Deaths due to prescription and illicit opioid overdose continue to rise. The Centers for Disease Control and Prevention estimates that approximately 29,000 lives are lost to opioid overdose each year in the United States. The majority of these deaths happen in the home. Although most deaths are in adults, data from 1999 to 2013 revealed an incidence of 2.6 deaths per 100,000 adolescents and young adults 15-24 years of age. Prescription opioid use has also been linked to the growing rate of heroin addiction. Use of heroin is highest in patients 18-25 years of age, with an increase from 3.5 to 7.3 per 1,000 people (108.6%) over the past decade. The frequency of heroin use in children 12-17 years has remained stable at 1.6 per 1,000, but remains unacceptably high.²

Reversal of opioid toxicity with naloxone is one of the primary means of preventing death due to opioid overdose. Initial attempts to provide naloxone to first responders or laypeople began with pilot programs in the 1990s. These initial programs were successful in reducing opioid-related fatalities, but the process of preparing naloxone injections required extensive training and was often difficult in chaotic situations. New products have been developed to provide naloxone in forms that allow faster and more accurate drug delivery in the prehospital setting. An auto-injector for intramuscular (IM) or subcutaneous naloxone administration was approved by the Food and Drug Administration (FDA) on April 3, 2014, and on November 18, 2015, the FDA approved the first naloxone nasal spray. Both products are approved for emergency use in children and adults suspected of having an opioid overdose and are designed for administration by first responders or non-medical personnel such as family members.³ ⁴

Mechanism of Action
Naloxone hydrochloride, 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride, is a synthetic derivative of oxymorphone. It acts as an antagonist, competing with opioids for their receptor binding sites and reversing opioid-induced respiratory depression, sedation, and hypotension. It may also reverse the psychotomimetic and dysphoric effects of opioid agonist-antagonists.³ ⁴

Pharmacokinetics and Pharmacodynamics
Naloxone is well absorbed after intravenous administration and is widely distributed throughout the body.³ ⁴ The onset of action after IV administration is approximately 2 minutes. It is weakly bound to serum proteins. Naloxone undergoes hepatic metabolism via glucuronide conjugation. It is important for those who will administer naloxone to remember that its duration of action is shorter than that of most opioids. After a single dose of naloxone, it should be expected that opioid-induced central and respiratory depression may return, requiring additional doses.

The pharmacokinetic profile of naloxone after IM or subcutaneous administration was evaluated in 30 adult volunteers.³ After a single 0.4 mg dose using the auto-injector, the median time to maximum concentration (T_max) was 15 minutes (range 5 minutes to 1.2 hours), with a mean maximum plasma concentration (C_max) of 1.24 ± 0.64 ng/mL. Mean half-life was 1.28 ± 0.48 hours. These results were similar to those obtained with administration of a 0.4 mg naloxone dose given IM or subcutaneously using a standard syringe: a T_max of 20 minutes (range 5 minutes to 2.03 hours), mean C_max of 1.07 ± 0.48 ng/mL, and mean half-life of 1.36 ± 0.32 hours.

The pharmacokinetics of naloxone nasal spray were evaluated in a study of 29 healthy adults.⁴
All subjects received three doses of naloxone: a single spray in one nostril (4 mg total), a single spray in each nostril (8 mg total), and a single 0.4 mg dose of naloxone given IM. Dose selection reflected the relative bioavailability of approximately 45% for intranasal administration. Maximum plasma concentrations (median %CV) for the 4 mg nasal, 8 mg nasal, and 0.4 mg IM doses were 4.83 ng/mL (43.1), 9.70 ng/mL (36.0), and 0.88 ng/mL (30.5). Time to maximum concentrations was similar among the groups: 0.50 hours, 0.33 hours, and 0.38 hours, respectively. Median area under the concentration-time curve (AUC) values were 7.95 hr•ng/mL (37.3), 15.5 hr•ng/mL (22.7), and 1.76 hr•ng/mL (22.6). Half-lives were 2.08 hours (29.5), 2.10 hours (32.4), and 1.24 hours (25.9).

Clinical Experience
While there is only limited information in the medical literature on the new auto-injector and nasal spray products, the safety and efficacy of naloxone for opioid overdose has been well established. Several studies have compared different routes of naloxone administration in the prehospital setting. In 2005, Kelly and colleagues compared intranasal and IM naloxone for prehospital treatment of suspected overdose. This prospective, randomized, unblinded study was conducted in 155 patients (ages 13-57 years) treated by paramedics from two ambulance services. Patients were randomized to receive a 2 mg naloxone dose given IM or intranasally using a mucosal atomizer device. The primary outcome was time to regain a respiratory rate greater than 10 breaths/minute. Secondary outcomes included the percentage of patients meeting the primary outcome and/or a Glasgow coma score over 11 within 8 minutes, the need for additional naloxone, and the rate of adverse effects.

The IM group had a more rapid response than the intranasal group (mean time 6 minutes versus 9 minutes, p = 0.006) and a greater percentage of IM patients met the 8 minute goals (82% versus 63%, p = 0.017). There was a smaller percentage of patients who required rescue naloxone in the IM group, but the difference was not statistically significant (13% versus 26%, p = 0.0558). No serious adverse effects were reported. A total of 74% of the intranasal patients had a response sufficient to reverse opioid toxicity. The authors concluded that intranasal naloxone was an effective means of reversing opioid-induced respiratory depression, but was not as effective as IM administration. They balanced this difference with the advantage of the intranasal route in avoiding needle sticks in the paramedics and suggested making the intranasal option more widely available.

The authors published a second randomized controlled trial in 2009 with a more concentrated naloxone nasal spray which confirmed their earlier findings. A total of 172 patients were enrolled (mean age 29 years). The proportion of patients who responded within 10 minutes was similar, 72.3% in the intranasal group and 77.5% in the IM group (difference −5.2%, 95% CI −18.2 to 7.7). No difference was observed in mean response time; 8.0 minutes in the intranasal group and 7.9 minutes in the IM group (difference 0.1, 95% CI −1.3 to 1.5). Supplementary naloxone was administered to fewer patients who received IM naloxone (4.5% versus 18.1%, difference 13.6%, 95% CI 4.2–22.9). Intranasal naloxone administration was considered successful in reversing opioid toxicity in 82% of patients.

Based on these and other studies, the ease of use, and elimination of needle exposure, intranasal naloxone has become a part of many public health programs. In 2009, Doe-Simkins and colleagues described a program utilizing bystander intranasal naloxone in Boston. This program was developed in response to a regulation passed by the Boston Public Health Commission that authorized the distribution of naloxone through its mobile needle-exchange program. Participants were given a 15-minute training session that included symptom recognition and a kit containing two prefilled syringes with a 2 mg naloxone dose and atomizers. Participants were able to return for additional naloxone. A total of 385 people took part in the program over the first 15 months. At follow-up, 278 were contacted. Fifty participants had administered naloxone and 74 successful reversals were reported. Complications included difficulty in connecting the atomizer in four cases, naloxone-induced withdrawal symptoms in two cases, and the return of sedation in two cases. Based on these results, the program was expanded to additional training sites.

In 2015, Edwards and colleagues compared the ease of administration with the naloxone auto-injector and intranasal naloxone given using an atomizer. This manufacturer-sponsored study was conducted in 42 healthy adults between 18 and 65 years of age. The primary outcome of the study was the proportion of participants who were able to successfully administer a simulated dose of naloxone. After training by a nurse on each product, 100% of the participants in the auto-injector group versus 57.1% in the intranasal atomizer group (p < 0.0001) successfully completed administration. The average time to task completion was also shorter in the auto-injector group (0.5 ± 0.15 minutes versus 2.0 ± 2.15 minutes).
Warnings and Precautions
Use of naloxone in opioid-dependent patients may precipitate severe opioid withdrawal. Patients may experience reversal of analgesia, agitation, anxiety, fever, tremor, weakness, tachycardia, hypertension, sneezing, yawning, nausea, vomiting, and diarrhea. Abrupt reversal of opioid-induced respiratory depression in the postoperative setting has been associated with similar symptoms, as well as seizures, arrhythmias, pulmonary edema related to a centrally-mediated massive catecholamine response shifting blood volume into the pulmonary vascular bed. Cardiac arrest and death have been reported after naloxone use in the postoperative setting.\(^3\)\(^4\)

Patients who have overdosed on a partial agonist or mixed agonist-antagonist (buprenorphine or pentazocine) may require larger or repeated naloxone doses to achieve a response. Buprenorphine exhibits a slow dissociation from opioid receptors, resulting in a long duration of action. Naloxone produces a more gradual reversal in buprenorphine overdoses and has a shorter duration of effect than the respiratory depression produced by the drug.\(^3\)\(^4\)

Naloxone should not be used in patients with a history of hypersensitivity to naloxone or other opioid antagonists. Patients who have underlying cardiovascular disease may be at greater risk for changes in blood pressure or arrhythmias after naloxone use and should be monitored in a healthcare setting.\(^3\)\(^4\)

Adverse Effects
In premarking trials of naloxone nasal spray, the most commonly reported adverse effects were transient hypertension, musculoskeletal pain, headache, and nasal dryness, congestion, edema, or inflammation. While the numbers of patients treated with the nasal spray are too small to determine the presence of rare serious adverse effects, information may be gained from use in other settings (see Warnings and Precautions).\(^3\)\(^4\)

Availability
The naloxone auto-injector, Evzio\textsuperscript{TM}, is a product of Kaléo, Incorporated.\(^7\) It is available in a carton containing two devices, each with a single 0.4 mg dose, and a trainer device. Information on the auto-injector is available on the manufacturer’s website at \url{http://evzio.com/hcp/index.php}. The Evzio\textsuperscript{TM} auto-injector is available at retail pharmacies or through a mail-order pharmacy described on the company’s website. The retail price of the 2-dose carton is approximately $3,500-$4,000, but the manufacturer offers programs to reduce co-pay requirements for insured patients and provides the drug at a reduced cost to uninsured patients.

Information on the manufacturer’s Evzio\textsuperscript{TM} Savings Program and the Kaléo Cares Patient Assistance Program is available on the manufacturer’s website.

Narcan\textsuperscript{®} nasal spray is available in a 4 mg/0.1 mL single-dose device, sold in a 2-dose package.\(^5\) Naloxone was first approved by the FDA in 1971 with the trade name Narcan\textsuperscript{®}. The manufacturer, Endo Pharmaceuticals, discontinued production in 2013, leaving two generic products on the market. Adapt Pharma purchased the rights to the Narcan\textsuperscript{®} name and is using it for their naloxone nasal spray.

Adapt Pharma has partnered with the National Association of Counties, the National Governors Association, the National League of Cities, and the United States Conference of Mayors to provide Narcan\textsuperscript{®} nasal spray at a discounted price of $37.50 per 4 mg dose ($75 per 2-dose package) to state and local law enforcement officials, first responders, Departments of Health, and other community groups.\(^9\) The public interest price may be obtained by contacting the manufacturer at \url{customerservice@adaptpharma.com} or by calling 844-461-7116. The retail price for Narcan\textsuperscript{®} nasal spray is approximately $130-$150 per 2-dose package.

A second naloxone nasal spray is currently under development by Indivior, the manufacturer of Suboxone\textsuperscript{®} (buprenorphine and naloxone) sublingual film.\(^10\) The FDA declined to approve Indivior’s New Drug Application based on concerns regarding its equivalency to the reference product (0.4 mg naloxone given IM). Indivior is evaluating its response. It is hoped that the availability of multiple products will make access easier and potentially reduce cost.

Dosing Recommendations
Before prescribing naloxone for use in the prehospital setting, healthcare providers should ensure that the patient and/or family can recognize the symptoms of opioid overdose. Both products instruct the user to look for signs of extreme sleepiness, slow or shallow breathing, extremely small or pinpoint pupils, and a slow heartbeat. Family members should also understand the importance of rapidly accessing emergency medical assistance, even in cases where the patient’s symptoms may have appeared to resolve.

The naloxone auto-injector provides a single 0.4 mg dose for use in patients of all ages.\(^3\) The device provides both visual and auditory instructions for use. After removing the red safety cap, the black end of the injector should be placed on the anterolateral aspect of the thigh.
In infants, the thigh muscle should be pinched to facilitate placement and delivery of the dose. The device should be held in place for 5 seconds after the audible click and hiss that signal administration of the dose. Depending on the patient size and the presence of clothing, the dose will be delivered either IM or subcutaneously. After injection the device retracts the needle into the housing, the black base locks into place, a red indicator appears in the viewing window, and visual and audible instructions are provided to the user to seek emergency medical attention.

If the patient does not respond, an additional dose may be given every 2 to 3 minutes as needed until medical assistance arrives. The naloxone auto-injector should be stored in its protective case at room temperature. Patients and all family members who may use the auto-injector should read the instructions provided and practice with the black and white training device. The auto-injector should only be used if the naloxone solution remains clear. The solution should be checked periodically through the viewing window to ensure that it remains clear. If the solution is discolored, cloudy, or contains particles, it should be replaced.

Intranasal naloxone is administered as a 4 mg dose for children as well as adults.1 The spray should be held with the thumb on the bottom of the plunger and the first and middle fingers on either side of the nozzle. It does not require priming or testing. The patient should be placed on his/her back and the head should be tilted back and supported under the neck. The tip of the nozzle should be inserted into the nose and the plunger pressed firmly. If administered by a friend or family member, the patient should be placed on his/her side and medical assistance should be contacted immediately after the first dose is administered. Instructions for using the device are included. Pediatric patients should be monitored by healthcare providers for a minimum of 24 hours prior to discharge.

If the patient does not respond to the initial dose or if symptoms return, additional doses may be given every 2-3 minutes while awaiting emergency medical assistance or during transport to a hospital. A new spray device must be used each time and subsequent doses should be administered into alternating nostrils. Unused nasal spray may be stored at room temperature.

Summary
Naloxone has been shown to be an effective tool in the initial management of opioid overdose in both the prehospital and hospital settings. Two new products make administration of naloxone by first responders and family members much easier, potentially shortening the time to reversal of opioid adverse effects and reducing opioid-related deaths. Both the auto-injector and nasal spray provide a standard dose for all patients and are designed to be easy to use. If prescribing a naloxone auto-injector or nasal spray to be kept in the home, it is imperative that all family members who may respond to an overdose recognize the symptoms, know how to use the product, and understand the importance of seeking emergency medical assistance immediately after the first dose is given.

References