Briefing Note:
Cost Coverage of Naloxone and Take-Home Naloxone Kits

Issue

Deaths related to opioids are a serious public health problem in Canada. During 2013 in Ontario alone, there were 577 opioid overdose deaths, continuing the upward trend in overall opioid deaths (Centre for Addiction and Mental Health, 2015). Researchers have found that many individuals who have died from prescription opioid poisoning had received a prescription for the medication in the months prior to death (Dhalla et al., 2009), illustrating the significant harms associated with prescription opioids. Furthermore, most opioid-related fatalities have been found to be accidental (Dhalla et al., 2009), highlighting an important role for prevention interventions.

Providing take-home naloxone (THN) kits to individuals at high risk of death due to opioid overdose is a critical part of an overall prevention strategy needed to reduce these deaths. The World Health Organization released a report on Community Management of Opioid Overdose (World Health Organization, 2014). The report included a strong recommendation that **people likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose**. From a public health perspective, a comprehensive strategy is required to make naloxone widely accessible to high-risk groups and to raise awareness about opioid overdose prevention.

Background

The effectiveness and safety of naloxone for the treatment of an opioid overdose is well established. It is a short-acting, competitive opioid antagonist used primarily by emergency medical personnel to reverse a suspected opioid overdose. Naloxone can also be prescribed or provided directly to out-patients at high risk for overdose, just as epinephrine auto-injectors like EpiPen® are prescribed to out-patients at risk for anaphylaxis. Similar to epinephrine, naloxone is a rescue medication, carried by the at-risk patient for use in a life-threatening emergency and is often administered by a bystander. Naloxone is usually provided to individuals through community-based THN programs, typically as part of a kit that includes:

- Two naloxone vials,
- Two syringes, and
- Two needles.

Kits can also contain additional supplies such as alcohol swabs, plastic gloves, one-way breathing barriers and a carrying case. Training for the recipient, as well as friends or family members, is a critical component of community-based THN programs.

Currently in Canada, there are community-based THN programs in several Ontario, British Columbia and Alberta cities. During the summer of 2015, Alberta expanded street-level THN programs across the province. More recently, community-based THN programs have been established in Montreal and Halifax, and proposed for Saskatoon.

A large Centers for Disease Control and Prevention study pointed out that although the majority (81.6%) of overdose reversals involved heroin, prescription drugs are actually responsible for twice as many deaths as heroin (Centers for Disease Control and Prevention, 2015). This report

emphasized the need for additional interventions to better target the population of people who use prescription drugs.

In Canada, providing naloxone kits at no cost or listing naloxone and THN kits on federal, provincial and territorial drug plan formularies would complement street-level THN programs by providing access to naloxone for those who do not interact with community-based THN programs, potentially preventing additional deaths due to prescription opioid overdose.

Proposed Reimbursement Criteria

Federal, provincial and territorial drug plans in Canada[1] are asked to consider providing naloxone kits at no cost, or listing naloxone and THN kits as unrestricted benefits on drug plan formularies to optimize access to naloxone for prevention of opioid-related overdose. As an alternative to open listing, the following criteria are proposed to restrict naloxone and THN kits to those at highest risk of opioid overdoses.

The proposed criteria closely align with those proposed by the Surviving Opioid Overdose with Naloxone, International Working Group (Orkin et al., 2015), and are similar to those indicated in the World Health Organization report (2014).

1. Individuals who may have a substance use disorder related to opioids and who are not in treatment, regardless of the reason

This group includes those who are:

- On wait lists for treatment or
- Not actively seeking treatment.

Rationale

In a systematic review of mortality studies involving individuals dependent on heroin (Degenhardt et al., 2011), the relative risk of death was 2.3 while out of treatment compared to in treatment, with overdose being the most common cause of death. In a large cohort study of those who use heroin in Italy (Davoli et al., 2007), the annual overdose death rate out of treatment was 1.1%, compared to 0.1% in treatment. The standardized mortality ratio for out of treatment among those who use heroin was 21.4, which is 20 times higher than the general population matched for age.

The overdose mortality rate among individuals who have a substance use disorder related to prescription opioids is probably lower than among those who use heroin, as injection use is a risk factor for overdose (Milloy et al., 2010; Fischer, Rehm, & Blitz-Miller, 2000); however, it still appears to be substantial. In a study on overdose deaths among Ontario Drug Benefit Program recipients, most cases involved those who used prescription opioids (Dhalla et al., 2009). Out-of-treatment individuals with substance use disorders related to prescription opioids are at high risk for overdose, because they use high doses, have variable levels of tolerance depending on drug availability, often use the opioid parenterally or intra-nasally, and combine opioids with benzodiazepines, alcohol and other sedating drugs. Additionally, if individuals are obtaining their opioids off the street, they cannot be sure what they are taking and can take something different from what they think.

[1] According to a the Canadian Agency for Drugs and Technologies in Health environmental scan, *Prescribing and Dispensing Policies to Address Harms Associated With Prescription Drug Abuse*, naloxone is only reimbursed by the Department of National Defence, Canadian Armed Forces drug plan. (Canadian Agency for Drugs and Technologies in Health, 2015).

2. Individuals who use opioids, including methadone, with known or suspected use of alcohol or benzodiazepines, or other drugs known to increase overdose risk

Rationale

Patients who are taking opioids, including those on a stable dose of methadone, are at elevated risk for overdose death if they also take benzodiazepines or alcohol. A report by the Ontario Drug Policy Research Network found that benzodiazepines were present in half of all opioid overdose deaths in Ontario between 1991 and 2010 (Gomes, Mamdani, Dhalla, Paterson, & Juurlink, 2014). A case control study found that patients who were prescribed both opioids and sedative hypnotics had a three-fold higher risk of overdose death compared to those prescribed opioids alone (Paulozzi et al., 2012). In a Norwegian study on opioid overdose deaths, alcohol or sedating drugs were detected in toxicological analyses in the majority of cases (Hakkinen, Launiainen, Vuori, & Ojanpera, 2012). In a study of methadone patients at the Centre for Addiction and Mental Health, benzodiazepine use was associated with an increased risk of non-fatal overdose (Brands et al., 2008).

3. Higher-risk patients on methadone-assisted treatment

This group includes methadone patients who are:

- About to start methadone for opioid use disorder or
- In the first two months of treatment.

Rationale

An Australian study (Caplehorn, 1998) found that there were 14 deaths in 1994 in the New South Wales methadone program that occurred during the first two weeks of methadone treatment. Ten of 14 deaths were due to iatrogenic methadone toxicity. In 2011, 103 people in Ontario died of a methadone overdose, more than the number of deaths from any other opioid except oxycodone (Ontario Drug Benefit Program, 2013). This figure reflects both the behaviour of methadone patients and the intrinsic pharmacological properties of methadone. Methadone has a half-life of 55 hours or longer in the first few weeks of treatment. As a result, it accumulates in the serum, creating a high risk of overdose death when combined with other opioids, benzodiazepines or alcohol. The half-life declines after several weeks, due to induction of hepatic enzymes that metabolize methadone.

4. Individuals who have stopped using opioids, but are at high risk for relapse

This group includes those who have:

- Recently discontinued methadone-assisted treatment;
- Been recently discharged from an abstinence-based treatment program or withdrawal management service;
- Been recently discharged from hospital with history of opioid use disorder; or
- Been recently discharged from a correctional centre (including remand) with history of opioid use disorder.

Rationale

Patients are at high risk for overdose death during periods of temporary abstinence (Clausen, Waal, Thoresen, & Gossop, 2009; Strang et al., 2003). An Italian cohort study (Davoli et al., 2007) found an annual mortality rate of 2.3% in the first month after completion of methadone or abstinence-based treatment, 26 times higher than the in-treatment mortality rate. Early relapse after discharge from abstinence-based treatment is common (Smyth, Barry, Keenan, & Ducray, 2010) and relapse can lead to death because patients lose their tolerance to opioids within two weeks of abstinence.

For similar reasons, individuals are at high risk for overdose death following discharge from prison. Opioid-dependent patients who have been incarcerated report that most of their overdoses occurred within one month of leaving prison (Wakeman, Bowman, McKenzie, Jeronimo, & Rich, 2009). A meta-analysis confirmed that in every country studied, prisoners had a three to eight-fold higher risk of a fatal overdose in the first two weeks of release from prison, compared to weeks three to twelve (Merrall et al., 2010).

5. Individuals with previous opioid-associated overdose

This group includes those with one or more previous:

- Unintentional overdoses involving opioids (accidental overdoses) or
- Intentional overdoses involving opioids (suicide attempts by overdose).

Rationale

One study found that individuals who had been injecting heroin for at least one year and who reported a previous overdose had an odds ratio of 28.6 for having a subsequent overdose (Coffin et al., 2007). In an analysis of coroners' reports in Ontario, the risk of opioid overdose death among decedents with a previous suicide attempt was 12.0 relative to other causes of death, higher than for any other risk factor, including a personal history of alcohol abuse or illicit drug use (Madadi, Hildebrandt, Lauwers, & Koren, 2013). An Australian study (Stoové, Dietze, & Jolley, 2009) found that after controlling for age and sex, those who had been attended by an ambulance for two non-fatal heroin overdoses had more than three and a half times the risk of fatal heroin overdose compared to those who had experienced only one previous overdose. Further, those who had experienced more than two previous non-fatal heroin overdoses had more than seven times the risk of fatal overdose.

6. Individuals on high doses of prescription opioids

Based on the literature, two different options for threshold morphine equivalent doses (MED) are proposed:

- More than 200 mg/day MED or
- More than 100 mg/day MED.

In some cases, it might be more appropriate to start with higher threshold doses while planning to monitor and lower threshold doses in the future.

Rationale

The risk of overdose is strongly associated with the dose prescribed. A study of Ontario Drug Benefit Program recipients found that the risk of fatal overdose death was increased by a factor of three in patients receiving 200 mg/day MED or more, compared to patients receiving 1–20 mg/day MED (Gomes et al, 2011). A cohort study of 10,000 patients in an Health Maintenance Organization in the United States found that patients receiving 100 mg/day MED or more had a 1.8% annual nonfatal overdose rate, nine times higher that of patients receiving 1–20 mg/day MED (Dunn et al., 2010). In a case control study, patients receiving 100 mg/day MED or more had a relative risk of fatal overdose of 4.5 to 11.9, compared to those receiving 1–20 mg/day MED. The relative risk was higher among chronic pain patients than among patients with addiction (Bohnert et al., 2011). The World Health Organization recommends a threshold of no more than 100 mg/day MED (World Health Organization, 2014).

A lower dose limit is suggested for patients with additional risk factors, such as heavy drinking, use of benzodiazepines or other sedating drugs, advanced age, or renal, hepatic or respiratory insufficiency.

Cost Implications

A Naloxone Costing Tool is provided to assist jurisdictions in estimating drug plan costs associated with providing naloxone kits at no cost or reimbursement of naloxone and THN kits. All proposed high-risk groups can be included in the cost estimate or jurisdictions can choose to select only some of the proposed high-risk groups for inclusion. The template is currently populated with our best general assumptions based on the literature, but can be modified to include data specific to a jurisdiction if available.

Note: Jurisdictions are encouraged to provide reimbursement for naloxone, regardless of its prescription status. Since naloxone has been moved to non-prescription status, jurisdictional coverage would still be required to ensure that financial barriers do not prevent those in need from accessing the drug.

Acknowledgements

This briefing note was originally drafted by Dr. Mel Kahan with subsequent review and input from the following members of the First Do No Harm, Overdose and Overdose Death Prevention Project Team: Dr. Brian Emerson, Dr. Michael Trew, Dr. Aaron Orkin, Katie Fleming and Dr. Terri O'Grady. We would also like to acknowledge Karen Lee, Director of Health Economics at Canadian Agency for Drugs and Technologies in Health for her review of the Naloxone Costing Tool.

References

Bohnert, A.S., Valenstein, M., Bair, M.J., Ganoczy, D., McCarthy, J.F., Ilgen, M.A., & Blow, F.C. (2011). Association between opioid prescribing patterns and opioid overdose-related deaths. *Journal of the American Medical Association, 305*(13), 1315–1321.

Brands, B., Blake, J., Marsh, D.C., Sproule, B., Jeyapalan, R., & Li, S. (2008). The impact of benzodiazepine use on methadone maintenance treatment outcomes. *Journal of Addictive Diseases, 27*(3), 37–48.

Caplehorn, J.R. (1998). Deaths in the first two weeks of maintenance treatment in NSW in 1994: identifying cases of iatrogenic methadone toxicity. *Drug and Alcohol Review*, 17, 9–17.

Canadian Agency for Drugs and Technologies in Health. (2015). *Prescribing and dispensing policies to address harms associated with prescription drug abuse*. Ottawa, Ont.: Author. Retrieved September 13, 2016, from www.cadth.ca/prescribing-and-dispensing-policies-address-harms-associated-prescription-drug-abuse.

Centers for Disease Control and Prevention. (2015). Opioid overdose prevention programs providing naloxone to laypersons — United States, 2014. *Morbidity and Mortality Weekly Report, 64*(23), 631–635.

Centre for Addiction and Mental Health. (2015). *Restrictions on prescribing oxycodone followed by increases in other strong opioid use and opioid-related deaths in Ontario, CAMH research shows* [webpage]. Retrieved September 13, 2016, from www.camh.ca/en/hospital/about_camh/newsroom/news_releases_media_advisories_and_backgrounders/current_year/Pages/Restrictions-on-prescribing-oxycodone.aspx.

Clausen, T., Waal, H., Thoresen, M., & Gossop, M. (2009). Mortality among opiate users: opioid maintenance therapy, age and causes of death. *Addiction*, *104*(8), 1356–1362.

Coffin, P.O., Tracy, M., Bucciarelli, A., Ompad, D., Vlahov, D., & Galea, S. (2007). Identifying injection drug users at risk of nonfatal overdose. *Academic Emergency Medicine, 14*(7), 616–623.

Davoli, M., Bargagli, A.M., Perucci, C.A., Schifano, P., Belleudi, V., Hickman, M., … VEdeTTE Study Group. (2007). Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE study, a national multi-site prospective cohort study. *Addiction*, *102*(12), 1954–1959.

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., & McLaren, J. (2011). Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. *Addiction*, *106*(1), 32–51.

Dhalla, I.A., Mamdani, M.M., Sivilotti, M.L., Kopp, A., Qureshi, O., & Juurlink, D.N. (2009). Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *Canadian Medical Association Journal, 181*(12), 891–896.

Dunn, K.M., Saunders, K.W., Rutter, C.M., Banta-Green, C.J., Merrill, J.O., Sullivan, M.D., & Von Korff, M. (2010). Opioid prescriptions for chronic pain and overdose: a cohort study. *Annals of Internal Medicine, 152*(2), 85–92.

Fischer, B., Rehm, J., & Blitz-Miller, T. (2000). Injection drug use and preventive measures: a comparison of Canadian and Western European jurisdictions over time. *Canadian Medical Association Journal*, *162*(12), 1709–1713.

Gomes, T., Mamdani, M.M., Dhalla, I.A., Paterson, J.M., & Juurlink, D.N. (2011). Opioid dose and drug-related mortality in patients with nonmalignant pain. *Archives of Internal Medicine, 171*(7), 686–691.

Gomes, T., Martins, D., Singh, S., Mamdani, M., Dhalla, I., Paterson, M., Tadrous M. & Juurlink, D. (2014). Opioid related deaths in Ontario between 1991 and 2010. Toronto, Ont.: Ontario Drug Policy Research Network. Accessed September, 13, 2016, from odprn.ca/wp-content/uploads/2015/04/Opioid-deaths-formal-report_19Nov2014.pdf.

Hakkinen, M., Launiainen, T., Vuori, E., & Ojanpera, I. (2012). Comparison of fatal poisonings by prescription opioids. *Forensic Science International, 222*(1–3), 327–331.

Madadi, P., Hildebrandt, D., Lauwers, A.E. & Koren, G. (2013). Characteristics of opioid-users whose death was related to opioid-toxicity: a population-based study in Ontario, Canada. *PLoS One*, *8*(4): e60600.

Merrall, E.L., Kariminia, A., Binswanger, I.A., Hobbs, M.S., Farrell, M., Marsden, J., … Bird, S.M. (2010). Meta-analysis of drug-related deaths soon after release from prison. *Addiction*, 105(9), 1545–1554.

Milloy, M.J., Wood, E., Reading, C., Kane, D., Montaner, J., & Kerr, T. (2010). Elevated overdose mortality rates among First Nations individuals in a Canadian setting: a population-based analysis. *Addiction*, *105*(11), 1962–1970.

Ontario Drug Benefit Program. (2013). Number of opioid-related deaths by drug in Ontario, 2002–2011. Internal document.

Orkin, A.M., Bingham, K., Klaiman, M., Leece, P., Buick, J.E., Kouyoumdjian, F., … & Hu, H. (2015). An agenda for naloxone distribution research and practice: meeting report of the Surviving Opioid Overdose with Naloxone (SOON) international working group. *Journal of Addiction Research & Therapy*, *6*, 212.

Paulozzi, L.J., Kilbourne, E.M., Shah, N.G., Nolte, K.B., Desai, H.A., Landen, M.G., … Loring, L.D. (2012). A history of being prescribed controlled substances and risk of drug overdose death. *Pain Medicine*, *13*(1), 87–95.

Strang, J., McCambridge J., Best, D., Beswick, K., Bearn, J., Rees S., & Gossop, M. (2003). Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. *British Medical Journal*, *3*(326), 959–960.

Smyth, B.P., Barry, J., Keenan, E., & Ducray, K. (2010). Lapse and relapse following inpatient treatment of opiate dependence. *Irish Medical Journal, 103*(6), 176–179.

Stoové, M.A., Dietze, P.M., & Jolley, D. (2009) Overdose deaths following previous non-fatal heroin overdose: recovered linkage of ambulance attendance and death registry data. (2009). *Drug and Alcohol Review*, *28*(4), 347–352.

Wakeman, S.E., Bowman, S.E., McKenzie, M., Jeronimo, A., & Rich, J.D. (2009). Preventing death among the recently incarcerated: an argument for naloxone prescription before release. *Journal of Addictive Diseases, 28*(2), 124–129.

World Health Organization. (2014). *Community management of opioid overdose*. Geneva, Switz.: Author. Retrieved September 13, 2016, from www.who.int/substance_abuse/publications/management_opioid_overdose/en/.

ISBN 978-1-77178-369-9