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**World Health  
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UNODC/WHO 2013

**Opioid overdose:  
preventing and reducing  
opioid overdose mortality**



UNITED NATIONS OFFICE ON DRUGS AND CRIME  
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# **Opioid overdose: preventing and reducing opioid overdose mortality**

Contribution of the United Nations Office on Drugs and Crime  
and the World Health Organization to improving responses  
by Member States to the increasing problem  
of opioid overdose deaths



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# I. Introduction

Although data are limited, an estimated 70,000-100,000 people die from opioid overdose each year. Opioid overdose was the main cause of the estimated 99,000-253,000 deaths worldwide related to illicit drug use in 2010.<sup>1</sup> Opioid overdose is both preventable and, if witnessed, treatable (reversible). In its resolution 55/7 on promoting measures to prevent drug overdose, in particular opioid overdose, the Commission on Narcotic Drugs called upon Member States to include effective measures to prevent and treat drug overdose in national drug policies.<sup>2</sup> In that resolution, the Commission requested the United Nations Office on Drugs and Crime (UNODC), in collaboration with the World Health Organization (WHO), to collect and circulate available best practices on the prevention and treatment of and emergency response to drug overdose, in particular opioid overdose, including on the use and availability of opioid receptor antagonists such as naloxone and other measures based on scientific evidence.

This discussion paper outlines the facts about opioid overdose, the actions that can be taken to prevent and treat (reverse) opioid overdose and areas requiring further investigation.

Opioids, which can be chemically synthesized or derived from the opium poppy plant, are a group of compounds that activate the brain's opioid receptors, a class of receptors that influence perceptions of pain and euphoria and are involved in the regulation of breathing. Some of the more commonly known and used opioids are morphine, heroin, methadone, buprenorphine, codeine, tramadol, oxycodone and hydrocodone. They are used as medicines to treat pain and opioid dependence. If used in excess or without proper medical supervision, opioids can cause fatal respiratory depression.

In cases of fatal overdose, the victim's breathing slows to the point where oxygen levels in the blood fall below the level needed to transfer oxygen to the vital organs. As oxygen saturation (normally greater than 97 per cent) falls below 86 per cent, the brain struggles to function. Typically, the individual becomes unresponsive, blood pressure progressively decreases and the heart rate slows, ultimately leading to cardiac arrest. Death can occur within minutes of opioid ingestion. But often, prior to death there is a longer period of unresponsiveness lasting up to several hours. This period is sometimes associated with loud snoring, leading to the term "unrousable snorers".

Worldwide, overdose is the leading cause of avoidable death among people who inject drugs.<sup>3</sup> However, it is difficult to accurately estimate the number of fatal opioid

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<sup>1</sup>World Drug Report 2012 (United Nations publication, Sales No. E.12.XI.1), p.11.

<sup>2</sup>B. Mathers and others, "Mortality among people who inject drugs: a systematic review and meta-analysis", *Bulletin of the World Health Organization*, vol. 91, No. 2 (2013), pp.102-123.

<sup>3</sup>L. Degenhardt and others, "Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies", *Addiction*, vol. 106, No. 1 (2011), pp. 32-51.

overdoses because of the poor quality or limited nature of mortality data available. According to UNODC estimates, drug-related deaths account for between 0.5 per cent and 1.3 per cent of all-cause mortality at the global level among persons aged 15-64.<sup>4</sup> In that regard, the recent Global Burden of Diseases, Injuries, and Risk Factors Study, 2010 found that there were an estimated 43,000 deaths in 2010 due to opioid dependence and 180,000 deaths due to drug poisoning, resulting in more than 2 million years of life lost.<sup>5,6</sup> In the United States of America alone, there were an estimated 38,329 drug poisoning deaths in 2010, including 16,651 fatal opioid overdoses related to prescription opioid analgesics in 2010,<sup>7</sup> with the remainder of those deaths largely involving heroin and/or cocaine.<sup>8</sup> Opioid overdose accounts for nearly half of all deaths among heroin injectors, exceeding HIV and other disease-related deaths.<sup>9</sup> Overdose was reported more frequently than were other causes in the 58 cohort studies examined in a 2011 meta-analysis. That meta-analysis also indicated that overdose represented the most common specific cause of death, at 6.5 deaths per 1,000 person-years.<sup>10</sup>

Among the 10 per cent of people living with HIV in the United States who also inject drugs, overdose is a common cause of non-AIDS related death.<sup>11</sup> A recent meta-analysis showed that HIV seropositivity is associated with an increased risk of overdose: people who use drugs have a 74-per-cent greater risk of overdose if they are HIV-positive compared with their HIV-negative counterparts.<sup>12</sup> In the Russian Federation, overdose is the second leading cause of death for people with HIV after tuberculosis.<sup>13</sup>

Nationally reported mortality data in both low-income and high-income countries are often insufficient to estimate overdose deaths. Current data on overdose mortality derive mostly from prospective cohort studies and national reporting systems, largely from high-income countries. To address these challenges, some countries have now adopted a standard case definition, contributing to an improved capacity for

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<sup>4</sup>World Drug Report 2012, p. 17.

<sup>5</sup>R. Lozano and others, "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010", *The Lancet*, vol. 380, No. 9859 (December 2012), pp. 2095-2128.

<sup>6</sup>L. Degenhardt and others, "The epidemiology and burden of disease attributable to opioid dependence: findings from the Global Burden of Disease Study 2010" (forthcoming).

<sup>7</sup>C. M. Jones, K. A. Mack and L. J. Paulozzi, "Pharmaceutical overdose deaths, United States, 2010", *Journal of the American Medical Association*, vol. 309, No. 7 (February 2013), pp. 657-659.

<sup>8</sup>M. Warner, L. H. Chen and D. M. Makuc, "Increase in fatal poisonings involving opioid analgesics in the United States, 1999-2006", *NCHS Data Brief*, No. 22 (Hyattsville, Maryland, National Center for Health Statistics, September 2009).

<sup>9</sup>M. Hickman and others, "Drug-related mortality and fatal overdose risk: pilot cohort study of heroin users recruited from specialist drug treatment sites in London", *Journal of Urban Health*, vol. 80, No. 2 (2003), pp. 274-287.

<sup>10</sup>Degenhardt and others, "Mortality among regular or dependent users of heroin and other opioids".

<sup>11</sup>J. E. Sackoff and others, "Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City", *Annals of Internal Medicine*, vol. 145, No. 6 (September 2006), pp. 397-406.

<sup>12</sup>T. C. Green and others, "HIV infection and risk of overdose: a systematic review and meta-analysis", *AIDS*, vol. 26, No. 4 (2012), pp. 403-417.

<sup>13</sup>Information received from the Russian Federation: Special Scientific Laboratory on Preventing and Fighting AIDS of the Federal Research and Methodological Center for AIDS Prevention and Control, Federal State Scientific Institute of Epidemiology (2010).

reliable overdose data.<sup>14</sup> However, in a significant number of countries, data on overdose are limited, with the result that alternative data sources, often combined with expert opinion, are required to estimate rates.<sup>15</sup>

Consequently, overdose mortality generally tends to be underestimated, and nationally reported statistics in that regard are likely to be conservative. For example, against the backdrop of negligible numbers of fatal overdoses reported by national authorities of Central Asian countries, 25.1 per cent of injecting drug users surveyed in Kazakhstan, Kyrgyzstan and Tajikistan in 2010 reported having witnessed someone die from an overdose in the previous 12 months.<sup>16</sup>

It is likely that people who use opioids also experience a high rate of non-fatal overdose. For instance, 59 per cent of known heroin injectors in a study conducted in 16 Russian cities reported having had at least one non-fatal overdose in their lifetime.<sup>17</sup> The proportion of heroin injectors reporting lifetime non-fatal overdose is similarly high in several other cities: 41 per cent in Baltimore,<sup>18</sup> 42 per cent in New York City,<sup>19</sup> 68 per cent in Sydney,<sup>20</sup> 38 per cent in London,<sup>21</sup> 30 per cent in Bangkok,<sup>22</sup> and 83 per cent in Bac Ninh, Viet Nam.<sup>23,24</sup>

Non-fatal overdose can significantly contribute to morbidity, including cerebral hypoxia, pulmonary oedema, pneumonia and cardiac arrhythmia, that may result in prolonged hospitalizations and brain damage.<sup>25</sup>

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<sup>14</sup>C. Cook and A. Fletcher, "Youth drug-use research and the missing pieces in the puzzle: how can researchers support the next generation of harm-reduction approaches?", in *Children of the Drug War: Perspectives on the Impact of Drug Policies on Young People*, D. Barrett, ed. (New York, International Debate Education Association, 2011).

<sup>15</sup>P. Coffin, S. Sherman and M. Curtis, "Underestimated and overlooked: a global review of drug overdose and overdose prevention", in *Global State of Harm Reduction 2010: Key Issues for Broadening the Response*, C. Cook, ed. (London, International Harm Reduction Association, 2010).

<sup>16</sup>Population Services International, "Central Asian republics (2010): HIV and TB TRaC study evaluating risk behaviors associated with HIV transmission and utilization of HIV prevention and HIV/TB co-infection prevention among IDUs in Almaty, Karaganda, Osh, Chu, and Dushanbe-round one" (2010). Available from [www.psi.org/sites/default/files/publication\\_files/2010-centralasia\\_trac\\_idu\\_hiv\\_tb.pdf](http://www.psi.org/sites/default/files/publication_files/2010-centralasia_trac_idu_hiv_tb.pdf) (accessed 31 October 2011).

<sup>17</sup>Sergeev and others, "Prevalence and circumstances of opiate overdose among injection drug users in the Russian Federation", as cited in P. Coffin, S. Sherman and M. Curtis, "Underestimated and overlooked: a global review of drug overdose and overdose prevention", in *Global State of Harm Reduction 2010: Key Issues for Broadening the Response*, C. Cook, ed. (London, International Harm Reduction Association, 2010).

<sup>18</sup>K. E. Tobin and C. A. Latkin, "The relationship between depressive symptoms and nonfatal overdose among a sample of drug users in Baltimore, Maryland", *Journal of Urban Health*, vol. 80, No. 2 (2003), pp. 220-229.

<sup>19</sup>P. O. Coffin and others, "Identifying injection drug users at risk of nonfatal overdose", *Academic Emergency Medicine*, vol. 14, No. 7 (2007), pp. 616-623.

<sup>20</sup>S. Darke, J. Ross and W. Hall, "Overdose among heroin users in Sydney, Australia: I. Prevalence and correlates of non-fatal overdose", *Addiction*, vol. 91, No. 3 (1996), pp. 405-411.

<sup>21</sup>B. Powis and others, "Self-reported overdose among injecting drug users in London: extent and nature of the problem", *Addiction*, vol. 94, No. 4 (1999), pp. 471-478.

<sup>22</sup>M. J. Milloy and others, "Overdose experiences among injection drug users in Bangkok, Thailand", paper presented at the 20th International Conference on the Reduction of Drug-Related Harm in Bangkok, 20-23 April 2009.

<sup>23</sup>A. Bergstrom and others, "A cross-sectional study on prevalence of non-fatal drug overdose and associated risk characteristics among out-of-treatment injecting drug users in North Viet Nam", *Substance Use and Misuse*, vol. 43, No. 1 (2008), pp. 73-84.

<sup>24</sup>Coffin, Sherman and Curtis, "Underestimated and overlooked: a global review of drug overdose and overdose prevention".

<sup>25</sup>M. Warner-Smith, S. Darke and C. Day, "Morbidity associated with non-fatal heroin overdose", *Addiction*, vol. 97, No. 8 (2002), pp. 963-967.



## II. Risk factors for opioid overdose

A number of risk factors associated with both fatal and non-fatal overdose have been identified.

### A. Opioid availability

Opioid overdose rates are associated with an increased availability of opioids, both illicit and prescribed. Likewise a reduction of heroin availability and purity has been linked to reduced opioid overdoses, thus confirming the link between availability and overdose.<sup>26</sup> The recent increase in prescribing rates of opioids in the United States appears to have contributed to the increase in cases of opioid-related overdose, from 4,000 opioid overdose deaths per annum in 1999 to more than 16,000 in 2010.<sup>27,28</sup>

### B. Combination of opioids and other psychoactive substances

In cases of fatal opioid overdose, other sedating psychoactive substances, especially alcohol and benzodiazepines (both of which act on *gamma*-aminobutyric acid (GABA) receptors in the brain), are very often present.<sup>29,30</sup> Both opioid and GABA receptors are involved in mediating respiration, with the result that the combination of opioid and GABA sedatives are more potent in inducing respiratory depression than either is alone. Further, a study comparing fatal and non-fatal opioid overdose in people using heroin determined that the main risk factor for fatal overdose was the use of those opioids combined with use of other sedatives and/or alcohol.<sup>31</sup> There is also substantial involvement of cocaine in fatal opioid overdoses in locations where cocaine use is prevalent, which may be due to impaired breathing from smoking “crack” cocaine, acute hypertension caused by cocaine at the time of an opioid overdose and other factors.<sup>32-34</sup> It has been reported that individuals who inject

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<sup>26</sup>L. Degenhardt and others, “The effect of a reduction in heroin supply upon trends on fatal and non-fatal drug overdoses in New South Wales, Australia”, *Medical Journal of Australia*, vol. 182, No. 1 (2005), pp. 20-23.

<sup>27</sup>United States of America, Centers for Disease Control and Prevention, “Prescription painkiller overdoses in the US” (2012). Available from [www.cdc.gov/Features/Vitalsigns/PainkillerOverdoses/](http://www.cdc.gov/Features/Vitalsigns/PainkillerOverdoses/).

<sup>28</sup>L. H. Chen, “QuickStats: number of deaths from poisoning, drug poisoning, and drug poisoning involving opioid analgesics—United States, 1999-2010”, *Morbidity and Mortality Weekly Report*, vol. 62, No. 12 (2013), p. 234.

<sup>29</sup>S. Bauer and others, “Mortality in opioid-maintained patients after release from an addiction clinic”, *European Addiction Research*, vol. 14, No. 2 (2008), pp. 82-91.

<sup>30</sup>S. M. Bird and J. R. Robertson, “Toxicology of Scotland’s drugs-related deaths in 2000-2007: presence of heroin, methadone, diazepam and alcohol by sex, age-group and era”, *Addiction Research and Theory*, vol. 19, No. 2 (2011), pp. 170-178.

<sup>31</sup>P. Dietze and others, “When is a little knowledge dangerous? Circumstances of recent heroin overdose and links to knowledge of overdose risk factors”, *Drug and Alcohol Dependence*, vol. 84, No. 3 (2006), pp. 223-230.

<sup>32</sup>M. Warner-Smith and others, “Heroin overdose: causes and consequences”, *Addiction*, vol. 96, No. 8 (2001), pp. 1113-1125.

<sup>33</sup>“Illicit drug use in New York City”, *NYC Vital Signs*, vol. 9, No. 1 (2010). Available from [www.nyc.gov/html/doh/downloads/pdf/survey/survey-2009drugod.pdf](http://www.nyc.gov/html/doh/downloads/pdf/survey/survey-2009drugod.pdf).

<sup>34</sup>N. G. Shah and others, “Unintentional drug overdose death trends in New Mexico, USA, 1990-2005: combinations of heroin, cocaine, prescription opioids and alcohol”, *Addiction*, vol. 103, No. 1 (2008), pp. 126-136.

heroin and cocaine in combination have a risk of overdose that is greater by a factor of 2.6.<sup>35</sup>

### C. A lack of treatment

Treatment of opioid dependence with opioid agonist maintenance treatment (also known as “opioid substitution treatment”) reduces opioid overdose risk by almost 90 per cent.<sup>36</sup> In many countries, there is little or no access to such treatment.<sup>37</sup> Many patients also cease opioid dependence treatment prematurely, which is associated with a return to out-of-treatment levels of opioid overdose risk.<sup>38</sup>

### D. Reduced tolerance due to a recent period of abstinence

Recent periods of abstinence (particularly when enforced, such as in a period of incarceration) are a major risk factor for fatal opioid overdose. Substantial evidence from a number of longitudinal studies indicates that the period immediately following release from prison<sup>39</sup> and the period immediately following discharge from a detoxification facility pose a significantly elevated risk of overdose.<sup>40</sup> The main causes of increased overdose mortality among released prisoners who were formerly opiate dependent were the individual’s loss of tolerance and erroneous judgement with respect to dosage when returning to opiate use following a period of abstinence.<sup>41</sup>

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<sup>35</sup>K. C. Ochoa and others, “Overdosing among young injection drug users in San Francisco”, *Addictive Behaviors*, vol. 26, No. 3 (2001), pp. 453-460.

<sup>36</sup>World Health Organization, *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence* (Geneva, 2009).

<sup>37</sup>World Health Organization, *ATLAS on Substance Use (2010): Resources for the Prevention and Treatment of Substance Use Disorders* (Geneva, 2010).

<sup>38</sup>L. Degenhardt and others, “Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved”, *Drug and Alcohol Dependence*, vol. 105, Nos. 1-2 (2009), pp. 9-15.

<sup>39</sup>World Health Organization, “Prevention of acute drug-related mortality in prison populations during the immediate post-release period” (Copenhagen, WHO Regional Office for Europe, 2010).

<sup>40</sup>European Monitoring Centre for Drugs and Drug Addiction, *Annual Report 2011: The State of the Drugs Problem in Europe* (Luxembourg, Publications Office of the European Union, 2011), chap. 7. Available from [www.emcdda.europa.eu/online/annual-report/2011](http://www.emcdda.europa.eu/online/annual-report/2011).

<sup>41</sup>J. Strang and others, “Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study”, *British Medical Journal*, vol. 326, No. 7396 (3 May 2003).

### III. Responding to opioid overdose

Opioid overdose is a growing public health problem that can be easily averted through the use of naloxone, a safe and non-abusable substance. While opioid dependence is a treatable disease, it is a chronic disease for which relapse is part of the natural history. Preventing overdose allows people to continue their progress towards recovery and may enable them to seek out other life-saving services.

Opioid overdose is identified by a combination of three signs and symptoms referred to as the “opioid overdose triad”. The symptoms of the triad are:

- Pinpoint pupils
- Unconsciousness
- Respiratory depression

Treatment of overdose should be initiated if the person is not rousable and the respiratory rate is visibly slowed (i.e. less than 10 breaths per minute). In managing opioid overdose, the primary focus should be to address respiration and oxygenation, including assisted ventilation with rescue breathing or bag and mask with supplemental oxygen, if possible.<sup>42</sup>

For the treatment (reversal) of opioid overdose, WHO recommends using naloxone. Naloxone is a short-acting opioid antagonist that binds very tightly to opioid receptors, replacing other opioids that may be there and blocking other opioids from binding. It has a long clinical history of successful use for the treatment of opioid overdose. Specifically, naloxone is used in opioid overdoses to counteract life-threatening depression of the respiratory system and the central nervous system, allowing an overdose victim to breathe normally. The medication has no effect if opioids are absent and naloxone has no potential for abuse. In addition to reversing respiratory depression, naloxone may induce withdrawal symptoms in the dependent user under the influence of opioids, which, although unpleasant, are short-lived. Significant adverse effects of naloxone are extremely rare. Naloxone is on the WHO Model List of Essential Medicines and should be available in all health-care facilities that may be called upon to respond to opioid overdose.

In the case of suspected opioid overdose, any respiratory arrest should be managed with assisted breathing and/or oxygen while waiting for naloxone to be administered and take effect. Naloxone is fast-acting, and adequate respiration will typically resume within 3-7 minutes of intramuscular administration of naloxone.

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<sup>42</sup>World Health Organization, *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence*.

The ideal dose of naloxone is one that improves respiration without inducing opioid withdrawal. If in doubt, it is better to err on the side of too large rather than too low a dose. If there is access to injecting equipment and adequate patient ventilation, smaller amounts can be given in repeated doses, which will minimize the potential for opioid withdrawal, until the patient is breathing at a rate greater than 10 breaths per minute. While the initial dose of naloxone may need to be repeated to reverse the opioid overdose, as described above, the effects will then last for 30-90 minutes, which, in most cases is sufficient to prevent death. Naloxone may be injected in the muscle, vein or under the skin, or it can be administered as a spray into the nose using an atomizer.

If naloxone is not available, overdose can be treated with respiratory support, either mouth-to-mouth, with a bag and mask, or with pressure-controlled ventilation.

Ideally, an overdose victim should then be transported to the hospital for observation for at least one hour, though it is not uncommon for illicit opioid users to decline emergency assistance for fear of police intervention. In cases where the individual refuses to be observed for the recommended duration of one hour, studies have shown that if the victim is able to walk and to speak coherently following the reversal of short-acting opioids such as heroin, the risk of sinking back into potentially fatal sedation when the naloxone wears off is relatively small. That risk was reported by one study to be 1 in 600.<sup>43</sup> It is strongly advised that a medical professional or other competent caregiver stay with the individual for several hours, counsel them not to use more opioids (at the very least until the naloxone has worn off) and keep the individual active rather than allowing him or her to fall asleep.

Overdoses of long-acting opioids are more challenging to manage. In such a situation, the duration of the sedation may outlast the effects of naloxone. The safest method of treating the overdose of a long-acting opioid is ventilation, if available. Patients can also be managed with repeated boluses of naloxone or naloxone infusions. However, death can occur if there is an unnoticed interruption to the naloxone infusion or if the patient wakes up and prematurely discharges him/herself from medical care. Nevertheless, these situations are rarely documented in literature or anecdotally.

The aftermath of an overdose should also include discussion of ongoing drug or pain treatment after the effects of the naloxone have worn off. All people using opioids, whether by prescription or illicitly, should receive education on the factors increasing the risk of overdose and on recognition of overdose symptoms, as well as on the need for respiratory support and medical assistance in cases of overdose. In addition, negative health outcomes associated with non-fatal overdose, such as respiratory infections, may develop later. Individuals should thus be advised to seek a basic health screening in the days following an overdose.

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<sup>43</sup>S. Rudolph and others, "Prehospital treatment of opioid overdose in Copenhagen: is it safe to discharge on-scene?", *Resuscitation*, vol. 82, No. 11 (2011), pp. 1414-1418.



While the procedures for management of opioid overdose recommended by WHO, described above, are relatively simple, a number of factors routinely prevent individuals from offering or accessing first aid in the event of an overdose. First, caring for someone with respiratory failure is routine in many emergencies, but in some settings, emergency medical services may not have incorporated naloxone into the routine response to overdose. Additionally, community members may not recognize overdose, may not be aware of the need for help or, depending on the culture, may not be comfortable with rescue breathing.

Secondly, timely emergency services are not available in many settings, and where they are available, studies have documented an unwillingness to call an ambulance when witnessing an overdose because of the high financial cost of receiving medical care; fear of police involvement, fear of arrest or fear of being placed on an official register of drug users; and the perception that emergency services will either not respond or will not treat an overdose effectively.<sup>44-49</sup>

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<sup>44</sup>J. Ataiants, A. Latypov and D. Ocheret, Drug overdose: a review of the situation and responses in 12 Eastern European and Central Asian countries (Vilnius, Eurasian Harm Reduction Network, 2011) (in Russian). Available from [www.harm-reduction.org/index.php/library/2238-overdose-review-of-the-situation-and-response-in-12-countries-in-eastern-europe-and-central-asia.html](http://www.harm-reduction.org/index.php/library/2238-overdose-review-of-the-situation-and-response-in-12-countries-in-eastern-europe-and-central-asia.html).

<sup>45</sup>N. Bartlett and others, "A qualitative evaluation of a peer-implemented overdose response pilot project in Gejiu, China", *International Journal of Drug Policy*, vol. 22, No. 4 (2011), pp. 301-305.

<sup>46</sup>Powis and others, "Self-reported overdose among injecting drug users in London".

<sup>47</sup>C. T. Baca and K. J. Grant, "What heroin users tell us about overdose", *Journal of Addictive Diseases*, vol. 26, No. 4 (2007), pp. 63-68.

<sup>48</sup>K. E. Tobin, M. A. Davey and C. A. Latkin, "Calling emergency medical services during drug overdose: An examination of individual, social and setting correlates", *Addiction*, vol. 100, No. 3 (2005), pp. 397-404.

<sup>49</sup>Coffin, Sherman and Curtis, "Underestimated and overlooked: a global review of drug overdose and overdose prevention".



## IV. Prevention of fatal overdose

### A. Effective measures

#### 1. *Reducing the availability of opioids and harmful opioid use*

The three international drug control conventions outline measures to limit illicit opioid availability while ensuring availability for medical and scientific purposes, in particular for addiction treatment, acute pain, cancer pain and palliative care, for which WHO recommends the use of opioids (pain ladder).<sup>50</sup> Measures to limit the contribution of prescription medicines to opioid overdose include addressing the inappropriate prescription of opioids and other sedatives and inappropriate sales by pharmacies without a prescription.<sup>51</sup> Effective drug prevention programmes indirectly reduce overdose risk through reduction in drug use.

#### 2. *Providing access to effective treatment for people with opioid dependence*

Probably the most proven long-term strategy to prevent opioid overdose in people dependent on heroin and other opioids is to provide opioid agonist maintenance treatment with either methadone or buprenorphine. Methadone increases the tolerance for opioids, and in so doing reduces the effects of additional opioid use. Methadone maintenance treatment reduces the risk of opioid overdose mortality approximately sixfold.<sup>52</sup> Buprenorphine also reduces the risk of overdose by partially blocking opioid receptors. The introduction and rapid medical use of buprenorphine in France in the 1990s was associated with a dramatic reduction in opioid overdose rates in that country.<sup>53</sup> Opioid agonist treatment is more effective if the doses are higher and the duration is long.<sup>54</sup>

In communities with a high prevalence of drug injecting persons, outreach programmes that facilitate access to sterile injecting equipment (including retrieval), information (including on overdose prevention), health care (including testing and counselling for HIV and hepatitis) can also facilitate entry to drug treatment programmes.<sup>55</sup>

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<sup>50</sup>World Health Organization, *Cancer Pain Relief: With a Guide to Opioid Availability*, 2nd ed. (Geneva, 1996).

<sup>51</sup>United States, Centers for Disease Control and Prevention, "Opioids drive continued increase in drug overdose deaths" (2013). Available from [www.cdc.gov/media/releases/2013/p0220\\_drug\\_overdose\\_deaths.html](http://www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.html).

<sup>52</sup>World Health Organization, *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence*.

<sup>53</sup>M. Auriacombe and others, "French field experience with buprenorphine", *American Journal on Addictions*, vol. 13, No. 1 (2004), pp. S17-S28.

<sup>54</sup>World Health Organization, *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence*.

<sup>55</sup>World Health Organization, *mh-GAP Intervention Guide for Mental, Neurological and Substance Use Disorders in Non-specialized Health Settings: Mental Health Gap Action Programme (mhGAP)* (Geneva, 2010).

### **3. Reducing the risk of overdose upon release from prison**

Both methadone and buprenorphine treatment, just prior to or immediately following release from prison, are also highly effective in preventing overdose in prisoners who were opioid-dependent when entering prison. Programmes that commence either methadone or buprenorphine administration more than two weeks before individuals leave the prison system can reduce post-release overdose mortality rates dramatically.<sup>56</sup> A further effective strategy is ensuring that people being released from prison establish contact with drug dependence treatment programmes in the community. In general, it is most beneficial to provide opioid-dependent persons with continuous drug treatment, including opioid agonist maintenance treatment, throughout that transition period.<sup>57</sup> Successful prison pre-release interventions ensure that prisoners participate in overdose prevention awareness programmes; include opioid maintenance either continuously during imprisonment, starting at least several weeks prior to release or commencing in the community on the day of release; and ensure that the release of drug-dependent prisoners is planned in coordination with drug treatment services in the community.<sup>58,59</sup>

Programmes that facilitate treatment as an alternative to imprisonment, as encouraged by the drug control conventions, also reduce the risk of imprisonment-related overdose.

## **B. Gap between existing practice and current recommendations for prevention and treatment**

### **1. Availability of opioids**

There is a high level of investment in reducing the availability of illicit heroin. However, the level of investment in reducing the harmful use of prescription opioids and other sedatives is less well developed in many countries.

### **2. Access to effective treatment of drug dependence**

The estimate produced by the WHO ATLAS global survey of resources for the prevention and treatment of substance use disorders estimates that opioid agonist treatment with methadone or buprenorphine is available in only 42 per cent of countries,

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<sup>56</sup>G. Khotari, J. Marsden and J. Strang, "Opportunities and obstacles for effective treatment of drug misusers in the criminal justice system in England and Wales", *British Journal of Criminology*, vol. 42, No. 2 (2002), pp. 412-432.

<sup>57</sup>World Health Organization, "Prevention of acute drug-related mortality in prison populations during the immediate post-release period".

<sup>58</sup>M. Farrel and J. Marsden, "Acute risk of drug-related death among newly released prisoners in England and Wales", *Addiction*, vol. 103, No. 2 (2008), pp. 251-255.

<sup>59</sup>World Health Organization, "Prevention of acute drug-related mortality in prison populations during the immediate post-release period".

and less than 10 per cent of people worldwide who need it have access.<sup>60</sup> Additionally, in even fewer countries are methadone and buprenorphine made available in the prison system.

### **3. Availability of drug dependence treatment in prisons**

An increasing number of countries have now made opioid agonist treatment available in prisons, but most prisoners remain without access to treatment with methadone or buprenorphine, either in prison or on release. Many countries do not coordinate release with treatment.

### **4. Effective treatment of opioid overdose**

Although naloxone is on the WHO Model List of Essential Medicines, it is reported that naloxone is often not available.<sup>61</sup>

## **C. Potential new areas for overdose prevention and treatment**

While naloxone has been traditionally used by medical staff to treat opioid overdose, a number of countries have recently adopted policies and procedures that allow medical staff to distribute naloxone to first responders (e.g., police and firemen) and to people dependent on opioids, their peers and family members who are likely to be present when an overdose occurs. Additionally, some countries are considering making naloxone a medicine that is available in pharmacies without a prescription due to the low risk/high benefit ratio associated with naloxone. For example, in Italy, naloxone is available in pharmacies without a prescription and is also distributed through outreach programmes, with anecdotal reports of success in reversing opioid overdose and no adverse events.<sup>62</sup>

In programmes that distribute naloxone, peers and family members are provided overdose prevention education and equipped with naloxone to be used in case of opioid overdose. In some cases, naloxone is prescribed to the person using opioids, who then entrusts it to someone else to administer when needed. This is similar to the practice of prescribing adrenaline to people with severe allergic reactions and placing it in the care of family members or others to administer to the person suffering the allergic reaction, if needed. In other cases, naloxone is provided directly to a friend or family member who is likely to be present during an overdose.

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<sup>60</sup>World Health Organization, *ATLAS on Substance Use (2010): Resources for the Prevention and Treatment of Substance Use Disorders* (Geneva, 2010).

<sup>61</sup>Ibid.

<sup>62</sup>A. Favaretto and others, "Prevenzione della morte per overdose da eroina: consegna di naloxone (Narcan®) ai tossicodipendenti afferenti all'unità di strada del Comune di Venezia" (2001). Available from [www.dronet.org/lineguida/ligu\\_pdf/narcan.pdf](http://www.dronet.org/lineguida/ligu_pdf/narcan.pdf).

Programmes in which naloxone is made available to the community, so-called “community-based naloxone distribution programmes”, exist to some extent in more than a dozen countries, including Afghanistan, Australia, Canada, China, India, Italy, Kazakhstan, Kyrgyzstan, Tajikistan, Thailand, the United Kingdom of Great Britain and Northern Ireland, the United States, Ukraine and Viet Nam, although generally on a pilot or experimental basis.

At the same time, some funding agencies have allowed the use of HIV funds for overdose prevention programmes, including making naloxone available to communities of people who use drugs. Since 2010, the Global Fund to Fight AIDS, Tuberculosis and Malaria, has permitted and encouraged grant applicants to include overdose services in national proposals.<sup>63</sup> The guidelines of the United States President’s Emergency Plan for AIDS Relief (PEPFAR), the United States HIV/AIDS relief programme, also permit funding of the provision of naloxone in the countries in which it is active, when in line with local laws and policies.<sup>64</sup>

There is a growing body of experience related to naloxone distribution programmes, both pilot programmes and clinical trials, and a number of trials are ongoing.<sup>65,66</sup> A recent survey in the United States found that the distribution of approximately 53,000 naloxone kits through local opioid overdose prevention programmes had resulted in 10,000 uses to treat overdoses.<sup>67</sup> Several cities in the United States reported declines in overdose mortality following the launch of overdose prevention programmes with naloxone distribution. For example, in the period extending from 2005, when New York City first began to scale up overdose programmes, until 2011, there was a 22-per-cent decline in the overall unintentional drug poisoning mortality rate,<sup>68</sup> and a 27-per-cent decline in the unintentional heroin poisoning mortality rate. In Massachusetts, where the health department permits non-governmental organizations to distribute naloxone using the authority of a prescribing physician (even when that physician is not physically present), overdoses decreased significantly in those areas where bystanders were trained to recognize overdose, perform rescue breathing and use naloxone compared with those areas where the medicine was unavailable.<sup>69</sup> In response to increasing overdose mortality among people using prescription opioids, other programmes, such as the United States-based Project Lazarus, have targeted physicians, pain patients and their families with overdose education and naloxone,

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<sup>63</sup> Global Fund to Fight AIDS, Tuberculosis and Malaria, “Harm reduction for people who inject drugs: information note” (February 2013).

<sup>64</sup> United States, President’s Emergency Plan for AIDS Relief (PEPFAR), “Comprehensive HIV prevention for people who inject drugs: revised guidance” (July 2010). Available from [www.pepfar.gov/documents/organization/144970.pdf](http://www.pepfar.gov/documents/organization/144970.pdf).

<sup>65</sup> L. Beletsky, J. D. Rich and A. Y. Walley, “Prevention of fatal opioid overdose”, *Journal of the American Medical Association*, vol. 308, No. 18 (2012), pp. 1863-1864.

<sup>66</sup> J. Strang, S. M. Bird and M.K.B. Parmar, “Take-home emergency naloxone to prevent heroin overdose deaths after prison release: rationale and practicalities for the N-ALIVE randomized trial”, *Journal of Urban Health*, 1 May 2013 (electronic journal).

<sup>67</sup> E. Wheeler and others, “Community-based opioid overdose prevention programs providing naloxone: United States, 2010”, *Morbidity and Mortality Weekly Report*, vol. 61, No. 6 (2012), pp. 101-105.

<sup>68</sup> D. Paone, E. Tuazon and Bradley O’Brien, “Unintentional opioid analgesic poisoning (overdose) deaths in New York City, 2011”, *Epi Data Brief*, No. 27 (New York City Department of Health and Mental Hygiene, May 2013).

<sup>69</sup> A. Y. Walley and others, “Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis”, *British Medical Journal*, vol. 346, 2013.

and have seen rates of fatal overdose decline—with a documented 43-per-cent drop between 2008 and 2010.<sup>70</sup>

Surveys indicate that people who use drugs are willing to provide appropriate first aid when witnessing an overdose.<sup>71-73</sup> Hence, training on overdose prevention and response techniques for this unique population could serve to improve and increase peer-delivered first aid.<sup>74,75</sup> Further, it has been demonstrated that the non-professional participants in training are capable of correctly identifying when rescue breathing and naloxone are required.<sup>76</sup> Mathematical modelling has shown distribution of naloxone to users of illicit opioids are likely to be cost-effective, with costs per quality-adjusted life year gained comparable to essential and affordable interventions such as checking blood pressure.<sup>77</sup>

On the other hand, the distribution of naloxone is not without risk. Encouraging people without medical training to inject an unconscious person could result in harm. The risks include unsterile injection (which may result in bacterial or viral infections), damage due to poor injection technique, or rare naloxone-induced adverse events.

The administration of medication by a non-medical professional on those unable to give their consent also raises some legal concerns. Use of injectable naloxone, in particular, raises questions, since some countries have prohibitions against injection by anyone except medical personnel. Some jurisdictions have passed specific legislation to eliminate legal liability for those who administer naloxone in an overdose emergency.

In some areas, emergency personnel, police, firemen and laypeople have been provided with more highly concentrated intranasal naloxone formulations, used by spraying medicine through an atomizer into each nostril. Naloxone is well absorbed through the nasal mucosa, and there are a number of studies demonstrating the feasibility of intranasal administration of naloxone in reversing opioid overdose.<sup>78</sup> One study found only minimal differences between the intranasal and intramuscular

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<sup>70</sup>S. Albert and others, "Project Lazarus: community-based overdose prevention in rural North Carolina", *Pain Medicine*, vol. 12, No. 2 (2011), pp. S77-S85.

<sup>71</sup>J. Strang and others, "Peer-initiated overdose resuscitation: fellow drug users could be mobilised to implement resuscitation", *International Journal of Drug Policy*, vol. 11, No. 6 (2000), pp. 437-445.

<sup>72</sup>B. Sergeev and others, "Prevalence and circumstances of opiate overdose among injection drug users in the Russian Federation", *Journal of Urban Health*, vol. 80, No. 2 (2003), pp. 212-219.

<sup>73</sup>Y. Liu and others, "Attitudes and knowledge about naloxone and overdose prevention among detained drug users in Ningbo, China", *Substance Abuse Treatment, Prevention, and Policy*, vol. 7, February 2012.

<sup>74</sup>K. H. Seal and others, "Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study", *Journal of Urban Health*, vol. 82, No. 2 (2005), pp. 303-331.

<sup>75</sup>K. E. Tobin and others, "Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives", *International Journal of Drug Policy*, vol. 20, No. 2 (2009), pp. 131-136.

<sup>76</sup>T. C. Green, R. Heimer and L. E. Grau, "Distinguishing signs of opioid overdose and indication for naloxone: an evaluation of six overdose training and naloxone distribution programs in the United States", *Addiction*, vol. 103, No. 6 (2008), pp. 979-989.

<sup>77</sup>P. O. Coffin and S. D. Sullivan, "Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal", *Annals of Internal Medicine*, vol. 158, No. 1 (2013), pp. 1-9.

<sup>78</sup>M. Doe-Simkins and others, "Saved by the nose: bystander-administered intranasal naloxone hydrochloride for opioid overdose", *American Journal of Public Health*, vol. 99, No. 5 (2009).

administration of naloxone in treating opiate-induced respiratory depression.<sup>79,80</sup> Given the potential for harm from injecting, there may be advantages in using intranasal formulations of naloxone.<sup>81</sup>

#### **D. Specific proposals to prevent the recent rise in prescription opioid overdoses**

The recent increase in prescription overdose in the United States has prompted some, such as the United States Office of National Drug Control Policy, to call for a multipronged approach to preventing prescription opioid overdose, including distribution of naloxone to first responders.<sup>82</sup>

In addition to naloxone distribution, other measures proposed include real-time monitoring of the prescription of opioids, and such systems are already used in a number of countries. These systems help ensure that patients are not receiving opioid prescriptions from multiple doctors and allow law enforcement officials to track prescribing and dispensing patterns. Additionally, opioids can be prescribed and dispensed in smaller quantities, and patients can be encouraged to dispose of opioids properly (in a safe manner) when no longer needed. Furthermore, there is a growing awareness of the need for health-care professionals to be better educated with respect to the risks of prescribing opioids, particularly for chronic non-malignant pain.

The use of opioids for chronic non-cancer pain remains controversial given the lack of clinical trials demonstrating long-term benefits of opioids, either in terms of pain relief or function.

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<sup>79</sup>A. M. Kelly and others, "Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose", *Medical Journal of Australia*, vol. 182, No. 1 (2005), pp. 24-27.

<sup>80</sup>D. Kerr, "Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose", *Addiction*, vol. 104, No. 12 (2009), pp. 2067-2074.

<sup>81</sup>H. Ashton and Z. Hassan, "Intranasal naloxone in suspected opioid overdose", *Emergency Medicine Journal*, vol. 23, No. 3 (2006), pp. 221-223.

<sup>82</sup>United States, Executive Office of the President, *National Drug Control Strategy 2013* (Washington, D.C., 2013). Available from [www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/ndcs\\_2013.pdf](http://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/ndcs_2013.pdf) (accessed 24 April 2013).



## V. Conclusion

It is critical that existing recommendations to reduce high rates of overdose among people who use opioids, both illicitly and prescribed, be systematically implemented and followed globally. Efforts to increase the uptake of existing recommended approaches (such as opioid agonist maintenance treatment and making naloxone available to medical staff and treatment facilities) should be a priority.

A number of additional approaches warrant further investigation and action. This includes addressing areas such as the growing issue of prescription opioid overdose and the use of opioids in chronic non-malignant pain.

Likewise, experiences with over-the-counter licensing for naloxone and peer distribution should be looked at in detail. The initial experiences with respect to the early treatment of overdose (including both resuscitation and the use of naloxone) by peers and family members show promising results, and there is clear interest in this area from funding agencies.

The complexities of interpretation of the data, the differing models of naloxone availability, and the lack of clear guidance for training and implementation in the field suggest that there is a demand for further evidence-based guidance from United Nations organizations on how to best structure and implement overdose prevention efforts.







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