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PHARMACOLOGY

Should naloxone be considered an essential medication in dental emergency kits?

Jason H. Goodchild, DMD ■ Mark Donaldson, BSP, ACPR, PHARMD, FASHP, FACHE ■ Stanley F. Malamed, DMD

Although it is often described as a new emergency, the opioid epidemic in the United States is not a recent development. Almost 10 years ago, the Centers for Disease Control and Prevention (CDC) determined that overdose deaths from painkillers had more than tripled in a decade, rising to the level of an epidemic.[1] Regardless of its origin, the opioid epidemic in the United States continues to challenge patients, families, healthcare professionals, and prescribers alike. According to the CDC, 68,400 drug overdose deaths occurred during the 12-month period ending in October 2017—up from 61,062 in the previous 12-month period (a 12% increase).[2] The estimated number of lives lost every day to drug overdoses in the United States is 142.[3] Even more tragically, drug overdoses have become the leading cause of unintentional deaths in the United States, surpassing motor vehicle accidents.[4] Many elements have contributed to the rise in unintentional opioid overdose deaths. Box 1 illustrates the timeline for the opioid epidemic in the United States.[5-7]

Proposed solutions to the opioid epidemic

Several strategies are being implemented to limit the improper use, overprescribing, and wide availability of prescription opioids (Box 2).[4,5,8-13] Beginning in 2016, the CDC issued evidence-based practice recommendations for prescribing opioids to patients 18 years or older in primary care settings, focusing on chronic pain treatment.[10] To date, however, no CDC guidelines exist for prescribing opioids for acute pain. Similarly, the American Dental Association (ADA) does not have specific guidelines for prescribing opioids to treat acute dental pain.[11] In January 2018, the ADA's president encouraged prescribers to take 4 steps to help opioids from harming patients: consider nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line analgesics, order fewer pills when opioids are indicated, counsel patients on the risks and benefits of opioids, and learn to recognize when a patient may have a substance use disorder or be prone to addiction.[12]

On April 5, 2018, the US Surgeon General released an advisory on naloxone and opioid overdose, stating[14]:

For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, knowing how to use naloxone and keeping it within reach can save a life.

Naloxone: history and pharmacology

Naloxone was synthesized by Jack Fishman in 1961 during attempts to develop a treatment for constipation following chronic opioid use.[15,16] By replacing the methyl group with an allyl group from the nitrogen atom in oxymorphone, the strong competitive and specific antagonist naloxone was formed.[17] In 1971, the US Food and Drug Administration (FDA) approved naloxone under the brand name Narcan (Adapt Pharma) for use by intravenous and intramuscular injection with a recommended initial dose of 0.4 mg.[17] In 1983, the World Health Organization added naloxone to its Model List of Essential Medicines.[18,19]

Naloxone has no clinical effects when given alone, but when it is administered to patients previously given opioid agonists, it competes for available opioid-binding sites, ultimately displacing the agonist and reversing its effects.[17] It can be used clinically to reverse respiratory depression in patients who breathe inadequately after opioid overdose or opioid anesthesia. In addition, naloxone can reduce or reverse opioid-induced nausea and vomiting, pruritus, urinary retention, rigidity, and biliary spasm associated with numerous opioid therapies.[17]

The onset of intravenous naloxone action is rapid—less than 2 minutes—and its half-life and duration of effect are short (30 and 60 minutes, respectively).[20] Because respiratory depression from opioids may outlast the effects of naloxone, repeated doses, bolus injections, or even a continuous infusion of naloxone may be required to maintain

Box 1. Opioid epidemic timeline.[5-7]

- Early 1990s: The American Pain Society suggests that there is a national epidemic of untreated pain and that pain should be classified as the fifth vital sign.
- 1995: New emphasis is placed on the aggressive treatment of pain.
- 1995: OxyContin is introduced to the US market.
- 1996: Prescriptions for opioids begin a sharp upsurge.
- 1999: The Veterans Health Administration launches the "Pain as the 5th Vital Sign" initiative.
- 2005: Hydrocodone becomes the most prescribed drug in the United States.
- 2010: Prescriptions for opioids peak.
- 2013: Drug overdose becomes the leading cause of accidental death in the United States.
- 2014: Hydrocodone combination products are reclassified as Schedule II by the US Drug Enforcement Administration.
- 2015: Heroin surpasses prescription drugs as the foremost cause of opiate overdose death.
- 2016: Synthetic opioids (eg, fentanyl and its analogs) become the foremost cause of opiate overdose death.
- 2017: The highest total number of drug overdose deaths is recorded.

Box 2. Strategies to restrict prescribing, abuse, and diversion of prescription opioids.[4,5,8-13]

- Evaluating guidelines for pain management
- Promoting public education about the risks posed by prescription opioids
- Limiting prescription of opiates
- Mandating checks of the appropriate state Prescription Drug Monitoring Program prior to prescribing
- Developing abuse-deterrent formulations
- Using triplicate prescription forms
- Rescheduling of drugs within US Drug Enforcement Administration categories
- Promoting public education for healthcare professionals about addiction and the risks posed by prescription opiates
- Eliminating "pill mills" and physician dispensing
- Ensuring proper disposal of unused prescription drugs (eg, "take back" days)
- Increasing naloxone distribution

reversal of respiratory depression.[21-24] Renarcotization occurs more frequently after the use of naloxone to reverse longer-acting opioids such as methadone and oxycodone.

Should naloxone be in dental office emergency kits?

In 2017, Sangrik postulated that "medical emergencies during dental treatment are increasing in frequency, intensity, and diversity" because of the increase in invasive dental treatment, an aging and more medically complex patient population, and an increasing trend of in-office sedation.[25] Dental patients do not always disclose their complete medical and drug history; although sedation medications are intrinsically safe, unintended combinations that may contain prescription or nonprescription opioids may occur.[22,26] In these cases, further central nervous system depression is possible and could precipitate a medical emergency.

The purpose of all emergency care is to rescue or stabilize and maintain the patient until additional help arrives. When a medical emergency arises, oral healthcare providers not only need to be familiar with the medications available in their emergency kit but also must know how to use them safely and correctly. Currently, many dental experts agree that the minimal emergency kit should comprise at least 7 medicines: epinephrine, an injectable antihistamine, nitroglycerin, aspirin, a β_2-adrenergic receptor agonist, glucose, and aromatic ammonia.[27-29]

Notwithstanding sedation cases, patients or other individuals in the dental office may suffer from opioid overdose, necessitating readily available naloxone. Because of these factors and in the context of the current opioid epidemic, oral healthcare providers should consider the addition of naloxone as the eighth drug in their minimal medical emergency kit. Already, at least one manufacturer of prepared medical emergency kits for dental offices has included naloxone in its product.[30]

Increasing availability of naloxone

In 2014, a new 2-mg intramuscular autoinjector, EVZIO (Kaléo), was approved by the FDA; this was followed in 2015 by approval of Narcan in 2-mg and 4-mg doses.[31-34] The FDA approved the first generic intranasal naloxone formulation in April 2019.[34,35] The intention of these formulations was to acknowledge the increasingly rampant availability of both prescription and illicit opioids in the public domain and to make available novel, lifesaving dosages of naloxone that could be safely, easily, and successfully administered by people who are not healthcare workers.

Naloxone is not classified by the US Drug Enforcement Administration as a controlled substance, nor is it a substance of abuse; while the injectable formulations remain prescription medications in most states, anyone can purchase the nasal spray from a pharmacy without a prescription under statewide standing orders or collaborative practice agreements. The product comes as a 2-pack with each individual spray formulation in separate and sealed foil packages that should not be opened until ready for use. The product should be stored at room temperature, and the shelf life is typically 2 years.

California was the first state to officially deregulate naloxone as a prescription medication in 2014, making it available to the general public for purchase without a prescription.[36] Among those who strongly supported the bill were parent groups concerned about the number of

Box 3. Instructions for using naloxone nasal spray.[38-40]

- Administer naloxone nasal spray as quickly as possible if someone is unresponsive and an opioid overdose is suspected.
- Hold the device with your thumb on the bottom of the plunger and 2 fingers on the nozzle. Place and hold the tip of the nozzle in either nostril until your fingers touch the bottom of the patient's nose.
- Do not press the plunger to test the device; this will waste necessary medication.
- Position the patient on his or her back with chin raised and head tilted back.
- Depress the plunger fully to deliver the entire contents of the device for the initial, 4-mg dose. Note: The device containing the 2-mg dose should be reserved for opioid-dependent patients at risk for severe opioid withdrawal and at low risk for accidental or intentional opioid exposure by household contacts.
- Contact emergency medical services as soon as possible after administering naloxone nasal spray.
- If the patient's respiratory depression persists after the initial dose or the patient relapses to unresponsiveness and/or respiratory depression, administer an additional dose after 2-3 minutes. Repeat additional doses every 2-3 minutes, if needed, until emergency medical assistance arrives.
- Alternate nostrils for each dose.
- If required, perform basic life support measures—being mindful of position, airway, breathing, circulation, and definitive care—until emergency medical assistance arrives.

young people who were being lost to unintentional overdoses without access to lifesaving naloxone.[36,37] The pharmaceutical industry has responded by producing naloxone in easier-to-administer dosage formulations (Box 3).[38-40] Currently, all 50 states and Washington, DC, allow paramedics to administer naloxone, while many other first responders, such as police officers and firefighters, also carry it.[41] With all of the progress being made, oral healthcare providers must ask themselves: Why not have naloxone available in the office?

From a dental regulatory perspective, Washington's Dental Quality Assurance Commission was the first to require the coprescription of naloxone with opioids for postoperative dental pain, effective January 2019.[42] The regulation mandates that dentists either provide a prescription for naloxone or refer the patient to a pharmacist for counseling and evaluation.[42] Other dental boards are expected to follow suit because research suggests that the risk of opioid overdose decreases when clinicians prescribe naloxone along with prescription opioids, even if the patient does not fill the naloxone prescription.[10,43] The CDC began recommending coprescriptions in its 2016 guideline, and detailed guidance was issued by the US Department of Health and Human Services in 2018.[10,44,45] Additional research suggests that naloxone prescription serves as an important educational strategy, and national rates for naloxone-opioid coprescriptions have steadily increased among patients with Medicare Part D insurance plans.[46]

Conclusion

The opioid epidemic has a longer history in the United States than most patients and prescribers realize. It may take an equally long time to reverse current trends, but strategies to combat this social plague are multifold, and some success is already being recorded. Recently published guidelines to limit the improper use, overprescribing, and availability of prescription opioids have helped to stem this tide, but the availability of naloxone to family, friends, emergency responders, and healthcare providers should be a priority.

Oral healthcare practitioners should continue to take a leadership role in the face of this epidemic. All dental offices should have a basic medical emergency kit containing lifesaving medications; as prescribers and healthcare facilitators in the midst of the opioid crisis, dentists should consider adding naloxone as the eighth essential medication in the kit. Proper recognition of a medical emergency and the use of appropriate medications, coupled with the basic life support algorithm (positioning, airway, breathing, circulation, and definitive care), can help ensure positive outcomes for patients.

Author information

Dr Goodchild is the vice president of clinical affairs, Premier Dental Products Company, Plymouth Meeting, Pennsylvania; an associate clinical professor, Department of Oral and Maxillofacial Surgery, Creighton University School of Dentistry, Omaha, Nebraska; and an adjunct assistant professor, Division of Oral Diagnosis, Department of Diagnostic Sciences, Rutgers School of Dental Medicine, Newark, New Jersey. Dr Donaldson is an associate principal, Vizient Pharmacy Advisory Solutions, Irving, Texas; a clinical professor, Skaggs School of Pharmacy, University of Montana, Missoula; a clinical assistant professor, School of Dentistry, Oregon Health & Sciences University, Portland; and an adjunct professor, Faculty of Dentistry, University of British Columbia, Vancouver. Dr Malamed is a dental anesthesiologist and an emeritus professor of dentistry, Ostrow School of Dentistry, University of Southern California, Los Angeles.

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