

## Evidence Brief: Mortality following non-fatal opioid overdose



### Key Messages

- The available evidence suggests mortality following non-fatal opioid overdose may occur within five years in up to 18% of individuals treated in prehospital care and in 9.4% of individuals within one year of treatment in the emergency department.
- Possible risk factors include previous opioid overdose, opioid prescriptions or substance use disorders.
- Prehospital and hospital settings represent a potential point of intervention to reduce mortality following non-fatal overdose.

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### Issue and Research Question

Opioid-related harms in the Ontario population continue to rise, including emergency department visits, hospitalizations and deaths.<sup>1</sup> Specifically, the rate of emergency department visits in Ontario for opioid poisoning increased from 15.2 to 26.3 per 100,000 between 2003 and 2015.<sup>1</sup> In 2015, there were 3,628 emergency department visits and 1,745 patients hospitalized for opioid poisoning, as well as 730 opioid-related deaths.<sup>1</sup> Together, these outcomes represent a large burden of opioid-related morbidity and mortality, as well as health care costs.

Comprehensive strategies to address opioid-related harms are developing in many jurisdictions in North America, including Ontario.<sup>2</sup> These strategies typically include aspects of prevention, treatment, harm reduction and law enforcement, which are also reflected in Canada's updated [Drugs and Substances Strategy](#).<sup>3</sup>

In developing specific interventions, it is important to understand risk factors, groups or settings to inform priority-setting or targeted programs. For example, evidence suggests that opioid prescriptions are associated with non-fatal and fatal overdose in a dose-response relationship. There is also an increased risk of

non-fatal and fatal overdose among patients on opioid therapy who have concurrent psychiatric disorders or substance use disorders.<sup>4</sup> New opioid guidelines in Canada aim to reduce risks related to prescribing.<sup>4</sup>

Furthermore, the current [American Heart Association Guidelines](#) outlines specific groups of people who may benefit from access to overdose education and naloxone training due to higher risk of experiencing or witnessing an overdose.<sup>5</sup> For example, the guidelines lists people who have presented for emergency care for opioid overdose. In addition, the guidelines list other groups, such as people enrolled in opioid dependence treatment programs and patients on opioid therapy with additional risk factors for adverse events.

The scope of the literature specifically on the risk of mortality after non-fatal overdose has not been well-characterized previously. A non-systematic narrative review of prehospital treat-and-release policies among patients with opioid overdose found five relevant studies.<sup>6</sup> These studies included patients with opioid overdose treated by paramedics, emergency medical technicians or other prehospital care providers (hereafter referred to as “paramedics”) and who refused transport to hospital. The authors found three patients in a pooled total of 3875 died of rebound overdose during short-term follow-up. One recent study suggested an incidence of 9% all-cause mortality within one year among patients seen in the emergency department for opioid overdose.<sup>7</sup>

There is a gap in understanding the current breadth of the literature on mortality, including risk factors, among patients with non-fatal opioid overdose treated in various settings and followed for longer periods.

Given the potential for intervention in settings that have contact with people who experience non-fatal overdose, we sought to review the published literature on mortality following non-fatal overdose and associated risk factors.

This Evidence Brief asks: *What is the incidence of, and risk factors for, opioid-related and all-cause mortality at any time point following a non-fatal opioid overdose?*

## Methods

The evidence base for this Evidence Brief consists of a review of the published literature. The detailed search strategy is available from PHO on request.

PHO Library Services conducted a database search on March 14, 2017 in line with a peer-reviewed search strategy. Two databases were searched (Ovid MEDLINE and Embase) using relevant search criteria (subject terms, key words, English language, from 2006 to 2017). Search terms included those related to opioids (e.g., “Analgesics, Opioid”) and non-fatal or fatal overdose (e.g., “drug overdose”). Duplicate references were removed by the library staff.

Studies were eligible if they were written in the English language, represented primary data or a systematic search and synthesis of the literature, and reported on adults with non-fatal opioid overdose, poisoning or toxicity (by any definition in the article, including self-reported, attended by paramedics or treated in a health care setting). We included studies with or without a comparison group. Outcomes of interest were opioid-related or all-cause mortality within any time period after non-fatal opioid overdose or associated risk factors.

Title and abstracts were screened for eligibility by two reviewers using standardized criteria and discrepancies were resolved by consensus. For articles potentially eligible on title and abstract screening, full text articles were retrieved and two reviewers assessed each article using the same eligibility criteria and consensus process for discrepancies.

For included articles, relevant information was extracted from each article by one reviewer. A second reviewer independently verified the data on just under half (n=6) of the included

articles and compared results with the other reviewer for reliability.

Two reviewers independently conducted quality appraisal selecting the appropriate tool for each included article based on the study design. Quality appraisal and tool selection was guided by the PHO Library Services Meta Quality Appraisal Tool (MetaQAT)<sup>8</sup> with advice from PHO's Knowledge Synthesis Services unit—Health Promotion, Chronic Disease and Injury Prevention (HPCDIP). Discrepancies in quality appraisal outcomes between the reviewers were resolved by consensus. More information on quality appraisal is available upon request.

## Main Findings

The search of the published literature identified 1990 articles, from which 64 unique articles met inclusion criteria on title and abstract screening. On full text review, a total of 14 primary studies were relevant to our Evidence Brief objectives.

The quality ratings for the articles were appraised as 6/9 for one study,<sup>9</sup> as 7/9 for five studies,<sup>10-14</sup> as 8/9 for five studies,<sup>7,15-18</sup> and as 9/9 for three studies<sup>19-21</sup> using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies.<sup>22</sup>

Below we summarize our findings organized by the setting where individuals were treated for a non-fatal opioid overdose. For findings where the setting was not specified or the overdose was not treated by a healthcare professional (e.g., reported on a survey), we have classified the setting as a general community setting.

### Community setting

Two studies reported on mortality and risk factors among cohorts of people who use drugs in the community (adults or youth), with mortality rates ranging from 6.4 to 9.1 per 1000 person years.<sup>16,20</sup> Darke et. al. found 5% (31/651) of people using heroin in a cohort study died during follow-up between 2001 to 2009, at a rate of 6.4 per 1000 person years.<sup>20</sup>

Among these deaths, 68% were related to overdose involving heroin (confirmed by personal communication with author).<sup>20</sup> The only significant correlate with all-cause mortality was history of heroin overdose prior to baseline. Similarly, among youth (under 30 years) with injection drug use, the death rate was 9.1 per 1000 person years (38/644), and was associated with heroin use most days in the past month but not associated with past heroin overdose.<sup>16</sup>

### Prehospital setting

There were four studies that reported on mortality among patients treated in a prehospital setting for opioid overdose<sup>9,11,14,21</sup> and three other studies that reported on mortality among related patient groups (such as drug-poisoning, heroin overdose, people with injection drug use).<sup>10,13,18</sup> Within these eight studies, one included patients who were not transported to hospital for further care,<sup>14</sup> five included a combination of patients who were or were not transported,<sup>9-11,13,21</sup> and one did not describe whether patients were transported after being treated.<sup>18</sup>

Among patients with opioid overdose, three studies reported on mortality after 48 hours,<sup>9,11,14</sup> and all-cause mortality ranged from 0% (0/552)<sup>14</sup> to 1.4% (12/863) when those who died on scene were excluded (including patients who were hospitalized or released on scene).<sup>11</sup> Wampler et. al. further studied 30-day mortality and found 1.6% (9/552) died.<sup>14</sup> One study included information on cause of death, and found 1 in 18 deaths within 48 hours was by suicide.<sup>9</sup> Wichman et. al. tested associations of various factors with 48 hour mortality and found that previous opioid overdose was not significantly associated.<sup>11</sup> The other two articles did not analyze risk factors.<sup>9,14</sup>

In follow-up of 2045 patients with drug poisoning seen in ambulance, outpatient or hospital settings, 14% died within five years (2% by suicide), and 1.4% (4/285) of deaths occurred within one week.<sup>10</sup> Among those with opioid as the main toxic agent, 18% (92/503) died within five years.<sup>10</sup> A factor that

significantly predicted death in the cohort in the multivariate Cox regression analysis was having opioids as the main agent for previous non-fatal drug poisoning [Hazard Ratio (HR) 2.3, Confidence Interval (CI) 1.6-3], in addition to older age (continuous variable) and male sex.<sup>10</sup>

Within 12 hours of receiving naloxone for treatment of heroin overdose, 0% (0/145) patients died.<sup>13</sup> Another study reported on follow-up of people treated for heroin or opioid overdose and found an overdose mortality rate of 1.2 per 100 person years (164/4884, mean follow-up 2.2 years) (defined as accidental or intentional drug/ toxic substance poisoning as primary or secondary cause of death).<sup>18</sup> Having been attended by paramedics for multiple non-fatal heroin overdoses was associated with increased mortality risk [two previous overdoses Adjusted Hazard Ratio (AHR) 3.71, 95%CI 2.54-5.45; >2 previous overdoses AHR 7.38, 95%CI 4.81-11.31].<sup>18</sup>

### **Emergency department setting**

Two studies reported on one-year all-cause mortality among patients that were treated for opioid overdose in an emergency department (ED).<sup>7,19</sup> Boscarino et. al. found a 9.4% (191/2039) all-cause mortality within one year.<sup>7</sup> This study did not have additional information on cause of death or test associations between multiple non-fatal overdoses and subsequent death.<sup>7</sup> Variables significantly associated with one-year mortality included receiving nine or more opioid prescription orders prior to non-fatal overdose versus none (OR 2.29, 95%CI 1.48-4.22) and substance use disorders prior to non-fatal overdose (OR 2.85, 95%CI 1.42-5.76).<sup>7</sup>

The study by Hasegawa et. al. reported only on in-hospital mortality among a cohort of 19,831 patients as a secondary outcome and did not use other sources of data to determine whether the person was still alive.<sup>19</sup> This study found 1.1% one-year in-hospital mortality (95%CI 1.0-1.3%), with 90% occurring at the same visit as the overdose. There was a significant association between male sex and cancer and no association with frequent ED visits.<sup>19</sup> This study was one of

two identified that collected data on whether the non-fatal overdose was intentional or unintentional and found 38% (95% CI, 37.3%-38.7%) of the cohort had at least one intentional opioid overdose.

Two other studies reported on mortality following emergency department visits among patient groups defined by drug poisoning or heroin overdose, rather than opioid overdose. One reported on patients with drug poisoning in general (including opioid poisoning) and found 0.1% (2/1731) died in the first week after discharge, both from new opioid poisoning.<sup>15</sup> Among the total group of all individuals with drug poisoning, 6% were classified as a suicide attempt.<sup>15</sup> The other study, reported on patients seen for heroin overdose and found 5.4% (12/224) died within five years (5/12 deaths were opioid-related).<sup>17</sup>

### **Hospital setting**

We did not identify any articles that described mortality following non-fatal opioid overdose admitted to hospital.

### **Intensive care setting**

Among 21 patients admitted to intensive care units (ICU) for drug poisoning involving opioids, five died in ICU and 25% (4/16) of those discharged alive had died within the follow-up period (median follow-up 31 months).<sup>12</sup>

## **Discussion and Conclusions**

Our review found a small body of literature with a wide range of mortality estimates among patients treated for opioid overdose in various settings. Studies also varied substantially in the population included and how overdose was defined.

The estimates ranged from 0% within 48 hours of prehospital care to 25% (4/16) all-cause mortality within a median 31 months after discharge from ICU from drug poisoning involving opioids. Yearly estimates from various



settings were found among three studies.<sup>7,18,21</sup> These ranged from 1.2% for mortality from intentional or unintentional drug poisoning<sup>18</sup> to 18% all-cause mortality for opioid overdose seen in the prehospital setting,<sup>21</sup> with an estimate of 9.4% following opioid overdose seen in emergency departments falling between these values.<sup>7</sup> An estimated five-year mortality after heroin overdose seen in emergency departments was 5.4% in one study.<sup>17</sup> In comparison, a recent study found a 6% one-year mortality among a large cohort of over 4,000 acute myocardial infarction patients followed between 2005 and 2008 among 24 US hospitals.<sup>23</sup>

Risk factors associated with mortality in relevant community-based cohorts included history of opioid overdose in one study (cohort of people with heroin use),<sup>20</sup> but no significant association was found in another study (cohort of youth with injection drug use).<sup>16</sup>

Among patients treated for opioid overdose in various settings, risk factors for mortality included previous episodes of opioid overdose (significant in two studies for all-cause mortality),<sup>21</sup> and overdose mortality;<sup>18</sup> and not significant in one study for all-cause mortality.<sup>11</sup>

Risk factors for all-cause mortality after opioid overdose treated in emergency department also included multiple opioid prescriptions and substance use disorders.<sup>7</sup> Among patients with drug poisoning seen in the emergency department, non-fatal overdose involving opioids was associated with higher risk of five-year mortality in comparison with other drug poisonings.<sup>10</sup>

Overall, we conclude that the available literature suggested an elevated risk of one-year mortality among patients following non-fatal opioid overdose treated in a prehospital or hospital setting. Possible risk factors included previous opioid overdose, opioid prescriptions or substance use disorders. More research is needed to understand the magnitude and the risks for death following non-fatal overdose, to understand opportunities for effective intervention.

## Implications for Practice

The best available evidence on the incidence of mortality following non-fatal opioid overdose indicates up to 18% of individuals seen in prehospital care may die within five years or 9.4% seen in the emergency department may die in the following year.

There is a need to identify effective points of intervention to reduce mortality following non-fatal overdose.

## Limitations

Limitations of our review include the search limits to review only the English language literature in the past ten years. We conducted a rapid review rather than a full systematic review of the literature. The search results were challenging to synthesize, as the definitions of non-fatal opioid overdose and classification of mortality outcomes varied widely and were often not described clearly.

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