HHS Public Access

Author manuscript

*Prev Med*. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

*Prev Med*. 2015 November ; 80: 41–43. doi:10.1016/j.ypmed.2015.05.016.

# Distribution of Naloxone for Overdose Prevention to Chronic Pain Patients

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Prescribing of opioids for pain, especially chronic non-malignant pain, has risen dramatically over the last decade with the number of opioid prescriptions tripling between 1991 – 2013 to ~207 million [1, 2]. The morbidity and mortality associated with the increased availability of opioids is substantial, including significant rises in prescription opioid-related poisonings and deaths [3, 4]. Between 1999 and 2012, opioid-involved drug poisoning deaths more than tripled from 1.4 to 5.1 per 100,000 [5]. Opioid analgesics are the most common prescription medication involved in overdose deaths, and by 2006, these deaths exceeded the number of deaths attributed to cocaine, heroin and psychostimulants combined [6]. One outstanding question related to the prescription opioid overdose epidemic is to what extent pain patients with legitimate opioid prescriptions contribute to these high mortality rates. Epidemiological studies reporting on fatal overdoses often rely on medical examiner reports with content and format that vary widely, thus making it difficult or impossible to discern if death cases are the result of accidental or intentional overdose in chronic pain patients or substance abusers or both.

Perhaps the most important studies in this area are those few that highlight key overdose risks among patients receiving opioids for chronic pain. Dunn and colleagues prospectively examined a large cohort of patients (n=9940) through a comprehensive care system in Washington state, who were starting a new episode of opioid use (with at least 3 opioid prescriptions in 90 days) for chronic non-cancer pain [7]. Using ICD coding to identify overdose events, it was determined that, during an average of 42 months of surveillance, 51 patients were identified as having one or more than one overdose event. The likelihood of a fatal or nonfatal overdose event was positively related to daily opioid dose, with the highest

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The authors have no conflicts of interest to report related this report.

dose category (≥100 mg/day morphine equivalents [MME]) demonstrating a 9-fold increase in risk compared to the lowest dose group (≤20 MME). Another population-based study examined a cohort of individuals from Canada who qualified for a public prescription drug coverage program and received an opioid prescription over an approximate 9-year period. Those individuals receiving high daily opioid doses (≥200 MME) were at nearly 3-fold greater risk for a fatal overdose compared to those on low daily doses (i.e., <20 MME). Moreover, the toxicology screening revealed that 39% of the decedents had more than one opioid detected at the time of autopsy, and 85% were co-prescribed a benzodiazepine at the time of death [8].

## Naloxone as an Overdose Prevention Tool

Naloxone, an opioid receptor antagonist, is marketed for reversal of opioid-associated respiratory depression for hospital and ambulance use [9, 10]. Naloxone produces little detectable pharmacological action unless opioid agonists are present but does require a physician's prescription in the U.S. The approved formulation [11] is a sterile solution that can be administered parenterally or intranasally. Emergency responders widely use intranasal administration of naloxone through an atomizer, as it obviates the need for needles. While both the atomizer and the drug are FDA-approved, their combination is not; however, they are widely used off-label because it is easy to deliver the spray into an unconscious person's nose, does not require venous access, and reduces needlestick risks. The FDA approved the first naloxone auto-injector (Evzio™) in 2014, but its widespread distribution may be cost-prohibitive [i.e., ≥$300/dose]. Other easy-to-use formulations, including single unit nasal sprays [e.g., 12], are at various stages of development with sponsors seeking rapid FDA-approval. In recent years, legislative changes in many states have reduced restrictions on naloxone use by emergency responders [13] and allowed for the development of programs for naloxone distribution to opioid abusers in order to reduce opioid-associated morbidity and mortality [14, 15]. There are at least 188 programs that currently distribute naloxone to IDUs throughout the U.S. [16].

Between 1996 and 2010, more than 10,000 successful opioid overdose reversals were reported by ~48 naloxone distribution programs [16], providing evidence that naloxone can be administered by bystanders with limited training to prevent overdose death. Using an interrupted time-series analysis to evaluate overdose education and naloxone distribution (OEND), Walley and colleagues discovered that communities with even low levels (<100 participants per 100,000 population) of OEND implementation had significantly lower rates of opioid overdose deaths compared to communities without programs [17]. The success of these programs has led the National Institute on Drug Abuse, the Office of National Drug Control Policy and other federal agencies to advocate for broader access to naloxone [18–20]. Amended laws in 30 states and the District of Columbia (DC) now make it easier for medical professionals to prescribe and dispense naloxone, and for bystanders to administer it, by removing or reducing liability if something goes wrong. Furthermore, Good Samaritan Laws in 22 states and DC allow bystanders to call 911 to report an overdose without fear of arrest [21].

## Naloxone overdose prevention: Targeting at-risk chronic pain patients

Many strategies should be employed clinically to reduce the risk of overdose in chronic pain patients who are receiving opioids, including avoiding concomitant prescribing of drugs with known risky interactions, careful monitoring of at-risk patients (e.g., those with sleep apnea), choosing appropriate opioid doses with care, and overall reduced prescribing. Indeed, opioid prescribing has been declining nationally from its peak at 219 million to 207 million in 2013 prescriptions [22]. Recent reports have suggested limited scientific evidence supporting the long-term efficacy of opioids in the treatment of chronic non-malignant pain [23, 24], which may lead to further reductions in prescribing. Nonetheless, we argue that, while naloxone has historically been distributed as a treatment for heroin overdose, its utility as a rescue agent for accidental overdose in pain patients must be considered. Project Lazarus, a community-based prevention program, partnered with local physicians to offer naloxone as part of their routine medical care to both suspected opioid abusers and pain patients who were at high risk for overdose and included additional interventions, such as enhanced education for prescribing physicians. In that program, opioid-associated death rates decreased by 50% in a single year [25]. Naloxone training and distribution to chronic pain patients and their families/friends could be incorporated into clinical practice to reduce opioid-related risks similar to the addition of other risk management tools (e.g., regular urine drug testing, querying of state prescription monitoring programs, pill counts, more cautious and circumscribed prescribing, and referral to drug abuse specialists when aberrant drug-using behavior is noted [26–28]. An outstanding resource was developed and available from the Substance Abuse and Mental Health Services Administration called the Opioid Overdose Toolkit [29]. This easy-to-read document outlines information for prescribers, community members, first responders, patients and family members. Moreover, it defines the critical five actions for first responders (i.e., call 911, check for signs of overdose, support breathing, administer naloxone and monitor the response). As the majority of patients receiving opioids for chronic pain may, indeed, be at low or no risk of opioid overdose, broad distribution of naloxone and training to all patients and their families is probably unnecessary and perhaps not practicable. However, distribution of naloxone reversal kits along with training to the subpopulation of chronic pain patients and their families who may be at greatest risk of adverse drug-related outcomes is an excellent preventive measure for physicians to consider. Based upon both clinical experience and the published literature, those at substantively greater risk of opioid overdose would be patients:

1. with a history or current diagnosis of alcohol or drug use disorders or harmful substance use,
2. maintained on relatively higher doses of opioids [7, 8],
3. initiating and/or receiving methadone, which, owing to its long-half, is recognized for risk of toxic accumulation during the start of therapy [30, 31],
4. with polypharmacy, especially use of benzodiazpines, and at risk of drug-drug interactions [8, 32–34],
5. with co-morbid psychiatric disorders and at greater risk for suicide by overdose [35, 36], and

6. with cognitive impairments that could lead to accidental ingestion of excess opioids.

Incorporation of naloxone overdose prevention for pain patients will require support from physicians, patients, patient families and health insurers. In order to obviate potential issues of stigma and mistrust that may surround naloxone, it may be helpful to frame the prescribing of naloxone overdose prevention as just one more risk management tool available for physicians to protect their patients who are prescribed opioids, a drug class whose beneficial therapeutic effects cannot be completely dissociated from the risk of respiratory depression. Physician reticence to provide naloxone may result from fear of legal ramifications; however, there are no restrictions on a physician's right to prescribe for a legitimate medical purpose [37]. Recent legislative changes (e.g., expansion of Good Samaritan Laws to bystanders calling for medical aid after an overdose, as well as retail pharmacy partnerships with physicians to allow for over-the-counter sales of naloxone) are indicative of a growing acceptance of naloxone as a safe agent capable of reducing overdose deaths. Patients' families, friends or cohabiters will ultimately be responsible for administering naloxone, and will need to receive training on how to identify an overdose, administer naloxone, and call emergency services as part of any rescue. This information can be conveyed directly by a doctor or pharmacist, instructions can be sent home with patients, and/or instructions may be recorded and delivered through a rescue device (e.g., Evzio™). Common objections to take-home naloxone (including the perceived inability of laypersons to safely and effectively administer naloxone and possibility of secondary opiate overdose due to the short half-life of naloxone and the notion that providing a naloxone "safety net" would encourage complacency and more risky behaviors) have been refuted numerous times elsewhere. With minimal training (i.e., as little as 10 minutes) [17], laypersons are fully capable of recognizing an opioid overdose and initiating naloxone rescue [14, 38, 39], and the success rate of naloxone rescue is equivalent in trained versus untrained rescuers [40]. Adequate training of potential rescuers to call 911 would obviate concerns about secondary overdose. Finally, evidence from IDUs (a groups of people already engaging in more high risk drug taking than chronic pain patients) shows that providing naloxone does not promote increased drug use [41–43]. These objections to naloxone programs are the result of stigma surrounding illegal drug use, and their persistence, despite compelling contrary evidence, is unfortunate but should not prevent the availability of naloxone for overdose prevention.

## Conclusions

Over the past 20 years, opioid prescribing has increased dramatically in the U.S. due, in part, to pain being designated as the "fifth vital sign," significant changes in clinical practice guidelines advocating for improved pain control, broader opioid prescribing for chronic non-malignant pain leading to increased availability of opioids, and increased marketing of opioids. As opioid prescribing has risen, significant increases in opioid-related poisonings and deaths have been observed. Naloxone is a life-saving therapeutic used for opioid overdose reversal in hospital and ambulance response settings. Naloxone distribution and training programs have demonstrated efficacy in reducing opioid-associated mortality, but have focused largely on distribution to opioid abusers. Here, we propose that physicians

prescribing opioids for chronic pain (general practitioners and specialists alike) consider adding naloxone prescription coupled with overdose training for patients, family members, co-habiters and/or friends as part of their clinical risk minimization strategy. The availability of naloxone as an intervention may be particularly important for sub-groups of chronic pain patients who are at known greater risk of opioid overdose (e.g., those on higher opioid doses and/or receiving numerous concomitant medications). In addition to following existing guidelines for opioid prescribing and incorporating other available harm reduction strategies into clinical practice, naloxone availability would likely improve the overall risk/benefit ratio of opioid prescribing in chronic pain patients and save lives.

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## Highlights

- Prescribing of opioids for pain has risen dramatically over the last decade, coinciding with increased morbidity and death rates.
- Chronic pain patients prescribed opioids are at increased risk of overdose death.
- Naloxone distribution programs have effectively reduced morbidity and mortality wherever they are implemented.
- Expanding naloxone access to at-risk chronic pain patients would reduce overdose death.