

## The Rising Price of Naloxone — Risks to Efforts to Stem Overdose Deaths

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New England Journal of Medicine

N Engl J Med 2016; 375:2213-2215 [December 8, 2016](#) DOI: 10.1056/NEJMp1609578

The Food and Drug Administration (FDA) first approved naloxone in 1971 as an injection (Narcan) for reversing opioid intoxication or overdose. Although the brand-name version has been discontinued, generic versions of naloxone have been available since 1985, and today injections are available in two doses (0.4 mg per milliliter and 1 mg per milliliter; **see table below**. Recent and Current Prices for Naloxone.). In 2014, the FDA fast-tracked approval of the first auto-injector formulation (Evzio), a fixed-dose single injection designed to allow people without medical training to reverse opioid overdose. In 2015, the agency fast-tracked approval of the first nasal-spray formulation (also marketed as Narcan); previously, naloxone injections (larger vials of a 1-mg-per-milliliter dose) had routinely been used off-label with an atomizer for nasal delivery.

In 2013, more than 80% of naloxone use was for heroin overdose, although there were twice as many deaths from prescription-opioid overdose as from heroin overdose.<sup>1</sup> Several U.S. federal agencies have therefore recommended increasing access to naloxone, particularly for prescription-opioid users. The Substance Abuse and Mental Health Services Administration developed an overdose-prevention tool kit in 2013, advising clinicians to coprescribe naloxone to patients taking opioids after considering a variety of factors, including whether these patients were receiving long-term or high-dose opioid therapy.

In 2015, the Department of Health and Human Services published its priorities in combating opioid overdoses, including accelerating development of new naloxone formulations and user-friendly products and expanding naloxone utilization by disbursing grants to states for naloxone-purchasing programs. Earlier this year, the Centers for Disease Control and Prevention (CDC) recommended that clinicians coprescribe naloxone to patients taking opioids and concurrently using benzodiazepines, patients taking higher opioid dosages ( $\geq 50$  morphine milligram equivalents per day), and patients with a history of overdose or substance use disorder. The 2016 Comprehensive Addiction and Recovery Act builds on these guidelines and calls for additional grants to expand access to naloxone — by means of provider training and drug purchasing, for instance.

Similarly, some states have increasingly pursued initiatives designed to improve access to naloxone. Historically, it has been illegal for physicians to prescribe naloxone to third parties, such as family members or friends of patients at risk for overdose. One new approach, adopted by 40 states so far, is to offer clinicians various levels of immunity from criminal or civil prosecution for third-party prescriptions. Laws in 42 states also grant criminal or civil immunity to bystanders who possess or use illegal drugs when they provide emergency services to someone who has overdosed, including administering naloxone or calling emergency responders.

A second strategy has been to allow people without a prescription to obtain naloxone at pharmacies through physicians' standing orders, collaborative practice agreements, or pharmacists' prescriptive authority; this approach has been authorized in 40 states, up from 1 in 2012. All told, the number of states with at least one law expanding access to naloxone increased from 8 in 2012 to 46 in 2016.

Beyond legislation, a rapidly growing number of community organizations now provide naloxone kits and education programs to laypersons,<sup>1</sup> and states and partnering agencies are doing the same with emergency medical services (EMS) providers.

Given the attention focused on naloxone and the initiatives broadening recommendations for its use, one would expect rapid increases in utilization. But between 2009 and 2015, the annual number of naloxone prescriptions increased only from 2.8 million to 3.2 million; while retail-prescription numbers were unchanged, the proportion attributed to clinics and EMS providers has grown from 14% to 29%.<sup>2</sup> The relatively slow adoption of naloxone may be due in large part to stigmatization and lack of familiarity with the treatment among clinicians and opioid users.<sup>3</sup> Another reason, however, may be its rising cost, which is probably enabled by the small number of manufacturers producing it.

Each formulation of naloxone — two injection doses, Narcan nasal spray, and Evzio auto-injector — essentially has one supplier. Though there are three manufacturers with FDA approval for 0.4-mg-per-milliliter-dose injections, the vast majority are sold by Hospira, which has increased the price by 129% since 2012 (see table below). Only Amphastar manufactures 1-mg-per-milliliter injections, the dose used off-label as a nasal spray, which currently costs \$39.60 after a 95% increase in September 2014. Newer, easier-to-use formulations are even more expensive. Narcan costs \$150 for two nasal-spray doses. A two-dose Evzio package was priced at \$690 in 2014 but is \$4,500 today, a price increase of more than 500% in just over 2 years.

Naloxone's price increase is part of an overall trend of increasing prescription-drug prices for both new brand-name drugs and old, off-patent generics. Public frustration with rising drug prices has led to a number of recent policy proposals, including Vermont's new legislation requiring companies to justify price increases, California's attempt to constrain drug payments, and the recently proposed and bipartisan-supported Fair Accountability and Innovative Research Drug Pricing Act. None of the federal or state initiatives expanding naloxone's availability, however, address the drug's rising cost.

We believe that such policies should explicitly call on manufacturers to reduce the price of naloxone and increase transparency regarding their costs, particularly those related to the development of new formulations. For example, Evzio's price jumped significantly and without explanation the month before the CDC's coprescription guidelines were released. Several U.S. senators — most recently, Susan Collins (R-ME) and Claire McCaskill (D-MO) — have sent letters asking naloxone manufacturers to explain their price increases. Though these requests recall recent investigations into Mylan, the manufacturer of the EpiPen, the naloxone situation has not garnered the type of attention or outrage inspired by that case, perhaps in part because of the stigma associated with opioid use.

There are additional steps governments could take to address naloxone's price increase. First, naloxone could be purchased in bulk, which would create stable demand that might motivate additional companies to begin manufacturing the medication — a strategy that's been used for vaccine manufacturing. Second, governments could invoke federal law 28 U.S.C. section 1498 to contract with a manufacturer to act on behalf of the United States and produce less costly versions of Evzio's patented auto-injector in exchange for reasonable royalties — an approach that was considered for procuring ciprofloxacin during the anthrax threat in 2001.<sup>4</sup> Third, in response to increases in generic drug prices, some observers have proposed allowing importation of generics from international manufacturers that have received approval from regulators with standards comparable to those of the FDA,<sup>5</sup> a strategy that could be pursued for naloxone.

In the long term, the FDA could also offer incentives to additional companies to obtain approval to market generic versions of naloxone by prioritizing more timely approval and waiving application user fees, which may require congressional action but would probably stimulate price competition. In the past, the FDA has discussed switching naloxone to over-the-counter status,<sup>2</sup> a conversation that could be revisited given the expected benefits for patient access. The relative ease of receiving FDA authorization for over-the-counter medications would also probably attract additional manufacturers.

Naloxone coprescribing and expanded availability represents only one of many potential strategies for reducing the number of prescription-opioid and heroin overdose deaths in the United States. But when governments promote naloxone use, they have a responsibility to ensure the drug's affordability. Taking action now is essential to ensuring that this lifesaving drug is available to patients and communities.

#### Source Information

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Recent and Current Prices for Naloxone.*			
Naloxone Product	Manufacturer	Previous Available Price (yr)	Current Price (2016)
Injectable or intranasal, 1 mg-per-milliliter vial (2 ml) (mucosal atomizer device separate)	Amphastar	\$20.34 (2009)	\$39.60
Injectable			
0.4 mg-per-milliliter vial (10 ml)	Hospira	\$62.29 (2012)	\$142.49
0.4 mg-per-milliliter vial (1 ml)	Mylan	\$23.72 (2014)	\$23.72
0.4 mg-per-milliliter vial (1 ml)	West-Ward	\$20.40 (2015)	\$20.40
Auto-injector, two-pack of single-use prefilled auto-injectors (Evzio)	Kaleo (approved 2014)	\$690.00 (2014)	\$4,500.00
Nasal spray, two-pack of single-use intranasal devices (Narcan)	Adapt (approved 2015)	\$150.00 (2015)	\$150.00

\* Price information was obtained from Medi-Span Price Rx (Wolters Kluwer Clinical Drug Information).