10 mg.

In November 2015, Narcan Nasal Spray (Adapt Pharma) became the first US Food and Drug Administration (FDA) approved non-injectable naloxone product for the treatment of opioid overdose. This new intranasal route of administration will provide great advantages over injection.

Overdose is a medical emergency in which response time is of the essence to save the person who is usually unconscious, hypoxic, and in the more severe cases, apneic. Initiating treatment of opioid an overdose as early as possible, even before the arrival of emergency medical services (EMS) at the scene [SAMHSA, 2013] is a medical imperative and a critical determinant of outcome in opioid overdose. As such, expanding access to those who are in close contact with a person at risk of overdose, such as close family contacts or police officers, is critical. In response to the increased use of opioids and the consequent risk for opioid overdose for patients and household contacts (ACMD, 2012; UNODC/WHO, 2013), World Health Organization guidelines (2014) on the prevention of opioid overdose deaths recommend that “people likely to witness an opioid overdose should have access to naloxone” (WHO, 2014).

Some EMS programs have now moved toward intranasal administration of naloxone because many patients needing naloxone are injection drug users; 80% of the injection drug user population in large metropolitan areas is Hepatitis C positive or HIV positive (Wermeling, 2013). The safety profile of intranasal naloxone appears to be no different than that of naloxone injection in the treatment of opioid overdose (Robinson and Wermeling, 2014). Increasing the

pool of individuals carrying naloxone increases the likelihood that the first person to arrive at an overdose is capable of initiating naloxone reversal (Hawk et al., 2015).

The opioid epidemic, along with the risk of blood-borne infection, reinforces the need for alternative routes of naloxone administration for the treatment of patients with suspected opioid overdose in the out-of-hospital setting.

Even though intranasal administration would be the preferred route for the person unresponsive due to opioid overdose, in other circumstances this may be less than optimal. As such, having a product that could be effectively administered via more than one route would be a definite advantage. Examples include cases involving damage to or obstruction of the nasal mucosa or cavity as may be the case with habitual cocaine or opioid abusers. Repeated use of cocaine (Millard & Mejia-2000; Patel et al., 2000; Goodger et al.,2005), heroin (Peyrière et al., 2013), other opioids (Greene, 2005) and methamphetamine (Bekhshaee et al., 2013) can cause destruction, scarring, perforation, loss of tissue and necrosis of the nasal septum, nasal mucosa, and associated naso- and oropharyngeal tissues including the soft palate. Absorption of intranasally administered drugs, such as naloxone, may consequently vary substantially in these individuals, making it difficult to achieve systemic drug levels rapidly and reliably. As stated by Robinson and Wermeling (2014), "Limitations to the use of intranasal naloxone depend in part on the structure of, or injury to, the nose. Contraindications to intranasal administration can include nasal septal abnormalities, nasal trauma, epistaxis, excessive nasal mucus, and intranasal damage caused by the use of substances such as cocaine."

In a study by Barton et al. (2005), it was shown that 9 out of 52 subjects (17%) who received intranasal naloxone for suspected opioid overdose were unresponsive to the treatment. Five (56%) of the nine non-responders had epistaxis (n=2), nasal mucus (n=1), trauma (n=1), or septal abnormality (n=1) while none of the intranasal naloxone responders had any nasal abnormalities. In another study (Barton et al., 2002), intranasal naloxone was administered to 30 patients who presented with altered mental status with suspected opioid overdose. Only one patient did not respond to intranasal naloxone but subsequently responded to IV naloxone. It was noted that the patient had epistaxis. The authors concluded that physical factors such as nasal septum abnormalities, trauma, epistaxis, excessive mucus, and mucosal destruction from other intranasal drug use (i.e., cocaine) may have a significant effect on the rate and amount of absorption of intranasal medications, making it difficult to achieve systemic drug levels rapidly and reliably and that drug abusers might be a population at higher risk for these nasal abnormalities.

Snorting a substance, such as cocaine or heroin, is one of the more rapid ingestion routes since the drug bypasses the digestive tract and, later, the liver – where the drug would otherwise be subjected to an initial round of process (e.g., first pass metabolism). Upon entering the bloodstream, the drugs travel quickly to the brain, thus eliciting a host of intense effects shortly after snorting. The cumulative irritation of the nostrils, nasal passages, and sinus structures can lead to irritation of the nasal mucosa, sinusitis, and perforation of the nasal septum (Crane 2016). Physical obstruction of the nasal passage(s) due to prior trauma and subsequent deflection of the passageways is another possibility. Increases in mucus production and changes in mucociliary

clearance rates could affect bioavailability. During the common cold, the efficiency of an intranasal medication is often compromised. Nasal pathology can also alter mucosal pH and thus affect absorption of drugs (Aurora 2002). These all suggest that another route of administration besides IV and intranasal is necessary for out-of-hospital management of opioid overdose.

Due to these limitations, there still remains a need for other non-invasive products that offer alternative routes of administration. Of 112 routes of drug administration listed by the US Food and Drug Administration (FDA, 1992; updated 2014), Strang et al. considered the potential applicability as a viable non-injectable route for emergency naloxone delivery by non-medical personnel, and identified buccal, nasal, and sublingual routes as suitable. These routes of administration do not require medical training, are publicly acceptable for administration by non-medical bystanders, provide adequate systemic drug concentration, and produce sufficiently rapid drug absorption relative to parenteral administration (Strang et al., 2016).

A challenge for expanding access to naloxone is that the medication is currently available only as an injection for intravenous (IV), intramuscular (IM), subcutaneous (SC) injection, and recently intranasal. Therefore, an unmet medical need is to have more user-friendly, needle-free naloxone delivery systems available for medical professionals, first-responders, and at-home family member use (Wermeling 2015). By making easy-to-use devices and training law enforcement officers to administer naloxone to opioid overdose victims can increase knowledge and confidence in managing opioid overdose emergencies (Wagner et al., 2016). Development and approval of reliable non-injectable formulations will facilitate wider naloxone provision across the community (Strang et al., 2016).

In a nonrandomized intervention study of naloxone co-prescription for primary care patients receiving long-term opioid therapy for pain, patients who were prescribed higher doses of opioids and with an opioid-related emergency department visit in the past 12 months were independently more likely to be prescribed naloxone. Patients who received a naloxone prescription had 47% fewer opioid-related ED visits per month in the 6 months after receipt of the prescription and 63% fewer visits after 1 year compared with patients who did not receive naloxone (Coffin et al., 2016).

Insys believes that this flexibility of administration is a beneficial gain in the hands of first responders especially when a preferred route of administration may be impractical or unavailable as in an agitated, injured or otherwise compromised patient. A major advantage of both sublingual and intranasal drug administration via the Insys device is that it is simple and easy to use, requires little expertise, pre-administration preparation or supervision (Stevens and Ghazi, 2000). It also requires limited training and coordination for proper usage and both routes result in a fast absorption, allowing for a rapid onset of action. Finally, both routes also bypass first pass elimination and enable therapeutic drug exposure levels to be achieved with relatively low administered doses.

2. DOSE

One US approved drug product label states that, in the absence of narcotics, naloxone exhibits essentially no pharmacologic activity (IMS, 2001). A small study including volunteers receiving 24 mg/70 kg did not demonstrate toxicity (Hospira, 2006). Naloxone has been used to reverse over 10,000 opioid-related overdoses since initial use of the drug in the US (Wheeler, 2012). Advocates insist that naloxone is safe and can be administered with minimal side effects other than those associated with opiate withdrawal (Massatti, 2013).

There are variations in the recommended doses with the British National Formulary advises 0.8-2 mg boluses, repeated as necessary up to 10 mg for adults (10 µg/kg followed by 100 µg/kg boluses for children), and Poisindex suggesting 0.4-2mg boluses. The dose of naloxone is influenced by the dose of opioid ingested or injected. Extremely 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 et al., 2005). Nine patients with narcotic analgesic overdosage recovered consciousness immediately after intravenous injection of 0.4-1.2 mg of naloxone given in divided doses over 3 minutes (Evans et al., 1973).

The major side effect associated with naloxone is the precipitation of acute withdrawal symptoms in chronic opioid users, provoking an often violent reaction. Acute withdrawal symptoms also include agitation, nausea, vomiting, piloerection, diarrhea, lacrimation, yawning, and rhinorrhea. These are not generally life threatening (Chiang and Goldfrank, 1990). Reported rates vary widely from 7-46% with 2-4 mg boluses (Clarke et al., 2005). Naloxone dose and route of administration can produce variable intensity of potential adverse reactions and opioid withdrawal symptoms: intravenous administration and higher doses produce more adverse events and more severe withdrawal symptoms in those individuals who are opioid dependent (Wermeling 2015). Withdrawal symptoms induced by naloxone administration tend to dissipate in a period of 30-60 minutes due to the relatively short half-life of naloxone (Ngai et al., 1976; Dowling et al., 2008).

In a study of 453 patients treated with naloxone, only 6 (1.3%) suffered complications such as cardiac arrest, pulmonary edema, and epileptic seizures, with the primary cause of cardiorespiratory complications from naloxone being a massive release of catecholamines (Osterwalder 1996). These risks, although small, warrant the cautious use of naloxone and adequate monitoring of the cardiorespiratory status of the patient after naloxone administration where indicated.

Kerr e al. compared safety and effectiveness of a specially prepared concentrated naloxone formulation (2 mg/mL) given via the IN versus IM routes in a randomized, controlled, open-label trial. Eighty three received 1 mg/0.5 mL into each nostril (2 mg total) and 89 patients received 2 mg/mL IM. The authors concluded that a low adverse event rate was observed in both arms (Kerr et al., 2009).

3. TIMING

The logic behind naloxone take-home programs is that when it comes to reversing an opioid overdose, time matters. It has been well reported that many overdoses are witnessed by individuals who would be willing to intervene and provide assistance (Clark et al, 2014, Wakeman et al., 2009).

IV administration can provide rapid and relatively higher exposure to naloxone in an emergency compared with routes requiring drug adsorption. Routes of administration having an absorption phase, depending upon the dose, may provide a slower onset of revival that may be better tolerated during the recovery period. New products with an absorption phase adequate to reverse the overdose, but not providing peak levels of naloxone similar to an IV dose are likely to be successful in the prehospital treatment context. A balance should be struck between rapidity of opioid reversal versus frequency and intensity of adverse reactions and opioid withdrawal symptoms (Wermeling 2015). Tremor and hyperventilation associated with an abrupt return to consciousness has occurred in some patients receiving naloxone for opiate overdosage.

Loimer conducted a study in 17 opioid-dependent patients to compare the efficacy of 1 mg of intranasal naloxone to intramuscular and intravenous naloxone administration. Withdrawal symptoms and vital sign changes were again used as endpoints at 1, 5, 15, 45, 90, and 180 minutes after administration. The data demonstrated that intranasal administration had a more rapid onset and intensity of withdrawal as compared to intramuscular administration, but was not as rapid or as intense as intravenous administration (Loimer et al., 1994). Barton demonstrated that eighty-three percent of the patients with an opioid overdose responded to intranasal naloxone, with an average response time of 3.4 minutes. Seven (16%) of the intranasal responders required additional doses of IV naloxone. Nasal abnormalities were noted in 5 (of 9) patients who did not respond to intranasal naloxone (Barton et al., 2005).

Naloxone has an onset of action within 1-2 minutes following IV administration and within 2-5 minutes following subcutaneous or IM administration. After 5 minutes, the naloxone dose Is repeated if the person is not awakening or breathing well enough (10 or more breaths per minute). A repeat dose may be needed 3-90 minutes later if sedation and respiratory depression recur (Wermeling 2015). This is because most opioids (heroin, morphine, fentanyl) used by addicts have relatively long half-lives, whereas naloxone has a half-life of only 30 min (White and Irvine, 1999). It is necessary to adequately dose and monitor the patient.

Naloxone administration by intranasal and intramuscular administration has been shown to be safe and effective with minimal training (Hawk et al., 2015). A study compared the pharmacokinetic properties of intranasal naloxone (2-8 mg) delivered in low volumes (0.1-0.2 mL) to an approved (0.4 mg) intramuscular dose. All doses of intranasal naloxone resulted in plasma concentrations and areas under the curve greater than observed following the intramuscular dose; the time to reach maximum plasma concentrations was not different following intranasal and intramuscular administration (Krieter et al., 2016). Another study found that the exposure levels resulting from intranasal and sublingual administration of Naloxone 8

mg exceed the exposure levels of the intramuscular (0.4 mg) at 2, 4, 6, 8, and 10 minutes (Data on file).

One study estimated that using EMTs to administer naloxone could reduce time for intranasal naloxone delivery between 5.7 and 10.2 minutes, which has the potential to significantly reduce the mortality and morbidity associated with opioid overdose (Belz et al., 2006). Thus, it is imperative that no matter the type of device used, it should provide naloxone PK levels higher than IM levels at 2 minutes and beyond.

4. PEDIATRICS

According to the American Academy of Pediatrics, "[t]here is insufficient evidence to evaluate safety and efficacy of administering naloxone to a new born with respiratory depression due to maternal opiate exposure. Animal studies and case reports cite complications from naloxone, including pulmonary edema, cardiac arrest, and seizures" (AAP/AHA 2015).

The following are off-label naloxone dosing recommendations, endorsed by the American Academy of Pediatrics and the American Heart Association, for cardiopulmonary resuscitation and emergency cardiovascular care for full reversal of opioid effects were used to recommend the doses indicated on the labeling:

- Younger than 5 years or body weight 20 kg or less: 0.1 mg/kg administered by IV push, intraosseous push, or by ET tube. Follow each dose given via ET tube with at least 5 mL of isotonic sodium chloride injection
- 5 years and older or body weight more than 20 kg: 2 mg administered by IV push, intraosseus or by ET tube. Follow each dose given via ET tube with at least 5 mL of isotonic sodium chloride injection

Studies in normal, healthy pediatric patients would not feasible to determine the appropriate dose of the intranasal devices. Moreover, although naloxone appears to be readily absorbed after oral administration, it low bioavailability renders it less suitable for this administration route. Additionally, following oral administration, naloxone undergoes extensive hepatic metabolism, indicating high first-pass effect (> 95%) (van Dorp et al., 2007). Thus, if naloxone cannot be administered through injection or intranasally, it will not provide the desired effect. However, it is not possible to design an ethical study to determine the correct dose for pediatric administration using the intranasal devices, thus the dose in pediatrics should be the same as the dose in adults.

5. CONCLUSION

The Agency is correct in encouraging Sponsors to explore alternative routes of administration of naloxone for opioid overdose. An easy -to-use and economical delivery system that achieves plasma levels of naoloxone above those obtained by IM injection in 2 to 5 minutes and the delivery stystems can be used by laypeopole intranasally or sublingually is likely to play a critical role in reducing the number of deaths due to opioid overdose. The Agency should continue encouraging development of these types of delivey systems without unnecessary obstacles.

6. REFERENCES

Barton ED, Ramos J, Colwell C, et al. Intranasal administration of naloxone by paramedics. Prehospital Emergency Care 2002;6:54-8.

Barton E, Colwell C, Wolfe T, Fosnocht D, Gravitz C., Bryan T. et al. Efficacy of intranasal naoloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. J Emerg Med 2005;29:265-71.

Bailey J, Campagna E and Dart R. The under recognized toll of prescription opioid abuse on young children. Ann Emerg Med 2009;53:419-24.

Belz D, Lieb J, Rea T, Eisenberg MS. Naloxone use in a tiered-response emergency medical services system. Prehosp Emerg Care. 2006;10(4):468-471. [PubMed]

Bond G, Woodward R, Ho M. The growing impact of pediatric pharmaceutical poisoning. J Pediatr 2012;160:265-270.

Boyer EW. Management of opioid analgesic overdose. N Engl J Med. 2012;367(2):146-155.

Burris S, Norland J, Edlin BR. Legal Aspects of Providing Naloxone to Herioin Users in the United States. Int J Drug Policy. 2001;12(3):237-248.

Chiang WK, Goldfrank LR. Substance withdrawal. Emerg Clin North Am 1990;8:613-32.

Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. J Addict Med. 2014;8(3):153-163.

Clarke SFJ, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope. Emerg Med J 2005;22:612-616.

Coffin PO, Behar E, Rowe C, Santos GM, Coffa D, Bald M, Vittinghoff E. Nonrandomized Intervention Study of Naloxone Coprescription for Primary Care Patients Receiving Long-Term Opioid Therapy for Pain. 2016 Aug 16;165(4):245-52.

Davis CS, Ruiz S, Glynn P, Picariello G, Walley AY. Expanded access to naloxone among firefighters, police officers, and emergency medical technicians in Massachusetts. Am J Public Health. 2014;104(8):e7-e9 [PubMed]

Evans LEJ, Roscoe P, Swainson CP, et al. Treatmentof drug overdosage with naloxone, a specific narcotic antagonist. Lancet 1973;1:452-5.

Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation. July 2002.

Hospira Naloxone hydrochloride injection solution prescribing information. 2006; Hospira Inc.

IMS Naloxone hydrochloride injection solution pescribing information. 2001; International Medication Systmes, Limited.

Kerr D, Kelly A, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009;104:2067-2074.

Krieter P, Chiang N, Gyaw S, Skolnick P, Crystal R, Keegan F, Aker J, Beck M, HarrisJ. Pharmacokinetic Properties and Human Use Characteristics of an FDA Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose. J Clin Pharmacol. 2016 May 5. [Epup ahead of print]

Hawk KF, Vaca FE, and D'Onofrio G. Reducing Fatal Opioid Overdose: Prevention, Treatment and Haarm reduction Strategies. Yale J Biol Med. 2015 Sep; 88(3):235-45.

Lorimer N, Hoffmann P, Chaudhry HR. Nasal administration of naloxone is as effective as the intravenous route in opiate addicts. Int J Addict. 1994;29:819-27.

Millard DR, Mejia FA. Reconstruction of the nose damaged by cocaine. Plast Reconstru Surg. 2001 Feb;107(2):419-24.

Massatti R, Beeghly C, Hall O, Kariisa M, Potts L. Increasing heroin overdoses in Ohio: Understanding the issue. Ohio Department of Mental Healht and Addiction Services; 2014.

Narcan, Solution for Injection, prescribing information 04/2004.

Narcan Nasal Spray, Prescribing Information 2016.

Ngai S, Berkowitz B, Yang J, Hempstead J, Spector S. Pharmacokinetics of naloxone in rats and in man: basis for its potency and short duration of action. Anesthesiology. 1976;44:3989-401.

Osterwalder JJ. Naloxone – for intoxications with intravenous herioin and heroin mixtures – harmless or hazardous? A prospective clinical study. J Toxicol Clin Toxicol 1996;34:409-16.

Peyriere H, Legise Y, Rousseau A, Cartier C, Gibaja V, Falland P. Necrosis of the intranasal structures and soft plalate as a result of heroin snorting: a case series. Subst Abus. 2013;34(4):409-14.

Robinson A, Wermeling DP. Intranasal naloxone administration for treatment of opioid overdose. Am J Health Syst Pharm. 2014 Dec 15;71(24):2129-35.

SAMHSA. State estimates of substance Use and mental disorders from 2010-2011 national surveys on drug Use and health. HHS Publication No. (SMA) 13-4641: Rockville, MD; 2013.

Strang J, McDonal R, Alqurshi A, Royall P, Taylor D, Forbes B. Naloxone without the needle – systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal. Drug Alcohol Depend. 2016 Jun 1;163:16-23.

Stevens RA, Ghazi SM. Routes of opioid analgesix therapy in the management of cancer pain. Cancer Control. 2000 Mar-Apr;7(2):132-41.

Summary AAP/AHA 2015 Guidelines for Cariopulmonary Resucitation and Emergency Cardiovascualr Care of the Neonate

Van Dorp E, Yassen A, Daha A. Naloxone treatment in opioid addiction: the risks and benefits. Expert Opin Drug Saf. 2007 Mar;6(2):125-32.

Volkow ND. Presciption Opioid and Heroin Abuse. National Institue on Drug Abuse [Internet] 2014.

Wnger K, Brough L, Macmillan I, Goulding J, MacPhail I, ChristensonJ. Intraenous vs subcutaneous naloxone for out-of-hospital management of presume opioid overdose. Acad Emerg Med. 1998;5:293-99.

Wakeman SE, Bowman SE, McKenzie M, Jeronimo A, Rich JD. Preventing death among the recently incarcerated: an argument for naloxone prescription before release. J Addict Dis. 2009;28(2):124-129.

Wermeling DP. A response to the opioid overdose epidemic: Naloxone nasal spray. Drug delivery Transl Res. 2013;3:63-74.

Wermeling DP. Review of naloxone safety for opioid overdose: practival considerations for new technology and expanded public access. Ther Adv Drug Saf 2015;6(1):20-31.

Wheeler E. Community-based opioid overdose prevention programs providing Naloxone. Center Dis. Control Prevention: Morbidity Mortality Weekly Rep. 2102;61:101-105.

World Health Organization: Community management of opioid overdose. Geneva: World Health Organization; 2014.