Expanded Access to Opioid Overdose Intervention: Research, Practice, and Policy Needs

Rates of fatal drug overdoses have more than doubled in the United States over the past decade to become one of the leading causes of preventable injury death. Overall drug overdose deaths increased to a record of 38,329 in 2010, outpacing deaths from motor vehicle traffic crashes nationally for 2 years running (1). Most of the increase in such deaths is related to prescription opioids and mirrors an increase in opioid prescribing (1, 2). Diversion of these medications contributes to the problem (3), and both higher opioid doses and poly substance use are significant contributing factors (3, 4).

Many actions are needed to address the complexity of the problem. In response, the Office of National Drug Control Policy has embarked on a 4-pronged effort to address prescription drug abuse: public and clinician education, controlled substance tracking and monitoring, proper medication disposal, and law enforcement (5). The Office of National Drug Control Policy and others have endorsed direct interventions to treat opioid overdoses as an important component of this comprehensive approach (6, 7). The article by Coffin and Sullivan in this issue (8) represents a significant step in the evolution of the science in this area: a detailed analysis of the cost-effectiveness of overdose intervention with naloxone administration for heroin abusers. The authors suggest that lay naloxone administration is likely to be highly cost-effective in this setting, a robust finding that holds up under various assumptions. Future analyses that extend their findings to the setting of prescription opioids would be welcome.

Naloxone is safe and effective for the treatment of opioid overdose (9). Its use is standard practice in emergency settings, where it is administered to patients with an opioid-induced coma or respiratory depression because of its rapid action as a μ-opioid–receptor antagonist. Despite its potential to safely, rapidly, and completely reverse an opioid overdose (7–9), the public health impact of this medication has not yet reached its full potential.

A key factor limiting widespread use of naloxone is that the only U.S. Food and Drug Administration (FDA)–approved formulation is injectable. Potential alternatives include formulations that could be delivered by an intranasal device (10) or an auto-injector, both of which show great promise but require additional research. Ultimately, approval of a naloxone formulation that could be used without a prescription would also help encourage broader use, although additional studies are needed in this area as well.

In April 2012, the FDA, the National Institute on Drug Abuse (NIDA), the Centers for Disease Control and Prevention, and the Office of the Assistant Secretary for Health jointly sponsored a public meeting on the potential for expanded access to naloxone, particularly its use outside of conventional medical settings (11). Researchers from various locations—both here and abroad—reported encouraging data on the ability of naloxone to reverse opioid overdose and emphasized the use of intranasal formulations administered in nonmedical settings. At the meeting, the FDA outlined the regulatory pathway for approval of both intranasal and auto-injector devices. The primary requirement would be to show bioequivalence of the new formulation to the existing approved injectable formulation, and additional required studies may be limited in number, of short duration, and modest in size. Switching naloxone from prescription to over-the-counter status to increase availability was also discussed; the necessary studies would center on the ability of consumers to accurately diagnose an overdose and correctly administer the medication.

Since the meeting, federal agencies have continued to address this urgent public health need through targeted educational efforts, research, and communications. For example, the NIDA is encouraging research on strategies to help prevent opioid tolerance; to develop opioid delivery systems that are less likely to be diverted; to evaluate the effectiveness of naloxone distribution among high-risk patients; and to lay the groundwork for the development of devices that deliver naloxone automatically when a preset threshold for oxygen concentration signals respiratory depression, even when patients are asleep. The FDA has continued to encourage the pharmaceutical industry to develop data on the comparability of injection and alternative formulations of naloxone (12) through discussions with naloxone manufacturers here and abroad. In addition, the Substance Abuse and Mental Health Services Administration has been developing an overdose “toolkit” to educate persons at high risk for overdose and their families (11).

However, prevention of overdose can be only 1 facet of an overall comprehensive approach to prescription drug abuse. Increases in both the number of prescriptions and the doses of opioids prescribed seem to be significant contributors to the problem (1, 2, 4, 5), suggesting that education and enhanced physician access to patient prescription records might be part of the solution. For instance, the NIDA, in partnership with the pain consortium at the National Institutes of Health, has funded “pain centers of excellence” to develop curricula to better prepare clinicians and nurses for screening and monitoring pain, including proper management of opioid medications. In July 2012, the FDA announced the approval of a Risk Evaluation and Mitigation Strategy for high-potency and extended-release opioids, which is focused on prescriber and patient education and has a goal of reducing the abuse of these powerful...
drugs. In addition, access to state Prescription Drug Monitoring Program data in a rapid, automated manner can inform clinicians about other controlled substances that may have been prescribed to their patients. Such information can change prescribing practices and may reduce both inadvertent and intentional medication misuse (13). Programs are currently operational in most states, but physician enrollment and utilization have been disappointing. Projects at the Substance Abuse and Mental Health Services Administration and the Office of the National Coordinator for Health Information Technology to enhance and simplify access to Prescription Drug Monitoring Program data in real-world clinical settings, such as emergency departments and primary care practices, are underway.

In parallel to these advances, there is an urgent need for continued research and practice development. The NIDA and the FDA are keen to work with public health and pharmaceutical company partners on pharmacokinetic studies of intranasal and injectable naloxone, and they welcome inquiries. Additional formative and implementation studies of naloxone distribution and overdose intervention in field settings, particularly for prescription opioid abusers, are also needed, as are studies of the ways to embed overdose intervention into a broader addiction intervention system (that is, to use overdose interventions as points of entry into drug treatment). Studies of the use of take-home naloxone for persons receiving high dosages of prescription opioids and of those abusing the drugs are warranted to determine whether such interventions reduce mortality and morbidity. In particular, studying the effectiveness of layperson-administered naloxone in reversing overdose from long-acting and extended-release opioids is essential (7, 9, 10).

We applaud Drs. Coffin and Sullivan for their important contribution to this public health effort, and we encourage much additional work that can bring such potentially life-saving interventions more firmly into the mainstream of both clinical practice and community programs for licit and illicit drug users.

Wilson M. Compton, MD, MPE
Nora D. Volkow, MD
National Institute on Drug Abuse
Bethesda, Maryland

Douglas C. Throckmorton, MD
Peter Lurie, MD, MPH
U.S. Food and Drug Administration
Silver Spring, Maryland

Disclaimer: The views and opinions expressed in this commentary are those of the authors and should not be construed to represent the views of the National Institute on Drug Abuse, the National Institutes of Health, the U.S. Food and Drug Administration, or the U.S. government.

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-2814.

Requests for Single Reprints: Wilson M. Compton, MD, MPE, National Institute on Drug Abuse, 6001 Executive Boulevard, MSC 9589, Bethesda, MD 20892-9589; e-mail, wcompton@nida.nih.gov.

Current author addresses are available at www.annals.org.


References


Current Author Addresses: Dr. Compton: National Institute on Drug Abuse, 6001 Executive Boulevard, MSC 9589, Bethesda, MD 20892-9589.
Dr. Throckmorton: U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Building 51, Room 6132, Silver Spring, MD 20993.
Dr. Lurie: U.S. Food and Drug Administration, Office of the Commissioner, 10903 New Hampshire Avenue, Building 1, Room 2320, Silver Spring, MD 20993.
Dr. Volkow: National Institute on Drug Abuse, 6001 Executive Boulevard, Bethesda, MD 20892.