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Preventing opioid overdose deaths with take-home naloxone

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for Drugs and Drug Addiction

Preventing opioid overdose deaths with take-home naloxone

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Foreword

Each year, between 6 300 and 8 000 drug-induced deaths are reported in Europe. In the 20 years since the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) started reporting on the drug situation, we have counted more than 140 000 drug overdose deaths. This is a conservative figure; the real number is likely to be much higher. Opioids, mainly heroin or its metabolites, are present in most overdose cases and we can say with confidence that these drugs account for the large majority of overdose deaths.

With appropriate intervention many opioid overdose deaths may be preventable. Naloxone is a life-saving overdose reversal drug that rapidly counteracts the effects of opioids. It has been used in emergency medicine in hospitals and by ambulance personnel since the 1970s to reverse the respiratory depression caused by opioid overdose, and it is included in the World Health Organization's list of essential medicines.

We know from research that many opioid overdoses occur when others are present. This means that an opportunity for potentially lifesaving action may exist, if bystanders can be empowered to act. Unfortunately, often this does not happen, either because there is a failure to recognise the seriousness of the situation or, for fear of police involvement, emergency services are called late — or not at all.

The rationale for making naloxone available at places where overdoses are likely to occur is that overdose is common among opioid users — over a third have experienced a (non-fatal) overdose and two-thirds have witnessed one — and that there is willingness among bystanders to intervene. After calls for the introduction of emergency naloxone as a harm-reduction measure in the 1990s, community-based programmes started to distribute naloxone kits to partners, peers and families of drug users and train them in overdose response and naloxone use.

With evidence on its effectiveness growing, 'take-home' naloxone provision has gained more attention in recent years. In Europe, take-home naloxone initiatives operate at city level in Denmark, Estonia, Germany, Italy, Norway, and at regional level in Spain (Catalonia) and the United Kingdom (Scotland and Wales).

A number of other European countries are currently exploring the topic and considering adding take-home naloxone to an existing range of interventions to prevent drug-related deaths. It is timely and appropriate for the EMCDDA to share existing experiences in order to broaden the knowledge base for decision-making. Authored by a group of experts who are well known in this field, this book provides an overview of take-home naloxone provision, describing the diffusion, practice and effectiveness of the intervention.

One of the main challenges for take-home naloxone programmes is to achieve sufficient coverage of at-risk populations, so that substantial reductions in opioid overdose deaths can be attained. The wider use of naloxone is often restricted by legal and regulatory barriers. In most jurisdictions, naloxone is a prescription-only medicine and its use is restricted to medical personnel or to patients to whom it is prescribed. The introduction of provision in some countries would therefore require adjustments to be made to current regulations, as has occurred in the United Kingdom and in some US states. Allowing local services in contact with high-risk drug users to stock naloxone kits for emergency use — as in Scotland — or handling it legally in the same way as another potentially life-saving drug that can be injected by bystanders — adrenaline to treat anaphylactic shock, for example — also merits serious policy consideration as does the introduction of 'Good Samaritan' legislation, which exempts drug users from prosecution when they call emergency services after witnessing an emergency.

Currently, available naloxone formulations are licensed for intramuscular, intravenous or subcutaneous injection. Whereas the use of a syringe can be an obstacle for non-medical responders, administration via nasal spray will offer advantages for wider dissemination of the intervention. While this book was being prepared for press, the US Food and Drug Administration approved a nasal naloxone preparation. The drug will be available through pharmacies across the United States, and in 15 states it will be available without prescription. These developments raise the prospect that nasal naloxone will be available in Europe in the near future.

Each of the 19 lives lost every single day to overdose in Europe is worth all our efforts to improve overdose prevention and response. Empowering bystanders to deliver a potentially life-saving intervention is an important next step in a diversified and balanced European response to drugs.

Alexis Goosdeel
Director, EMCDDA

Executive summary

Individuals who overdose on heroin or other opioids classically receive treatment when the ambulance or emergency medical care arrives, at which point the opioid antagonist naloxone is typically given. Naloxone is a semi-synthetic competitive opioid antagonist, which reverses opioid overdose and has been used in clinical and hospital overdose management since the 1970s. However, over the past 20 years, the provision of naloxone kits to opioid users and others likely to witness opioid overdoses has emerged as a novel harm-reduction intervention to make the antidote available in situations of need. Several countries in Europe and elsewhere have introduced take-home naloxone programmes that combine provision of the antidote with training in overdose prevention and emergency management. In November 2014, the World Health Organization (WHO) released new guidelines, recommending that take-home naloxone should be made available to anyone likely to witness an overdose.

This Insights publication provides both practitioners and policymakers with an analysis of the current evidence base on take-home naloxone. Specifically, it includes a comprehensive review of take-home naloxone initiatives in Europe. It also guides the reader through key issues of implementation, including training and programme evaluation. Finally, it engages in current debates around naloxone availability, including the development of non-injectable formulations and facilitating laws.

Chapter 1 describes the pharmacological basis of opioids and opioid reversal. Opioids have unique pain-relieving, anti-anxiolytic and sedative effects, but in the event of overdose this group of drugs can suppress the rate of breathing to the point of loss of consciousness, organ failure and death. The potential dangers of opioid drugs are illustrated by the example of heroin and its effects on the respiratory system. The chapter also explores risk factors that influence the likelihood of overdose. The chapter then introduces the opioid antagonist naloxone and summarises its pharmacology, how it is metabolised and other factors that influence its mechanism of action, such as the half-life of opioid agonists. The high specificity of naloxone in blocking opioid action is described as its defining feature, explaining why, 50 years after its original manufacture, naloxone remains the antidote of choice for reversing opioid overdose.

Chapter 2 covers the use of emergency naloxone by healthcare professionals in the emergency department and ambulance settings. In addition to comparing the different licensed routes of administration, it addresses the side effects of naloxone, with particular focus on precipitated withdrawal in opioid-dependent individuals. Naloxone administration also bears the risk of post-recovery re-intoxication due to the short half-life of naloxone relative to some of the opioids: the naloxone-induced blockade of opioid receptors wears off with time, and naloxone doses may need to be repeated to ensure that the overdose victim does not drift back into overdose. A concluding section discusses dosage recommendations and dose titration.

Chapter 3 highlights the significant contribution of heroin and the opioids to the high level of premature and preventable drug-induced deaths in Europe. The chapter contains a comprehensive review of the risk factors for opioid overdose. Personal correlates and predictors of risk of overdose include age, gender, history of use and comorbid medical conditions. Behavioural risk determinants include route of administration, co-use of other substances, reduced tolerance and using alone. Overdose deaths are typically clustered around specific situations, most prominently the periods following release from prison and discharge from residential detoxification and recovery treatment. In consideration of the fact that most overdoses occur in the presence of others, take-home naloxone is presented as a harm-reduction intervention that offers lay bystanders direct access to a potentially life-saving medication.

Chapter 4 describes the historical development of take-home naloxone provision, from its grassroots origins in Chicago to its current role in government-funded public health programmes in Europe and beyond. Take-home naloxone was first proposed in the mid-1990s as a previously overlooked opportunity to prevent deaths by providing naloxone to peers and family and consequently reducing the time between overdose onset and naloxone administration. The chapter reviews two decades of take-home naloxone research, covering its first mention in the peer-reviewed literature, through initial exploration of feasibility and attitudes among potential target populations, the assessment of safety and legal concerns, to reports and programme evaluations. The chapter includes a summary of current take-home naloxone programmes in Europe and beyond, which is enriched by outcome data, examples of good practice and lessons learnt. A timeline of the history of take-home naloxone development is also provided.

Chapter 5 explains how take-home naloxone programmes can be implemented in practice, identifying the main target populations as well as necessary resources. Training is described as an essential part of take-home naloxone distribution programmes that can effectively increase participants' knowledge, confidence and skills in managing an opioid overdose. Training can be offered to opioid users (former or current), carers and staff in frequent contact with users. It should be tailored to each setting, taking into account participant needs and available resources. Three levels of training are described: brief, standard and advanced. The chapter also includes assessment tools that can be used to test overdose-related knowledge and competence before and after training. The chapter concludes with a summary of methods for monitoring post-training impact.

The final chapter addresses naloxone options for the future, covering new products in development, new research initiatives and new legislation. It briefly summarises available systematic reviews on the effectiveness of naloxone programmes and gives an overview of recent WHO guidelines on community management of opioid overdose, which recommend widespread take-home naloxone provision. Barriers to naloxone access in the European Union are identified from policy, provider and research perspectives. The final sections of the chapter address the latest developments in the area of non-injectable naloxone products as well as initiatives to improve legal frameworks and raise awareness among healthcare service providers. These are identified as crucial facilitators for the wider availability of a life-saving intervention.

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Introduction

Drug use is one of the major causes of avoidable mortality among young people in Europe, and a large proportion of the yearly 6 000–8 000 drug-induced deaths in Europe are caused by opioids, which are potent respiratory depressants. Overall, opioid users are at least 10 times as likely to die in any one year than their peers of the same age and gender (EMCDDA, 2015a). However, many of these deaths are preventable.

An effective medication that reverses the central nervous system-depressant effects caused by opioid overdose is naloxone, an opioid-receptor antagonist. Naloxone is used in hospital emergency departments and by ambulance staff, is highly effective and is inexpensive. Traditionally it is given by intravenous, intramuscular and subcutaneous routes, but paramedics also administer the drug intranasally to treat suspected opioid overdose. Although naloxone is a prescription medicine in most countries, it is not a controlled substance and has no abuse potential.

Based on the rationale that more opioid-overdose deaths could be prevented if people who witness overdoses recognised the danger in which the victims are and were able to administer the overdose-reversal drug, 'take-home' naloxone programmes have been developed to increase the availability of the antidote in places where overdoses are especially likely to occur. Under these programmes, an emergency supply of naloxone is given out, together with instructions about its administration, to drug users and their close friends, partners and families, as well as other individuals likely to witness overdoses, so that, in the event of an opioid overdose, naloxone is readily available and can be administered to the overdose victim before the arrival of an ambulance.

The first programmes in the United States and Europe began distributing naloxone in 1996 and a report on outcomes in two European sites — Berlin, Germany, and Jersey, Channel Islands — was published in 2001 (Dettmer et al., 2001). Besides nationwide programmes in the community and before release from prison in Scotland and Wales, further naloxone initiatives in Europe have been implemented in Catalonia, Denmark, Estonia, Italy and Norway.

Evidence about naloxone programmes has grown. Since 2005, several studies have been published addressing different aspects of these programmes. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) recently reviewed the effectiveness of education and training interventions complemented by take-home naloxone, including 21 studies, and found evidence that these programmes decrease overdose-related mortality (EMCDDA, 2015b).

As interest in 'take-home' naloxone is greater than ever before among policymakers, agency staff and drug-user interest groups across Europe, it is the aim of this publication to bring together available background information, evidence and best-practice examples of take-home naloxone programmes.

Chapter 1 addresses the pharmacology and physiological mechanisms of opioid overdose and response by describing the specific dangers of heroin and other opioid drugs, explaining the impact of opioids on the breathing mechanism and the risks inherent in different routes of administration, and naloxone's effects on the human body.

Chapter 2 addresses the use of emergency naloxone in clinical practice by medical professionals in the emergency department or in a pre-hospital setting by ambulance staff. In addition to comparing the different licensed routes of administration, it addresses the side effects of naloxone and discusses dosage recommendations and dose titration.

Chapter 3 highlights the role of opioids in drug-induced deaths in Europe and reviews personal correlates and predictors of risk of overdose, including behavioural risk determinants as well as situational aspects of overdose risk.

Chapter 4 gives an overview of the history of take-home naloxone projects in Europe and beyond, reviewing project reports and programme evaluations, and research about feasibility and attitudes among potential target populations, assessing safety and legal concerns. Good practice and lessons learnt in current take-home naloxone programmes in Europe are described.

Chapter 5 presents how take-home naloxone programmes can be set up and run. It provides an overview of the main target populations for and the importance and effectiveness of training, as well as of the resources necessary to implement a comprehensive take-home naloxone programme, including training curriculum, materials and personnel.

The final chapter briefly summarises available evidence on the effectiveness of naloxone programmes and gives an overview of recent World Health Organization (WHO) guidelines on community management of opioid overdose, which recommend naloxone provision. It addresses barriers to the wider availability of take-home naloxone programmes, and future challenges, presenting an overview of the latest developments regarding products and initiatives to improve legal frameworks and to raise awareness among healthcare service providers.

References

Dettmer, K., Saunders, B. and Strang, J. (2001), 'Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes', *BMJ* 322(7291), pp. 895–896.

EMCDDA (2015a), *European drug report: Trends and developments 2015,* Publications Office of the European Union, Luxembourg.

EMCDDA (2015b), *Preventing fatal overdoses: A systematic review of the effectiveness of take-home naloxone,* EMCDDA Papers, Publications Office of the European Union, Luxembourg.

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CHAPTER 1

Pharmacology and physiological mechanisms of opioid overdose and reversal

Basak Tas and Ed Day

The first part of this chapter describes the pharmacological basis of opioids, with a particular focus on the potential dangers of heroin and its effects on the respiratory system. The second part introduces and describes the drug naloxone, and summarises its pharmacology, how it is metabolised and other factors that influence its function. It shows the accuracy and specificity of naloxone's action as an opioid antagonist, how we understand its functions and why, 50 years after its original manufacture, naloxone remains the opioid antagonist of choice for reversal of overdose.

TABLE 1.1
Definitions

Opiate	One of a group of alkaloids derived as natural products from the opium poppy (*Papaver somniferum*), with the ability to relieve pain, induce euphoria and induce sleep, and, at higher doses, to induce respiratory depression and coma. Examples are morphine and codeine. The term excludes synthetic opioids.
Opioid	A generic term applied to natural opium alkaloids, their synthetic and semi-synthetic analogues (which in some cases may have a very different chemical structure from natural opium alkaloids) and molecules (e.g. β-endorphin, enkephalins, dynorphin) synthesised in the body which interact with opioid receptors in the brain and have the ability to induce analgesia, euphoria (a sense of well-being) and, at higher doses, respiratory depression and coma.

Heroin and other opioids: understanding their particular dangerousness

What are opioids?

Although the terms 'opiate' and 'opioid' are sometimes used interchangeably (see Table 1.1 for definitions), in medicine 'opiate' describes any of the opioid analgesic chemicals found as natural products in the opium poppy plant (*Papaver somniferum*) (Shook et al., 1990). Both opiates and opioids have been used medicinally, predominantly for pain relief but also for their strong sedative (sleep disorders), anxiolytic (reducing anxiety), anti-tussive (cough suppressant) and anti-diarrhoeal properties. Since the nineteenth century, it has been possible to obtain opiate products through the chemical isolation and extraction of the active ingredient from the opium poppy plant (Berridge, 1999). Major opium alkaloids are morphine, codeine and thebaine, of which morphine and codeine have analgesic properties and depressant effects, while thebaine has no direct therapeutic effect.

'Opioid' is a wider term that includes the semi-synthetic analogues such as methadone and buprenorphine, and also heroin. Heroin, which has the chemical name diacetylmorphine (also called diamorphine) is produced by a simple chemical reaction from morphine, a natural extract of the opium poppy, and was first marketed in 1898 by the chemical company Bayer in Germany under the trade name 'Heroin'. The chemical processes of converting opium into diacetylmorphine (i.e. diamorphine or heroin) involve first processing opium into morphine before acetylation to produce heroin. The term 'opioid' also encompasses the naturally occurring opiate and opiate-like drugs, including molecules that are very different from natural opiates but nevertheless activate the opioid receptors in the human body, producing similar effects to natural opioids (e.g. endorphins).

Some people experience a euphoric reaction to opioid medications, as opioids also affect the areas of the brain involved in reward (NIDA, 2014). Their strong medicinal effects and their euphoric properties may explain why the opioids are among the most commonly used groups

of drugs for recreational and self-medication purposes. The distinct properties of opioids that will be explored in this publication can lead to physical and psychological dependence, and carry a high risk of overdose.

Most of the heroin found in the illicit market in Europe at present is in the form of a brown powder (base) which originates from south-west Asia. The base is not water-soluble but is suitable for vaporisation with heat ('chasing', sometimes also called 'smoking', although no combustion of heroin takes place). It requires an acidifier (e.g. vitamin C) and heat to dissolve it in water and allow it to be injected. The white powder (salt) form of heroin, traditionally originating from south-east Asia, is soluble in water and can more easily be injected (although it often still requires heat).

How do heroin and other opioids work?

Heroin and the opioids affect a number of different areas in the human body. The primary areas of action are the brain, spinal cord and gastrointestinal tract, where the opioids bind to receptors in the nervous system and produce their actions through processes of activation or inhibition. Receptors act as a 'key' in controlling physiological and psychological responses such as analgesia (pain reduction), sedation, euphoria, reduced breathing (respiratory depression), drowsiness, constricted pupils and nausea. The physiological and psychological effects differ depending on the particular opioid and the type of receptor that is activated or inhibited.

Agonist and antagonist

An agonist is a substance that elicits a response when it interacts with a receptor, whereas an antagonist prevents the effect of an agonist. If they both have an affinity for the same type of receptor (i.e. ability to bind to it), an antagonist acts by competing with the agonist to bind to the receptor, thus preventing the agonist from being able to promote its action and thereby eliminating the agonist's effects. This is called 'competitive antagonism'. The extent to which an agonist effect still occurs in the presence of an antagonist depends on the power balance between the agonist and the antagonist, namely their binding affinity to the receptor and the intrinsic activity of each. Full agonists bind to the receptor and produce a full effect on it, whereas partial agonists bind in the same way but exert only part of the effect on the receptor. Examples of full opioid agonists include morphine, heroin, methadone and fentanyl. Partial agonists include buprenorphine.

An opioid antagonist is a substance that blocks opioid receptors. Opioid antagonists differ in their pharmaceutical uses: some have a quick, strong and short action and can be used for immediate reversal of opioid-induced respiratory depression (as with the emergency medicine naloxone, which is effective only with opioids) whereas others bind to the receptors for longer and can be used to block the potential longer-term effects of heroin as part of a treatment programme for heroin dependence (as with naltrexone).

Opioid receptors

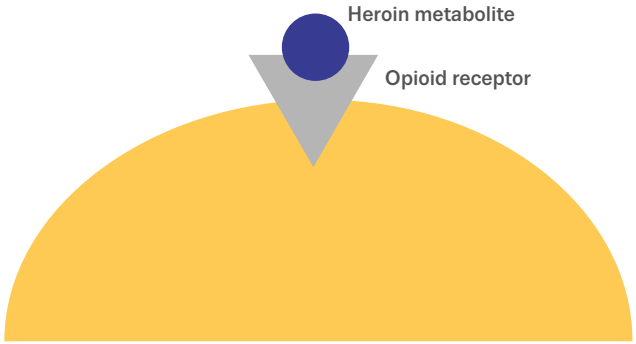
Opioid receptors are located in various locations of the brain that are implicated in the control of breathing and respiration, euphoria and pain control. They are also located in peripheral regions such as the intestinal tract, and in areas relating to respiratory feedback drive, for example in the carotid bodies and the vagi (Pattinson, 2008) (see section 'Impact of opioids on breathing mechanisms' for a more detailed description).

There are three main groups of opioid receptors: mu (μ), delta (δ) and kappa (κ). All three produce analgesia when activated, but differ in other effects. The μ-opioid receptor is the most widespread opioid receptor in the body and the primary target for a great variety of therapeutic drugs. However, μ-opioid receptors can also produce undesirable effects such as respiratory depression and constipation (Pasternak, 2006). The group of μ-opioid receptor agonists includes heroin, morphine, oxymorphone, methadone and fentanyl. The effect of other opioid receptors on respiration is less well understood. Δ-opioid receptors appear to have some inhibitory action on respiration and κ-opioid receptors have little or no effect on respiration (Shook et al., 1990).

Heroin pharmacology

Heroin is regarded as a powerful opioid. In its pharmacologically purest form it is more powerful than morphine, weight for weight. If consumed orally it enters the digestive system and then undergoes metabolism in the liver, with a considerable proportion becoming deactivated. However, if injected intramuscularly or intravenously it enters straight into the bloodstream and crosses the blood–brain barrier, a cellular system that exists to protect the brain from potentially toxic molecules. The effect of heroin peaks within 20 seconds of intravenous injection, and slightly later following intramuscular administration (eMC,

FIGURE 1.1
Illustration of a heroin metabolite (blue) attaching to an opioid receptor (grey triangle)



NB: This simplified illustration represents the metabolites of heroin, 3-monoacetylmorphine, 6-monoacetylmorphine and morphine.

2013; Klous et al., 2005). Heroin rapidly crosses the blood–brain barrier but is also rapidly broken down into the active metabolites morphine, morphine glucuronide and 6-acetylmorphine (Inturrisi et al., 1983). Heroin could therefore be considered not only as a drug in its own right but also as a pro-drug ([1]) for morphine (Sawynok, 1986). A key feature of heroin is that its chemical structure allows it to cross the blood–brain barrier more easily than most other opioids. As a result, heroin has a very fast onset of action for brain effects and associated euphoric effects, which contributes to its high potential for addiction relative to other opioids.

Heroin is a strong agonist for opioid receptors, with particular affinity for the μ-opioid receptor: the heroin metabolite occupies the receptor until it loses its ability to bind. Figure 1.1 demonstrates the binding fit of a heroin metabolite (or any other opioid agonist) onto an opioid receptor.

Other opioids

Opioids differ greatly in their duration of action, and this is influenced by their elimination half-life, that is, the amount of time it takes for half of the drug to be eliminated from the body. The half-life of a drug does not necessarily equate to its peak effects or its concentration at the relevant receptors, and in fact all drugs will continue to produce some effects after the stated half-life duration. Table 1.2 summarises some of the more commonly used opioids and their approximate half-lives.

([1]) 'A pro-drug is a pharmacologically inactive substance that is the modified form of a pharmacologically active drug to which it is converted by a metabolic conversion process in the body' (Merriam–Webster dictionary, 2014).

TABLE 1.2
Opioids along with their respective half-life approximations (Pasternak, 2006)

Drugs	Approximate half-life
Heroin (diamorphine)	6 minutes
Morphine	120 minutes
Hydromorphone	150 minutes
Oxymorphone	150 minutes
Codeine	180 minutes
Fentanyl	220 minutes
Tramadol (immediate release)	6 hours
Methadone	24 hours
Buprenorphine	37 hours

Heroin/opioid metabolism

There are two ways in which opioids are broken down in the liver (metabolised): by the enzymes known as the cytochrome P450 system ([2]); and by other types of reactions, most commonly by a reaction known as glucuronidation ([3]). Some opioids (e.g. methadone, tramadol and fentanyl) undergo only the former process and some undergo only the latter process (e.g. heroin and morphine). If taken orally, heroin undergoes extensive metabolism as it enters the liver and consequently does not reach the systemic circulation. In this instance, heroin is largely converted to morphine before it reaches the general circulation (and hence before it reaches the brain). Heroin absorbed by the gastrointestinal tract travels directly to the liver, where this conversion occurs (known as hepatic first-pass metabolism). Consumption through the intranasal, inhalatory, intramuscular and intravenous routes bypasses this initial stage in the liver, and therefore produces more prominent brain effects than the oral route (Brunton et al., 2008; Smith, 2009).

Definition of overdose and pharmacological overdose risk factors

The EMCDDA (2015) defines drug-related death as a death 'directly due to use of illegal substances, although these often occur in combination with other substances, such as alcohol or psychoactive medicines. These deaths occur generally shortly after the consumption of the substance' and are therefore considered 'directly caused by drugs'. They are also known as 'drug-induced

([2]) This is one of two systems of enzymes (the other, less significant, group is known as UDP-glucuronosyltransferases) involved in the breakdown of opioids and has gained great attention since we have developed a stronger understanding of the genetic influences on the effectiveness of the breakdown pathway (Holmquist, 2009).
([3]) Glucuronidation is a general process that occurs in the breakdown of chemicals, mainly in the liver.

deaths' (a term used in the United States and increasingly in the European Union), as 'poisonings' (which corresponds to the terminology used in the *International Classification of Diseases*) or in more common language as 'overdoses'.

There are many factors that contribute to the risk of overdose in general and to fatal overdose in particular. Non-fatal overdoses are more common than fatal ones but the risk factors for both are the same. According to Frisher et al. (2012), the more risk factors are present, the more likely it is that the overdose will be fatal. Behavioural and situational risk factors are examined in detail in Chapter 4. The focus below is on the pharmacological aspects of overdose.

Route of administration and relevant risk of overdose

A high bioavailability (the proportion of the actual drug that reaches the systemic bloodstream) usually equates to a high rate of absorption and increased risk of overdose. Bioavailability is considerably affected by the route of administration, which determines what type of metabolism (breakdown) the drug undergoes, but also by the dose taken and the purity of the drug. The combination of the last two factors will determine the total amount of active substance consumed.

In Table 1.3, routes of administration are listed in order of increasing risk of overdose, assuming that dose and purity are constant.

Unknown purity

'Street' heroin is subject to unpredictable variations in drug purity and may contain a variety of adulterants or contaminants mixed in, making it difficult for the user to determine the amount of active substance to use. However, the picture is far from clear, as large numbers of fatal overdose sufferers have low concentrations of morphine in the blood, often below, or similar to, those of living intoxicated heroin users or of heroin users who died from other causes (Darke et al., 2010; Darke and Farrell, 2014; Davidson et al., 2003). Additional important factors may be the individual's tolerance level, consumption of other depressants or organ (lung, liver) failure. Furthermore, harmful contaminants that may have contributed to the fatal outcome of the overdose may often not be detected in toxicological analyses of blood, drugs and used syringes.

Concurrent use of other drugs

There is an increased risk of overdose from heroin or other opioids if alcohol and other sedative drugs (e.g.

TABLE 1.3

Risk of overdose by route of administration (descending order)

Route	Characteristics
Intravenous (injecting into vein)	Powder or crushed tablets are prepared for injection, usually using water and an acidifier (e.g. heroin or crushed pharmaceutical opioid drugs); this is typically self-administered (or given by fellow drug user) as a bolus, thus delivering sudden full onset of drug effect when the bolus of drug reaches and crosses the blood–brain barrier. Because delivery following the pushing of the syringe plunger is instant, there is no scope to reduce the dose if the effect of the heroin is greater than expected. Heroin through this route has 100 % bioavailability.
Intramuscular (injecting into muscle)	Similarly, this is typically self-administered quickly but, by virtue of being injected into muscle (instead of into a vein), it is absorbed more slowly, so, even if eventually fully absorbed, it does not produce the same front-end bolus effect as intravenous use. As with intravenous use, there is no scope to reduce the dose if the effect of the heroin is greater than expected. Bioavailability is slightly lower than that of intravenous (Girardin, 2003).
Inhalation (smoking, 'chasing')	Vaporising heated heroin base (brown powder), usually on foil, is known as 'chasing the dragon'. By utilising the vast surface area of the lungs (as with cigarette smoking), 'chasing' produces rapid absorption and hence rapid brain effect. However, the technique involves running the melted heroin up and down the heated foil and inhaling the sublimate in the vapours. This technique is not instant in the same way as pushing a syringe plunger and, consequently, does not produce the rapid bolus effect. Hence, inhalation results in a slightly slower onset, which thereby gives the opportunity to reduce the dose if the effect is larger than expected.
Intranasal (snorting)	Although not common, the white powder (salt) form of heroin occurs in some countries and communities. Snorting results in a mix of effects, some of fairly rapid-onset and other of more extended duration. Heroin bioavailability intranasally is approximately half that of the intramuscular route (Cone et al., 1993).
Oral	Ingesting any drug orally as a tablet/capsule/liquid (e.g. methadone, morphine sulphate or dihydrocodeine) is likely to produce a slow-onset effect as it is gradually absorbed from the stomach or further down the alimentary tract. The extent to which it then produces effects on the brain varies greatly among the different opioid drugs, and is markedly affected not only by how comprehensively it is absorbed but also, crucially, by the extent of first-pass metabolism (see section 'Heroin pharmacology'). Thus there is no opportunity to reduce the dose if the effect is larger than expected, but there is also no sudden-onset bolus effect. Heroin has < 35 % bioavailability when taken orally (Rook et al., 2006).

benzodiazepines) are also consumed. This 'cocktail' of drugs and alcohol contributes to a great number of overdose deaths. In the presence of other drugs that depress the central nervous system , a dose of heroin that is usually well-tolerated can prove fatal.

Impact of opioids on breathing mechanisms

To understand why heroin and other opioids are particularly dangerous, it is important to consider the fundamentals of breathing and lung physiology.

Introduction to respiration

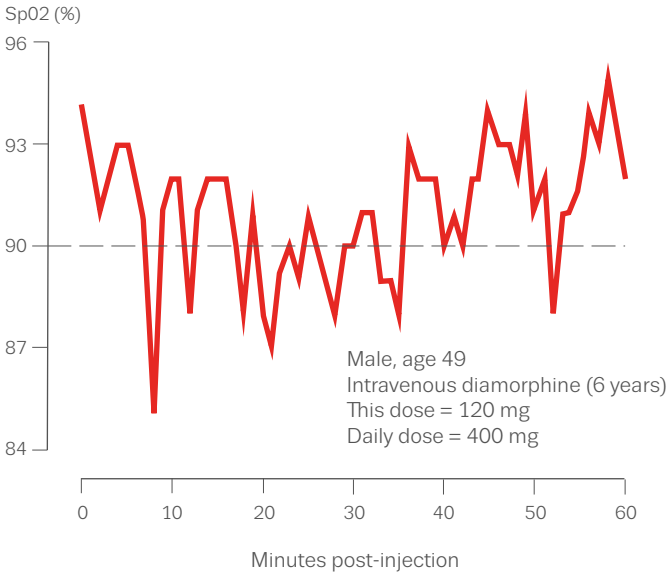
The lungs function to exchange oxygen and carbon dioxide continually with the external environment in order to maintain low concentrations of carbon dioxide and high concentrations of oxygen in the tissues of the body (Levitzky, 2013). Normal resting breathing is driven by the respiratory centres of the brain, located in the medulla and pons regions of the brainstem. Blood oxygen is monitored by sensors (also known as chemoreceptors) located in the body (peripheral sensors, e.g. the carotid body, see Table 1.4), and in the brain. Together these support a precise self-regulating system by constantly monitoring blood oxygen to detect any drops in levels. These chemoreceptors are also sensitive to increasing levels of carbon dioxide, as a failsafe second-level detection system. The respiratory centres monitor the feedback from the peripheral sensors and send the appropriate stimuli to initiate breathing.

A build-up of carbon dioxide in the blood is poisonous. If not adequately expelled via the lungs, an accumulation of carbon dioxide can lead to the condition known as hypercapnia. This in turn causes a decrease in blood pH (known as acidosis, the accumulation of acid substances in the body) and is typically accompanied by a decrease in blood oxygen (hypoxaemia) and finally hypoxia (a condition in which the tissue in a region of the body or the whole body is deprived of oxygen). If this state of low oxygen and high carbon dioxide in the blood is prolonged, it is usually fatal (Levitzky, 2013).

TABLE 1.4
Glossary

Alkaloid	A naturally occurring chemical, mainly found in plants
Carotid body	A group of receptors of the carotid artery (supplying blood to the head and neck) that detect small changes in oxygen and carbon dioxide
Medullary and pontine nuclei	Areas of the brainstem involved in respiration
Partial pressure (P_a)	An estimate of the pressure of a gas (e.g. oxygen and carbon dioxide) if it were alone in the volume of blood. It is a hypothetical figure but is the standard measurement to provide
Ventilation rate	The volume of air that the lungs exchange per minute; basic indicator of pulmonary physiology

FIGURE 1.2
Oxygen saturation levels after intravenous opioid injection



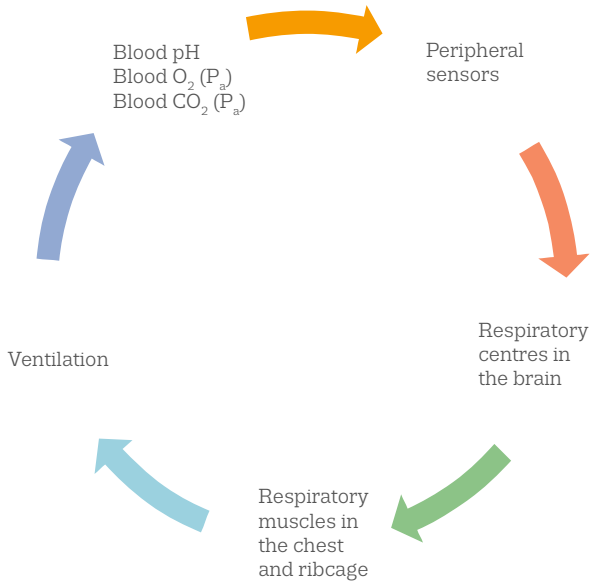
SpO_2, peripheral capillary oxygen saturation.

Why do these drugs cause respiratory depression?

Morphine, heroin and other opioids with agonist activity at the μ-opioid receptor in the respiratory centre produce depressant effects soon after binding. The activity in brain areas associated with inspiration (taking air in) is reduced by opioids, but the areas associated with expiration (breathing air out) are unaffected, so the breathing rhythm becomes slow and irregular (Leino et al., 1999). This causes hypercapnia (elevated CO_2 levels in the blood) and hypoxaemia (low levels of blood oxygen). The effect on oxygen levels is demonstrated by Figure 1.2, which shows a considerable drop in oxygen just after intravenous heroin injection.

In the absence of opioids, any dampening of the ventilatory system leads the peripheral sensors to relay information to the respiratory centres of the brain to command the lungs to increase the rate of ventilation in order to counter hypercapnia and hypoxaemia (see feedback loop mechanism in Figure 1.3). However, in the presence of opioids, this protective regulatory mechanism is stunted (Pattinson, 2008). If the ventilatory drive is reduced for an extended time, the individual will eventually stop breathing (respiratory

FIGURE 1.3
Respiratory feedback loop



NB: Ventilation is the depth and frequency (breaths per minute) of breathing.

arrest) and/or there will be excessive build-up of carbon dioxide in the blood (hypercapnia), leading to respiratory acidosis. Vital organs and tissues no longer receive sufficient oxygen (hypoxia), ultimately leading to risk of organ failure, coma or death. The severity of this respiratory depressant effect varies between opioids, but there is no opioid that does not have this effect.

It should be noted that respiratory depression caused by opioids, particularly μ-opioid receptor agonists, is more likely in people who have underlying pulmonary disease (e.g. emphysema or chronic bronchitis). It is thus much more common in cigarette smokers. However, the risk of overdose is still significant in heroin users without pre-existing lung pathology.

Polydrug use

In some cases, combined use of other depressant drugs (e.g. benzodiazepines) with opioids (see section 'Concurrent use of other drugs') also leads to respiratory difficulties. Emergency overdose cases that involve other drugs are often not affected by the use of naloxone, and require use of other forms of resuscitation. For example, flumazenil is used to reverse benzodiazepine overdoses.

Summary of physiology

Opioids act on specific receptors, which are predominantly located in the regions of the brain that control respiration and breathing, such as the medullary and pontine nuclei of the brainstem (see Table 1.4), but which are also found in the carotid body.

Heroin and other opioids bind to these receptors, reduce their responsivity and thereby cause a 'dampening' effect on the respiratory system of the body, which causes breathing to slow down to potentially dangerous rates. When breathing slows down significantly, the level of carbon dioxide in the blood rises and the level of oxygen falls to dangerously low levels. However, because the respiratory centres of the brain are dampened by opioids, the feedback loop between the central respiratory centres and the lungs is interrupted. In normal circumstances (without any opioid agonistic effect), the breathing rate increases to counter the changes in blood gases. However, when respiratory centres are dampened, the lungs are not signalled to increase the breathing rate. This exacerbates the abnormal levels of oxygen and carbon dioxide in the blood, and, as the combined losses of hypercapnic and hypoxic drives deprive the victim of the stimulus to breathe (Doyon et al., 2014), results in respiratory acidosis, respiratory arrest and possibly death.

Naloxone: pharmacology and mechanisms of action

What is naloxone?

Naloxone is a medication that counters the effects of heroin and other opioids by reversing respiratory depression caused by these drugs. It was first synthesised in the early 1960s: the Japanese company Sankyo submitted the first patent application, and a second application by Fishman and Lewenstein of Endo Laboratories (New York) followed in March 1961 (Yardley, 2013). Naloxone was conceived of as a safer and more powerful opioid antagonist with fewer side effects than its predecessors. In 1971, naloxone received regulatory approval from the US Food and Drug Administration (US FDA) for intravenous, intramuscular, and subcutaneous administration.

Naloxone is made from a component of the opium poppy plant called thebaine. Thebaine is a minor component of the poppy, contributing to between 0.1 % and 2 % of all the extracts from the plant (UNODC, 1953). As described earlier, these extracts of the poppy plant, including morphine and thebaine, are collectively known as alkaloids and all have different uses and properties. The commonly found opium poppy alkaloids are

morphine, thebaine, narcotine, papaverine and codeine. To create the final naloxone molecule, thebaine undergoes many reactions after extraction, which is why naloxone is commonly referred to as a semi-synthetic antagonist. Extracted thebaine is also used in the production of semi-synthetic medicinal drugs such as hydrocodone, oxycodone and buprenorphine (Machara et al., 2012; Rinner and Hudlicky, 2012). Thebaine has no direct therapeutic uses itself. The WHO has included naloxone as a specific antidote in its Model List of Essential Medicines (WHO, 2013), a listing of the most efficacious, safe and cost-effective medicines for priority conditions.

Administration of naloxone

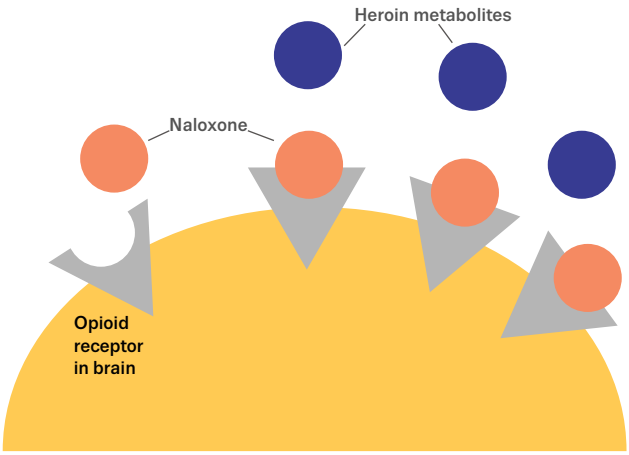
Naloxone is produced for injection, and is commercially available in formulations ranging from 0.4 mg/ml to a more concentrated 1-mg/ml solution. In paediatric formulations, this dose is diluted to 0.02 mg/ml (NIH, 2007a; Joint Formulary Committee, 2014). It is licensed for administration into a vein (intravenous), into a muscle (intramuscular), or under the skin (subcutaneous) (NIH, 2007a). Work is under way to develop an adequately formulated naloxone nasal spray for pre-hospital use; in the interim, some clinical services have improvised a nasal spray by combining a naloxone syringe with a spray adapter (see Chapter 6). A pilot project about the nasal use of naloxone is currently under way in Norway. The possibility of a buccal tablet (in the mouth, against the cheek) is also being explored (EudraCT: 2014-001802-16).

How does naloxone work?

General mechanism of action

Naloxone is a μ-opioid competitive antagonist (see section 'How do heroin and other opioids work?' for further information on agonists and antagonists). It has an affinity for the μ-opioid receptor and works by competing with other relevant drugs for a space on the receptor. Thanks to its ability to compete and control the specific opioid receptors, naloxone can reverse the effects (e.g. respiratory depression) that were caused by heroin (or another opioid) by preventing heroin metabolites from exercising influence on the receptor's normal functioning (see Figure 1.4). Reversal is a fairly rapid event at the μ-opioid receptor, and partly at the δ-opioid receptor, the main instigators of respiratory depression in heroin/opioid consumption (Pazos and Florez, 1984; Shook et al., 1990) (see section 'Impact of opioids on breathing mechanisms').

FIGURE 1.4
Illustration of naloxone competing with heroin metabolites for μ-opioid receptors



Pharmacodynamics: how does naloxone affect the body?

Naloxone produces effects only if opioids are present in the body. If opioids have been taken and are producing an effect (e.g. pain relief, euphoria, sedation, respiratory depression), then a dose of naloxone will compete with the opioid at the receptor and will partially or completely reverse the opioid effect. The extent of this reversal will depend on the dose of naloxone, the dose of opioids that had previously been taken and their relative affinities for the opioid receptor. In persons with physical dependence on opioids, small subcutaneous doses of 0.5 mg of naloxone can produce moderate to severe withdrawal symptoms, which appear within minutes of administration and subside after around 2 hours (McEvoy, 2012). The duration and severity of withdrawal symptoms will depend on the dose of naloxone, the route of naloxone administration, and the degree and type of opioid dependence.

Where opioids are administered during surgery, naloxone can be used for partial reversal of opioid depression in a post-operative setting (McEvoy, 2012). The dose of naloxone is usually titrated to effect, as this is less likely to cause undesirable cardiovascular side effects. Small doses (0.1–0.2 mg) of naloxone are used for the reversal of respiratory depression, and the patient's response is observed. Sometimes repeat doses are required and are given at 2- to 3-minute intervals.

In an emergency, non-clinical overdose setting, titration is often not possible, as the person administering naloxone may see the urgent reversal of the heroin effect as the priority. Injection (0.4–0.8 mg) of naloxone can

produce a prompt reversal of the effects produced by heroin/opioids. Where respiratory depression is present, naloxone typically causes increased respiratory rate within 1–2 minutes of intravenous administration (Nguyen et al., 2012; NIH, 2007a) and within 3–4 minutes of intramuscular or subcutaneous (McEvoy, 2004; MHRA, 2011) administration. Generally speaking, 1 mg of naloxone administered intravenously will completely block the effects of a standard dose (around 25 mg) of heroin.

Pharmacokinetics: how does the body handle naloxone?

Once absorbed, naloxone is distributed around the body very rapidly (NIH, 2007a). When administered intravenously its onset of action (i.e. the time required after administration of a drug for a response to be observed) is rapid, i.e. within 1 to 2 minutes. It is slightly slower in onset when administered subcutaneously or intramuscularly, after which onset of action is typically reached within 3 to 7 minutes (McEvoy, 2004; UNODC and WHO, 2013). The duration of action depends on the dose and route of administration (intramuscular administration leads to a longer duration of action than intramuscular administration), but the effect of naloxone generally lasts for up to 2 hours. The half-life of naloxone in serum (the period of time required for the amount of drug in the body to be reduced by one-half) is variable (e.g. from 30 to 80 minutes), with an average time of about an hour (NIH, 2007a).

The pharmacokinetics of intranasal naloxone have been published in only one study (Dowling et al., 2008) to date. The study tested intranasal naloxone doses of 0.8 mg/2 ml and 2 mg/5 ml and found intranasal absorption to be rapid, but only low amounts of naloxone were absorbed into the bloodstream. The bioavailability of intranasal naloxone was only 4 % of that of intravenous administration. The authors pointed out that subjects might have swallowed some of the naloxone solution (Dowling et al., 2008). Future studies will therefore need to study more concentrated nasal naloxone formulations.

It is important to note that the duration of action of naloxone is shorter than that of some opioids. Heroin is one of the shorter-acting opioids, so its effects have usually dissipated by the time naloxone wears off. However, with longer-acting opioids, the effects of the opioid may return once the effects of naloxone start to disappear (see section 'The heroin substitutes' and Chapter 2), leading to a requirement for repeat doses of naloxone.

Metabolism of naloxone

As described in the section 'Heroin/opioid metabolism', opioids are mainly broken down (metabolised) by the cytochrome P450 enzyme system in the liver, or by the process known as glucuronidation. Naloxone, like heroin and morphine, is metabolised predominantly by the latter process and is broken down to naloxone-3-glucuronide. This is an inactive metabolite, but can be used as a marker when measuring the levels of naloxone in the body (Smith et al., 2008). Naloxone is completely metabolised in one pass through the liver, and when taken orally only a small proportion reaches the systemic circulation. Consequently it has to be given by a route that bypasses this initial stage in the liver (i.e. by injection) for maximum effectiveness (Brunton et al., 2008).

After a parenteral dose of naloxone, 25–40 % of the drug will have been excreted in urine within 6 hours, 50 % within 24 hours and 60–70 % within 72 hours.

Paediatric use of naloxone

In a post-operative setting, naloxone has been shown to reverse respiratory depression caused by opioids in children and new-borns, and appears to be safe and effective in reversing respiratory depression (Fischer and Cook, 1974; McEvoy, 2012; Segal et al., 1980). It is not known whether or not naloxone is excreted into human milk, but it crosses the placenta readily, and its effect on the foetus is not well understood.

Naloxone's actions with other opioids

Chemical differences

The effects of naloxone differ slightly according to the opioid that it is countering. Naloxone competes for the opioid receptors, μ, κ and σ, with the greatest affinity (attraction) for the μ receptor. Similarly, morphine and heroin also act on the μ and κ receptors, with greatest affinity for the μ receptor (Table 1.5). This similarity explains why naloxone is particularly effective at reversing the respiratory depressant actions of heroin and morphine.

Furthermore, the chemical structures of the opioids and naloxone are generally very similar. Naloxone is particularly similar to both heroin and morphine in its structure but with four slight variations to its functional groups (Figure 1.5). These slight tweaks to the bonds and atoms of the molecule create the difference between a pure agonist and a pure antagonist.

FIGURE 1.5
Chemical structures of heroin, naloxone, morphine and buprenorphine

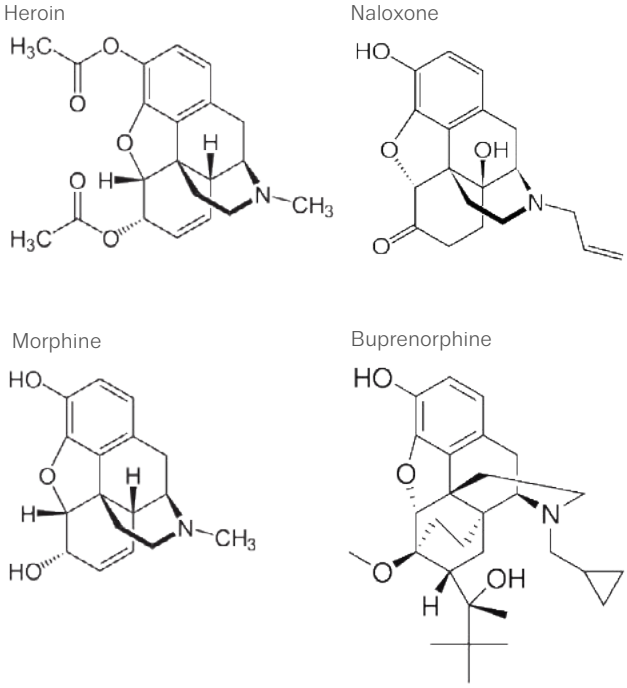


TABLE 1.5
Opioids and their relative opioid receptor affinities (Brunton et al., 2008)

Drug	Opioid receptor		
	μ	δ	κ
Naloxone	– – –	–	– –
Morphine	+++	No effect	+
Methadone	+++	No effect	No effect
Buprenorphine	P	No effect	– –
Fentanyl	+++	+	+

–, antagonist action; +, agonist action; strength of action is indicated by number of signs; P, partial agonist action.

The heroin substitutes

Heroin substitutes such as methadone and buprenorphine display similar respiratory depressant effects to heroin or morphine (Mégarbane et al., 2010), but these effects are not as effectively reversed by naloxone, particularly those of buprenorphine (Yassen et al., 2007).

Although rare, buprenorphine overdoses can occur, often due to the co-ingestion of benzodiazepines (e.g. Hakkinen, 2015). Buprenorphine is referred to as a partial agonist (Table 1.5) and sometimes as a mixed agonist/antagonist, with the agonist or antagonist effect varying by dose, by receptor and between individuals (Jacob et al., 1979). Therefore, the mechanism of naloxone's reversal of buprenorphine effects differs from the mechanism of its reversal of heroin effects. Furthermore, buprenorphine has a very high affinity for the μ-opioid receptor and attaches to the receptor with greater affinity and for much longer than naloxone; in some circumstances, this means that naloxone cannot compete for a space on the receptor for a long enough time (Yassen et al., 2007).

Because buprenorphine's effects on opioid receptors vary, the effect of naloxone administration is a little more complicated. If high-dose buprenorphine has been consumed, it may be necessary to administer a higher dose or more frequent doses of naloxone. However, individual variability plays a crucial role here. Therefore, it is difficult to specify a dose of naloxone to counter respiratory depression caused by buprenorphine.

Methadone, a synthetic opioid agonist, is administered either in oral form, as a liquid or tablet, or in injectable form. It binds to the μ-opioid receptor strongly and has a long duration of action (NIH, 2007b; AHFS, 2014). Methadone can be used as a maintenance medication in the treatment of opioid dependence, as it has minimal euphoric effects and can relieve craving (Joseph et al., 2000). It can also be used in the treatment of chronic pain.

Once the peak effects of naloxone disappear, respiratory-depressant effects in longer-acting opioids are more likely to reappear; this is known as recurrence of toxicity. The long-acting nature of methadone means that recurrence of toxicity is more likely than with heroin, and naloxone may be required in repeated doses (Waldron et al., 1973; Wanger et al., 1998). In a study looking at naloxone responses to opioid overdose in an emergency department, 30 % of those patients who responded to naloxone showed recurrence of toxicity, which was significantly correlated to long-acting opioids (Watson et al., 1998) (see Chapter 2 for further details on recurrence of toxicity).

Other opioids

Tramadol, a synthetic opioid analgesic that can cause significant respiratory depressant effects, also contributes to opioid-related overdoses (in the United Kingdom, 100 tramadol-related deaths were recorded in 2013; ONS, 2014). It has a fairly long half-life of around 6 hours (Dayer et al., 1994) and thus, as with methadone, there is a chance of recurrence of toxicity. In the few reported cases of naloxone reversal of tramadol, naloxone appears to be effective at reversing respiratory depression at standard doses (Stamer et al., 2008; Sachdeva and Jolley, 1997).

Slow-release morphine (or extended-release morphine sulphate) is a long-acting opioid agonist used for its analgesic properties as well as in the treatment of opioid dependence as an opioid maintenance medication (Jegu et al., 2011). Naloxone is considered effective at increasing the respiratory rate in morphine-related overdose cases (McEvoy, 2012); however, because of the long-acting effects of slow-release morphine, toxicity is likely to occur. Similarly to the previously listed long-acting opioids, repeated doses are often required for slow-release morphine, although very few clinical cases have been reported.

Fentanyl is a strong opioid receptor agonist with analgesic properties and is commonly used to relieve cancer-related pain or breakthrough pain (pain that appears suddenly and is not relieved by standard pain medication). The duration of action of fentanyl ranges from 6 minutes (intranasal) to 27 hours (transdermal patch) (Foster et al., 2008; NIH, 2014). Again, the standard resuscitation procedure is to administer repeat doses of naloxone, but the clinical outcome may vary from case to case.

Adverse effects

Naloxone has not been found to produce any independent psychoactive or physiological effects of note. However, if opioids are already present in the system, naloxone competitively displaces them from opioid receptors in both the brain and the periphery. This may trigger a secondary loss of opioid pain relief, the emergence of a time-limited acute withdrawal syndrome, or both (see also Chapter 2, section on 'Side effects of emergency naloxone', such as precipitated withdrawal and renarcotisation). Patient-specific effects of naloxone, including pulmonary oedema, have been reported, although these may be related to the individual's underlying health conditions and independent of the actions of naloxone. Adverse effects usually occur when naloxone is provided during or after an operation, after administration of morphine as an analgesic. In non-opioid-dependent patients, the most commonly reported side effect of using naloxone is the reversal of the analgesia (Pasternak, 2006).

Naloxone may sometimes be administered in cases where respiratory depression is not due to opioid overdose. If naloxone is administered in the absence of opioid drugs (or of physiological dependence and an ongoing abstinence syndrome), it is unlikely to produce any pharmacological activity at all. Studies of subcutaneous naloxone administration have not found any subjective effects, and even very high doses of naloxone (24–30 mg) have been found to cause only slight drowsiness (McEvoy, 2012; Palermo, 1999). In other studies, extremely high-dose intravenous naloxone (up to 5.4-mg/kg boluses and 4 mg/kg/h) has been administered without adverse effects (Bracken et al., 1990; Groeger and Inturrisi, 1987), although mild elevations in blood pressure and decreased performance in memory tests were seen with doses exceeding 20 mg (Terman, 2012). However, with the high risk of mortality in opioid overdose, the risk–benefit ratio of naloxone administration is clearly acceptable (Kim et al., 2009).

Summary

Opioids are a particularly interesting group of drugs that have been used for centuries (in particular, opium, before morphine was originally isolated) for their pain-relieving, sedative, anti-anxiolytic and cough-suppressant effects. However, they also possess a negative side effect that has been the crux of pharmaceutical development over many decades: respiratory depression, a dangerous reduction in breathing. Opioids act on a wide range of areas of the brain and body through molecules that elicit or inhibit effects (known as receptors).

In an opioid overdose, the impact of opioids on breathing centres of the brain can cause respiratory depression, which leads to low levels of oxygen in the blood and, if prolonged, can cause loss of consciousness, organ failure and death. There are numerous risk factors influencing the likelihood of an overdose, including, but not limited to, the type of opioid, its strength and the amount that is absorbed into the blood. Individual factors, such as tolerance, current health status, duration of use and genetic influences, among others, add to the intricacy and complexity surrounding opioid overdose.

Naloxone is a safe and effective antidote to the respiratory-depressant effects of heroin and other opioids. It works best in reversing the effects of a heroin or morphine overdose, but, depending on dose and route of administration, it also works to reverse respiratory depression caused by other opioids, including methadone. The short duration of action of naloxone means that repeated doses may be required for full effectiveness at reversing respiratory depression.

Naloxone has a strong affinity for the opioid receptors, particularly μ receptors, and it works by competing with the opioid and taking its space on the receptor, thereby

deactivating the receptor and reversing overdose. Naloxone itself has very few independent effects but does precipitate an acute withdrawal syndrome if given to a person who is dependent on opioids. The following chapters will explore the evidence surrounding the use of naloxone in preventing overdose deaths, with a particular focus on the provision of emergency naloxone to those who are likely to be present at an overdose.

Recommended reading

Darke, S. (2011), *The life of the heroin user: Typical beginnings, trajectories and outcomes*, Cambridge University Press, Cambridge.

EMCDDA (2015), *Preventing overdose deaths in Europe* (http://www.emcdda.europa.eu/topics/pods/preventing-overdose-deaths).

Pattinson, K. T. S. (2008), 'Opioids and the control of respiration', *British Journal of Anaesthesia* 100, pp. 747–758 (http://bja.oxfordjournals.org/content/100/6/747.long).

References

AHFS (2014), *Methadone*, MedlinePlus, National Institutes of Health, US National Library of Medicine (https://www.nlm.nih.gov/medlineplus/druginfo/meds/a682134.html).

Berridge, V. (1999), *Opium and the people: opiate use and drug control policy in the nineteenth and early twentieth century England*, Free Association Books, London.

Bracken, M. B., Shephard, M. J., Collins, W. F., Holford, T. R., Young, W., Baskin, D. S. Eisenberg, H. M., Flamm, E. et al. (1990), 'A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury: results of a the second national acute spinal cord injury study', *The New England Journal of Medicine* 322, pp. 1405–1411.

Brunton, L., Blumenthal, D., Buxton, I. and Parker, K. (editors) (2008), *Goodman and Gilman's manual of pharmacology and therapeutics*, McGraw Hill Medical, New York.

Cone, E. J., Dickerson, S., Paul, B. D. and Mitchell, J. M. (1993), 'Forensic drug testing for opiates: V. Urine testing for heroin, morphine, and codeine with commercial opiate immunoassays', *Journal of Analytical Toxicology* 17, pp. 156–164.

Darke, S., Duflou, J. and Torok, M. (2010), 'A reduction in blood morphine concentrations amongst heroin overdose fatalities associated with a sustained reduction in street heroin purity', *Forensic Science International* 198, pp. 118–120.

Darke, S. and Farrell, M. (2014), 'Would legalizing illicit opioids reduce overdose fatalities? Implications from a natural experiment', *Addiction* 109, pp. 1237–1242.

Davidson, P. J., McLean, R. L., Kral, A. H., Gleghorn, A. A., Edlin, B. R. and Moss, A. R. (2003), 'Fatal heroin-related overdose in San Francisco, 1997–2000: a case for targeted intervention', *Journal of Urban Health* 80, pp. 261–273.

Dayer, P., Collart, L. and Desmeules, J. (1994), The pharmacology of tramadol, *Drugs* 47, pp. 3–7.

Dowling, J., Ibister, G. K., Kirkpatrick, C. M., Naidoo, D. and Graudins, A. (2008), 'Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers', *Therapeutic Drug Monitoring* 30, pp. 490–496.

Doyon, S., Aks, S. E. and Schaeffer, S. (2014), 'Expanding access to naloxone in the United States: position statement', *Journal of Medical Toxicology* 10, pp. 431–434.

eMC (Electronic Medicines Compendium) (2013), Diamorphine hydrochloride injection 30mg: pharmacological properties (http://www.medicines.org.uk/emc/medicine/28258).

Fischer, C. G. and Cook, D. R. (1974), 'The respiratory and narcotic antagonistic effects of naloxone in infants', *Anesthesia and Analgesia* 53, pp. 849–852.

Foster, D., Upton, R., Christrup, L. and Popper, L. (2008), 'Pharmacokinetics and pharmacodynamics of intranasal versus intravenous fentanyl in patients with pain after oral surgery', *Annals Pharmacotherapy* 42, pp. 1380–1387.

Frisher, M., Baldacchino, A., Crome, I. and Bloor, R. (2012), 'Preventing opioid overdoses in Europe : a critical assessment of known risk factors and preventative measures', EMCDDA technical reports (available at http://www.emcdda.europa.eu/scientific-studies/2012/preventing-overdoses).

Girardin, F. (2003), 'Pharmacokinetics of high doses of intramuscular and oral heroin in narcotic addicts', *Clinical Pharmacology and Therapeutics* 74, pp. 341–352.

Groeger, J. and Inturrisi, C. E. (1987), 'High-dose naloxone: pharmacokinetics in patients in septic shock', *Critical Care Medicine* 15, pp. 751–756.

Hakkinen, M. (2015), 'Buprenorphine/pregabalin/temazepam overdose: fatal poisoning following abuse: 2 Case reports', *Reactions Case Reports* 1556, p. 67.

Holmquist G. L. (2009), 'Opioid metabolism and effects of cytochrome P450', *Pain Medicine* 10, pp. 20–29.

International Classification of Diseases (2016), International Statistical Classification of Diseases and Related Health Problems 10th Revision. World Health Organisation, Geneva, Switzerland.

Inturrisi, C. E., Schultz, M., Shin, S., Umans, J. G., Angel, L. and Simon, E. J. (1983), 'Evidence from opiate binding studies that heroin acts through its metabolites', *Life Sciences* 33 (Suppl. 1), pp. 773–776.

Jacob, J. J., Michaud, G. M. and Tremblay, E. C. (1979), 'Mixed agonist–antagonist opiates and physical dependence', *British Journal of Clinical Pharmacology* 7 (Suppl. 3), pp. 291s–296s.

Jegu, J., Gallini, A., Soler, P., Montastruc, J-L. and Lapeyre-Mestre, M. (2011), Slow-release oral morphine for opioid maintenance treatment: a systematic review, *British Journal of Clinical Pharmacology* 71, pp. 832–843.

Joint Formulary Committee (2014), 'Naloxone hydrochloride', in *British National Formulary for Children,* Pharmaceutical Press, London (available at https://www.medicinescomplete.com/mc/bnfc/current/).

Joseph, H., Stancliff, S. and Langrod, J. (2000), 'Methadone maintenance treatment (MMT): a review of historical and clinical issues', *Mount Sinai Journal of Medicine* 67, pp. 347–364.

Kim, D., Irwin, K. S. and Khoshnood, K. (2009), 'Expanded access to naloxone: options for critical response to the epidemic of opioid overdose mortality', *American Journal of Public Health* 99, pp. 402–407.

Klous, M. G., Van den Brink, W., Van Ree, J. M. and Beijnen, J. H. (2005), 'Development of pharmaceutical heroin preparations for medical co-prescription to opioid dependent patients', *Drug and Alcohol Dependence* 80, pp. 283–295.

Leino, K., Mildh, L., Lertola, K., Seppala, T. and Kirvela, O. (1999), 'Time course of changes in breathing pattern in morphine- and oxycodone-induced respiratory depression', *Anaesthesia* 54, pp. 835–840.

Levitzky, M.G. (2013), *Pulmonary physiology*, 8th edition, McGraw Hill, New York.

Machara, A., Werner, L., Endoma-Arias, M. A., Cox, D. P. and Hudlicky, T. (2012), 'Improved synthesis of buprenorphine from thebaine and/or oripavine via palladium-catalyzed N-demethylation/acylation and/or concomitant O-demethylation', *Advanced Synthesis and Catalysis* 354, pp. 613–626.

Merriam–Webster dictionary (2015), 'Pro-drug', *Encyclopaedia Britannica* (available at http://www.merriam-webster.com).

McEvoy, G. K. E. (2004), 'Naloxone', *American Hospital Formulary Service (AHFS) drug information*, American Society of Health-System Pharmacists, Bethesda, MD, pp. 2093–2095.

McEvoy, G. K. E. (2012), 'Naloxone hydrochloride', *American Hospital Formulary Service (AHFS) drug information*, American Society of Health-System Pharmacists, Bethesda, MD, pp. 2236–2239.

Mégarbane, B., Buisine, A., Jacobs, F., Résière, D., Chevillard, L., Vicaut, E. and Baud, F. J. (2010), 'Prospective comparative assessment of buprenorphine overdose with heroin and methadone: clinical characteristics and response to antidotal treatment', *Journal of Substance Abuse Treatment* 38, pp. 403–407.

MHRA (Medicines and Healthcare Products Regulatory Agency) (2011), *Naloxone hydrochloride 400 micrograms/ml solution for injection* (http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con114431.pdf).

Nguyen, T., Englin, E., Palecek, W. and Wombwell, E. (2012), 'Use of naloxone for the management of opioid overdose', *IOSR Journal of Pharmacy* 2, pp. 8–11.

NIDA (2014), *Prescription drug abuse*, Research Report Series 15, National Institute of Drug Abuse, National Institutes of Health, Bethesda, MD.

NIH (2007a), *Naloxone hydrochloride injection*, National Institutes of Health (NIH), US National Library of Medicine (available at http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=76f7eee1-d524–43a4-a868-ffa9f29638a6).

NIH (2007b), *Methadone hydrochloride injection, solution*, National Institutes of Health (NIH), US National Library of Medicine (available at http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5581).

NIH (2014), *Duragesic – fentanyl patches*, National Institutes of Health, US National Library of Medicine (available at http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d7aade83–9e69–4cd5–8dab-dbf1d7b89bb4).

ONS (2014), *Deaths related to drug poisoning in England and Wales, 2013*, Office for National Statistics: Statistical Bulletin (available at http://www.ons.gov.uk/ons/rel/subnational-health3/deaths-related-to-drug-poisoning/england-and-wales---2013/stb---deaths-related-to-drug-poisoning-in-england-and-wales--2013.html).

Palermo, P. (2001), *A method of preventing abuse of opioid dosage forms,* Google Patents (https://docs.google.com/viewer?url=patentimages.storage.googleapis.com/pdfs/US6228863.pdf).

Pasternak, G. W. (2006), 'Opioids', in Hemmings, H. C. and Hopkins, P. M. (editors), *Foundations of anaesthesia: basic sciences for clinical practice*, 2nd edition, Elsevier, Oxford, pp. 373–383.

Pattinson, K. T. (2008), 'Opioids and the control of respiration', *British Journal of Anaesthesia* 100, pp. 747–758.

Pazos, A. and Florez, J. (1984), 'A comparative study in rats of the respiratory depression and analgesia induced by mu- and delta-opioid agonists', *European Journal of Pharmacology* 99, pp. 15–21.

Rinner, U. and Hudlicky, T. (2012), 'Synthesis of morphine alkaloids and derivatives', in Knölker, H.-J. (editor), *Alkaloid Synthesis: Topics in Current Chemistry* 309, Springer, Berlin, pp. 33–66.

Rook, E. J., Van Ree, J. M., Van Den Brink, W., Hillebrand, M. J. X., Huitema, A. D. R., Hendriks, V. M. and Beijnen, J. H. (2006), 'Pharmacokinetics and pharmacodynamics of high doses of pharmaceutically prepared heroin, by intravenous or by inhalation route in opioid-dependent patients', *Basic and Clinical Pharmacology and Toxicology* 98, pp. 86–96.

Sachdeva, D. K. and Jolley, B. T. (1997), Tramadol overdose requiring prolonged opioid antagonism, *The American Journal of Emergency Medicine* 15, pp. 217–218.

Sawynok, J. (1986), 'The therapeutic use of heroin: a review of the pharmacological literature', *Canadian Journal of Physiology and Pharmacology* 64, pp. 1–6.

Segal, S., Anyan, W. R., Hill, R. M., Kauffman, R. E., Mofenson, H., Pruitt, A. W. et al. (1980), 'Naloxone use in newborns', *Pediatrics* 65, pp. 667–669.

Shook, J. E., Watkins, W. D. and Camporesi, E. M. (1990), 'Differential roles of opioid receptors in respiration, respiratory

disease, and opiate-induced respiratory depression', *American Review of Respiratory Disease* 142, pp. 895–909.

Smith, H. S. (2009), 'Opioid metabolism', *Mayo Clinic Proceedings* 84, pp. 613–624.

Smith, K., Hopp, M., Mundin, G., Leyendecker, P., Bailey, P., Grothe, B. et al. (2008), 'Single- and multiple-dose pharmacokinetic evaluation of oxycodone and naloxone in an opioid agonist/antagonist prolonged-release combination in healthy adult volunteers', *Clinical Therapeutics* 30, pp. 2051–2068.

Stamer, U., Stuber, F., Muders, T. and Musshoff, F. (2008), Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication, *Anaesthesia and Analgesia* 107, pp. 926–929.

Terman, G. W. (2012), 'Naloxone: effects and side effects', paper presented at conference on the role of naloxone in opioid overdose fatality prevention (http://www.fda.gov/downloads/Drugs/NewsEvents/UCM300866.pdf).

UNODC (1953), 'The opium alkaloids', in *Bulletin on narcotics*, United Nations Office on Drugs and Crime, Vienna, Austria pp. 13–14.

UNODC and WHO (2013), *Opioid overdose: preventing and reducing opioid overdose mortality*, discussion paper, United Nations Office on Drugs and Crime, Vienna.

Waldron, V. D., Klimt, C. R. and Seibel, J. E. (1973), '*Methadone Overdose Treated With Naloxone Infusion', JAMA* 225, pp. 53.

Wanger, K., Macmillan, I., Goulding, J., MacPhail, I. and Christenson, J. M. (1998), 'Intravenous vs subcutaneous naloxone for out-of-hospital management of presumed opioid overdose', *Academic Emergency Medicine* 5, pp. 293–299.

Watson, W. A., Steele, M. T., Muelleman, R. L. and Rush, M. D. (1998), 'Opioid toxicity recurrence after an initial response to naloxone', *Journal of Toxicology: Clinical Toxicology* 36, pp. 11–17.

WHO (2013), *WHO Model List of Essential Medicines*, 18th edition, World Health Organization, Geneva.

Yardley, W. (2013, 14 December), 'Jack Fishman dies at 83: saved many from overdose', *The New York Times* A30.

Yassen, A., Olofsen, E., van Dorp, E., Sarton, E., Teppema, L., Danhof, M. and Dahan, A. (2007), 'Mechanism-based pharmacokinetic–pharmacodynamic modelling of the reversal of buprenorphine-induced respiratory depression by naloxone: a study in healthy volunteers', *Clinical Pharmacokinetics* 46, pp. 965–980.

2

CHAPTER 2

Emergency naloxone in regular clinical practice

Kylie Reed

Naloxone availability, pricing and formulations

Naloxone is a prescription-only medication in most countries. Globally, access to naloxone is generally limited to health professionals, and in many countries there is limited availability of naloxone even in medical settings, including ambulances (WHO, 2014).

There is variation across Europe in the authorisation and availability of naloxone in emergency settings, and the administration of naloxone may be restricted to medically trained staff (see Chapter 4). In some jurisdictions the notification of overdose events can trigger a report to the police, which may discourage overdose witnesses from contacting emergency medical services (WHO, 2014).

Naloxone is formulated as naloxone hydrochloride and available in vials of 0.02 mg, 0.4 mg and 1 mg per 1 ml, 2-mg/1 ml, 2-mg/2 ml and 2-mg/5 ml pre-filled syringes and a 4-mg/10 ml multi-dose vial. It is currently not under patent and is available through generic manufacturers (WHO, 2014).

According to a survey among selected European countries conducted as follow-up to a 2014 EMCDDA expert meeting on take-home naloxone ([4]), naloxone is most frequently supplied in a concentration of 0.4 mg/ml. There is considerable variation in the price of naloxone between countries; for example, 1-ml glass ampoules cost the equivalent of EUR 8.20 in the United Kingdom versus EUR 1.38 in Poland, a unit cost five times greater. National economics do not fully account for the variation in cost; to illustrate, the United Kingdom ranks tenth in the European Union in terms of per capita gross domestic product according to Eurostat, but in Austria, which has the fourth highest per capita gross domestic product level in the European Union, a 1-ml glass ampoule of the same formulation costs just EUR 4.14, half the UK price.

This variation in cost between products can partly be explained by factors such as manufacturing and licensing costs (not explored further here). Pre-filled syringes are also typically more expensive than ampoules. In countries where naloxone products are disproportionately expensive, it is likely that cost has a substantial impact on clinical practice, especially when it concerns the introduction of a new expenditure for which no financial allowance had previously been made.

Side effects of emergency naloxone

Precipitating the acute opioid withdrawal syndrome

Naloxone is a potentially life-saving medication, and failing to use it at the earliest opportunity in cases of opioid overdose may result in the death of the overdose victim. It is essential to know how to use naloxone safely, what potential side effects can occur and how these can be managed (see Chapter 1). A rapid reversal of opioid effects by naloxone may precipitate an acute withdrawal syndrome in physiologically dependent individuals. The side effects, or unwanted effects, of naloxone can therefore include symptoms of the opioid withdrawal syndrome. Opioid withdrawal symptoms may include nausea, stomach cramps, muscular tension, muscle spasms/twitching, aches and pains, insomnia, vomiting, sweating, tachycardia, hyperventilation, increased blood pressure, trembling and violent behaviour, and the objective signs listed in Table 2.1 (Taylor et al., 2012). Most commonly, the side effects will be a component of the opioid withdrawal syndrome in varying proportions and to varying degrees.

([4]) For more information see www.emcdda.europa.eu/events/2014/meetings/naloxone

TABLE 2.1
Objective opioid withdrawal signs, based on the Objective Opioid Withdrawal Scales

Symptom	No withdrawal	Mild to moderate withdrawal	Severe withdrawal
Lactorrhoea	Absent	Eyes watery	Eyes streaming/wiping eyes
Rhinorrhoea	Absent	Sniffing	Profuse secretion (wiping nose)
Agitation	Absent	Fidgeting	Cannot remain seated
Perspiration	Absent	Clammy skin	Beads of sweat
Piloerection	Absent	Hairs barely palpably standing up	Readily palpable, visible
Pulse rate (BPM)	< 80	80–100	> 100
Vomiting	Absent	Absent	Present
Shivering	Absent	Absent	Present
Yawns/10 minutes	< 3	3–5	≥ 6
Dilated pupils	Normal < 4 mm	Dilated 4–6 mm	Widely dilated > 6 mm

Source: Taylor et al. (2012).

Acute withdrawal syndrome affects all systems of the body. It is an extremely unpleasant experience for the patient and difficult to medicate fully while maintaining reversal of toxicity. The syndrome is effectively characterised by the same aversive symptoms that would cause an opioid-dependent individual to seek opioids in the natural environment because of craving. If some of these symptoms occur following naloxone administration, support and encouragement are essential, and symptomatic medication for withdrawal may be required.

The alpha-2 adrenergic agonist lofexidine is licensed for the treatment of opioid withdrawals in the United Kingdom. It inhibits the release of noradrenaline in the central and peripheral nervous system and thereby reduces those opioid withdrawal symptoms that are due to adrenergic hyperactivity. Lofexidine is prescribed initially as 800 µg daily in divided doses, and can be increased as necessary in steps of 400–800 µg daily up to a maximum of 2.4 mg daily in divided doses, the maximum single dose being 800 µg (Joint Formulary Committee, 2015). The recommended duration of treatment is 7–10 days (without opioid use) but longer treatment may be required (Joint Formulary Committee, 2015). Further symptomatic management may also be needed.

Recurrence of toxicity

On the other side of the pharmacotherapeutic see-saw, it is possible that a patient can re-enter respiratory depression; as naloxone has a shorter half-life than some opioids that may cause overdose, the naloxone-induced blockade of opioid receptors can wear off (leading to relief from withdrawal symptoms) and respiratory depression may return. To quote Clarke et al. (2005), 'clinicians are clearly walking a tightrope between precipitating acute withdrawal symptoms and avoiding recurrence of toxicity'. Therefore, naloxone doses may need to be repeated. Furthermore, the length of time for which further monitoring is needed depends on the type of opioid used (if known to the medical professionals assessing the case); for example, if heroin has been used in combination with methadone, the latter having a longer half-life, a more protracted monitoring period may be needed.

One-quarter (12 of 47; Boyd et al., 2006) to almost one-third (26 of 84; Watson et al., 1998) of presumed heroin overdose patients need repeat doses of naloxone to avoid recurrent opioid toxicity.

In a Finnish study of the incidence of recurrent opioid toxicity and how long after pre-hospital treatment it occurs in presumed heroin-overdose patients, of the 47 patients taken to the emergency department for further monitoring who had been given naloxone and responded to it, 25 % (12 people) needed further naloxone to be administered in the emergency department because of signs of recurrent opioid toxicity, including respiratory depression in all 12 cases, or other adverse events within 1 hour after administration of naloxone before entry to hospital (Boyd et al., 2006). In the same study, however, 71 patients who had naloxone administered to them did not come to the emergency department after receiving pre-hospital naloxone, and during a 12-hour follow-up period no life-threatening events were recorded. However, the authors noted that in some cases, in this retrospective study, false identification details, such as names, dates of birth and identity numbers, may have been given, so that following up and correctly matching the data may not always have been possible. Moreover, in terms of comparing these data with results from other countries,

it should be noted that, in the majority (87 %) of cases in this study, an emergency physician was on scene to evaluate the condition of the patient, and, even when patients were treated solely by paramedics, the paramedics consulted an emergency physician before leaving a patient at the scene or in police custody. All patients had therefore been carefully assessed, including those allowed not to come to the emergency department, and the more unwell or those deemed most likely to have a recurrent respiratory depression were taken to hospital (Boyd et al., 2006). This would explain the high incidence of repeat naloxone administered to those taken to the emergency department. It also suggests that the findings regarding the low incidence of complications after leaving patients at the assessment scene should be treated with caution when making comparisons with other parts of Europe if other healthcare systems do not always provide the same level of expert on-scene assessment; without such expert assessment, a higher degree of caution would need to be applied regarding those who refuse to attend the emergency department. Expert assessment is needed to ascertain who is at greatest risk and requires ongoing monitoring. Under these circumstances of careful assessment, the authors concluded that allowing presumed heroin-overdose patients to sign out after pre-hospital care with naloxone is safe and that, if patients had been transported to an emergency department, a 1-hour observation period after naloxone administration seemed to be adequate for recurrent heroin toxicity (Boyd et al., 2006).

In a study addressing the frequency of opioid toxicity recurrence after a response to naloxone in adult emergency department patients, Watson et al. (1998) carried out a retrospective case–control study of naloxone-treated patients with opioid toxicity over an 8-year period, and found that, in approximately one-third of cases, opioid toxicity recurred after a response to naloxone. Over the study period, 221 people were given a diagnosis of opioid toxicity, of whom 90 were treated with naloxone and 84 were included in their analysis. There was a response to naloxone in 50 % of the 84 cases and, in approximately one-third of adult emergency department opioid overdose cases treated with naloxone over the 8-year period, opioid toxicity recurred after a response to naloxone (Watson et al., 1998). This is a higher figure than found in the later Finnish study (Boyd et al., 2006), where the authors had noted that only the more serious cases or those more likely to have a recurring respiratory depression attended the emergency department. Recurrence of toxicity was more common in patients who had used long-acting opioids, and was not associated with the route of opioid exposure (Watson et al., 1998).

Other authors have reported higher frequencies of repeat naloxone dosing. In one study, over 70 % of patients received two naloxone doses following continued medical assessment in the field before being signed off (Vilke et al., 2003).

Paramedics in San Diego County have a protocol that allows patients who have received naloxone to be signed off 'against medical advice' (AMA) without being admitted to hospital if they are oriented in time and place, not impaired by drugs or alcohol, are competent to refuse care, have discussed the risks and consequences and have been advised that medics will return if called back. In a retrospective study that covered a 5-year period during which a total of 998 patients were given naloxone after heroin overdoses in the field and then allowed to sign out AMA if this stringent list of safety criteria was checked first, the authors found no identifiable opioid overdose deaths (Vilke et al., 2003). It should be noted that over 70 % of the patients received two naloxone doses following continued medical assessment in the field before being signed off AMA; in other words, they did receive some continued assessment before the AMA status was reached. Moreover, of those receiving two doses, more than three in four patients (77 %) received intravenous followed by intramuscular naloxone. Intramuscular administration has slower onset than intravenous but the naloxone effect acts for longer (Vilke et al., 2003). This dosing regimen also has the potential to be explored further in future study protocols.

The risk of recurrence of toxicity and the potential need for re-administration of naloxone emphasise the importance of transferring patients to the emergency department whenever possible. Expert assessment is needed to ascertain who is at greatest risk and requires ongoing monitoring.

Other adverse reactions to naloxone

Besides the risks of precipitated withdrawals and re-intoxication, other side effects may more rarely occur. The other potential adverse effects are influenced by underlying conditions present at the time of naloxone administration (MHRA, 2011):

- cardiac disorders — tachycardia, pulmonary oedema, cardiac arrest/failure and ventricular fibrillation;
- gastrointestinal disorders — nausea and vomiting;
- nervous system disorders — convulsions, paraesthesia and grand mal convulsion;

- psychiatric disorders — agitation, hallucinations and tremulousness;
- respiratory and thoracic disorders — dyspnoea, respiratory depression and hypoxia;
- skin and subcutaneous tissue disorders — non-specific injection-site reaction and sweating;
- vascular disorders — hypertension, hypotension and hot flushes.

Evaluations of the safety and efficacy of hospital-based naloxone administration suggest that naloxone is associated with a moderately low rate (< 1.5 %) of serious adverse events (e.g. convulsions, cardiovascular problems, pulmonary oedema) and hypotension (Osterwalder, 1995, 1996; Taylor et al., 2012). Based on case studies, surveillance for at least 8 hours has been advocated in some cases after successful treatment, to exclude delayed pulmonary oedema in patients intoxicated with heroin or heroin mixtures (Osterwalder, 1995).

In the United Kingdom in 2014, following three patient safety incidents, including two that resulted in death, NHS England released advice stating that 'naloxone must be given with great caution to patients who have received longer-term opioid treatment for pain control or who are physically dependent on opioids' and pointing out that according to the *British National Formulary*, a reference book with prescribing recommendations, the doses used in acute opioid overdose may not be appropriate for palliative patients and other chronic opioid users (NHS England, 2014). The advice noted that use of naloxone in larger doses than recommended can cause a rapid reversal of the physiological effects for pain control, leading to intense pain and distress, and an increase in sympathetic nervous stimulation and cytokine release, precipitating an acute withdrawal syndrome.

Clarification regarding naloxone dosing in palliative care and for chronic pain patients receiving long-term opioids is required internationally; after naloxone administration there is still a need for careful monitoring and for maintaining or restoring pain relief (NHS England, 2014).

Route of administration of naloxone in the pre-hospital clinical setting

Naloxone is approved for administration intravenously, intramuscularly or subcutaneously. There has been particular interest in the intramuscular route because of the greater ease with which a member of the public without medical training may administer the dose, especially given that long-term drug injecting often makes it relatively difficult to find access to a vein.

Emergency medical systems vary across Europe. This may affect how and where naloxone is given, and what assessments and follow-up care take place. In 2006, for example, Boyd et al. described the emergency medical system in Helsinki as three tiered. The first tier consists of firefighters, trained as emergency medical technicians (EMTs), staffing the ambulances. The second tier consists of three advanced life-support units staffed by paramedics and one paramedic supervisor unit. The paramedics are licensed to administer drugs intravenously, such as naloxone, after physician consultation or by following written standing orders. The third tier is made up of a mobile intensive-care unit staffed by two EMT-firefighters and one emergency physician (Boyd et al., 2006).

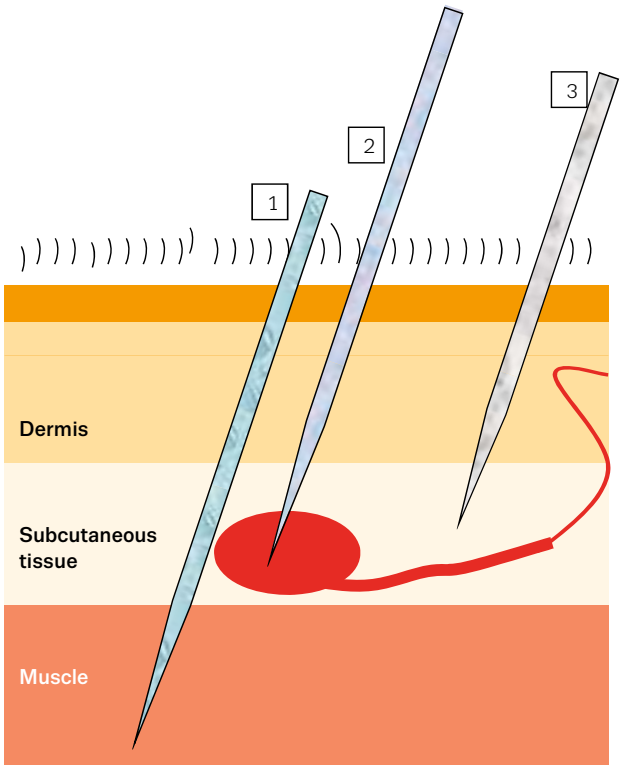
Internationally, in paramedical settings, there is a drift away from the original reliance on intravenous naloxone, with increasing numbers of ambulance crews preferring the alternative intramuscular route (Horowitz, 1998; Wanger et al., 1998), and some studies finding the intramuscular route to be as effective as the intravenous route (Sporer et al., 1996). Although other variables are introduced by intramuscular administration, such as depth of injection and muscle blood flow (Clarke et al., 2005), the greater ease of intramuscular or subcutaneous administration is also important, especially when many patients have challenging venous access (Horowitz, 1998; Wanger et al., 1998). Some studies have found the slower rate of absorption via the subcutaneous route to be offset by the greater ease of use of this route over intravenous administration, for example if there is a delay in establishing an intravenous route (Wanger et al., 1998). Also important is the likely greater ease of use by the passer-by Samaritan (Wanger et al., 1998).

The existing opioid overdose management, provision and use of naloxone within drug, ambulance and police services was surveyed throughout England in 2005 to determine the feasibility of extended naloxone access to reduce fatalities from opioid overdose. The largest group of drug services reported that they would administer naloxone intramuscularly (49 %, 36 of 73), 16 % intravenously and only 1 % subcutaneously, and 19 services reported that they used a combination of routes, predominantly intravenously and intramuscularly (23 %, 17 of 73) (Strang et al., 2007).

Horowitz (1998) notes that either an subcutaneous or an intramuscular injection of naloxone may awaken the patient more gradually than one administered intravenously and reduce the risk to the paramedic of needle-induced blood exposure. She also suggests that repeat doses and/or intravenous naloxone administration may be needed in patients who do not respond to the initial intramuscular or subcutaneous dose. An important factor to consider when comparing routes is that any future approved intranasal naloxone product — not currently licensed, and explored further in Chapter 6 — would presumably be easier to administer, primarily because it does not involve a needle. Venous access can be difficult to achieve in individuals with a history of intravenous drug use; and even intramuscular administration runs the risk of a needle-stick injury, which is hazardous in a population with a relatively high prevalence of blood-borne viruses.

Figure 2.1 illustrates the relative positions of where a naloxone dose can be administered, showing where the vein runs, set in the muscle, with the subcutaneous ('under the skin') layer above this. Above the subcutaneous layer are the three skin (cutaneous) layers, subdermal, dermal and subepidermal, illustrated here as the dermis and epidermis. The naloxone dose may be administered into a vein, muscle or the subcutaneous layer.

FIGURE 2.1
Anatomy of soft tissue layers



NB: The naloxone dose may be administered into muscle (needle 1), a vein (needle 2), or the subcutaneous layer (needle 3).

Naloxone doses

Naloxone is a registered medication in all western European countries, but advice about use and its availability vary between and within countries.

Clinically, the scenarios to consider are whether to start at a lower or higher dose within the accepted dose range (0.4–2 mg); how many repeated doses may be needed; which route would be best (intravenous, intramuscular or subcutaneous, with intranasal potentially being a future additional option; see Chapter 6); and whether or not the patient is using opioids in the long term for palliative care, which creates a different scenario from those using opioids for other reasons or overdoses in naive users.

The doses used in acute opioid overdose may not be appropriate for the management of opioid-induced respiratory depression and sedation in those receiving long-term opioids for palliative care and other chronic opioid use. The recommended dose for adults in post-operative respiratory depression and for palliative care and chronic opioid use by intravenous injection is 100–200 µg (1.5–3 µg/kg). If the response is inadequate, a subsequent dose of 100 µg should be given every 2 minutes (Joint Formulary Committee, 2014; NHS England, 2014).

Following reports of fatalities (see section 'Other adverse reactions to naloxone'; NHS England, 2014), NHS England has noted a need for further clarification on the recommended dosing regimens to be used for a patient following a suspected acute opioid overdose (as distinct from the advice for management of reduced consciousness and/or respiratory depression in chronic opioid users including some palliative care patients, which had prompted the initial report), given this lack of clarity around dosing. Within single countries there may be conflicting dosing advice from different sources (such as that provided in the *British National Formulary*, in the manufacturers' individual product characteristics documents, in ToxBase and in the Palliative Care Formulary) (NHS England, 2015). NHS England therefore emphasised that low starting doses are recommended in all of these clinical scenarios (NHS England, 2015). Arguably, however, more cautious starting doses may heighten the need for monitoring for recurrent respiratory depression (see section 'Recurrence of toxicity'), but this has yet to be explored prospectively.

UK Medicines Information has agreed to undertake the production of a document addressing the naloxone doses to be used in adults, which will consider the

relevant literature base and consult with experts in the field (NHS England, 2015). Dosing coherence across Europe would have the potential to further enhance patient safety.

With regard to naloxone dosing, the WHO guidelines on the management of opioid overdose (2014) note that 'the choice of initial dose will depend on the formulation of naloxone to be used and the context'. The guidelines note that dose titration is usually standard practice in the medical setting, and advise that, although the initial dose should be 0.4–2 mg, in most cases a dose of between 0.4 mg and 0.8 mg will be effective at targeting recovery of breathing. The guidelines also highlight the importance of achieving a balance between treating the overdose and avoiding marked opioid withdrawal symptoms, with initial doses above 0.8 mg administered intramuscularly, intravenously or subcutaneously increasing the risk of precipitating significant withdrawal symptoms.

Most European injectable naloxone formulations are dosed as 0.4 mg. In adults suffering from opioid overdose, a single dose of 0.4 mg should be administered immediately. The dose of 0.4 mg can be repeated every 2–3 minutes in subsequent resuscitation cycles until the contents of a syringe are used up (Joint Formulary Committee, 2014); or an initial adult dose of 400 µg to 2 mg of naloxone may be administered intravenously. If the desired degree of counteraction and improvement in respiratory function is not obtained, doses may be repeated at 2- to 3-minute intervals. Further doses may be needed if respiratory function deteriorates.

A dose range (rather than a specific dose) is provided in part because the amount needed to provide the necessary antagonistic effect depends upon the number of opioid receptors that have been occupied (Clarke et al., 2005), which cannot be known in advance, so, effectively, the response must be a titrated one or a higher one-dose-fits-all style solution. However, the latter risks causing a more aversive withdrawal reaction in the individual, which in the longer term could reduce the likelihood of the opioid user community engaging with naloxone.

The debate lies in the question of whether or not emergency naloxone treatment should be more explicitly based on giving an initial dose judged to be probably adequate, with the option of further doses if the overdose is not promptly reversed (i.e. titrating dose against effect).

References

Boyd, J. J., Kuisma, M. J., Alaspää, A. O., Vuori, E., Repo, J. V. and Randell, T. T. (2006), 'Recurrent opioid toxicity after pre-hospital care of presumed heroin overdose patients', *Acta Anaesthesiologica Scandinavica* 50, pp. 1266–1270.

Clarke, S. F., Dargan, P. I. and Jones, A. L. (2005), 'Naloxone in opioid poisoning: walking the tightrope', *Emergency Medicine Journal* 22, pp. 612–616.

Handelsman, L., Cochrane, K. J., Aronson, M. J., Ness, R., Rubinstein, K. J and Kanof, P. D. (1987), 'Two new rating scales for opiate withdrawal', *American Journal of Drug and Alcohol Abuse* 13, pp. 293–308.

Horowitz, Z. (1998), 'Subcutaneous naloxone: a less rude awakening?', *Academic Emergency Medicine* 5, pp. 283–285.

Joint Formulary Committee (2014), *British National Formulary (BNF),* Pharmaceutical Press, London.

MHRA (2011), 'Naloxone hydrochloride 400 micrograms/ml solution for injection' (http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con114431.pdf).

NHS England (2014), 'Patient safety alert: risk of distress and death from inappropriate doses of naloxone in patients on long-term opioid/opiate treatment' (http://www.england.nhs.uk/wp-content/uploads/2015/02/psa-naloxone-supp-info.pdf).

NHS England (2015), 'Further supporting information: patient safety alert. Risk of distress and death from inappropriate doses of naloxone in patients on long-term opioid/opiate treatment' (http://www.england.nhs.uk/wp-content/uploads/2015/02/psa-naloxone-supp-info.pdf).

Osterwalder, J. J. (1995), 'Patients intoxicated with heroin or heroin mixtures: how long should they be monitored?', *European Journal of Emergency Medicine*, 2, pp. 97–101.

Osterwalder, J. J. (1996), 'Naloxone for intoxications with intravenous heroin and heroin mixtures: harmless or hazardous? A prospective clinical study', *Journal of Toxicology — Clinical Toxicology* 34(4), pp. 409–416.

Sporer, K. A., Firestone, J. and Isaacs, S. M. (1996), 'Out-of-hospital treatment of opioid overdoses in an urban setting', *Academic Emergency Medicine* 3, pp. 660–667.

Strang, J., Manning, V., Mayet, S., Kelleher, M., Semmler, C., Offor, L. et al. (2007), *The naloxone programme: Investigation of the wider use of naloxone in the prevention of overdose deaths in pre-hospital care*, National Treatment Agency for Substance Misuse, London.

Taylor, D., Paton, C. and Kapur, S. (2012), *Maudsley prescribing guidelines in psychiatry*, 11th edition, Wiley-Blackwell, Chichester.

Vilke, G. M., Sloane, C., Smith, A. M. and Chan, T. C. (2003), 'Assessment for deaths in out-of-hospital heroin overdose patients treated with naloxone who refuse transport', *Academic Emergency Medicine* 10, pp. 893–896.

Wanger, K., Brough, L., Macmillan, I., Goulding, J., MacPhail, I. and Christenson, J. M. (1998), 'Intravenous vs subcutaneous naloxone for out-of-hospital management of presumed opioid overdose', *Academic Emergency Medicine* 5, pp. 293–299.

Watson, W. A., Steele, M. T., Muelleman, R. L. and Rush, M. D. (1998), 'Opioid toxicity recurrence after an initial response to naloxone', *Journal of Toxicology — Clinical Toxicology* 36, pp. 11–17.

WHO (2014), *Community management of opioid overdose*, WHO, Geneva (available at http://www.who.int/substance_abuse/publications/management_opioid_overdose/en/).

3

CHAPTER 3

Opioid overdose deaths: risks and clusterings in time and context

Anna Williams and John Strang

Overdose deaths in the European Union: trends over time

The EMCDDA epidemiological key-indicator 'drug-related deaths and mortality' has two components: deaths directly caused by illegal drugs (drug-induced deaths, commonly referred to as poisonings or drug overdoses) and deaths among problem drug users as a consequence of drug-related diseases, violence or accidents. In line with the EMCDDA definition (EMCDDA, 2010), in this publication, the term 'overdose' is used to describe a drug-induced death that occurs generally shortly after the consumption of the substance.

Since the EMCDDA assumed its role of monitoring the European drug situation in 1995, more than 140 000 drug-related deaths have been reported in Europe. This is an underestimate of the real number, as data gaps exist and under-reporting or under-ascertainment ([5]) of drug-induced deaths occur in some countries.

Overall, across the 30 countries reporting to the EMCDDA (the 28 EU Member States, Norway and Turkey), between 6 000 and 8 000 drug-induced deaths (overdoses) a year are reported, and the majority of them are associated with heroin and other opioids (EMCDDA, 2015). Most countries reported an increasing trend in overdose deaths from 2003 until around 2008/9, when overall levels first stabilised and then began to decline, but this stalled and, in recent years, deaths have remained at high levels with no clear trend. For 2013, the average mortality rate due to overdoses in Europe was estimated at 16 deaths per million inhabitants in the age range of 15–64 years, with some countries, including Estonia, Norway and Sweden, reporting multiples of that rate (between 70 and 127 deaths per million population). Direct comparison of countries is, however, difficult, as national differences exist in coding and reporting practices, and systematic under-reporting in some countries may also happen (EMCDDA, 2015, pp. 56–57).

Opioid-related deaths are of particular importance for policy and public health action, since many of them are potentially preventable by a number of different interventions, including the timely emergency administration of the opioid antagonist naloxone. Besides heroin, other opioids including methadone, buprenorphine, fentanyls and tramadol are regularly mentioned in toxicological reports, and these substances are now associated with a substantial share of overdose deaths in some countries (EMCDDA, 2015, p. 57). Other central nervous system depressants including alcohol and medicines, in particular benzodiazepines, may also be causally implicated.

Personal predictors of risk

Compared with the beginning of the heroin epidemics in Europe in the 1980s, there is now more knowledge about which individuals are at greatest risk of overdose death, as well as a more precise understanding of when they are at particularly increased risk (see Frisher et al., 2012).

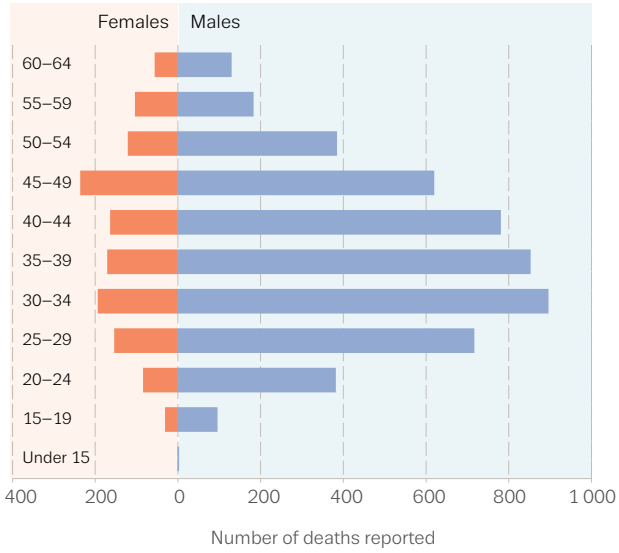
Variation in overdose mortality by age and gender

Examination of overall patterns reveals some important characteristics, which have a direct bearing on personal predictors of risk. Patterns of deaths and their distribution by age and gender are of obvious importance.

Europe's opioid-using population is ageing, and risk of overdose death increases with age. The ageing trend among the user population is reflected in mortality data: between 2006 and 2013, overdose deaths decreased

([5]) Under-ascertainment refers to false negatives, i.e. cases that fulfil the criteria of a drug-induced death but are not identified as such.

FIGURE 3.1
Age pyramid of drug-induced deaths reported in 2014



among younger users, but increases were found among older users (EMCDDA, 2015, p. 56).

Of all recorded drug-induced deaths in Europe, 43 % occur in individuals aged 40 and older, with a further 47 % in the 25–39 age bracket and only 10 % among those aged under 25 years (EMCDDA, 2014; see Figure 3.1).

A gender imbalance is evident in data, with 77 % of all reported drug-induced deaths being of males. This reflects the predominance of males in the current opioid user population. For example, 80 % of all clients who entered drug treatment with heroin as their primary drug in 2013 were men (EMCDDA, 2015). This suggests that drug-induced deaths are only half as likely to happen to women as to their male drug-using counterparts. This greater mortality risk due to drug overdose among men using opioids remains striking even after controlling for other variables (Bird, 2010; Bird et al., 2003; Merrall et al., 2012; Pierce et al., 2015). The gender difference could perhaps be related to female opioid users being less likely to inject, using smaller amounts and using in the company of others (Powis et al., 1996). Female users might also be better at perceiving risk than males, while males tend to take greater risks (Sheedy et al., 2003; Spigner et al., 1993). However, study of these data has thus far not adequately explained either the age difference or the gender difference.

Heroin use career

Length of exposure to injection drug use has also been identified as an important risk factor for overdose death. Chronic users are at greater risk than naive users; nevertheless, recreational users can also become fatal cases (Zador et al., 1996). Other common characteristics of overdose victims have been identified as being single, being in deprived circumstances, having severe depressive symptoms and not being in treatment (Cornish et al., 2010; Warner-Smith et al., 2001).

Poor health

Overdose can also be associated with poor health. Opioid users have poorer health status than the general population, and some factors such as impaired liver function resulting from chronic viral infections could put them at greater risk of overdosing. Hepatitis B and C are highly prevalent among drug users and also among fatal cases. An association between heroin overdose mortality and liver disease (hepatitis B and C) has been suggested (Sheedy et al., 2003). It is likely that reduced metabolism of opioids in a damaged liver may prolong the depth and duration of intoxication, increasing the risk and dangers of overdose (Warner-Smith et al., 2001). Finally, it is also important to consider the effect that changes in body function related to normal ageing might have in increasing overdose risk. This is particularly relevant because the heroin-using population in Europe is ageing.

A typology of drug overdose

Drug overdoses can usually be considered as being either accidental or with clear suicidal intent. Although suicidal ideation contributes to at least some drug overdoses, it is clearly a minor contribution. In general, the vast majority of overdoses in this population are in the category of accidental drug overdose (Farrell et al., 1996). It is worth noting that toxicological tests can be inconsistent and opioid overdose nomenclature can vary, so some deaths might be misidentified. Some opioid-related deaths will also fall into an overlap zone where, despite the absence of overt suicidal intent, there was nevertheless a lack of regard to safety as a result of personal mood state and circumstances (Vingoe et al., 1999). Regarding the potential contribution of wider use of naloxone, it is likely that we will observe the biggest benefit from take-home naloxone in accidental drug overdoses that occur in the presence of peers or in a family home.

From a pharmacological and physiological perspective, overdoses can be further distinguished into sudden- and slow-onset cases. In sudden-onset (also called catastrophic) overdoses, the victim may lose

consciousness with the needle still in situ, whereas in slow-onset (also called insidious) overdose cases the victim may be thought to be sleeping soundly when in reality they are drifting into coma; death may occur not as a result of lack of emergency medication but simply because friends or family fail to realise the danger. The sudden-onset, catastrophic overdose occurs classically after intravenous administration of heroin, whereas overdose with oral methadone or oral pharmaceutical opioids would typically be a slow-onset, insidious overdose.

Identification of further drug-use risk factors

The risk of overdose from heroin (and other opioids) is increased by a range of individual and behavioural factors (pharmacological aspects of opioid overdose are explored in Chapter 1). Firstly, blood morphine concentrations detected in instances of apparently clear heroin overdose death are often not significantly different from the blood levels detected in individuals taking heroin without detectable overdose (Darke and Zador, 1996; Zador et al., 1996). Secondly, even in the context of supervised heroin maintenance treatment, sudden-onset heroin overdose still occasionally occurs, even though the individual patient has had their dose personally titrated and is being supervised (Oviedo-Joekes et al., 2009; Strang et al., 2010). We need to realise that factors that we do not easily recognise nevertheless contribute to unexpected overdose events in ways that neither we nor heroin users themselves adequately understand.

However, some factors are within our understanding (some increasing the risk of overdose and of fatal outcome, and others decreasing it). Below, we will look at these, first those that are related to behaviour and then the factors related to situation.

Behavioural risk factors

Injection use

Heroin overdose is particularly associated with the use of the drug by injection. The stark difference in risk of overdose was evident in the London-based study comparing heroin users who were taking their heroin by injection with those who were 'chasing the dragon' (see Table 1.3 in Chapter 1) (Griffiths et al., 1994; Strang et al., 1999a). Only 2 % of the heroin chasers had overdosed, compared with 31 % of the heroin injectors (Gossop et al., 1996). Whatever various factors may influence this difference in overdose risk, they are likely to include the irreversibility of pressing the syringe-plunger compared with the slower process of 'chasing the dragon', which, by occurring over several minutes, allows for the possibility of titrating the drug dose against effect (and perhaps stopping any further heroin use if the heroin is found to be exerting an unexpectedly powerful effect, for example).

Of the possible injection routes (intravenous, intramuscular, subcutaneous), it is intravenous drug use, which is most likely to cause sudden-onset overdose, presumably because of the rapid induction of respiratory depression by the bolus of heroin as it reaches the respiratory drive centres in the brain.

Although injecting heroin presents a greater risk of mortality, it needs to be remembered that routes with a slower onset of action may contribute to slow-onset overdose. Non-injecting routes may be a greater risk when other substances are ingested simultaneously (Darke and Ross, 2000). Another particular risk moment in the heroin user's career is when a heroin smoker chooses to inject for the first time. It is a common scenario for drug addicts to initiate their heroin use by snorting or 'chasing the dragon' and then change their habit to injecting as their tolerance increases (Donoghoe, 1999). This change in the route of administration increases their chances of overdose and also puts them at greater risk for contracting a blood-borne virus.

It is possible to rank routes of administration (assuming dose and purity are not influences in this consideration) by descending risk of overdose: intravenous, intramuscular, inhalation, intranasal, and oral (see Table 1.3 for detailed description).

The influence of concurrent use of other substances

There is an increased risk of overdose from heroin or other opioids if alcohol and other sedative drugs (e.g. benzodiazepines) are also consumed (Pierce et al., 2015). The use of a 'cocktail' of drugs (or of drugs and alcohol) contributes to a great number of the deaths caused by a drug-induced overdose. In the presence of other depressant drugs, a dose of heroin that is usually well tolerated can prove fatal.

Experimental research in a clinical laboratory setting has tested the extent to which benzodiazepines aggravate the degree of respiratory depression resulting from opioids (Lintzeris et al., 2006, 2007). The co-administration of benzodiazepines makes respiratory depression more severe, thus giving laboratory

confirmation of the effects observed clinically, epidemiologically and in forensic analyses.

There is now good awareness that the risk overdose from heroin or other opioids is increased if alcohol or other sedative drugs such as benzodiazepines have also been taken, and it is probable that such combined overdoses contribute prominently to drug overdose deaths (Bird and Robertson, 2011). However, general management remains similar, and the life-saving potential of emergency naloxone remains valid, even though the resuscitated overdose victim may still be under the influence of the sedative drug or alcohol.

Using alone

By its very nature, risk of overdose death is greatest when the overdose occurs in the absence of any witnesses. As with many other medical emergencies (epilepsy, diabetes, anaphylaxis), it often falls to others present to implement the essential initial resuscitation procedures. Additional risk factors include other situations of social isolation and marginalisation, at least partly through an increase in solitary drug use. Fear of calling official services or agency personnel (e.g. hostel staff) can further increase risk of overdose, and increase the dangerousness of overdose when it occurs.

Emergency resuscitation is obviously more likely to be effective if the person present is familiar with resuscitation techniques. Training programmes have now been established, and training both for drug users themselves (Strang et al., 2008b) and for families (Strang et al., 2008a; Williams et al., 2014) has been shown to improve knowledge and confidence regarding overdose emergency management (see Chapter 5).

Loss of tolerance

Reduced tolerance has been found to be an important risk factor for opioid-overdose deaths. Many studies have reported low blood-morphine concentrations found in autopsies of people who died of overdoses (Darke et al., 2002; Tagliaro et al. 1998). Darke and Zador (1996) reported a considerable overlap between the blood-morphine levels of people who died of overdoses and the blood-morphine levels of living heroin users. Supporting this evidence, hair analysis of a sample in Verona in Italy found that heroin-overdose fatalities occurred mainly after a period of abstinence (Tagliaro et al. 1998). Darke et al. (2002) replicated the Italian study in Australia and confirmed that people who died of heroin overdose had lower concentrations of morphine in their hair compared with current living heroin users.

Situational risk factors

Release from prison

Prisons are important for at least two different reasons. First, society produces (for other reasons, admittedly) an extraordinary concentration of drug misusers in its prison population (Fazel and Baillargean, 2011). Regarding the potential of naloxone to prevent overdose deaths, we are particularly interested in opioid users. The prevalence rates in prison compared with those in the community are startling: the population lifetime prevalence in most European countries is less than 1 % among the general public, but this contrasts sharply with prevalence rates in the region of 30 % in the prison population, both in sentenced populations (Bird et al., 1992, 1995; Fazel et al., 2006; Maden et al., 1992; Rounds-Bryant and Baker, 2007) and also in remand populations (Brooke et al., 1998; Mason et al., 1997). This disproportion is confirmed in recent European data, with the highest prevalence of heroin use reported among prisoners in Italy, Portugal, Spain and the United Kingdom, (Montanari et al., 2014). It is particularly high among (the smaller number of) female prisoners (Maden et al., 1990). Prisons can also be places where heroin use is initiated (Boys et al., 2002; Gore at al., 1995).

The second reason why we need to pay particular attention to the prison setting is that there is an extraordinarily high rate of drug overdose deaths (mostly involving heroin or other opioids) in the weeks immediately following release from prison (Binswanger et al., 2007; Bird and Hutchinson, 2003; Farrell and Marsden, 2008; Merrall et al., 2010; Seaman et al., 1998) — so much so that a commentary described this post-release period as a 'period of extremely high risk' during which we observe 'carnage among recently released prisoners' (Darke, 2008). This post-release clustering of overdose deaths has now been demonstrated in many different countries, with risk of overdose death increased more than sevenfold in the first fortnight after release (and remaining significantly elevated in the second fortnight) before gradually subsiding back to heroin users' baseline (but still high) mortality rate. Of prisoners with a previous history of heroin injecting who are released from prison, one in every 200 will die of a heroin overdose within the first 4 weeks following release from prison (Bird and Hutchinson, 2003).

Discharge from residential rehab/detox

A similar phenomenon appears to exist in the period following discharge from inpatient detoxification or following return to the general community after residential rehabilitation, although this has not been studied so intensively and rigorously. At an earlier point, Strang et al. (2003) found that opioid-dependent patients who had successfully completed detoxification treatment were more likely to die of overdose than those who had failed to complete the programme. Subsequent investigations with stronger designs have confirmed this observation (Bauer et al., 2008; Cornish et al., 2010; Davoli et al., 2007; Merrall et al., 2012; Pierce et al., 2015; Ravndal and Amundsen, 2010). These periods of abstinence may leave opioid users vulnerable to overdose when a relapse occurs. If this is correct, then it points to another instance of localisation in time and context, which can guide future initiatives to prevent opioid overdose deaths.

Start of opioid agonist treatment

Treatment is generally protective against risk of overdose death, not only in those receiving treatments involving total abstinence (such as drug-free residential rehabilitation, and naltrexone antagonist treatments) but also in ambulatory opioid-substitution treatment (most commonly methadone or buprenorphine maintenance). There is robust international research evidence that opioid substitution treatment with either methadone or buprenorphine reduces mortality from all causes, including reducing risk of drug overdose deaths (Mattick et al., 2009, 2014). However, there are complexities to the relationship between the treatment and the reduction of risk of overdose death. Several independent research studies in different countries have identified an increased risk of death for a short period of time during the first few weeks of treatment (Caplehorn and Drummer, 1999; Cornish et al., 2010) before it reaches the reduced mortality rate generally associated with this treatment (Faggiano et al., 2003). In a pattern similar to the increased mortality after release from prison, there is also a transient increased mortality rate in the weeks immediately after treatment ends.

Unexpected change of purity

It is unclear to what extent unexpected changes in purity contribute to drug overdose deaths. Even though this factor is often presented by the media, and sometimes by drug experts, as the explanation for heroin overdose deaths, it is unlikely to be a sufficient explanation. It is certainly true that there are variations in drug purity and a variety of adulterants or other psychoactive drugs are often also part of illicit heroin samples (for an analysis of the significance of different added components of illicit heroin, see Strang et al., 1997). The picture is far more complicated than the simple descriptions from coroner's courts, from newspaper reports or from expert opinions. Indeed, for many fatal overdose cases, post-mortem analyses find only relatively low blood morphine concentrations, often below or similar to those of living intoxicated heroin users, or of heroin users who died from other causes (Darke and Zador, 1996; Zador et al., 1996). Furthermore, although illicit heroin may contain a wide variety of other psychoactive or inert substances, it is rare for harmful contaminants to be detected (or tested for) in toxicological analyses of blood, drugs and used syringes.

A related protective effect is apparent from reduction in the purity (and increase in price) of street heroin, as was observed in the prolonged 'heroin drought' in Australia in the early 2000s, over which period there was a marked reduction in heroin overdose deaths (Degenhardt et al., 2005, 2006).

Speed of response of emergency services

The longer the delay between recognition of the overdose and the arrival of emergency medical services, the greater will be the risk that severe damage or overdose death may occur. This will be a greater problem in rural areas, and in communities that have poor access and poor emergency medical services. The actions of family or peers as 'first responders', including the use of naloxone, can make the difference between life and death.

Individuals likely to witness an overdose

Over recent years, we have learnt much about drug overdose deaths by interviewing individuals about their overdose experiences, using study methods such as privileged access interviewing (Griffiths et al., 1993). Such interviews typically address overdoses the individual has taken (sometimes followed by detailed debriefing on the last such event) as well as overdoses the individual has witnessed (with debriefing about the circumstances and the actions then taken). More than half of all fatal overdoses occur in the victim's home and more than half occur with another person present (Zador et al., 1996). Even greater proportions are identified when the examination is of the contexts and circumstances of all drug overdose events (Strang et al., 1999b).

Drug users and peers

The circumstances in which overdoses happen indicate that a fatal outcome can often be prevented. First, overdoses seldom take place in isolation. Most overdoses occur at private homes (McGregor et al. 1998) and, most importantly, between 70 % and 80 % of them occur in the presence of someone else: peers, family members or partners (Best et al., 2002; Darke et al., 1996; Lagu et al., 2006; McGregor et al., 1998; Powis et al., 1999; Strang et al., 2000; Tobin et al., 2005).

Another crucial characteristic of opioid overdoses is that, in the majority of cases, death will not occur instantaneously. Many deaths happen 2 or 3 hours after injection (Sporer, 1999; Zador et al., 1996). Only one-quarter of deaths happen immediately after drug administration (Darke and Zador, 1996). This time frame provides a window of opportunity for interventions to take place.

The majority of witnesses have made active interventions to address the emergency situation (Best et al., 2002; Beswick et al., 2002), even though many of the actions taken may have been incorrect. In many cases, witnesses fail to recognise the early signs of these symptoms or to distinguish them from a state of intoxication. In a London audit of overdose fatalities, Hickman et al. (2007) found that, in most of the 148 cases, the overdose symptoms were not noticed until it was too late to intervene. This may be a result of lack of knowledge and lack of training, so it should be easily remediable through the prior provision of training.

In many situations of overdose, medical help is not sought or is sought too late. One of the reasons for not calling an ambulance is fear of police involvement (Sporer, 1999). However, other reasons for not summoning emergency services have been identified, among them related costs, possible eviction from hostel accommodation or loss of tenancy, previous negative experience with hospital staff and that the victim had regained consciousness (Davidson et al., 2002; Wright et al., 2006). An ambulance is most frequently called in the fatal cases (Davidson et al., 2002), probably after failure of attempts to resuscitate the victim.

There is a mistaken belief that drug users do not help each other in overdose situations. In a naloxone feasibility survey among opioid users, 89 % of those who had witnessed an overdose death said they would have administered naloxone to the victim if they had had access to the antidote (Strang et al., 1999b). Drug users are thus willing to help, but in many cases they do not know which actions to take (or are mistaken in the beliefs they hold). A sense of responsibility and 'duty of care' for each other is clearly expressed by fellow users (Wright et al., 2006). Best and colleagues (2000b) highlight the fact that most witnesses try to assist the victims in many ways, but some actions that are not taken are among the most important ones, such as calling for an ambulance. Hickman et al. (2007) estimated that one in four fatalities could have been prevented if the witness had acted differently. Beliefs that putting the person in a cold bath, injecting salt solution or giving stimulants would help have been reported among drug users (Beswick et al., 2002; Davidson et al., 2002). All those beliefs are incorrect and can be potentially dangerous, delaying appropriate assistance being given to the victim.

Drug users need to be made aware of the particular danger of intravenous use, of injecting alone, and of mixing heroin with sedative drugs, including alcohol. Harm-reduction measures targeted at preventing overdose need to increase awareness, with the explicit objective of promoting behaviour change away from injecting, and, if not, then away from mixing drugs and from solitary injecting.

Case 1: peer-user setting, London

I was using with someone else. Their lips went blue and they stopped breathing — I knew they had gone over. Didn't have a problem putting it [naloxone] together — they came round in about 3 minutes ... I saw him walking on the street yesterday.
Clinical case studies, Davis and Finch, 2008, unpublished

Case 2: peer user/passer-by setting, Berlin

Three days ago, I was walking along the canal with a friend of mine. We saw a guy lying on the ground ... The guy was blue in the face and hardly breathing any more ... I gave him one ampoule of naloxone ... We tried to give him CPR and we called 911. Then the guy started to wake up and he started to breathe and shake a little bit. He was so thankful ... When the medics came I told them I had given him the naloxone. The medics said "Wow! So you guys have even got naloxone now?" But he thought it was great. He said we had probably just saved the guy's life.
Dettmer et al., 2001

Family members and carers

Family members of heroin users can get closely involved with their relatives' drug use. It is likely that family members may witness an overdose event, particularly when part of the same household.

Strang et al. (2008a) found that family members of opioid users do indeed witness overdose events. Most family members were concerned about a problem drug user who was currently injecting heroin and about half of these drug users had previously overdosed. About a third of family members had seen heroin being taken, and 20 % of them had already personally witnessed an overdose. About 74 % of them had not received any guidance or advice on how to manage an overdose. As a result, many family members had inaccurate knowledge of signs and of actions to take in the event of an opioid overdose. The vast majority of the sample showed high levels of motivation to receive training in overdose prevention and naloxone administration.

Case 3: partner/family setting, London

My son died of a heroin overdose, but I couldn't get to him quick enough, the paramedics couldn't revive him. My daughter is still on drugs.
Parent-carer, female, aged 49 (Strang et al., 2008a)

Case 4: partner/family setting, London

My husband injected heroin and went over, I phoned an ambulance, he stopped breathing, so I had to give CPR. He died three days later.
Peer-carer, female, aged 46 (Strang et al., 2008a)

Case 5: partner/family setting, London

I heard a noise in the bathroom and found him lying there, blue, with breathing difficulties.
Parent-carer, male, aged 55 (Strang et al., 2008a)

Case 6: partner/family setting, London

My son injected himself in our toilet, came out and then collapsed. I looked at his eyes and realised he must have used.
Parent-carer, female, aged 59 (Strang et al., 2008a)

Health workers and other settings at a macro level

Health professionals working closely with opioid users, for example professionals at treatment services, professionals at outreach services and hostel workers, are in work environments where there is a real risk of witnessing an overdose, and they should receive appropriate training. They also have an important role in providing training and information. Therefore, it is important that they feel competent and confident in their overdose management skills.

Overdose prevention is a pivotal topic for those involved with opioid users, who are already recognised as a group that has an excessive risk of mortality which is largely caused by overdoses. Proposals for the provision of take-home naloxone have been well accepted by many clinicians but translation into clinical practice has been slow. Moreover, take-home naloxone could be offered on its own or as part of a harm-reduction package which would also include training on preventing blood-borne virus transmission (hepatitis C and human immunodeficiency virus) and safer injecting. Please see further information in Chapter 5.

Conclusion

Training of family and friends is increasingly being recognised as an essential component of urgent interim management and maintenance of breathing and airway while awaiting arrival of emergency medical care.

Willingness to take part in training is greatest when people realise a family member or friend is potentially at risk of overdosing (Seal et al., 2003; Worthington et al., 2006; Wright et al., 2006). On the other hand, the fact that naloxone administration involves the use of a syringe and a needle can act as a major psychological barrier for many non-medical professionals who could otherwise give a life-saving dose of naloxone.

Training of family and peers and provision of take-home naloxone are important strategies that can prevent or minimise the excessive mortality among opioid users.

References

Bargagli, A. M., Hickman, M., Davoli, M., Perucci, C. A., Schifano, P., Buster, M. et al. (2006), 'Drug-related mortality and its impact on adult mortality in eight European countries', *European Journal of Public Health* 16, pp. 198–202.

Bauer, S. M., Loipl, R., Jagsch, R., Gruber, D., Risser, D., Thau, K. and Fischer, G. (2008), 'Mortality in opioid-maintained patients after release from an addiction clinic', *European Addiction Research* 14, pp. 82–91.

Best, D., Gossop, M., Man, L. H., Stillwell, G., Coomber, R. and Strang, J. (2002), 'Peer overdose resuscitation: multiple intervention strategies and time to response by drug users who witness overdose', *Drug and Alcohol Review* 21, pp. 269–74.

Beswick, T., Best, D., Bearn, J., Rees, S., Gossop, M., Coomber, R. and Strang, J. (2002), 'From salt injection to naloxone: accuracy and myths in peer resusucitation methods for opiate overdose', *Journal of Drug Issues*, 32, pp. 1103–1114.

Binswanger, I. A., Stern, M. F., Deyo, R. A., Heagerty, P. J., Cheadle, A., Elmore, J. G. and Koepsell, T. D. (2007), 'Release from prison: a high risk of death for former inmates', *New England Journal of Medicine* 356, pp. 157–165.

Bird, A. G., Gore, S. M., Jolliffe, D. W. and Burns, S. M. (1992), 'Anonymous HIV surveillance in Saughton Prison, Edinburgh', *AIDS* 6, pp. 725–733.

Bird, A. G., Gore, S. M., Cameron, S., Ross, A. J. and Goldberg, D. J. (1995), 'Anonymous HIV surveillance with risk factor elicitation at Scotland's largest prison, Barlinnie', *AIDS* 9, pp. 801–808.

Bird, S. M. (2010), 'Over 1200 drugs-related deaths and 190000 opiate-user-years of follow-up: relative risks by sex and age-group', *Addiction Research and Theory* 18, pp. 194–207.

Bird, S. M. and Hutchinson, S. J. (2003), 'Male drugs-related deaths in the fortnight after release from prison: Scotland, 1996–99', *Addiction* 98, pp. 185–190.

Bird, S. M. and Robertson, J. R. (2011), '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* 19, pp. 170–178.

Bird, S. M., Hutchinson, S. J. and Goldberg, D. J. (2003), 'Drug-related deaths by region, sex, and age group per 100 injecting drug users in Scotland, 2000–01', *The Lancet* 362(9388), pp. 941–944.

Boys, A., Farrell, M., Bebbington, P., Brugha, T., Coid, J., Jenkins, R. et al. (2002), 'Drug use and initiation in prison: results from a national prison survey in England and Wales', *Addiction* 97, pp. 1551–1560.

Brooke, D., Taylor, C., Gunn, J. and Maden, A. (1998), 'Substance misusers remanded to prison: a treatment opportunity?', *Addiction* 93, pp. 1851–1856.

Caplehorn, J. R. M. and Drummer, O. H. (1999), 'Mortality associated with New South Wales methadone programs in 1994: lives lost and saved', *Medical Journal of Australia* 170, pp. 104–109.

Cornish, R., Macleod, J., Strang, J., Vickerman, P. and Hickman, M. (2010), 'Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database', *BMJ* 341, pp. c5475.

Darke, S. (2008), 'From the can to the coffin: deaths among recently released prisoners', *Addiction* 103, pp. 256–257.

Darke, S. and Ross, J. (2000), 'Fatal heroin overdoses resulting from non-injecting routes of administration, NSW, Australia, 1992–1996', *Addiction* 95, pp. 569–573.

Darke, S. and Zador, D. (1996), 'Fatal heroin 'overdose': a review'. *Addiction* 91, pp. 1765–1772.

Darke, S., Ross, J. and Hall, W. (1996), 'Overdose among heroin users in Sydney, Australia: II. Responses to overdose', *Addiction* 91, pp. 413–417.

Darke, S., Hall, W., Kaye, S., Ross, J. and Duflou, J. (2002), 'Hair morphine concentrations of fatal heroin overdose cases and living heroin users', *Addiction 97*, pp. 977–984.

Davidson, P. J., Ochoa, K. C., Hahn, J. A., Evans, J. L. and Moss, A. R. (2002), 'Witnessing heroin-related overdoses: the experiences of young injectors in San Francisco', *Addiction* 97, pp. 1511–1516.

Davoli, M., Bargagli, A. M., Perucci, C. A. et al. (2007), 'Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE study, a national multi-site prospective cohort study', *Addiction* 102, pp. 1954–1959.

Degenhardt, L., Day, C., Dietze, P., Pointer, S., Conroy, E., Collins, L. and Hall, W. (2005), 'Effects of a sustained heroin shortage in three Australian States', *Addiction* 100, pp. 908–920.

Degenhardt, L., Day, C., Gilmour, S. and Hall, W. (2006), 'The "lessons" of the Australian "heroin shortage"', *Substance Abuse Treatment, Prevention, and Policy* 1, pp. 1–7.

Dettmer, K., Saunders, B. and Strang, J. (2001), 'Take-home naloxone and the prevention of deaths from opiate overdose: two pilot schemes', *BMJ* 322, pp. 895–896.

Donoghoe, M. (1999), 'Opioid overdose: an international perspective', *Addiction* 94, p. 1745.

EMCDDA (2010), *EMCDDA standard protocol to collect data and report figures for the key indicator drug-related deaths* (DRD-Standard, version 3.2), European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

EMCDDA (2014), *European drug report 2014: Trends and developments*, Publications Office of the European Union, Luxembourg.

EMCDDA (2015), *European drug report 2015: Trends and developments*, Publications Office of the European Union, Luxembourg.

Faggiano, F., Vigna-Taglianti, F., Versino, E. and Lemma, P. (2003), *Methadone maintenance at different dosages for opioid dependence*, The Cochrane Library.

Farrell, M. and Marsden, J. (2008), 'Acute risk of drug-related death among newly released prisoners in England and Wales', *Addiction* 103, pp. 251–255.

Farrell, M., Neeleman, J., Griffiths, P. and Strang, J. (1996), 'Suicide and overdose among opiate addicts', *Addiction* 91, pp. 321–323.

Fazel, S. and Baillargean, J. (2011), 'The health of prisoners', *The Lancet* 377, pp. 956–965.

Fazel, S., Bains, P. and Doll, H. (2006), 'Substance abuse and dependence in prisoners: a systematic review', *Addiction* 101, pp. 181–191.

Frisher, M., Baldacchino, A., Crome, I. and Bloor, R. (2012), *Preventing opioid overdoses in Europe,* EMCDDA technical report (available at www.emcdda.europa.eu/scientific-studies/2012/preventing-overdoses).

Gore, S. M., Bird, A. G. and Ross, A. J. (1995), 'Prison rites: starting to inject inside', *BMJ* 311, pp. 1135–1136.

Gossop, M., Griffiths, P., Powis, B., Williamson, S. and Strang, J. (1996), 'Frequency of non-fatal heroin overdose: survey of

heroin users recruited in non-clinical settings', *BMJ* 313, p. 402.

Griffiths, P., Gossop, M., Powis, B. and Strang, J. (1993), 'Reaching hidden populations of drug users by the use of Privileged Access Interviewers: report on methodological and practical issues', *Addiction* 88, pp. 1617–1626.

Griffiths, P., Gossop, M., Powis, B. and Strang, J. (1994), 'Transitions in patterns of heroin administration: a study of heroin chasers and heroin injectors', *Addiction* 89, pp. 301–309.

Hickman, M., Carrivick, S., Paterson, S., Hunt, N., Zador, D., Cusick, L. and Henry, J. (2007), 'London audit of drug-related overdose deaths: characteristics and typology, and implications for prevention and monitoring', *Addiction* 102, pp. 317–323.

Lagu, T., Anderson, B. J. and Stein, M. (2006), 'Overdoses among friends: drug users are willing to administer naloxone to others', *Journal of Substance Abuse Treatment 30*, pp. 129-133.

Lintzeris, N., Mitchell, T. B., Bond, A., Nestor, L. and Strang, J. (2006), 'Interactions on mixing diazepam with methadone or buprenorphine in maintenance patients', *Journal of Clinical Psychopharmacology* 26, pp. 274–283.

Lintzeris, N., Mitchell, T. B., Nestor, L., Bond, A. J. and Strang, J. (2007), 'Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients', *Drug and Alcohol Dependence* 91, pp. 187–194.

Maden, A., Swinton, M. and Gunn, J. (1990), 'Women in prison and use of illicit drugs before arrest', *BMJ* 301, p. 1133.

Maden, A., Swinton, M. and Gunn, J. (1992), 'A survey of pre-arrest drug use in sentenced prisoners', *Addiction* 8, pp. 27–33.

Mason, D., Birmingham, L. and Grubin, D. (1997), 'Substance use in remand prisoners: a consecutive case study', *BMJ* 315(7099), pp. 18–21.

Mattick, R. P., Breen, C., Kimber, J. and Davoli, M. (2009), 'Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence', *Cochrane Database of Systematic Reviews* 3.

Mattick, R. P., Kimber, J., Breen, C. and Davoli, M. (2014), 'Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence', *Cochrane Database of Systematic Reviews* 2.

McGregor, C., Darke, S., Ali, R. and Christie, P. (1998), 'Experience of non-fatal overdose among heroin users in Adelaide, Australia: circumstances and risk perceptions', *Addiction* 93, pp. 701–711.

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

Merrall E. L. C., Bird, S. M. and Hutchinson, S. J. (2012), 'Mortality of those who attended drug services in Scotland 1996–2006: record linkage study', *International Journal of Drug Policy* 23, pp. 24–32.

Montanari, L., Royuela, L., Pasinetti, M., Giraudon, I., Wiessing, L. and Vicente, J. (2014), 'Drug use and related consequences among prison populations in European countries in WHO', in Enggist, S., Møller, L., Galea, G. and Udesen, C. (editors) *Prisons and Health,* WHO Regional Office for Europe, Copenhagen, pp. 107–112.

Oviedo-Joekes, E., Brissette, S., Marsh, D. C., Lauzon, P., Guh, D., Anis, A. and Schechter, M. T. (2009), 'Diacetylmorphine versus methadone for the treatment of opioid addiction', *New England Journal of Medicine* 361, pp. 777–786.

Pierce, M., Hayhurst, K., Bird, S. M., Hickman, M., Seddon, T., Dunn, G. and Millar, T. (2015), 'Quantifying crime associated with drug use among a large cohort of sanctioned offenders in England and Wales', *Drug and Alcohol Dependence* 155, pp. 52–59.

Powis, B., Griffiths, P., Gossop, M. et al. (1996), 'The differences between male and female drug users: community samples of heroin and cocaine users compared', *Substance Use & Misuse* 31, pp. 529–543.

Powis, B., Strang, J., Griffiths, P. et al. (1999), 'Self-reported overdose among injecting drug users in London: extent and nature of the problem', *Addiction* 94, pp. 471–478.

Ravndal, E. and Amundsen, E. J. (2010), 'Mortality among drug users after discharge from inpatient treatment: an 8-year prospective study', *Drug and Alcohol Dependence* 108, pp. 65–69.

Rounds-Bryant, J. L. and Baker, L. (2007), 'Substance dependence and level of treatment need among recently-incarcerated prisoners', *American Journal of Drug and Alcohol Abuse* 33, pp. 557–561.

Seal, K. H., Downing, M., Kral, A. H., Singleton-Banks, S., Hammond, J.-P., Lorvick, J. et al. (2003), 'Attitudes about prescribing take-home naloxone to injection drug users for the management of heroin overdose: a survey of street-recruited injectors in the San Francisco Bay Area', *Journal of Urban Health 80*, pp. 291–301.

Seaman, S. R., Brettle, R. P. and Gore, S. M. (1998), 'Mortality from overdose among injecting drug users recently released from prison: database linkage study', *BMJ* 316, pp. 426–428.

Sheedy, D. L., Garrick, T. M., Fortis, A. H. and Harper, C. G. (2003), 'Changing trends in heroin-related deaths in Sydney, Australia: 1995 to 1999', *American Journal on Addictions* 12, pp. 52–59.

Spigner, C., Hawkins, W. and Loren, W. (1993), 'Gender differences in perception of risk associated with alcohol and drug use among college students', *Women and Health* 20, pp. 87–97.

Sporer, K. A. (1999), 'Acute heroin overdose', *Annals of Internal Medicine* 130, 584–590.

Strang, J., Best, D., Man, L.-H., Noble, A. and Gossop, M. (2000), 'Peer-initiated overdose resuscitation: fellow drug

users could be mobilised to implement resuscitation', *International Journal of Drug Policy* 11, pp. 437–445.

Strang, J., Griffiths, P. and Gossop, M. (1997), 'Heroin in the UK: different forms, different origins, and the relationship to different routes of administration', *Drug and Alcohol Review* 16, pp. 329–337.

Strang, J., Griffiths, P., Powis, B. and Gossop, M. (1999a), 'Heroin chasers and heroin injectors: differences observed in a community sample in London, UK', *American Journal on Addictions* 8, pp. 148–160.

Strang, J., Powis, B., Best, D., Vingoe, L., Griffiths, P., Taylor, C., Welch, S. and Gossop, M. (1999b), 'Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability', *Addiction* 94, pp. 199–204.

Strang, J., McCambridge, J., Best, D., Beswick, T., Bearn, J., Rees, S. and Gossop, M. (2003), 'Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study', *BMJ* 326(7396), pp. 959–960.

Strang, J., Manning, V., Mayet, S. et al. (2008a), 'Family carers and the prevention of heroin overdose deaths: unmet training need and overlooked intervention opportunity', *Drugs: Education, Prevention, and Policy* 15, pp. 211–218.

Strang, J., Manning, V., Mayet, S., Best, D., Titherington, E., Santana, L., Offor, E. and Semmler, C. (2008b), 'Overdose training and take-home naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses', *Addiction* 103, 1648–1657.

Strang, J., Metrebian, N., Lintzeris, N., Potts, L., Carnwath, T., Mayet, S. and Groshkova, T. (2010), 'Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): a randomised trial', *The Lancet* 375(9729), pp. 1885–1895.

Tagliaro, F., De Battisti, Z., Smith, F. P. and Marigo, M. (1998), 'Death from heroin overdose: findings from hair analysis', *The Lancet* 351, pp. 1923–1925.

Tobin, K. E., Gaasch, W. R., Clarke, M. C., MacKenzie, E. and Latkin, C. A. (2005), 'Attitudes of emergency medical service providers toward naloxone distribution programs', *Journal of Urban Health* 82, pp. 296–302.

Vingoe, L., Welch, S., Farrell, M. and Strang, J. (1999), 'Heroin overdose among a treatment sample of injecting drug misusers: accident or suicidal behaviour?', *Journal of Substance Use* 4, pp. 88–91.

Warner-Smith, M., Darke, S., Lynskey, M. and Hall, W. (2001), 'Heroin overdose: causes and consequences', *Addiction* 96, pp. 1113–1125.

Williams, A. V., Marsden, J. and Strang, J. (2014), 'Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes', *Addiction* 109, 250–259.

Worthington, N., Markham Piper, T., Galea, S. and Rosenthal, D. (2006), 'Opiate users' knowledge about overdose prevention and naloxone in New York City: a focus group study', *Harm Reduction Journal* 3, p. 19.

Wright, N., Oldham, N., Francis, K. and Jones, L. (2006), 'Homeless drug users' awareness and risk perception of peer', *Substance Abuse Treatment, Prevention, and Policy* 1, p. 28.

Zador, D., Sunjic, S. and Darke, S. (1996), 'Heroin-related deaths in New South Wales, 1992: toxicological findings and circumstances', *Medical Journal of Australia* 164, pp. 204–207.

4

CHAPTER 4

Historical summary of the development and spread of take-home naloxone provision

Rebecca McDonald

Background: discovery of naloxone and usage in emergency room and pre-hospital emergency care

Naloxone, an opioid-receptor blocker that antagonises the effect of opioid drugs, was discovered at the beginning of the 1960s and approved for intravenous, intramuscular and subcutaneous administration in 1971 (see Chapter 1). The antidote was initially marketed under the trade name Narcan, and now also exists as a generic prescription medicine. For the quickest absorption into the bloodstream and onset of action, naloxone was recommended for intravenous administration, which became standard clinical practice for nearly two decades.

Hospital emergency departments routinely used naloxone intravenously for the antidote's three indications: to reverse respiratory and central nervous system depression in opioid overdose, to reverse the therapeutic effects of opioids in medical use (e.g. after general anaesthesia) and as a diagnostic tool (opioid challenge test; i.e. naloxone can be used to diagnose illicit opioid use, as it precipitates withdrawal symptoms). In the 1990s, in a move towards improving the prevention of overdose deaths in the community, ambulance services in the United States started to train their staff in the management of suspected opioid overdose, including intramuscular naloxone administration in conjunction with bag–valve–mask ventilation, and positive outcomes were reported (Sporer et al., 1996).

Spurred by the AIDS epidemic, clinicians became increasingly wary of the risk of needle-stick injury. As a result, there was pronounced interest in non-injecting routes of naloxone administration as a safer alternative for use in the high-risk opioid user population. Loimer et al. (1994) explored the intranasal administration of naloxone, which is still under investigation today (see Chapter 6). Alongside this line of work, a Vancouver-based ambulance study by Wanger et al. (1998) compared time to recovery (interval from crew arrival to reversal of respiratory depression) between intravenous and subcutaneous administration. The study found that the slower absorption rate from subcutaneous administration was offset by the delay in establishing intravenous access in overdose victims, thus resulting in equal clinical efficacy for both routes. Similarly, for the intramuscular route, it has been established that adequate breathing in opioid overdose victims will resume on average 5 minutes after naloxone delivery (UNODC and WHO, 2013). In addition, Horowitz (1998) noted that subcutaneous (or intramuscular) administration led to a more gradual patient recovery from overdose, compared to intravenous administration.

This shift from intravenous towards subcutaneous and intramuscular administration of naloxone in clinical practice, and the growing awareness that most overdoses are witnessed by others, set the scene for the development of take-home naloxone provision, which enables bystanders without formal medical training to administer an emergency dose of naloxone in order to save the life of an opioid overdose victim.

Take-home naloxone: original proposal and first implementation

Compared with over 40 years of naloxone use in medical care, the notion of providing the antidote directly to opioid users and family members ('take-home emergency naloxone') is relatively new.

The possibility was originally mooted at the Third International Harm Reduction Conference in March 1992 (Strang, 1992) as a throwaway example of harm reduction alternatives that were being overlooked. The first serious consideration of take-home emergency naloxone followed in a 1996 *BMJ* editorial (Strang et al., 1996), which explored the possibility of take-home naloxone distribution more thoroughly. Analogous to other harm reduction measures, take-home naloxone was presented as a strategy to give users direct access to the best available treatment.

Firstly, the editorial explored several different potential applications, such as the provision of a take-home dose to individuals believed to be at high risk of overdose, including patients leaving residential treatment after detoxification and former users on release from prison.

Secondly, it identified the need to consider wider populations beyond those in treatment for their addiction, including active users with lower levels of engagement with treatment (such as attendees of needle and syringe exchange schemes) and users not in contact with treatment services.

Thirdly, the poor suitability of existing naloxone products was identified, as was the medico-legal challenge of the probable need to instruct third parties, such as friends or family members, in how to administer naloxone in an emergency.

First implementation

The first instance of actual provision of take-home naloxone occurred in Chicago (Cook County), where the Chicago Recovery Alliance began dispensing naloxone as early as autumn 1996. The Chicago Recovery Alliance had been conducting harm-reduction outreach since 1992. Following the death of one of its founding members in May 1996, the Chicago Recovery Alliance started training users in overdose prevention and equipped them with take-home naloxone kits. The distribution volume grew between 1997 and 1999, and, because of high user demand for the antidote, naloxone distribution was continued and converted into a formal programme with a standardised training curriculum in 2001 (Bigg, 2002; Maxwell et al., 2006). The programme was initiated after a fourfold increase in drug-induced deaths reported by the Medical Examiner Officer from 1996 to 2000.

In the late 1990s, take-home naloxone was also introduced in Germany (Berlin), the Channel Islands (Jersey) and Italy (Turin, Bologna and Padua), as described in more detail later in this chapter in the section 'Take-home naloxone in Europe' (see also Table 4.1).

Testing the notion

Is take-home naloxone necessary?

When the take-home naloxone proposal was published (Strang et al., 1996), the rate of heroin overdose deaths in Europe was on the rise (Davoli et al., 1993). Despite fluctuations in the total number of opioid-induced deaths in subsequent years and differences in trends between countries, heroin and other opioids continue to be the main contributors to drug-related deaths today, as opioid users in Europe and beyond experience markedly elevated excess mortality rates compared with not only the general population but also users of other illicit drugs (e.g. cocaine) (Degenhardt et al., 2011; EMCDDA, 2015b) (see Chapter 3).

Who should be trained in take-home naloxone?

Based on the probability of witnessing an overdose, three target populations for take-home naloxone programmes were identified: users, carers (close contacts of users including peers and family members) and agency staff likely to interact with users.

People who use drugs: Opioid users and in particular those who inject are the primary target group for take-home naloxone because of their double function of potentially having an overdose in the future (50–70 % lifetime risk) as well as constituting willing interventionists highly likely to become bystanders of an overdose (Strang et al., 1999; Warner-Smith et al., 2001). Research identified the following groups of users as prone to overdose: current injecting opioid users (Gossop et al., 1996), heroin injectors upon release from prison (Bird and Hutchinson, 2003; Seaman et al., 1998), former opioid users upon release from in-patient detoxification/rehabilitation (Davoli et al., 2007; Strang et al., 2003) and individuals starting methadone maintenance treatment (Caplehorn and Drummer, 1999; Degenhardt et al., 2009) (see Chapter 3). More recently, Merrall et al. (2013) have shown a high rate of drug-related death among persons registered for drug misuse treatment in the first 4 weeks after hospital discharge, irrespective of the reason for hospitalisation. Among high-risk users, those who are currently in treatment or re-entering the community after a stay in an institution (e.g. prison or hospital) can be accessed reasonably

TABLE 4.1
Implementation timeline of take-home naloxone (THN)

Year	Event
1961	First patent is filed for naloxone
1971	United States: FDA licenses naloxone as prescription-only medication; naloxone enters clinical practice in Europe in subsequent years
1992	Notion of THN is mooted at International Harm Reduction Conference (Strang, 1992)
1994	First reported use of intranasal naloxone for overdose reversal (Loimer et al., 1994)
1996	*BMJ* editorial states 'Home based supplies of naloxone would save lives' (Strang et al., 1996)
	United States: Chicago Recovery Alliance distributes first THN kits
	Italy: Reports of THN distribution in Padua
1998	Channel Islands: Island of Jersey starts THN distribution
1999	Germany: Fixpunkt Berlin starts THN distribution
2001	Spain: Reports of underground THN distribution in Barcelona
	United States: New Mexico and San Francisco launch THN programmes
	First published report of THN distribution (Dettmer et al., 2001)
	United Kingdom: Introduction of first mainland THN scheme (south London)
2002	Chicago programme reports first lives saved in *BMJ* (Bigg, 2002)
2005	United States: Intranasal naloxone is distributed as part of THN kits in Massachusetts
	United Kingdom: Legal status of naloxone changed to permit emergency administration of naloxone by any member of the general public (Schedule 7 of the Medicines Act)
2006	United Kingdom: National Treatment Agency for Substance Misuse (NTA) funds THN training initiative for users and carers in 16 pilot sites
2007	United Kingdom: Scotland and Wales establish THN pilots
2008	United Kingdom: Medical Research Council funds N-ALIVE trial
	Spain: Formal THN programme launched in Barcelona
2011	United Kingdom: Scottish Lord Advocate issues new guidelines
	United Kingdom: Scotland and Wales launch national THN programmes
	Australia: First THN programme is introduced in Canberra
2012	Wales: first evaluation of national naloxone programme (Bennett and Holloway)
	UNODC Resolution 55/7 states 'Opioid overdose treatment, including the provision of opioid receptor antagonists such as naloxone, is part of a comprehensive approach to services for drug users'
2013	Denmark: THN programme starts (intranasal)
	Estonia: THN distribution launched in Harju and East-Viru counties
2014	Norway: THN programme starts (intranasal)
	WHO releases new guidelines, stating 'People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration' (WHO, 2014)
	EMCDDA hosts meeting 'Take home naloxone to reduce fatalities: scaling up a participatory intervention across Europe'
2015	EMCDDA publishes systematic review, stating 'There is evidence that educational and training interventions with provision of THN decrease overdose-related mortality' (EMCDDA, 2015a)

easily. Harder to reach are the estimated 50 % of opioid users in the European Union who are thought not to be engaged with formal addiction treatment services (EMCDDA, 2015b).

A separate target group that may also benefit from take-home naloxone is prescription opioid users, such as chronic pain patients. This group will need different recruitment approaches and language in information material from 'street opioid users'.

Carers (family members and other close contacts of drug users): Research in the late 1990s revealed that most opioid overdoses occur in private homes (McGregor et al., 1998) and in the presence of others: peers, family members or partners (Best et al., 2002; McGregor et al., 1998; Powis et al., 1999). Consequently, close contacts of opioid users were identified as the second target group. A postal survey of carers in England (Strang et al., 2008) underlined close contacts' willingness to intervene in an overdose emergency and administer naloxone, with nearly 90 % of carers wanting training in overdose management and the same proportion wanting training in naloxone administration. In practice, peers or family members may accompany users to overdose-education training and can also be accessed through support groups and advertising at health facilities and social service agencies.

Agency staff (those who work with people who use drugs): Thirdly, there are trained health professionals at drug treatment agencies as well as other professionals who work with at-risk individuals (e.g. at hostels or shelters for the homeless, needle and syringe programmes and outreach programmes) and first responders, such as ambulance, fire, police and other staff of law enforcement and criminal justice services. For all of the above, 'targeting' refers to the need to engage employees, educate them on the need for overdose intervention and train them in the provision of take-home naloxone treatment (see Chapter 5). It has been documented that in the United States, jurisdictions in 24 states have passed legal provisions to authorise law enforcement officers and firefighters to administer naloxone and that over 220 law enforcement agencies currently carry the antidote, which represents a significant shift from the traditional role of police officers (Davis et al., 2015). Evaluations of the public health benefit and cost-effectiveness of these programmes are forthcoming.

Is take-home naloxone acceptable to those involved?

Following the 1996 take-home naloxone proposal, research efforts focused on testing the feasibility of the proposed intervention and assessing the attitudes of users, carers and providers.

People who use drugs: Surveys investigating the practical feasibility of take-home naloxone found substantial support for the proposal among drug users. Attitudes of drug users towards take-home naloxone were first explored in London in the late 1990s. In a cohort of 454 drug users from a deprived area (Strang et al., 1999), 70 % agreed with the proposal that naloxone should be provided for emergency management of future possible overdose, with nearly 90 % of those who had witnessed an overdose stating they would have used the medication if it had been available. Subsequent UK-based surveys found that heroin users were willing to take part in training to manage overdoses and administer naloxone (Bennett and Higgins, 1999), store naloxone at home and intervene in an overdose situation (Best et al., 2002; Strang et al., 2000). These findings have since been replicated internationally. For instance, in a cohort of 82 street users in the San Francisco Bay Area (Seal et al., 2003), 84 % expressed the wish to carry naloxone and train peers. Similar results were obtained in a New York-based focus group study with 13 representatives from a naloxone distribution programme (Worthington et al., 2006) as well as among a sample of 99 needle and syringe programme participants in Melbourne (Kerr et al., 2008). However, drug users also expressed some concerns surrounding take-home naloxone, such as the fear of experiencing withdrawal symptoms after naloxone administration, the potential that they might increase their drug use, and having to contend with management difficulties in those revived such as hostility or the urge to re-administer heroin to counteract possible withdrawal symptoms (Kerr et al., 2008; Seal et al., 2003; Strang et al., 1999; Worthington et al., 2006). Moreover, several drug users were doubtful of bystanders' competency in using the medication (Worthington et al., 2006), and the majority of the Melbourne-based sample of drug users (75 %) pointed out that that they preferred intranasal administration to injectable naloxone to reduce the risk of infection with blood-borne viruses (Kerr et al., 2008). With an eye to possible legal repercussions, drug users expressed reservations about contacting ambulance services and voiced concern over naloxone being confiscated by the police (Richert, 2015; Seal et al., 2003).

Carers: Family members too have been found to be supportive of the proposal. In an England-based postal survey of 147 carers attending support groups (Strang et al., 2008), the majority were caring for a heroin user, and half of those cared for had already overdosed. The study found that only a third of carers had relevant knowledge or awareness of overdose management. It also highlighted carers' strong interest in both training and emergency use of naloxone. A randomised controlled trial showed that training family members in emergency recovery procedures and naloxone administration led to greater overdose-related knowledge than controls (who had received only basic information) and that these training gains were maintained over a 3-month follow-up period (Williams et al., 2014).

Agency staff: 'Technology transfer' of naloxone supply from standard medical settings (i.e. ambulance and emergency rooms) to layperson use constitutes the foundation of take-home naloxone distribution. Several studies have explored whether or not healthcare providers would be supportive of the practice, yielding mixed results. A New York-based postal survey (Coffin et al., 2003) of professionals with prescribing authority (i.e. physicians, physician assistants and nurse practitioners) showed that a third were willing to prescribe naloxone, whereas two-thirds of respondents were unsure or unwilling to do so. A survey (Tobin et al., 2005) of emergency service providers in Baltimore (Maryland) revealed overall negative attitudes towards take-home naloxone programmes, and 56 % felt that training would not have an impact on drug-related deaths. Willingness to prescribe was correlated with positive attitudes towards drug users, and vice versa (Beletsky et al., 2007). Some of the areas of potential concern raised by clinicians mirror those highlighted by drug users, such as competency in administering naloxone (Byrne, 2006; Tobin et al., 2009),

the possibility of implicitly promoting drug use (Tobin et al., 2005) and the risk of unsafe disposal of needles (Tobin et al., 2005). Potential use as street currency was also mentioned (Byrne, 2006). Most importantly, perhaps, providers voiced strong concerns over the uncertain medico-legal status of take-home naloxone and potential liability issues (Burris et al., 2001).

Is take-home naloxone safe?

Providers and also some users raised concerns over the safety of the technology transfer of naloxone into the public sphere. In particular, it was unclear whether or not the availability of take-home naloxone might encourage heroin use, and if the duration of action of naloxone (half-life: 1–1.5 h) would be sufficient to prevent overdose victims from re-entering overdose (so-called rebound toxicity). Similarly, there was concern that an overdose victim, once revived with naloxone, might inject another dose of heroin to overcome withdrawal symptoms, provoking an even more serious overdose by the time the naloxone wore off.

Surveys of drug users conducted at the end of the 1990s concluded that take-home naloxone was unlikely to lead to more risky heroin consumption (Strang et al., 1999), and there were no reports of revived overdose victims injecting heroin after overdose reversal (Vilke et al., 1999).

Early implementation pilots provided the first data on the safety of take-home naloxone provision. In the first published Europe-based take-home naloxone pilot, conducted in Berlin (Germany) and in Jersey (Channel Islands), the researchers reported 34 peer rescues from overdose in Berlin and found naloxone administration to be inappropriate in only one case (a cocaine overdose). All overdose victims were successfully revived. No increased use of heroin or occurrence of adverse effects (other than withdrawal symptoms) was observed. Among the five overdose reversals reported in Jersey, none involved adverse events (Dettmer et al., 2001).

The first US-based take-home naloxone programme in Chicago reported 319 overdose reversals between 2001 and 2006 (Maxwell et al., 2006). Adverse events included one death and two cases of severe adverse reactions; however, the latter were likely to have been associated with polydrug use.

A recent evaluation of the Massachusetts-based take-home naloxone programme reported that average heroin use in the previous 30 days among a subsample of programme participants (n = 325) who participated in a pre–post survey was not affected by naloxone availability (Doe-Simkins et al., 2014).

Similarly, in a more recent Danish study of 3 245 cases of naloxone administration, death from rebound toxicity occurred in only three cases (0.09 %) while all remaining 3 242 overdose victims survived (Rudolph et al., 2011).

To conclude, empirical findings on the safety of take-home naloxone programmes are favourable, and there have been very few reports of adverse effects beyond the expected onset of withdrawal symptoms and agitation in the revived overdose victim.

Is take-home naloxone legal?

Parallel to the first take-home naloxone pilots, explorations of regulatory obstacles were undertaken (Burris et al., 2001). Two central legal challenges were identified. Firstly, could naloxone be lawfully administered to the overdose victim by a bystander, who would not be the person to whom naloxone was prescribed? Secondly, would it be lawful for a take-home naloxone recipient to use the naloxone that was prescribed to him-/herself to rescue an overdose victim, even though that particular naloxone kit was never prescribed to the overdose victim? The first scenario is similar to the provision of other emergency medications to patients and family; for example, family members of patients known to suffer from severe allergies can be trained to administer adrenaline in case of an acute allergic anaphylactic reaction. The second scenario is more challenging, as it involves doctors issuing a prescription-only medication to a patient, without knowledge about the eventual recipient of the antidote. Medical providers as well as service users raised concerns about civil or criminal liability. Service users in the United States also expressed concerns over the risk of naloxone confiscation by the police.

Certain jurisdictions have passed Good Samaritan laws to free lay responders from liability and facilitate the availability of take-home naloxone. The legal situation and availability of take-home naloxone in Europe is explored in the following sections of this chapter.

Take-home naloxone in Europe

Naloxone: the legal situation in the European Union

According to Article 71 of the EU Medicinal Products Directive (2001/83), 'Medicinal products shall be subject to medical prescription where they [...] are normally prescribed by a doctor to be administered parenterally.' Since naloxone is currently licensed only

for injection, it follows that naloxone should normally be available only by prescription. Prescription-only status implies that, self-administration being unlikely during overdose, naloxone can be administered to the patient to whom the prescription was issued by only a medical practitioner (e.g. doctor or nurse) or those acting under the medical practitioner's instructions (e.g. family members).

In 2014, the EMCDDA consulted networks of experts from the 28 EU Member States to assess naloxone availability in the European Union (Hughes, 2014). National drug policy experts from 24 Member States completed one survey; no response was obtained from Finland, Ireland, Italy or Slovakia. These results were combined with data from a separate survey of experts via the national focal points. The results should be regarded with some caution, as inconsistencies were found in the data, possibly due to differing interpretation of some questions. Nevertheless, some numbers serve to illustrate the general picture of naloxone provision in Europe.

It was reported that naloxone is available by general medical prescription in 13 countries, but limited to prescription by clinicians in certain settings (e.g. hospitals) in 11 countries. None of the 24 countries participating in the survey reported that naloxone is available as over-the-counter medicine. One country reported that naloxone is not officially authorised as a medication and that any needs must be addressed through emergency imports of naloxone.

The respondents indicated that naloxone is permitted for hospital use or emergency response in 15 countries, and can be prescribed by any medical doctor in 17 countries. Naloxone is part of standard ambulance equipment in 16 countries, and 14 countries confirmed that all ambulance personnel are trained to administer naloxone.

Asked about potential obstacles to wider naloxone availability (i.e. take-home naloxone), two respondents said that the prevalence rate of opioid overdoses in their country was too low to encourage naloxone provision. Most respondents mentioned potential legal concerns; for example, the possession or use of naloxone without authorisation could be considered an offence in seven countries. In at least five countries, first responders could theoretically be held liable for injury or death of an overdose victim, while one respondent considered that doctors could be held liable for prescribing naloxone.

However, in several European countries, examples were given of the legal code protecting first responders, as follows:

- In Germany, first responders are protected by the civil law, with its basic principle of duty to rescue those in need to avoid greater harm. If a person is in danger, a bystander is obliged to provide aid. In fact, failure to provide aid may constitute a violation of Section 323c of the German criminal code (*Strafgesetzbuch*): 'Who fails to provide help in cases of disaster or imminent danger or distress, although this [help] is necessary and reasonable under the circumstances, [and is] especially without considerable danger for his own and without violation of other important duties possible, will be penalised with imprisonment up to one year or fined'.

- In the Netherlands, the law makes 'no objection' to the administration of prescription medicines by third parties in emergencies, if the medication (naloxone) is needed (Hughes, 2014).

- In Luxembourg, a duty-to-rescue law has been embedded in the national penal code since 1985 (*Article 410-1 Code Pénal 1879*). In addition, the national drug legislation (first introduced in 1973) was amended in 2001 to promote harm-reduction measures. With regard to overdoses, Articles 7 and 8c of the law state that a drug user who witnesses an emergency and immediately seeks qualified assistance for the drug user in need (i.e. overdose victim) cannot be prosecuted for drug possession. Further, if the assisting overdose witness has committed a drug-related offence, a reduction of penalties may be granted (EMCDDA, 2012).

- In the United Kingdom, parenteral (injectable) medicines can be administered only by the patient him-/herself, or by 'an appropriate practitioner or a person acting in accordance with the directions of an appropriate practitioner' (s.58(2)(b) Medicines Act 1968, UK Government, 1968). However, in 2005, naloxone was added to Schedule 7 of the Medicines Act, which allows any member of the general public to administer naloxone in the event of an emergency, with the aim of saving a life, placing naloxone alongside adrenaline and other rescue medications. Although naloxone is a prescription-only medication, the Scottish Lord Advocate passed guidelines in 2011 to allow local services in contact with high-risk drug users to stock naloxone kits for emergency use.

Take-home naloxone programmes in European countries

Currently, take-home naloxone programmes exist in seven European countries: Denmark, Estonia, Germany,

Italy, Norway, Spain and the United Kingdom (EMCDDA, 2015c). The programmes vary largely in their format: some are small and time-limited pilots, whereas Scotland and Wales have recently launched nationwide programmes.

Denmark

According to 2006 capture–recapture estimates, there are around 13 000 injection drug users in Denmark (EMCDDA, 2015d). During the 1990s and 2000s, Denmark has seen 250–275 direct drug-induced deaths (overdoses) registered per year, the majority of which are related to methadone and heroin.

As a result of the high number of opioid-related overdoses, the Danish Ministry of Health decided in 2012 to introduce a take-home naloxone programme, based on the positive outcomes of a pilot project in the capital city, and starting in March 2013 (Saelan, 2014).

Opioid users and potential bystanders, such as family members, friends and social service agency staff, are eligible to participate in the Danish take-home naloxone programme, which forms part of a wider agenda of harm-reduction measures. The government-funded project was initially rolled out in four Danish municipalities (Copenhagen, Aarhus, Odense and Glostrup) known to have a street scene of opioid use, but there are plans to expand the programme to other municipalities, provided the results of the ongoing evaluation — expected for mid-2015 — are positive. Training, data collection and project coordination are centrally managed by the municipality of Copenhagen.

After attending a training on overdose prevention and management, participants receive the naloxone kit, which contains a 2-mg/2 ml pre-filled naloxone syringe with nasal atomiser as well as three pieces of paper: a training certificate, an action card with overdose management instructions, and a data card (to complete and return to the Copenhagen team after an overdose event). Trainees are instructed to regard the 2-mg/2 ml formulation as five doses of 0.4 mg each: the first three doses are for intranasal administration and, in case of non-response, the fourth and fifth doses should be used for intramuscular administration.

As of October 2014, 100 people had been trained as trainers, and 121 drug users had received overdose prevention training and take-home naloxone kits. There have been seven instances of reported naloxone use for overdose reversal. However, because the evaluation design is not controlled, it is unclear whether or not a parallel downward trend in drug-related deaths in Denmark, which has occurred since, but had already begun before the project started, reflects the effectiveness of take-home naloxone.

The project coordinators point out that there is a heavy administrative burden associated with take-home naloxone distribution due to the antidote's prescription-only medication status, but are hopeful that intranasal naloxone may become available in Denmark as an over-the-counter medication after the end of the project (Saelan, 2014).

Estonia

Estonia has the highest drug-related mortality rate among adults (aged 15–64 years) in the European Union, with 111 deaths per million inhabitants in 2013, and most drug overdose fatalities are associated with the use of fentanyl, a highly potent synthetic opioid (EMCDDA, 2015d).

In September 2013, the National Institute for Health Development (NIHD) launched the Estonian take-home naloxone programme. The programme operates in Harju and East-Viru counties, which have the country's highest prevalence of injection drug use. Persons at risk of opioid overdose (including patients enrolled in opioid substitution treatment as well as their family members are eligible to partake in the programme. Moreover, opioid substitution treatment providers and harm-reduction outreach workers are eligible to take part. All programme participants must be at least 16 years of age, which has to be proven by the production of an identity document.

Programme participants receive training in overdose management, naloxone administration and infectious disease prevention, and receive a take-home naloxone kit if they pass an overdose prevention knowledge test. Like the Scottish take-home naloxone programme (see box below), patient lists are generated (instead of issuing individual prescriptions) and the distribution of naloxone kits is logged to comply with national legislation. Take-home naloxone kits contain the Prenoxad injection and an information leaflet. Since pre-filled syringes are not licensed in Estonia, Prenoxad kits are imported from the United Kingdom using a special authorisation from the Estonian State Agency of Medicines. The Estonian take-home naloxone is fully government funded, and provision of the service is carried out in cooperation with local healthcare providers and harm-reduction services. As of October 2014, 552 naloxone kits had been

distributed, which led to 72 repeat prescriptions and 71 overdose reversals.

Future goals for programme development include (1) to increase the number of distributed naloxone kits to at least 1 000 and (2) to scale the programme up in other regions with high overdose prevalence. Moreover, NIHD plans to actively involve Estonian police in the programme (Abel-Ollo, 2014; Andrey Rylkov Foundation for Health and Social Justice, 2013).

Germany

Together with Jersey (see below), a Berlin-based pilot constitutes the first published report on take-home naloxone provision to heroin users for community-based overdose management (Dettmer et al., 2001). In January 1999, take-home naloxone was introduced for clients attending a mobile needle and syringe exchange scheme and community programme (Fixpunkt). Within 16 months, 124 take-home naloxone kits were issued, and 22 users reported having administered the naloxone in a total of 29 overdose sufferers, all of whom recovered. The project continued until December 2002 and was well received among Fixpunkt clients, but could not secure funding beyond the pilot's duration (Dettmer, 2014; Deutsche AIDS-Hilfe, 2013). Nonetheless, Fixpunkt continued to distribute take-home naloxone at a low volume. Furthermore, a counselling and treatment centre in Frankfurt (Integrative Drogenhilfe e.V.) runs a small-scale naloxone action research project in close partnership with the University of Applied Sciences Frankfurt/Main, with a special focus on identifying obstacles to establishing naloxone programmes as part of standard service provision. A first visible result of this cooperation was a guideline about how to set up and run programmes adapted to the German context (Stöver, 2015).

Ireland

The number of drug-related deaths in Ireland increased from 105 in 2003 to 181 in 2012. The majority of overdose fatalities registered in 2012 were opioid-related, and toxicology results revealed that methadone was present in more cases than heroin (EMCDDA, 2015d). In October 2014, the Irish Health Service Executive announced that it would fund a take-home naloxone demonstration project with an initial target sample size of 600 opioid users (Sheehan, 2014). Opioid users willing to participate in the project are required to attend a video-based training session and complete a post-training knowledge questionnaire. If project participants can demonstrate sufficient understanding of opioid overdose signs and risk factors, naloxone administration and overdose emergency management (calling an ambulance, recovery position and basic life support), they are issued a take-home naloxone kit by prescription. The project was launched in May 2015 (Department of Health, 2015). No data have been published to date, but a project website has been established (www.drugs.ie/resources/naloxone).

Italy

The latest estimate of the number of high-risk opioid users in Italy suggests that there were about 168 000 problem opioid users in Italy in 2013 (EMCDDA, 2015b). For the same year, Italy reported a total number of 344 directly drug-induced deaths — the lowest number since 1999. A total of 196 drug-induced deaths had toxicology-testing results available, which indicated opioids as the most prevalent substance causing death in 146 cases. However, the prevalence of opioid use (including heroin) varies widely by region (EMCDDA, 2015d). Italy is the only country where naloxone is available without a prescription (so-called SOP status, *Senza Obbligo di Prescrizione* (WHO, 2014)). Italian pharmacists can issue naloxone without a medical prescription, but naloxone cannot be publicly displayed on shelves to which customers have direct access, and customers need to request naloxone directly from the pharmacist. Take-home naloxone distribution was introduced in the cities of Bologna, Padua and Turin as early as 1996 (Schifano, 2001; Simini, 1998). In Padua, about 150 naloxone vials were given out to carers of methadone patients over the course of 18 months. However, there was no formal assessment and, although overdose deaths went down citywide, the trial was abandoned (Schifano, 2001). The current availability of community-based naloxone varies regionally.

Norway

Norway is among the countries with the highest drug-induced mortality rates in Europe, with 70 overdose deaths per million adult inhabitants in 2013 (EMCDDA, 2015d). There are an estimated 8 400 people who inject drugs in Norway and the number of high-risk opioid users in the country is estimated to be 7 700 (EMCDDA, 2015d). In 2012, a total of 246 drug-induced deaths were recorded, and toxicological confirmations, available for nearly all drug-induced deaths, confirmed that 192 involved opioids with or without additional drugs.

In April 2014, the Norwegian Minister for Health launched the national overdose-prevention campaign. The campaign covers a 5-year overdose-prevention strategy, including take-home naloxone distribution.

The Norwegian naloxone pilot, which officially started in late June 2014, involves take-home naloxone implementation in the country's two largest cities (Bergen and Oslo) over a 2-year period. The initiative is mainly run out of 10 sites: primarily low-threshold health and care facilities, but also housing facilities, drop-in day centres and services 'on wheels'. The project targets drug users (in and out of treatment), users' families and peers, police officers and treatment facility staff members. At the end of a training session, which takes approximately 10 minutes, participants receive a 2-mg/2 ml pre-filled syringe equipped with a nasal adapter (MAD300). Unlike the Danish pilot, the Norwegian naloxone kit does not contain a needle for naloxone injection, and only intranasal administration is possible. Since no needles are provided, no individual prescription is needed either. To distribute this off-label naloxone nasal spray formulation, the Norwegian pilot had to obtain special approval from the Norwegian drugs regulatory authority before the pilot started.

As of October 2014, 456 naloxone kits had been distributed, including 12 to police officers and 11 to family members. Seventy-six individuals returned for naloxone refills. As part of evaluation efforts, the project aims to link naloxone and questionnaire data with registry data on emergency medical service usage and mortality records.

Future aims include the expansion of the pilot to prisoners on release, detoxification units and maintenance treatment facilities. One setback for the pilot has been that the manufacturer of the nasal spray increased the product price by 50 % as soon as the project had received regulatory approval.

Spain (Catalonia)

In Barcelona, 64 overdose deaths were reported in 2012 (Rodríguez-Sanz et al., 2014). A recent study estimates that Barcelona has the highest mortality rate in Spain (Espelt et al., 2015).

Early reports point to 'underground' distribution of take-home naloxone in Barcelona as early as 2001, which allegedly led to 60 successful overdose reversals (Trujols, 2001). However, medico-legal concerns prevented the authorisation of a take-home naloxone pilot study at the time.

In 2008, the Public Health Agency of Barcelona and the Public Health Agency of Catalonia launched a formal take-home naloxone programme. The Catalonian take-home naloxone programme was integrated into the Catalan Drug Abuse Care Centres Network (XADC), which covers 64 drug-treatment centres, 17 therapeutic communities, 10 detox units and 13 drug-consumption rooms, among other facilities. At participating sites, most staff members received training (on site or online) in overdose prevention and response, and at each site a project champion for implementation of the take-home naloxone programme from January 2009 onwards was identified. People who injected drugs received a financial incentive to attend training that covered overdose risk factors and overdose emergency management (including naloxone administration). As of December 2013, 1 007 professionals and 4 738 injecting drug users had been trained and 5 830 naloxone kits had been distributed since start of the programme in 2008. Among those who received naloxone and witnessed an overdose, 40 % reported using the naloxone kit. In a cross-sectional study of 306 opioid users in Catalonia, 44 % reported having participated in an overdose prevention programme (Arribas-Ibar et al., 2014), suggesting substantial coverage of the target population.

However, overdose deaths in Catalonia had been decreasing since well before the start of the take-home naloxone project, and it remains unclear whether or not the continuous decline in overdose deaths is the result of the take-home naloxone project. Major obstacles to the project are that (1) abstinence-oriented services have been reluctant to distribute naloxone and (2) some users are unwilling to carry naloxone. Both points need to be explored in more detail. Future aims of the Catalonian programme include offering shorter, more flexible training sessions, involving peers in the training and expanding take-home naloxone provision to prisons. Moreover, the project coordinators recommend that all drug care centres should systematically assess clients' overdose risk, and that such programmes should also be deployed in prisons, since drug users have a higher risk of death from overdose in the weeks following their release from prison.

United Kingdom and Crown dependencies

Take-home naloxone distribution was first piloted through a community-based drug clinic on the island of Jersey (Dettmer et al., 2001), a Crown dependency, before it was introduced in the United Kingdom. Between October 1998 and January 2000, 101 drug users were trained in overdose management and received take-home naloxone kits. During this period,

five successful overdose reversals were reported, none of which involved adverse events. Together with a Berlin-based pilot, the Jersey initiative was documented in the first published report on take-home naloxone provision by Dettmer et al. (2001).

In the United Kingdom, naloxone distribution was first introduced in 2001, when south London-based addiction treatment services began prescribing take-home naloxone to methadone and detox patients at treatment initiation and discharge (Strang, 2001), which was later extended to diamorphine patients. In 2005, the legal status of naloxone was changed to open the doors to naloxone administration by lay first responders (including peers, family members, hostel workers): naloxone was added to Schedule 7 of the Medicines Act, which allows any member of the general public to administer the drug in an emergency with the aim of saving a life, placing naloxone alongside adrenaline and other rescue medications. By 2011, at least 16 sites had implemented pilots in England (NTA, 2011).

The prescription-only status of naloxone has been under review by the Medicines and Healthcare Products Regulatory Agency (MHRA) since 2013, and new regulations are expected to come into effect in October 2015. Public Health England (PHE) expects that, under the new regulations, naloxone will be 'made exempt from prescription only medicine requirements when it is supplied by a drug service commissioned by a local authority or NHS' (DrugScope, 2015).

Take-home naloxone projects under consideration in Europe

France

Data from 2011 suggest that there are approximately 210 000 opioid users in France, and opioids (mostly heroin) account for about a third of the country's new entries into treatment. At seven deaths per million of the population aged 15–64 in 2012, the French drug-induced mortality rate among adults is less than half the European average. Toxicological data reveal that opioids are involved in more than three-quarters of all drug-related deaths in France (EMCDDA, 2015d).

To reduce opioid-related overdose mortality, the introduction of take-home naloxone programmes in France was recommended by the Addiction Committee in 2008 (Direction Générale de la Santé, 2008) and by the National Narcotics and Psychotropic Substances Commission in 2009 (Agence Française de Sécurité Sanitaire et des Produits de Santé, 2009). Emergency overdose management by a layperson without medical training was already legal, as French law places the onus

Example of good practice: Scotland

In Scotland, three local take-home pilots (in Glasgow, Lanark and Inverness) were launched in or after 2007 (McAuley et al., 2012). In 2011, the Lord Advocate passed guidelines that allowed naloxone to be provided to services without prescription for use in an emergency (ACMD, 2012). Moreover, the guidelines allowed the storage of naloxone in non-medical facilities. The guidelines facilitated the introduction of the Scottish National Naloxone Programme (SNNP) in 2011. The programme involves take-home naloxone distribution in the community as well as in prisons (upon release). Community-based services can issue take-home naloxone to the person at risk of opioid overdose, to family members and peers (with documented consent of the person at risk) and to agency staff. The Scottish government funds the programme centrally, and all service providers are reimbursed for the number of naloxone kits issued.

During a 12-month period in 2013/14 alone, the SNNP issued a total of 6 472 naloxone kits, of which 5 395 (83 %) were in the community and 1 077 (17 %) to prisoners on release. Among Scottish prisoners supplied with take-home naloxone, mortality within 4 weeks after release had decreased to 4.7 % by 2013, compared with the pooled 2006–10 baseline of 9.8 % (Information Services Division, 2014). Similar reductions of overdose deaths were observed after hospital discharge. In fact, since the programme's start in 2011, the number of heroin-related deaths within 4 weeks of prison release has decreased gradually every year, coinciding with a steady increase in the number of take-home naloxone kits provided. The significance of this reduction has been examined (Bird et al., 2015a), with study rationale as described by Bird et al. (2015b).

Example of good practice: N-ALIVE and prison-based overdose prevention

In 2008, the UK Medical Research Council awarded funding for the N-ALIVE pilot trial. The trial constitutes the first randomised controlled trial that assesses the impact of take-home naloxone provision on overdose mortality following discharge from prison (Strang et al., 2013). Specifically, the trial compares the rate of overdose deaths in the first 12 weeks of prison release between (former) heroin injectors who received a supply of take-home naloxone at release and those who did not.

Any prison inmate of at least 18 years of age, with a minimum duration of imprisonment of 7 days and a history of injection heroin use, was eligible for participation in the trial, which started in May 2012. Participants from 16 prisons in England were randomised to participate in the N-ALIVE trial. Upon release from prison, those randomised to the take-home naloxone arm would receive an N-ALIVE wallet containing a pre-filled naloxone syringe and an instruction leaflet, as well as a DVD containing video instructions on overdose management and naloxone administration. Study subjects in the control group learnt, at the point of their release, that the N-ALIVE wallet given to them contained no naloxone.

Following the release of the 2013/14 data report from the Scottish National Naloxone Programme, and with the N-ALIVE finding from interim analysis that twice as many naloxone kits were used to resuscitate another person (whereas the trial was measuring only death or survival of the actual prison releasees), recruitment into N-ALIVE was terminated for ethical reasons: with this new information, the committee that oversaw the N-ALIVE pilot trial deemed it unnecessary to continue the trial, especially as most overdose victims who were benefiting from the N-ALIVE naloxone were not those who were being followed up in the trial (or, even worse from the point of view of the trial, might even be subjects allocated to the control condition). Randomisation to the N-ALIVE trial ended on 8 December 2014. The committee recommended that, following the end of randomisation, take-home naloxone provision on release should be continued for all prisoners with a history of opioid use. In total, 1 685 subjects were recruited into the N-ALIVE trial. The results of the trial will be released in 2015 (MRC, 2014).

Following N-ALIVE, non-randomised prison-based naloxone provision has been introduced in the United States, in San Francisco and Rhode Island (Clear, 2015). In Russia, the AIDS Foundation East–West (AFEW) has recently funded a take-home naloxone programme that targets prisoners in the Tomsk prison system in Siberia (Open Society Foundations, 2013): upon release, (ex-)prisoners can choose to attend community-based overdose prevention training, where they are supplied with take-home naloxone.

on a bystander to assist in the event of an emergency: 'The French Law intends to punish — both in criminal and civil law — the bystander who, directly witnessing a dangerous incident, does not intervene even though to do so would pose no risk to him or a third party' (DAN Legal Network, 2014). However, in the absence of political support, the implementation of a take-home naloxone programme did not appear on the government's agenda. In February 2015, the National Narcotics and Psychotropic Substances Commission voted in favour of a take-home naloxone programme for drug users and third parties, which would use a naloxone nasal spray in the long term, depending on its market launch. As an interim solution, the commission also issued a favourable opinion for distribution of injectable naloxone, so that naloxone could be made available more rapidly (Agence Nationale de Sécurité du Médicament et des produits de santé, 2015). The take-home naloxone programme will prioritize newly released inmates and patients after opioid withdrawal as target populations.

Germany

A counselling and treatment provider in Cologne (Vision e.V.; www.vision-ev.de/) is planning to start a naloxone programme using a peer-based approach, and a regional drug user advocacy group in North Rhine-Westphalia (www.jesnrw.de/) is developing a concept for low-threshold training and distribution of naloxone to drug users and their peers in a street setting, starting in 2016 (JES e.V. NRW, personal communication).

Naloxone initiatives outside the European Union

There is an increasingly well-connected network of practitioners and policymakers interested in take-home naloxone, as well as interest and activism from injecting drug users and harm-reduction organisations. Consequently, it is important to track developments from outside Europe, to understand the potential for wider implementation and more effective prevention of opioid overdose deaths across Europe and beyond.

United States

Following the pioneering Chicago Recovery Alliance take-home naloxone pilot, early adopters in the United States included New Mexico (Baca, 2001; Baca and Grant, 2005) and the San Francisco DOPE (Drug Overdose Prevention and Education) project (Seal et al., 2005), which both introduced naloxone distribution in 2001.

Take-home naloxone programmes have since been established in at least 15 US states and the District of Columbia. The rapid dissemination of take-home naloxone was made possible by the introduction of Good Samaritan laws (granting legal immunity to bystanders) and the amendment of medical liability laws (relieving naloxone prescribers of liability) (NPHL, 2014).

A recent US survey among 136 organisations (84 community-based organisations, 28 healthcare facilities, 18 public health departments and six pharmacies) reported providing overdose training and take-home naloxone kits to 152 283 individuals between 1996 and mid-2014, and documented 26 463 overdose reversals (Wheeler et al., 2015). Many of these programmes were introduced in response to rising mortality from prescription opioid overdose.

Canada

In Canada, take-home naloxone initiatives of varying sizes exist in several regions. The only published Canadian study (Leece et al., 2013) reports on a

Spotlight: Massachusetts

In the United States, the most comprehensive programme evaluation to date has been conducted by the Massachusetts Department of Public Health.

In the early 2000s, amidst rising overdose rates, Boston-based harm reduction activists began distributing take-home naloxone without formal approvals, through underground needle-exchange schemes. However, the activists maintained a log of the number of naloxone vials distributed and the number of overdose events reversed, and documented these numbers in a 2005 letter to the mayor of Boston. In response, the mayor convened a joint meeting with the activists and the Department of Public Health. As a result of the meeting, the Boston Public Health Commission (BPHC) authorised the development of an overdose-prevention programme with naloxone distribution through its mobile needle-exchange programme. This programme was the first take-home naloxone programme that involved the distribution of intranasal naloxone (see Chapter 6), as opposed to the standard naloxone injection. Moreover, a standing order was passed by the Medical Director to allow trained, non-medical public health workers to issue the naloxone to injecting drug users and potential overdose bystanders. By 2009, the Massachusetts Department of Public Health had expanded the programme to seven more communities. At present, the Massachusetts take-home naloxone programme provides overdose education and naloxone supplies at needle-exchange sites, methadone clinics, homeless shelters, inpatient detoxification programmes, community meetings, outpatient and residential addiction-treatment programmes and emergency departments. Taken together, as of 2014, the Massachusetts take-home naloxone programme had trained 4 926 drug users, of whom 373 (7.6 %) reported administering naloxone (Doe-Simkins et al., 2014). A 2013 interrupted-time series analysis compared overdose rates in Massachusetts-based communities with take-home naloxone programmes and those without and found that those communities where take-home naloxone was available had significantly lower overdose mortality rates (adjusted rate ratio 0.71; 95 % confidence interval 0.57–0.90) (Walley et al., 2013).

Toronto-based take-home naloxone programme that trained 209 injecting drug users in overdose prevention and naloxone administration, and registered 17 overdose reversals. In Vancouver and surrounding British Columbia, a multi-site take-home naloxone programme has dispensed over 1 200 naloxone kits since 2012, and 125 overdose reversals have been reported (Canadian Drug Policy Coalition, 2014).

Australia

The first Australian take-home naloxone programme was started in Canberra in December 2011. In a preliminary evaluation, 140 injecting drug users had been trained in overdose prevention and reported 23 successful overdose reversals (ACT Health, 2014). Naloxone access in Australia has been facilitated by the addition of the antidote to the Pharmaceutical Benefit Scheme (Australian government programme that provides subsidised prescription drugs) in December 2012, whereby Australian residents can now obtain naloxone made by an Australian manufacturer at a concession rate of AUD 5.90 (approximately EUR 4.20), rather than the previous AUD 60 (EUR 43) (Fowlie, 2013). Provision of take-home naloxone is coordinated by different agencies, including charities such as the Salvation Army.

Low- and middle-income countries

Over the course of the past 5 years, take-home naloxone programmes have been established as pilot projects in a number of low- and middle-income countries (LMICs), including Afghanistan, China, Georgia, India, Kazakhstan, Kyrgyzstan, Tajikistan, Thailand, Ukraine and Vietnam (UNODC and WHO, 2013). Funding of these programmes is heavily dependent on foreign aid. The need for such programmes in LMICs, where opioid substitution treatment availability is often limited, was a particular focus of the new guidelines on community-based management of opioid overdose from the WHO (2014).

Take-home naloxone programmes are considered a central element of overdose prevention efforts across LMICs, where opioid users face significant barriers to medical care, such as the fear of arrest or forced detox following disclosure of opioid use, and prohibitive cost of treatment. Particularly in rural areas, emergency medical services are limited in availability, and lack of transport makes it difficult for individuals to access existing clinics. Some take-home naloxone pilot programmes provide naloxone directly to users and family members for lay administration, while others deliver naloxone free of charge to existing clinics or trained peer groups.

Initial results are promising: in Kyrgyzstan and Tajikistan, where overdose deaths are common because of the geographical proximity to Afghanistan and easy access to high-purity heroin, naloxone usage rates (i.e. naloxone kits used as a proportion of all kits distributed) were calculated for two take-home naloxone programmes. The analysis was based on questionnaire data obtained from programme participants who returned for naloxone refills. In both countries, a high proportion of naloxone kits (Kyrgyzstan 47 %; Tajikistan 78 %) were used in overdose incidents (Kan et al., 2014).

Lessons learnt

Largely run on a pilot basis, a wide range of naloxone distribution programmes currently exist. This variety of programme features is reflective of the need to tailor each individual programme to the available resources, local context and regulations. Despite these structural differences, the following joint lessons learnt may apply to the implementation of future take-home naloxone programmes:

- Governmental support facilitates roll-out legally and financially (see Denmark, Estonia, Massachusetts, Norway, Scotland and Wales).
- Gaining the support of local police is crucial for programme success (see Estonia and Norway), as it decreases users' fear of contacting ambulance services.
- Integrating naloxone provision into standard care at existing healthcare facilities promotes project sustainability (Norway).
- Involvement of user groups facilitates outreach and promotes project acceptability (Massachusetts and Norway).
- Family members and other carers can be vocal advocates to receive training themselves and to support wider provision to the user community (England and Scotland).
- First-responder services such as ambulance services, firefighters and police are an important workforce to be trained and can be influential advocates (England and United States).

- Good practices can be promoted through development of model legislation (e.g. Good Samaritan laws) and protocols (e.g. Scotland protocol by Bird et al., 2015).
- Reliance on one naloxone product or manufacturer can create financial risk (Norway).
- Naloxone programmes should include prisoners on release (N-ALIVE, Scotland and Wales).

Emergence of stronger science

Most take-home naloxone initiatives have been made possible through strong advocacy by local early adopters who have pioneered naloxone-prescribing schemes in various cities and communities, mostly in the United States and the United Kingdom thus far (CDC, 2015; NTA, 2011). The early pilot studies suggested that take-home naloxone had a number of benefits, but methodological limitations made it impossible to quantify the impact of take-home naloxone provision on overdose mortality and possible associated risks. Limitations included small sample sizes, lack of systematic follow-up, short duration of observation (not taking into account any possible late complications), lack of randomisation or control groups, reliance on self-report, selection bias largely determined by participants' motivation, attrition and the inability to quantify the number of lives saved. As a result, the lack of scientific underpinning of these case or project reports made it difficult to bring about policy change.

In recent years, however, a series of well-designed studies and two systematic reviews (Clark et al., 2014; EMCDDA, 2015a) have been published (see Chapter 6). Among others, studies include two randomised controlled trials comparing the administration of intranasal naloxone with intramuscular naloxone as well as a randomised controlled trial assessing the impact of training on knowledge and attitudes (for an overview see EMCDDA, 2015a). In addition, recent studies address the effect of take-home naloxone on mortality after release from prison (Strang et al., 2013); the impact of take-home naloxone provision on local overdose rates (interrupted time-series analysis in Massachusetts by Walley et al., 2013); and the cost-effectiveness of such programmes (Coffin and Sullivan, 2013a,b). Moreover, mortality impact studies by Bird and colleagues are forthcoming, as part of the evaluation of the Scottish National Naloxone Programme.

Based on these new research results, WHO published new guidelines on community management of opioid overdose (WHO, 2014), which are further described in Chapter 6 and recommend that 'People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration'.

Nonetheless, dissemination of take-home naloxone has been remarkably slow: almost 20 years after take-home naloxone was first proposed (1996), only Scotland and Wales have systems aiming at full national coverage of take-home naloxone. However, a growing number of EU Member States have introduced local take-home naloxone provision and a European exchange of experience and expertise on take-home naloxone was organised in October 2014 at the EMCDDA. Important remaining issues around implementation and scaling-up of take-home naloxone provision in Europe are addressed in the next chapter.

References

Abel-Ollo, K. (2014), *Take-home naloxone in Estonia* (available at http://www.emcdda.europa.eu/events/2014/meetings/naloxone).

ACMD (Advisory Council on the Misuse of Drugs) (2012), *Consideration of naloxone*, The Stationery Office, London.

ACT Health (2014), *Key interim findings: independent evaluation of the 'Implementing Expanding Naloxone Availability in the ACT (I-ENAACT)' program, 2011–2013* (http://www.atoda.org.au/wp-content/uploads/Summary-of-Interim-Findings-summary-for-release-2.pdf).

Agence Française de Sécurité Sanitaire et des Produits de Santé (2009), *Compte-rendu de la réunion du 8 janvier 2009 de la Commission nationale des stupéfiants et des psychotropes* (http://ansm.sante.fr/var/ansm_site/storage/original/application/8db592cc5f6bdbb78ce48ce3c0eb41a3.pdf).

Agence Nationale de Sécurité du Médicament et des produits de santé (2015), *Retour sur la séance du 12 février 2015 de la commission des stupéfiants et psychotropes*, ANSM, Saint-Denis.

Andrey Rylkov Foundation for Health and Social Justice (2013), *New take-home naloxone programme started in Estonia* (available at http://en.rylkov-fond.org/blog/other-eeca-countries/new-take-home-naloxone-programme-started-in-estonia/).

Arribas-Ibar, E., Sánchez-Niubò, A., Majó, X., Domingo-Salvany, A. and Brugal, M. T. (2014), 'Coverage of overdose prevention programs for opiate users and injectors: a cross-sectional study', *Harm Reduction Journal* 11, p. 33.

Baca, C. T. (2001), 'Take-home naloxone to prevent deaths from opiate overdose', rapid response, *BMJ* (322) p. 895

(available at http://.bmj.com/content/322/7291/895/rapid-responses).

Baca, C. T. and Grant, K. J. (2005), 'Take-home naloxone to reduce heroin death', *Addiction* 100, pp. 1823–1831.

Beletsky, L., Ruthazer, R., Macalino, G. E., Rich, J. D., Tan, L. and Burris, S. (2007), 'Physicians' knowledge of and willingness to prescribe naloxone to reverse accidental opiate overdose: challenges and opportunities', *Journal of Urban Health* 84, pp. 126–136.

Bennett, G. A. and Higgins, D. S. (1999), 'Accidental overdose among injecting drug users in Dorset, UK', *Addiction* 94, pp. 1179–1189.

Best, D., Gossop, M., Man, L.-H., Stillwell, G., Coomber, R. and Strang, J. (2002), 'Peer overdose resuscitation: multiple intervention strategies and time to response by drug users who witness overdose', *Drug and Alcohol Review* 21, pp. 269–274.

Bigg, D. (2002), 'Data on take home naloxone are unclear but not condemnatory', *BMJ* 324(7338), p. 678.

Bird, S. M. and Hutchinson, S. J. (2003), 'Male drugs-related deaths in the fortnight after release from prison: Scotland, 1996–99', *Addiction* 98, pp. 185–190.

Bird, S. M., McAuley, A., Perry, S., and Hunter, C. (2015a), 'Effectiveness of Scotland's national naloxone programme for reducing opioid-related deaths: a before (2006-10) versus after (2011-13) comparison', *Addiction* doi:10.1111/add.13265.

Bird, S., Parmar, M. and Strang, J. (2015b), 'Take-home naloxone to prevent fatalities from opiate-overdose: protocol for Scotland's public health policy evaluation, and a new measure to assess impact', *Drugs: Education, Prevention and Policy* 22, pp. 66–76.

Burris, S., Norland, J. and Edlin, B. R. (2001), 'Legal aspects of providing naloxone to heroin users in the United States', *International Journal of Drug Policy* 12, pp. 237–248.

Byrne, A. (2006), 'Emergency naloxone for heroin overdose: over the counter availability needs careful consideration', *BMJ* 333(7571), p. 754.

Canadian Drug Policy Coalition (2014), 'Canada is ignoring easy, uncontroversial ways to prevent overdose deaths' (available at http://drugpolicy.ca/2014/10/canada-is-ignoring-easy-uncontroversial-ways-to-prevent-overdose-deaths/).

Caplehorn, J. R. M. and Drummer, O. H. (1999), 'Mortality associated with New South Wales methadone programmes in 1994: lives lost and saved', *Medical Journal of Australia* 170, pp. 104–109.

CDC (Centers for Disease Control and Prevention) (2015), *Opioid overdose prevention programs providing naloxone to laypersons — United States, 2014* (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6423a2.htm).

Clark, A. K., Wilder, C. M. and Winstanley, E. L. (2014), 'A systematic review of community opioid overdose prevention and naloxone distribution programs', *Journal of Addiction Medicine* 8, pp. 153–163.

Coffin, P. O. and Sullivan, S. D. (2013a), 'Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal', *Annals of Internal Medicine* 158, pp. 1–9.

Coffin, P. O. and Sullivan, S. D. (2013b), 'Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal in Russian cities', *Journal of Medical Economics* 16, pp. 1051–1060.

Coffin, P. O., Fuller, C., Vadnai, L., Blaney, S., Galea, S. and Vlahov, D. (2003), 'Preliminary evidence of health care provider support for naloxone prescription as overdose fatality prevention strategy in New York City', *Journal of Urban Health* 80, pp. 288–290.

DAN Legal Network (2014), *The Good Samaritan law across Europe* (http://www.daneurope.org/c/document_library/get_file?uuid=c09228f3-a745-480b-9549-d9fc8bbbd535&groupId=10103).

Davis, C. S., Carr, D., Southwell, J. K. and Beletsky, L. (2015), 'Engaging law enforcement in overdose reversal initiatives: authorization and liability for naloxone administration', *American Journal of Public Health* 105, pp. 1530–1537.

Davoli, M., Perucci, C. A., Forastiere, F., Doyle, P., Rapiti, E., Zaccarelli, M. and Abeni, D. D. (1993), 'Risk factors for overdose mortality: a case-control study within a cohort of intravenous drug users', *International Journal of Epidemiology* 22, pp. 273–277.

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

Degenhardt, L., Randall, D., Hall, W., Law, M., Butler, T. and Burns, L. (2009), 'Mortality among clients of a state-wide opioid pharmacotherapy programme over 20 years: risk factors and lives saved', *Drug and Alcohol Dependence* 105, pp. 9–15.

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M. and 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, pp. 32–51.

Department of Health (2015), *Ministers welcome availability of life-saving antidote to heroin-related overdoses aimed at reducing drug-related deaths* (available at http://health.gov.ie/blog/press-release/ministers-welcome-availability-of-life-saving-antidote-to-heroin-related-overdoses-aimed-at-reducing-drug-related-deaths/).

Dettmer, K. (2014), *Der Einsatz von Naloxon durch geschulte Laien* (http://www.aidshilfe.de/sites/default/files/2014-06-30%20ADSB%20Cover%20innen.pdf).

Dettmer, K., Saunders, B. and Strang, J. (2001), 'Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes', *BMJ* 322(7291), pp. 895–896.

Deutsche AIDS-Hilfe (2013), *Leben retten mit Naloxon* (http://blog.aidshilfe.de/2013/08/31/leben-retten-mit-naloxon/).

Direction Generale de la Santé (2008), *Projet de mise à disposition de la naloxone (Narcan®) chez les usagers de drogues pour prévenir les décès par overdoses aux opiacés* (http://www.sante.gouv.fr/IMG/pdf/avis_narcan.pdf).

Doe-Simkins, M., Quinn, E., Xuan, Z., Sorensen-Alawad, A., Hackman, H., Ozonoff, A. and Walley, A. Y. (2014), 'Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programmes: a retrospective cohort study', *BMC Public Health* 14, p. 297.

DrugScope (2015), *Bite-sized briefing: take-home naloxone for opioid overdose in people who use drugs* (http://drugscope.blogspot.co.uk/2015/02/bite-sized-briefing-take-home-naloxone.html).

EMCDDA (2012), *Country legal profiles: Luxembourg* (http://www.emcdda.europa.eu/html.cfm/index5174EN.html?pluginMethod=eldd.countryprofiles&country=LU&language=en).

EMCDDA (2015a), *Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone*, EMCDDA papers, Publications Office of the European Union, Luxembourg.

EMCDDA (2015b), *European drug report 2015: trends and developments*, Publications Office of the European Union, Luxembourg.

EMCDDA (2015c), *Preventing overdose deaths in Europe* (http://www.emcdda.europa.eu/topics/pods/preventing-overdose-deaths).

EMCDDA (2015d), *Country overviews* (www.emcdda.europa.eu/publications/country-overviews/).

Espelt, A., Major, X., Parés-Badell, O., Carvajal, S., Gasulla, L., Bosque-Prous, M. and Brugal, M. (2015), 'Implementation of systematic programs of overdose training at drug treatment and prevention centres in Catalonia, 2008–2012' (pp. 83–95), in Stöver, H. and Dichtl, A. (editors), *Drogennotfallprophylaxe: Training und Naloxonvergabe*, Fachhochschulverlag, Frankfurt.

Fowlie, C. (2013), *Community development, priorities, staged approach: implementing expanded naloxone availability in the ACT* (www.atoda.org.au/wp-content/uploads/Fowlie_presentation_CREIDU_Colloquium_July_2013_Final.pdf).

Gossop, M., Griffiths, P., Powis, B., Williamson, S. and Strang, J. (1996), 'Frequency of non-fatal heroin overdose: survey of heroin users recruited in non-clinical settings', *BMJ* 313(7054), p. 402.

Horowitz, Z. (1998), 'Subcutaneous naloxone: a less rude awakening?', *Academic Emergency Medicine* 5, pp. 283–285.

Hughes, B. (2014), *Distribution and use of naloxone: legal issues* (available at http://www.emcdda.europa.eu/events/2014/meetings/naloxone).

Information Services Division (2014), *National Naloxone Programme Scotland: naloxone kits issued in 2013/14 and trends in opioid-related deaths* (https://isdscotland.scot.nhs.uk/Health-Topics/Drugs-and-Alcohol-Misuse/Publications/2014-10-28/2014-10-28-Naloxone-Report.pdf?2581423522).

Kan, M., Gall, J. A., Latypov, A., Gray, R., Alisheva, G., Rakhmatova, K. and Sadieva, A. S. (2014), 'Effective use of naloxone among people who inject drugs in Kyrgyzstan and Tajikistan using pharmacy- and community-based distribution approaches', *International Journal of Drug Policy* 25, pp. 1221–1226.

Kerr, D., Dietze, P., Kelly, A.-M. and Jolley, D. (2008), 'Attitudes of Australian heroin users to peer distribution of naloxone for heroin overdose: perspectives on intranasal administration', *Journal of Urban Health* 85, pp. 352–360.

Leece, P. N., Hopkins, S., Marshall, C. et al. (2013), 'Development and implementation of an opioid overdose prevention and response programme in Toronto, Ontario', *Canadian Journal of Public Health* 104, pp. e200–e204.

Loimer, N., Hofmann, P. and Chaudhry, H. R. (1994), 'Nasal administration of naloxone is as effective as the intravenous route in opiate addicts', *International Journal of the Addictions* 29, pp. 819–827.

Maxwell, S., Bigg, D., Stanczykiewicz, K. and Carlberg-Racich, S. (2006), 'Prescribing naloxone to actively injecting heroin users: a programme to reduce heroin overdose deaths', *Journal of Addictive Diseases* 25, pp. 89–96.

McAuley, A., Best, D., Taylor, A., Hunter, C., and Robertson, R. (2012), 'From evidence to policy: the Scottish national naloxone programme', *Drugs: Education, Prevention and Policy* 19, pp. 309–319.

McGregor, C., Darke, S., Ali, R. and Christie, P. (1998), 'Experience of non-fatal overdose among heroin users in Adelaide, Australia: circumstances and risk perceptions', *Addiction* 93(5), pp. 701–711.

Merrall, E. L. C., Bird, S. M. and Hutchinson, S. J. (2013), 'A record-linkage study of drug-related death and suicide after hospital discharge among drug-treatment clients in Scotland, 1996–2006', *Addiction* 108, pp. 377–384.

MRC (2014), *Update for people who have taken part in the N-ALIVE pilot trial* (www.ctu.mrc.ac.uk/13391/13399/n-alive_update_12.14).

NPHL (2014), *Legal interventions to reduce overdose mortality: naloxone access and overdose Good Samaritan laws* (https://www.networkforphl.org/_asset/qz5pvn/network-naloxone-10-4.pdf).

NTA (2011), *The NTA overdose and naloxone training programme for families and carers* (http://www.nta.nhs.uk/uploads/naloxonereport2011.pdf).

Open Society Foundations (2013), *Inside information: overdose trainings in prisons and jails* (http://naloxoneinfo.org/case-studies/prisons-and-jails#sthash.cccfEGeE.dpuf).

Powis, B., Strang, J., Griffiths, P., Taylor, C., Williamson, S., Fountain, J. and Gossop, M. (1999), 'Self-reported overdose

among injecting drug users in London: extent and nature of the problem', *Addiction* 94, pp. 471–478.

Richert, T. (2015), 'Wasted, overdosed, or beyond saving: to act or not to act? Heroin users' views, assessments, and responses to witnessed overdoses in Malmo, Sweden', *International Journal of Drug Policy* 26, pp. 92–99.

Rodríguez-Sanz, M., Borrell, C., Martos, D., Cunillé, M. and Llimona, P. (2014), *La mortalitat a la ciutat de Barcelona: Any 2012*, Agència de Salut Pública de Barcelona, Barcelona (http://aspb.cat/quefem/docs/Mortalitat_2012.pdf).

Rudolph, S. S., Jehu, G., Nielsen, S. L., Nielsen, K., Siersma, V. and Rasmussen, L. S. (2011), 'Prehospital treatment of opioid overdose in Copenhagen: Is it safe to discharge on-scene?', *Resuscitation* 82, pp. 1414–1418.

Saelan, H. (2014), *The Danish naloxone scheme* (available at http://www.emcdda.europa.eu/events/2014/meetings/naloxone).

Schifano, F. (2001), *Take home naloxone: a contribution for ongoing debate* (available at www.bmj.com/content/322/7291/895/rapid-responses).

Seal, K. H., Downing, M., Kral, A. H., Singleton-Banks, S., Hammond, J.-P., Lorvick, J. and Edlin, B. R. (2003), 'Attitudes about prescribing take-home naloxone to injection drug users for the management of heroin overdose: a survey of street-recruited injectors in the San Francisco Bay Area', *Journal of Urban Health* 80, pp. 291–301.

Seal, K. H., Thawley, M. R., Gee, M. L., Bamberger, J., Kral, A. H., Ciccarone, D. et al. (2005), 'Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study', *Journal of Urban Health* 82, pp. 303–311.

Seaman, S., Brettle, R. and Gore, S. (1998), 'Mortality from overdose among injecting drug users recently released from prison: database linkage study', *BMJ* 316(7129), pp. 426–428.

Sheehan, M. (2014), *Heroin users get antidote syringe for overdoses* (http://www.independent.ie/irish-news/health/heroin-users-get-antidote-syringe-for-overdoses-30693210.html).

Simini, B. (1998), 'BOLOGNA: naloxone supplied to Italian heroin addicts', *The Lancet* 352(9132), p. 967.

Sporer, K. A., Firestone, J. and Isaacs, S. M. (1996), 'Out-of-hospital treatment of opioid overdoses in an urban setting', *Academic Emergency Medicine* 3, pp. 660–667.

Stöver, H. (2015), *Analyse der Drogennotfallprophylaxe bei Poiatabhängigen (DroNoPro)* (https://www.frankfurt-university.de/fachbereiche/fb4/forschung/forschungsinstitute/isff/projekte3/analyse-der-drogennotfallprophylaxe.html).

Strang, J. (1992), 'Harm reduction: defining the concept, exploring the boundaries, and identifying operational possibilities', paper presented at the Third International Harm Reduction Conference, Melbourne.

Strang, J. (2001), 'Take home naloxone for opiate addicts', *BMJ* 323, p. 934.

Strang, J., Darke, S., Hall, W., Farrell, M. and Ali, R. (1996), 'Heroin overdose: the case for take-home naloxone', *BMJ* 312(7044), p. 1435.

Strang, J., Powis, B., Best, D., Vingoe, L., Griffiths, P., Taylor, C. et al. (1999), 'Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability', *Addiction* 94, pp. 199–204.

Strang, J., Best, D., Man, L.-H., Noble, A. and Gossop, M. (2000), 'Peer-initiated overdose resuscitation: fellow drug users could be mobilised to implement resuscitation', *International Journal of Drug Policy* 11, pp. 437–445.

Strang, J., McCambridge, J., Best, D., Beswick, T., Bearn, J., Rees, S. and Gossop, M. (2003), 'Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study', *BMJ* 326(7396), pp. 959–960.

Strang, J., Manning, V., Mayet, S., Titherington, E., Offor, L., Semmler, C. and Williams, A. (2008), 'Family carers and the prevention of heroin overdose deaths: unmet training need and overlooked intervention opportunity of resuscitation training and supply of naloxone', *Drugs: Education, Prevention, and Policy* 15, pp. 211–218.

Strang, J., Bird, S. M. and Parmar, M. K. (2013), '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* 90, pp. 983–996.

Tobin, K. E., Gaasch, W. R., Clarke, M. C., MacKenzie, E. and Latkin, C. A. (2005), 'Attitudes of emergency medical service providers toward naloxone distribution programmes', *Journal of Urban Health* 82, pp. 296–302.

Tobin, K. E., Sherman, S. G., Beilenson, P., Welsh, C. and Latkin, C. A. (2009), 'Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives', *International Journal of Drug Policy* 20, pp. 131–136.

Trujols, J. (2001), *Take home naloxone: life-saving intervention, medico-legal concern and heroin users' competence* (available at www.bmj.com/content/322/7291/895/rapid-responses).

UK Government (1968), *Medicines Act 1968* (available at http://www.legislation.gov.uk/ukpga/1968/67/part/III).

UNODC and WHO (2013), *Opioid overdose: preventing and reducing opioid overdose mortality* (http://www.unodc.org/docs/treatment/overdose.pdf).

Vilke, G. M., Buchanan, J., Dunford, J. V. and Chan, T. C. (1999), 'Are heroin overdose deaths related to patient release after prehospital treatment with naloxone?', *Prehospital Emergency Care* 3, pp. 183–186.

Walley, A. Y., Xuan, Z., Hackman, H. H., Quinn, E., Doe-Simkins, M., Sorensen-Alawad, A. et al. (2013), 'Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis', *BMJ* 346, pp. f174.

Wanger, K., Brough, L., Macmillan, I., Goulding, J., MacPhail, I. and Christenson, J. M. (1998), 'Intravenous vs subcutaneous naloxone for out-of-hospital management of presumed opioid overdose', *Academic Emergency Medicine* 5, pp. 293–299.

Warner-Smith, M., Darke, S., Lynskey, M. and Hall, W. (2001), 'Heroin overdose: causes and consequences', *Addiction* 96, pp. 1113–1125.

Wheeler, E., Jones, S. J., Gilbert, M. K. and Davidson, P. J. (2015), 'Opioid overdose prevention programs providing naloxone to laypersons: United States, 2014', *Morbidity and Morality Weekly Report* 64, pp. 631–635.

WHO (2014), *Community management of opioid overdose* (http://apps.who.int/iris/bitstream/10665/137462/1/9789241548816_eng.pdf?ua=1&ua=1).

Williams, A. V., Marsden, J. and Strang, J. (2014), 'Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes', *Addiction* 109, pp. 250–259.

Worthington, N., Markham Piper, T., Galea, S. and Rosenthal, D. (2006), 'Opiate users' knowledge about overdose prevention and naloxone in New York City: a focus group study', *Harm Reduction Journal* 3, p. 19.

5

CHAPTER 5

Setting up take-home naloxone training and distribution programmes

Anna Williams

Take-home naloxone training programmes overview

Training and advice on overdose management are recognised as key components of overdose prevention. The proposal to prescribe naloxone to opioid users, in a similar way to how adrenaline (epinephrine) is prescribed to someone with a severe allergy, has been welcomed by clinicians, patients and their family members. However, the enthusiasm for this new harm-reduction strategy has been accompanied by concerns related to the ability of patients to deal safely with an overdose emergency. These concerns included dealing with the potential recurrence of opioid toxicity, withdrawal symptoms of the overdose victim, summoning ambulance services and risk of blood-borne virus transmission.

Some of these concerns can be minimised by delivering good-quality training. However, implementing a take-home naloxone programme can be challenging, particularly if services lack support and funding. Lack of training, time and prioritisation are some of the barriers cited by new programmes in England (Mayet et al., 2011), but information and training materials are now available to assist services willing to provide naloxone distribution.

Is training necessary?

Training is an essential part of take-home naloxone distribution programmes. Most witnesses of overdoses try to assist the victims in many ways, but some actions that are often not taken are among the most important ones, such as calling for an ambulance (Darke et al., 1996). Mistaken beliefs that overdoses can be reversed by putting the person in a cold bath, injecting salt solution or giving stimulants have also been reported by drug users (Beswick et al., 2002; Davidson et al., 2002). These beliefs are incorrect and can be potentially dangerous, as well as delaying appropriate medical assistance.

Community distribution of naloxone is a fairly recent intervention and individuals without a medical background are unlikely to be familiar with emergency overdose cases and the intramuscular administration of naloxone. Training helps bystanders to become familiar with this medication and to feel competent to use it in the event of witnessing an overdose.

Is training effective?

Training in take-home naloxone can be beneficial to those at risk of witnessing an overdose. The short-term benefits can be seen immediately after training, in the increase of knowledge, confidence and skills of trainees. Several studies have assessed the short-term impact of take-home naloxone through knowledge acquisition and confidence enhancement (McAuley et al., 2009; Seal et al., 2005; Strang et al., 2008). A randomised controlled trial in England found that knowledge and positive attitudes relating to overdose and naloxone administration improved to a greater extent in the group receiving take-home naloxone training than in the control group, which received basic information only through leaflets. Positive outcomes were detected 3 months after the intervention (Williams et al., 2014). Another study found that drug users can be trained to be as competent as medical experts at distinguishing opioid overdose symptoms and administering naloxone appropriately (Green et al., 2008).

Long-term benefits of naloxone training have also been reported. A number of studies documented significant increases in the identification of overdoses and correct administration of naloxone by most trained individuals (Lopez Gaston et al., 2009; McAuley et al., 2009; Strang et al., 2008).

Take-home naloxone training may also help to increase clients' self-worth and give them a sense of empowerment by offering clients the knowledge, skills and competence necessary for them to increase control over their own opioid use. Take-home naloxone has the ability to transfer some of this control from the hands of health professionals into the hands of the clients and their social networks. This has the major additional advantage of greatly increasing the number of people who are competent at overdose management. For information on the effectiveness of training, see Chapter 6.

Who needs training?

Most overdoses are reported to occur in private homes, and between 70 % and 90 % of them occur in the presence of someone else (Best et al., 2002; Lagu et al., 2006; Tobin et al., 2005; Tracy et al., 2005). The groups known to be at risk of witnessing an opioid overdose are (see Chapter 4 for more information):

- current and former drug users, especially those who use opioids, people who inject drugs, (former) users upon release from prison, (former) users upon release from inpatient drug treatment, ever-injectors upon release from any hospitalisation and all drug users with a personal history of opioid overdose;
- family members, close friends, partners and other family members;
- health professionals, drug workers, staff at supervised drug-consumption facilities, outreach workers, hostel staff and ambulance staff;
- police officers, prison guards and firefighters.

Development and implementing training

Careful consideration needs to be given to how take-home naloxone training is going to be delivered. These are some of the aspects that should be considered.

Trainers

Anyone can become a take-home naloxone trainer, as long as they themselves have received appropriate training and feel confident and competent to train other individuals. Trainers should take time to understand opioid-overdose risk factors, the effects of opioids in the body and how an overdose can be reversed through the use of naloxone. Trainers should be able to explain step by step which actions need to be taken if someone witnesses an overdose. Trainers also need to feel competent to respond to trainees' questions and to deal with sensitive information. A practical way of implementing take-home naloxone is by using the 'Cascadian Approach' detailed by Mayet et al. (2011). In the Cascadian Approach, training is delivered to substance-misuse workers, who then take the lead in training their caseloads. To maximise impact, clients can also be asked to bring a friend to the training session (McAuley et al., 2009; Seal et al., 2005).

Trainers can be counsellors, ambulance service personal, harm-reduction workers, nurses, doctors, service users and carers. Adequate preparation is vital, as drug users have expressed concerns over professionals' lack of credibility and understanding about the effects of heroin (Wright et al., 2006). It is extremely beneficial for the programmes to involve service users fully. Service users should be involved from the planning stages, so that their views and ideas are taken into account. It is also helpful to involve service users in the implementation and delivery of take-home naloxone training. Their support is likely to increase the credibility of the programme and facilitate recruitment of individuals at risk of overdosing.

To become a trainer, individuals should access good-quality reading materials and have meetings with emergency medical personnel to discuss areas of conflicting information and clarify any doubts. It can be helpful to put together a simple protocol or manual for guiding the trainers in covering all the training content. Alternatively, available manuals (Perry and Mackintosh, 2007; Williams et al., 2014) can be adopted or adapted. Before launching the programme, trainers could run a couple of 'mock' training sessions among their colleagues. This might be a good opportunity to receive feedback on the planned programme. Finally, a system of supervision for the trainers should also be put in place, so that trainers can receive adequate support throughout the programme.

Setting

Take-home naloxone training can take place in a variety of settings, such as treatment settings (hospital-based, residential treatment centres or outpatient clinics), prisons or hostels, or through needle-exchange

programmes and outreach/mobile services. Training can take the format of a structured teaching session (in small or large groups) or a friendly individual dialogue. These types of training might take longer and require more resources, but brief training sessions can also be beneficial and increase the accuracy in overdose identification. A brief training session might take place in a waiting room or while other interventions or checks are under way.

Training content

The training has focused on educating individuals about what naloxone is, how to use it and the possible risks and benefits involved. In some services, the naloxone component has simply been added to their already established overdose-management training. Over the years, different services have produced a range of training protocols, varying in their format, content and prescribing procedures.

Training content needs to be consistent and based on good-quality information. Some common themes covered are risk factors for an overdose, how to recognise an opioid overdose, actions to take and aftercare procedures (McAuley et al., 2009; Seal et al., 2005; Strang et al., 2008; Wagner et al., 2010). The possibility of adverse reactions needs to be presented, alongside a balanced assessment of the dangers of an untreated overdose. The importance of calling for an ambulance needs to be emphasised, as some studies have reported a decrease in ambulance calls after implementation of take-home naloxone programmes (Bennett and Higgins, 1999; Dettmer et al., 2001; Doe-Simkins et al., 2009).

One point of divergence in terms of content has been the inclusion of cardiopulmonary resuscitation (CPR) training. Some programmes have liaised with local ambulance services to deliver naloxone training and CPR training together (McAuley et al., 2009; Seal et al., 2005; Tobin et al., 2005). However, CPR cannot be taught in a brief intervention, so other training programmes have excluded full CPR training, giving emphasis to the importance of airway and breathing and to consideration of naloxone administration (Strang et al., 2008).

Different training levels

- *Brief training:* A brief training session can be delivered when time is short, for instance to patients waiting for an appointment. During this brief training, individuals should be advised on how to recognise an opioid overdose, actions to take and how to administer naloxone safely, as well as on safe disposal of used naloxone kits. This information could be transmitted to patients individually or in pairs.

- *Standard training:* The standard training could be delivered when more time and resources are available. This training session can include additional information on how opioid overdoses can be prevented and more detailed information on actions to take, with a focus on checking the airways and recovery measures. Practising how to check airways and breathing and how to place someone in the recovery position could be encouraged. This training session could be delivered individually, in pairs or in small groups. This type of training could also be delivered during a counselling session with a drug worker or key worker.

- *Advanced training:* Services might wish to invest time, resources and personnel in a more extensive training programme, which could include practising how to inject naloxone intramuscularly (possibly using an injection trainer; see Figure 5.2) and also including some CPR training. For this extensive training session, ambulance personnel can be included in the delivery. The delivery can occur in larger groups. This training would be more directed to health professionals, as well as to drug users and their family members.

It is important that the training session be practical and dynamic, as well as educational. Practising life-saving skills at the training session will help reinforce knowledge and contribute to building clients' confidence. The practical stage of training can be implemented in a systematic fashion, for instance using the four-stage method described in the Glasgow Manual (Perry and Mackintosh, 2007). This method makes use of adult learning principles by transferring the skills gradually further away from the instructor to the trainee (Peyton, 1998). The four-stage teaching method consists of:

- *Conceptualisation:* The trainer performs the skill, so the participants know what is expected of them.

- *Visualisation:* The trainer performs the skill again but this time the trainer explains all the actions while performing them.

- *Verbalisation:* The trainer performs the skill and the participants verbalise each action while the trainer is performing it.

- *Practice:* Participants practise the skills themselves.

Dealing with an overdose: step-by-step for advanced training

The specific step-by-step approach to managing an opioid overdose should be decided by each individual programme. Existing national or local guidelines for dealing with opioid overdose should be taken into account. Suggested steps are detailed below. This step-by-step approach will be most suitable when time and resources are available to implement advanced training.

- *Approach with care:* In a suspected drug overdose the witness should be aware of any hazards to him-/herself and to the suspected overdose victim. They should check for danger, such as being careful with needles that might be around.

- *Check for response:* One of the first steps is to check if the overdose victim is conscious by calling their name, gently shaking their shoulders, talking loudly into their ears, rubbing their sternum or pinching their ears or the bed of the finger nail.

- *Call for assistance:* The importance of calling for assistance should be emphasised. If there are other people nearby, the witness could ask them to call emergency services, so that the witness can continue to look after the overdose victim. If the witness is alone, they should call for an ambulance immediately. It is important to tell emergency services the exact address and directions, what substances they think the overdose victim may have taken and whether or not the overdose victim is conscious and breathing. Witnesses might be afraid of calling an ambulance for fear of the police attending. In many European countries the police might indeed come, either because it is routine practice or to make sure the ambulance crew is safe or in case a death has occurred. This will vary across countries and jurisdictions, so it is important to check local police practice and consider involving them in the programme, following the example of some US programmes (Davis et al., 2015; Rando et al., 2015).

- *Check airways and breathing:* The mouth should be checked for any obvious obstructions. Any blockage should be cleared by kneeling by the side of the overdose victim and rolling the victim towards the person kneeling. If the blockage does not come away, the person should turn the overdose victim's head to the side, hook two fingers together and sweep them through the mouth. Breathing should also be checked by opening the airways — lifting the chin and tilting the head — and then placing their ear above the victim's mouth and looking along the chest and abdomen. Breathing should be checked for 10 seconds by:

  - looking to see if the chest is moving;
  - listening near the face for breathing sounds;
  - feeling for a breath on the cheek.

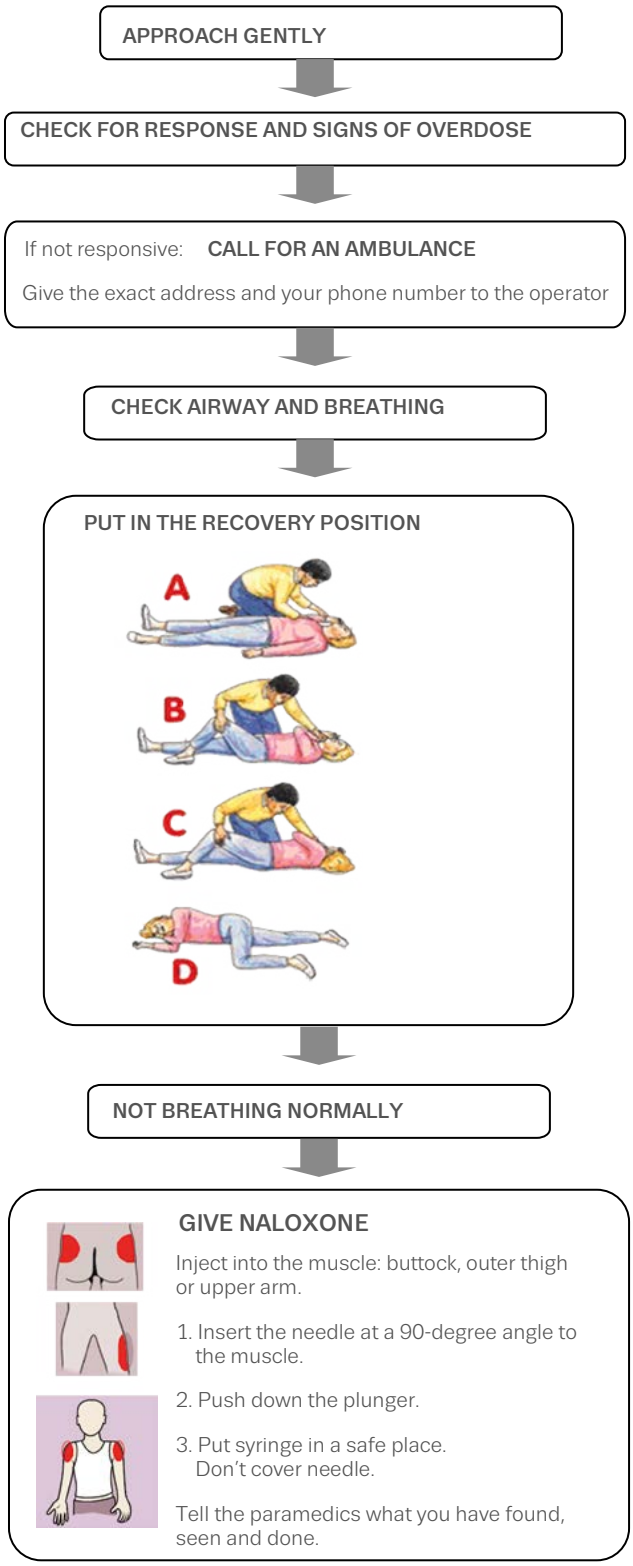
- *Practise how to put someone in the recovery position:* The recovery position is basically putting someone on their side. In this position the airway is open, the person is balanced on their side and if the person vomits they are unlikely to choke. If the bystander needs to leave the scene, they should put the overdosed person in the recovery position before leaving. To place someone on the recovery position:

  - Put the right hand of the victim by the head as if they were waving.
  - Put the left arm across the chest, so that the back of the hand rests against the cheek.
  - Hold the hand in place and lift up the left knee.
  - Turn the person on their side by pushing down on the knee (see Figure 5.1).

- *Practise how to inject naloxone:* Sometimes the overdose victim may make grunting, gasping or snoring-type breathing sounds for a couple of minutes. This is a sign that the person desperately needs oxygen. If a bystander observes this type of breathing, they should not delay naloxone administration. If a heroin user is unresponsive and not breathing (or is breathing abnormally), then they should call emergency services, put the person in the recovery position and give them naloxone. How to inject naloxone:

  - Take the syringe from box/pack.
  - Choose an injection site: the outer thigh, upper arm or buttock.
  - Hold needle at 90 degrees to skin.
  - Insert needle into the muscle.
  - Slowly and steadily push the plunger down.
  - Put the used syringe in a sharps box or in a safe place.
  - Do not cover needle, as this is how needle-stick injuries can happen.

FIGURE 5.1
Take-home naloxone training: step-by-step for advanced training (adapted from Williams, 2010, p. 415)



An injection trainer (Figure 5.2) is a device that looks like an arm muscle and is made of multi-layered soft tissue pad for the practice of injection techniques. An injection

FIGURE 5.2
Injection trainer

trainer can be used to practise how to give an intramuscular injection of naloxone. Expired naloxone syringes can be pre-filled with water solution by a team member and used to practise naloxone injection at the training session. Alternatively, an orange can be used to practise giving an injection.

- After administering naloxone: It is important to stay with the overdose victim, assist their breathing if necessary and evaluate if a second dose is necessary. The dose can be repeated if there is no response after 2 minutes. It is essential to let the paramedics know that naloxone has been given. If naloxone was used, the used naloxone kit, including any needles, should be disposed of safely in a sharp bin container (e.g. the paramedics').

Training material

Training packs

A training pack can also be provided to the participants at the training session (Ashton and Hassan, 2006). The training pack can contain a number of useful items, such as a sharps box, gloves, face shield, swabs, leaflets and an emergency card.

Incentives/contingency management

If resources are available, a small incentive can be used to increase attendance. Common incentives are gift vouchers, food vouchers and public transport vouchers (Piper et al., 2008; Seal et al., 2005; Wagner et al., 2010). A certificate of training completion can also be issued in the trainee's name.

Naloxone prescription

Naloxone can be prescribed just after the training in a one-to-one session with a physician. In the United Kingdom, for example, naloxone can be prescribed by a nurse or non-medical health worker if a 'patient group direction' is in place. A patient group direction is a special document developed by services and approved by senior doctors and pharmacists, which allows professionals other than doctors to dispense certain medicines, enabling nurses or pharmacists to dispense naloxone legally to a named patient (Department of Health, 2000). Some aspects to be considered in regard to naloxone prescription are the following (see Chapter 3 for more information).

Formulation

In Europe, preference has been given to dispensing pre-filled formulations of naloxone for intramuscular administration. Currently, intranasal naloxone is not licensed in most countries and has not undergone sufficient pharmacological testing to confidently support its use by community distribution programmes. Nevertheless, it has already been used by some take-home naloxone programmes (Doe-Simkins et al., 2009) and developments are under way to produce and test an adequate formulation for intranasal administration.

The dose prescribed has varied, with doses ranging from 0.4 mg (Galea et al., 2006; Seal et al., 2005) to a 10-ml multi-dose vial (Maxwell et al., 2006). A 2-mg/2 ml pre-filled formulation with nasal atomiser has been provided in the training programme described by Doe-Simkins et al. (2009). Some training programmes have also opted to prescribe two supplies to each trainee (Piper et al., 2008; Seal et al., 2005; Wagner et al., 2010), but a first dose ranging from 0.4 mg to 2 mg has been most recommended by programmes (see Chapter 3 for more information).

Legitimacy of prescription

Some programmes have also provided a 'proof of medication legitimacy' (Maxwell et al., 2006; Piper et al., 2008) to avoid problems with naloxone confiscation by police. Contacting local ambulance and police services might be an important first step when setting up a take-home naloxone programme (Seal et al., 2005).

Consent for medication collection

Naloxone is a prescription-only medication in almost all countries and consequently it needs to be prescribed to a named patient for their personal use. Naloxone provision to family members can sometimes seem complicated. However, family members are normally allowed to collect the medication for a named patient. One approach is for the family member to be sent a consent form by post, which they need to have signed by the user/patient and bring along to the training session, and then collect the prescription at the service requiring the consent.

Another example for dealing with this issue has been seen in Scotland, where a 'letter of comfort' by the Lord Advocate was provided in 2011, authorising prescribers to supply naloxone to individuals likely to come into contact with those at risk of opioid overdose (Angiolini, 2011). This legal document safeguards the prescriber from prosecution when prescribing naloxone to individuals other than the opioid-user patient.

Assessing knowledge and competence: before and after

Overdose and naloxone training is fundamentally an educational programme that aims to increase trainees' knowledge and confidence in managing an emergency overdose. Questionnaires can be used to assess pre-training gaps and then be repeated to measure post-training gains in knowledge and confidence. However, their use should not become a barrier to receiving training and naloxone.

Knowledge and confidence have been assessed in several take-home naloxone programmes by asking participants before and after training to respond to questions related to heroin overdose, risk factors, overdose prevention and management strategies. Wagner and colleagues (2010), for example, assessed the likelihood that trainees would administer naloxone, call emergency services and teach someone else how to use naloxone. Other programmes looked at trainees' level of comfort with naloxone administration (Piper et al., 2008; Tobin et al., 2009). Checklists, open-ended questions and recognition tests have also been used to evaluate overdose knowledge (Maxwell et al., 2006; Seal et al., 2005; Strang et al., 2008). However, few of these programme evaluations employed established instruments with known validity and reliability. When a scale of unknown validity is used, it is not possible to determine if it actually measures what it claims to measure and if the questions are relevant and clear to the trainees. To date, research measures in this field have been mostly ad hoc.

The Brief Overdose Recognition and Response Assessment (BORRA) is one of the few standardised scales available to take-home naloxone training evaluators (Green et al., 2008). BORRA evaluates the ability to recognise overdose symptoms and naloxone indication through 16 overdose scenarios. The Opioid Overdose Knowledge Scale (OOKS) is a more comprehensive knowledge questionnaire that has been validated and tested (Williams et al., 2013). The OOKS assesses the level of knowledge of opioid overdose management, including risk factors of overdose, signs of an opioid overdose, actions to be taken in an overdose situation, naloxone effects and administration, adverse effects and aftercare procedures. The scale also identifies misinformation and myths about opioid overdose. The Opioid Overdose Attitudes Scale (OOAS) is also a validated questionnaire, which assesses positive attitudes towards managing an opioid overdose (Williams et al., 2013). It assesses self-perceived ability to manage an overdose, concerns on dealing with an overdose and willingness to intervene in an overdose situation. The OOKS and OOAS are brief self-administered instruments that can be used before and after training. Both scales have been validated in samples of patients and family members and can also be administered to professionals (Ray et al., 2015). Full versions of the OOKS and the OOAS are available in the appendix to this publication.

Post-training monitoring

It is important to consider that not all supplies of naloxone distributed by a programme will be used to reverse an opioid overdose (Bird et al., 2015). Some supplies will be lost, some will be confiscated by police and some will simply not be used. Therefore, many more naloxone supplies need to be distributed than the actual number of overdoses. Bird et al. (2015) analysed the data from the SNNP and estimated that 'a country's annual provision of THN-kits should be at least nine times its recent-past mean annual number of opiate-related deaths' (p. 71), but ideally it should aim at distributing around 20 times as many.

Expired supplies and refresher sessions

Developing a strategy for the replacement of used naloxone supplies has been shown to be an easy method of keeping a record of the usage rate of naloxone kits (Dettmer et al., 2001; Maxwell et al., 2006). Refresher sessions could also be offered after a certain period of time (McAuley et al., 2009). However, re-training should not be a barrier to prescribing another supply.

Follow-up and evaluation

When training users or family members on how to deal with an overdose and supplying them with a naloxone kit, it is important to determine the long-term impact of the programme by evaluating whether or not trainees will attempt to use the medication in the future. Studies have reported the number of overdoses reversed with naloxone administered by the trained individual (Doe-Simkins et al., 2009; McAuley et al., 2009). Systematic follow-up should be conducted to evaluate the quality and impact of take-home naloxone programmes. If resources do not allow systematic follow-up with all take-home naloxone recipients, then contacting a random subsample represents a viable follow-up strategy.

Many take-home naloxone programmes rely on the spontaneous self-report of programme participants who return for naloxone refills. When returning for refills, programme participants are typically interviewed or given a brief questionnaire to assess how they used their naloxone supply. Although this follow-up strategy is less labour-intensive than systematic follow-up, it is also more prone to selection bias, as those who may have had a negative naloxone experience will be less likely to return for a naloxone refill. Systematic follow-up (of all trainees or of a random subsample) is thus a superior evaluation method to relying on self-report data from those returning for naloxone refills.

Systematic follow-up assessments usually take place at 3 months (Strang et al., 2008) and 6 months (Seal et al., 2005). Arguably, a longer follow-up assessment, of at least 1 year, would be important, as an overdose is a relatively uncommon event. Take-home naloxone programmes might also choose to validate overdose reports by confirming information with emergency service records or by interviewing other witnesses (McAuley et al., 2009; Seal et al., 2005).

Conclusion

Take-home naloxone training may vary in intensity and how much it covers. The choice of training level will be determined by the setting, the needs of the target group and the available resources. Regardless of the training level, good preparation and planning is the basis for an effective programme. The quality and benefits of

programmes can also be evaluated and monitored by using validated assessment tools and by implementing systematic follow-ups of trained individuals.

The idea of providing naloxone to prevent opioid overdose deaths has come a long way and over the years we have gathered knowledge and experience of how to implement naloxone distribution effectively. The range of training formats, contents and procedures developed so far offers a number of options for services planning to set up a new take-home naloxone service. Training has been an important part of take-home naloxone programmes not just for the clients but also for professionals, who can see the benefits of their work by witnessing clients' increase in knowledge, competence and self-worth, as well as positive reports of lives saved.

References

Angiolini, E. (2011), *Lord Advocate's guidelines on allowing the supply of naloxone to extend to staff working for services in contact with people at risk of opiate overdoses* (http://sdf.org.uk/sdf/files/LordAdvocatesGuidelines.pdf).

Ashton, H. and Hassan, Z. (2006), 'Best evidence topic report: intranasal naloxone in suspected opioid overdose', *Emergency Medicine Journal* 23, pp. 221–223.

Bennett, G. A. and Higgins, D. S. (1999), 'Accidental overdose among injecting drug users in Dorset, UK', *Addiction* 94, pp. 1179–1189.

Best, D., Gossop, M., Man, L. H., Stillwell, G., Coomber, R. and Strang, J. (2002), 'Peer overdose resuscitation: multiple intervention strategies and time to response by drug users who witness overdose', *Drug and Alcohol Review* 21, pp. 269–274.

Beswick, T., Best, D., Bearn, J., Rees, S., Gossop, M., Coomber, R. and Strang, J. (2002), 'From salt injection to naloxone: accuracy and myths in peer resuscitation methods for opiate overdose', *Journal of Drug Issues* 32, pp. 1103–1114.

Bird, S. M., Parmar, M. K. B. and Strang, J. (2015), 'Take-home naloxone to prevent fatalities from opiate-overdose: protocol for Scotland's public health policy evaluation, and a new measure to assess impact', *Drugs* 22, pp. 66–76.

Darke, S., Ross, J. and Hall, W. (1996), 'Overdose among heroin users in Sydney, Australia: II. Responses to overdose', *Addiction* 91, pp. 413–417.

Davidson, P. J., Ochoa, K. C., Hahn, J. A., Evans, J. L. and Moss, A. R. (2002), 'Witnessing heroin-related overdoses: the experiences of young injectors in San Francisco', *Addiction* 97, pp. 1511–1516.

Davis, C. S., Carr, D., Southwell, J. K. and Beletsky, L. (2015), 'Engaging law enforcement in overdose reversal initiatives: authorization and liability for naloxone administration', *American Journal of Public* Health 105, pp. 1530–1537.

Department of Health (2000), *Patient group directions*, Department of Health, London (http://www.england.nhs.uk/london/wp-content/uploads/sites/8/2014/09/lr-pat-dir-policy.pdf).

Dettmer, K., Saunders, B. and Strang, J. (2001), 'Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes', *BMJ* 322, pp. 895–896.

Doe-Simkins, M., Walley, A. Y., Epstein, A. and Moyer, P. (2009), 'Saved by the nose: bystander-administered intranasal naloxone hydrochloride for opioid overdose', *American Journal of Public Health* 99, pp. 788–791.

Galea, S., Worthington, N., Piper, T. M., Nandi, V., Curtis, M. and Rosenthal, D. M. (2006), 'Provision of naloxone to injection drug users as an overdose prevention strategy: early evidence from a pilot study in New York City', *Addictive Behaviors* 31, pp. 907–912.

Green, T. C., Heimer, R. and Grau, L. E. (2008), 'Distinguishing signs of opioid overdose and indication for naloxone: an evaluation of six overdose training and naloxone distribution programs in the United States', *Addiction* 103, pp. 979–989.

Lagu, T., Anderson, B. J. and Stein, M. (2006), 'Overdoses among friends: drug users are willing to administer naloxone to others', *Journal of Substance Abuse Treatment* 30, pp. 129–133.

Lopez Gaston, R., Best, D., Manning, V. and Day, E. (2009), 'Can we prevent drug related deaths by training opioid users to recognise and manage overdoses?', *Harm Reduction Journal* 6, pp. e1–e8.

McAuley, A., Lindsay, G., Woods, M. and Louttit, D. (2009), 'Responsible management and use of a personal take-home naloxone supply: a pilot project', *Drugs: Education, Prevention and Policy* 17, pp. 388–399.

Maxwell, S., Bigg, D., Stanczykiewicz, K. and Carlberg-Racich, S. (2006), 'Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths', *Journal of Addictive Diseases* 25, pp. 89–96.

Mayet, S., Manning, V., Williams, A., Loaring, J. and Strang, J. (2011), 'Impact of training for healthcare professionals on how to manage an opioid overdose with naloxone: effective, but dissemination is challenging', *International Journal of Drug Policy* 22, pp. 9–15.

Perry, S. and Mackintosh, G. (2007), *Glasgow naloxone programme: Instructor manual* (http://www.glasgow.gov.uk/CHttpHandler.ashx?id=7742&p=0).

Peyton, J. (1998), *Teaching and learning in medical practice*, Manticore Europe, Herts.

Piper, T. M., Stancliff, S., Rudenstine, S., Sherman, S., Nandi, V., Clear, A. and Galea, S. (2008), 'Evaluation of a naloxone distribution and administration program in New York City', *Substance Use & Misuse* 43, pp. 858–870.

Rando, J., Broering, D., Olson, J. E., Marco, C. and Evans, S. B. (2015), 'Intranasal naloxone administration by police first responders is associated with decreased opioid overdose

deaths', *American Journal of Emergency Medicine* 33, pp. 1201–1204.

Ray, B., O'Donnell, D. and Kahre, K. (2015), 'Police officer attitudes towards intranasal naloxone training', *Drug and Alcohol Dependence* 146, pp. 107–110.

Seal, K. H., Thawley, R., Gee, L., Bamberger, J., Kral, A. H., Ciccarone, D. and Edlin, B. R. (2005), 'Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death', *Journal of Urban Health* 82, pp. 303–311.

Strang, J., Manning, V., Mayet, S., Best, D., Titherington, E., Santana, L. and Semmler, C. (2008), 'Overdose training and take-home naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses', *Addiction* 103, pp. 1648–1657.

Tobin, K. E., Davey, M. A. and Latkin, C. A. (2005), 'Calling emergency medical services during drug overdose: an examination of individual, social and setting correlates', *Addiction* 100, pp. 397–404.

Tobin, K. E., Sherman, S. G., Beilenson, P., Welsh, C. and Latkin, C. A. (2009), 'Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives', *International Journal of Drug Policy* 20, pp. 131–136.

Tracy, M., Piper, T. M., Ompad, D., Bucciarelli, A., Coffin, O., Vlahov, D. and Galea, S. (2005), 'Circumstances of witnessed drug overdose in New York City: implications for intervention', *Drug and Alcohol Dependence* 79, pp. 181–190.

Wagner, K. D., Valente, T. W., Casanova, M., Partovi, S. M., Mendenhall, B. M., Hundley, J. H. and Unger, J. B. (2010), 'Evaluation of an overdose prevention and response training programme for injection drug users in the Skid Row area of Los Angeles, CA', *International Journal of Drug Policy* 21, pp. 186–193.

Williams, A. V. (2010), *Training on overdose management and naloxone administration for family members and carers of opioid users: An evaluation of the short-term benefits using validated measures*, unpublished doctoral dissertation, King's College London.

Williams, A. V., Strang, J. and Marsden, J. (2013), 'Development of Opioid Overdose Knowledge (OOKS) and Attitudes (OOAS) Scales for take-home naloxone training evaluation', *Drug and Alcohol Dependence* 132, pp. 383–386.

Williams, A. V., Marsden, J. and Strang, J. (2014), 'Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes', *Addiction* 109, pp. 250–259.

Wright, N., Oldham, N., Francis, K. and Jones, L. (2006), 'Homeless drug users' awareness and risk perception of peer "take home naloxone" use: a qualitative study', *Substance Abuse Treatment, Prevention, & Policy* 1, p. 28.

6

CHAPTER 6

Options for the future: new products, new legislation, new initiatives

Rebecca McDonald and John Strang

Introduction

As reviewed earlier in this volume, naloxone can reverse opioid overdose and save lives. We have a good understanding of how the drug works as an opioid antagonist, competing with opioids to bind to receptors and preventing opioids from influencing the body. The use of naloxone in emergency medicine is well established, but emergency services do not always reach overdose victims in time to act, and it is now twenty years since providing naloxone to laypersons likely to witness or experience an overdose was first suggested. We have reviewed the problems that have prevented the routine provision of naloxone — in combination with training in recognising and managing overdoses — to drug users, their peers and family for use in the event of an overdose. In addition, we have described how take-home naloxone programmes can be implemented. In this final chapter, the focus will be on the future. The World Health Organization's (WHO) recently issued guidelines, which recommend naloxone provision for the community management of opioid overdose, provides a good starting point, and the EMCDDA's systematic review highlights the evidence in support of the WHO recommendations.

The WHO guidelines and evidence of effectiveness of take-home naloxone

The 2014 WHO guidelines: release and potential impact

On 5 November 2014, WHO launched guidelines on the community management of opioid overdose (WHO, 2014) (see box 'WHO guideline development: community management of opioid overdose'). The guidelines recommend that people who are likely to witness an opioid overdose, including people who use opioids and their families and friends, should be given access to naloxone and training in its use so that they can provide an emergency response to opioid overdose, while awaiting the arrival of an ambulance. A global panel of experts, the Guideline Development Group, 'judged the risk–benefit profile to be strongly in favour of naloxone distribution, due to its clear potential for saving lives and apparent low risk of significant adverse effects' (WHO, 2014, p. 8). The Guideline Development Group recommended that, in addition to the use of naloxone, emergency care of suspected opioid overdose should include ventilation support, airway management and management of withdrawal effects. While basic training on the effective use of emergency naloxone was considered important, the Guideline Development Group considered that the lack of extensive emergency intervention training should not impede the use of naloxone in the community. The panel noted that, while minor adverse events from naloxone administration (such as vomiting and opioid withdrawal) were not uncommon, serious adverse events were extremely rare (WHO, 2014, p. 8). The guidelines further clarify that naloxone can be injected or administered intranasally and stipulate that 'while naloxone administered by bystanders is a potentially life-saving emergency interim response to opioid overdose, it should not be seen as a replacement for comprehensive medical care'.

Historically, the use of naloxone had been limited to ambulance workers and medical staff at hospitals. The new guidelines constitute a paradigm shift in the pre-hospital management of opioid overdose, by identifying the responsibility of non-medical (and medical) bystanders to intervene in an overdose emergency and administer naloxone.

EMCDDA systematic review of evidence

In January 2015, the EMCDDA published a systematic review of the effectiveness of take-home naloxone

WHO guideline development: community management of opioid overdose

After the feasibility of naloxone distribution programmes had been demonstrated in several countries and a 2012 UN resolution had called for the widespread adoption of this approach (UNODC, 2012), WHO, in collaboration with the United Nations Office on Drugs and Crime (UNODC), was tasked by the United Nations Economic and Social Council to provide evidence-based guidance on preventing mortality from drug overdose, in particular opioid overdose (WHO, 2014). The guideline-development process included a systematic literature review, a stakeholder consultation in the form of an online survey among those affected by such guidelines, a key informant survey and assessments by a global expert group, nominated by WHO. The quality of available evidence regarding several key questions was assessed and evidence graded using standardised methodology (Guyatt et al., 2008, 2011). This process included 'a narrative assessment of benefits versus risks and harms, the estimated values and preferences of those who might be affected by the guidelines, and the costs, resource utilisation and feasibility of the proposed interventions. Where necessary, these narrative descriptions also referred to other relevant evidence, not included in the systematic reviews' (WHO, 2014, p. 6). All studies and relevant outcomes were thoroughly documented.

WHO made the following recommendations:

1. 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.

2. Naloxone is effective when delivered by intravenous, intramuscular, subcutaneous and intranasal routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting and the local context.

3. In suspected opioid overdose, first responders should focus on airway management, assisting ventilation and administering naloxone.

4. After successful resuscitation following the administration of naloxone, the level of consciousness and breathing of the affected person should be closely observed until full recovery has been achieved.

programmes that combine overdose education and training interventions with the distribution of naloxone kits (EMCDDA, 2015b). Relevant outcomes were (1) overdose-related knowledge; (2) naloxone-related attitudes; (3) naloxone use during witnessed overdose; (4) naloxone-induced adverse events; and (5) overdose deaths.

The Cochrane databases, PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature and the Web of Science databases were searched for relevant entries. A total of 1 045 unique records were retrieved and assessed for eligibility. Studies reporting on take-home naloxone programmes involving opioid users, their family members or peers were deemed eligible for inclusion in the analysis if their designs featured randomised controlled trials, controlled clinical trials, controlled cohort studies, interrupted time-series analyses, cross-sectional surveys, case series or population-based results of programme implementations.

A total of 21 studies (one randomised controlled trial, three case series and 17 pre–post studies) were identified, included in the analysis and evaluated, using a qualitative synthesis method.

Results of the analysis showed (1) evidence from all studies that take-home naloxone programmes increased overdose-related knowledge and (2) evidence from four studies (including the randomised controlled trial) that the programmes improved naloxone-related attitudes, whereas in three studies no improvement was observed.

With regard to naloxone usage, results showed that (3) naloxone was used in a median of 67 % of overdoses witnessed (range 0–100 %; in the seven studies based on active follow-up by researchers) and (4) adverse

events beyond naloxone-induced withdrawal symptoms were rarely reported. In terms of (5) overdose deaths, results showed that opioid-overdose mortality was significantly lower in communities with active take-home naloxone programmes, and all take-home naloxone programmes had a high survival rate. The authors concluded: 'there is evidence that educational and training interventions with provision of take-home naloxone decrease overdose-related mortality.'

The conclusion of the EMCDDA systematic review is in line with a previously published review by Clark et al. (2014) covering 19 of the 21 studies included in the EMCDDA review. Clark et al. did not analyse the impact of take-home naloxone programmes on opioid-overdose mortality but found that take-home naloxone programs were effective at training opioid users and potential bystanders in overdose-emergency management and that take-home naloxone recipients were likely to intervene and administer naloxone to reverse opioid overdoses.

Barriers to naloxone access in the European Union

Despite evidence of the effectiveness of take-home naloxone, a number of barriers to wider naloxone access in the European Union persist at the levels of providers and policy, as well as research and development.

Policy-level barriers

In 2014, an EMCDDA network consultation (see Chapter 4, section 'Take-home naloxone in Europe') gathered evidence that some medico-legal concerns could continue to represent a central barrier to wider take-home naloxone provision in Europe. National policy experts were asked if, in their respective countries, possession or use of naloxone without authorisation could be considered an offence; if first responders could be held liable for injury or death of an overdose victim; and if doctors could be held liable for prescribing naloxone.

Policy experts from 13 EU Member States responded, and the results showed that in seven out of the 13 countries the possession or use of naloxone without authorisation could theoretically constitute an offence. Bystanders could be held liable in five countries if the overdose victim died and in eight countries if the overdose victim incurred serious harm. Doctors could be held liable for prescribing naloxone in only one of the 13 countries.

Provider-level barriers

Lack of awareness and legal concerns

Many clinicians and local, national and international organisations have endorsed take-home naloxone (e.g. ACMD, 2012; AMA, 2012; ASAM, 2013; WHO, 2014). Nonetheless, awareness among practitioners is often low (Beletsky et al., 2007; Binswanger et al., 2015; Green et al., 2013) and can be shrouded in misperceptions around legal risks associated with naloxone prescribing (Tobin et al., 2005). The systematic review by Clark et al. (2014) found that most take-home naloxone programme participants did not call an ambulance when witnessing an overdose emergency, and it identified bystanders' fear of possible legal repercussions as a central barrier.

Some of the expressed concerns are genuine challenges, such as the legal limitation of parenteral drug administration to medically trained staff or only to medical doctors, while others are merely perpetuation of misperceptions about obstacles that are in large part imaginary, for example the real-world likelihood of police action or prosecution of bystanders who administer naloxone to an overdose victim.

Lack of accountability (opt-in versus opt-out)

The dissemination of take-home naloxone is more difficult to achieve when providers and patients need to 'opt in', that is, when patients need to ask their doctors for a naloxone prescription or when providers consider prescribing take-home naloxone only on a case-by-case basis when specifically indicated (as opposed to 'opt out', where take-home naloxone provision would be standard; see also section 'Increasing healthcare provider awareness'). Providers often struggle with competing clinical demands, and opt-in medical services that are not part of standard care are low priority. In a recent US qualitative survey (Binswanger et al., 2015), primary care providers mentioned insufficient time during patient appointments and the inability to follow up with patients as main organisational barriers to prescribing take-home naloxone. Similarly, a UK study found the integration of overdose prevention services to be challenging even among specialist addiction-treatment staff (Mayet et al., 2011).

Lack of research and development

Continued research is needed to establish beyond reasonable doubt to what extent take-home naloxone can reduce mortality among specific populations, along

with investigations into the optimal dose range of naloxone for take-home kits, the identification of reliable injection-free routes of administration, and the suitability of take-home naloxone to reverse overdoses induced by long-acting prescription opioids.

Unsystematic take-home naloxone programme evaluations

The very nature of overdoses poses significant challenges for programme-evaluation designs. Firstly, while most opioid users have suffered overdoses (and survived), overdose death is a statistically rare event that is difficult to capture as a key outcome in a study. Randomisation of opioid users into intervention and control groups is ethically tricky, as it would imply denying members of the control group access to a potentially life-saving medication. Methodological limitations of many of the pilot studies on take-home naloxone include lack of systematic follow-up, lack of randomisation or control groups, reliance on self-report, selection bias largely determined by participants' motivation, drop-out and the inability to quantify the number of lives saved.

What is the optimal dose range for take-home naloxone?

Disappointingly, it is currently unclear what the correct naloxone dose for community-based lay administration is, and clinical guidelines differ across EU Member States. In international take-home naloxone implementation trials, the amount of naloxone given out in the 'kits' has varied from two 1-ml vials of 0.4 mg/1 ml (Galea et al., 2006; Seal et al., 2005) to a 10-ml multi-dose vial of the same concentration (Maxwell et al., 2006).

A recent NHS England Patient Safety Alert (NHS England, 2014) warned prescribers that 'larger than recommended doses [of naloxone] can cause a rapid reversal of the physiological effects [of opioids], leading to intense pain and distress, and an increase in sympathetic nervous stimulation and cytokine release precipitating an acute withdrawal syndrome.'

In qualitative interviews, opioid users have voiced concerns about administering take-home naloxone for fear of disturbing someone else's high and inducing abrupt withdrawal (Richert, 2015). Moreover, a study by Neale and Strang (2015) assessed the views on naloxone of users who had themselves overdosed and received naloxone treatment in an ambulance or hospital setting. Many reported negative views, which were probably caused by excessive naloxone dosing; negative effects ranged from acute withdrawal and associated aggression towards staff to premature self-discharge from hospital and the need to use more illicit drugs to counter the effects of the antagonist (Neale and Strang, 2015).

In practice, potential overdose witnesses should be instructed to administer as little naloxone as possible (even if this means requiring a second dose) and as much naloxone as necessary (Strang et al., 2014), but research has yet to identify the upper and lower limits of this dose range. No studies comparing response to different naloxone doses or to different dosing regiments (e.g. single bolus versus titration) exist to date (WHO, 2014).

Existing naloxone formulations are not well suited

Currently available formulations of naloxone are licensed for administration only by intramuscular, subcutaneous or intravenous injection. In terms of suitability for use by non-medical personnel, injectable naloxone is not ideal and this may be limiting its use by laypersons (Beletsky et al., 2012); among the reasons cited are logistical challenges, including fear of needle/syringe preparation and injecting procedures, potential lack of sterile needles, and delays in administration due to insufficient training. Moreover, applying the injection can put first responders at risk of needle-stick injury and of contracting blood-borne diseases (e.g. hepatitis C) (Wermeling, 2013), which are highly prevalent among the target population.

The absence of naloxone formulations for non-injectable administration can present a twofold barrier: on a clinical level, a layperson who witnesses an overdose may be less likely to intervene and administer an injection for fear of needle-stick injury or for lack of familiarity with needle-and-syringe assembly; on a policy level, the exclusive availability of naloxone as formulated for injection may represent the main legal barrier, limiting its wider use, as certain jurisdictions restrict the administration of injections to medical professionals (Hughes, 2014).

How suitable is take-home naloxone for reversal of overdose from synthetic opioids?

The majority of take-home naloxone implementation studies have been conducted in the United States and have focused on heroin users, largely because participants are recruited via needle and syringe programmes. Less is known about the impact of take-

home naloxone on the prevention of overdose deaths from synthetic (e.g. fentanyl, methadone or tramadol) and semi-synthetic opioids (e.g. hydromorphone, oxycodone, oxymorphone or buprenorphine). Overdose from synthetic and semisynthetic opioids is characterised by slow onset, as their half-life (2 hours and upwards) is more than 20 times the half-life of heroin (6 minutes; see Table 1.2 in Chapter 1). The interaction between naloxone and some of the synthetic opioids is more complex; especially long-acting opioids may require specific attention during the intervention with naloxone (see Chapter 3).

In addition to diverted prescription opioids, the supply of synthetic and semisynthetic opioids onto the European drug market includes illicit production and online sales (Mounteney et al., 2015).

The use of synthetic and semisynthetic opioids is growing in the European Union, and in some countries fatal overdoses from such substances even exceed deaths attributable to heroin. In Estonia, where the synthetic opioid fentanyl has replaced heroin in the illicit drug market, the highest per capita rate of opioid-related deaths in the European Union has been registered (EMCDDA, 2014). Even small amounts of fentanyl can be lethal: fentanyl is considered to be the most potent opioid analgesic, with a potency 30–50 times higher than that of heroin (Cassels, 2015).

In two EU Member States, overdoses from methadone (mostly diverted) exceed those from heroin (EMCDDA, 2014). The implementation of take-home naloxone provision for the emerging target groups of individuals using synthetic or semisynthetic opioids needs to be further studied. The supply of take-home naloxone will be used only when overdose witnesses realise the danger. If someone slips slowly into overdose from synthetic or semisynthetic opioids, for example, the person may go to sleep and mistakenly be presumed to be safe. This means that risk awareness needs to be emphasised in training.

Paving the way to wider naloxone availability

Non-injectable naloxone products

As discussed above, the licensed naloxone injections are not well suited for out-of-hospital use by lay bystanders who lack medical training. The available naloxone products need improvement, and alternative routes of administration (such as nasal) need development and validation.

In the following sections, we describe the nasal spray and give examples of other potential non-injectable routes that may warrant consideration.

Intranasal naloxone

Naloxone can be used 'off label' as a nasal spray by attaching a mucosal atomiser device to a pre-filled naloxone syringe. In the early 2000s, a number of ambulance services in the United States, Australia and the United Kingdom began using nasal naloxone to treat cases of suspected opioid overdose (Barton et al., 2005). The advantages are twofold: firstly, the nasal spray is quick to administer and, secondly, it protects ambulance workers from risk of needle-stick injury. These trained ambulance workers used nasal naloxone as the first line of treatment, and in cases of non-response administered a naloxone injection as a last resort.

Currently, no licensed nasal naloxone product is commercially available ([6]), as basic pharmacokinetics and safety data are still lacking. The only published pharmacokinetics study reported very low bioavailability (4 %) (Dowling et al, 2008), relative to 100 % intravenous bioavailability.

The non-response rate to intranasal naloxone has been assessed in studies in Australia and the United States. In an ambulance-based randomised controlled trial in Australia, intranasal naloxone recipients were found to be less likely to restore normal breathing than intramuscular naloxone recipients (63 % versus 82 %) and more likely to require a 'rescue' naloxone injection (26 % versus 13 %) (Kelly et al., 2005; Kerr et al., 2009). Similarly, an observational trial based in Denver (Colorado) found a non-response rate of 16 % among intranasal naloxone recipients (Barton et al., 2005).

In recent years, intranasal naloxone has also been introduced off label ([7]) in take-home naloxone schemes in

([6]) While this book was in press, the FDA approved a naloxone nasal spray product on 18 November 2015 (FDA, 2015). The FDA approval only applies to US territory, and the nasal spray product has been licensed as a prescription-only medicine. A competitor nasal naloxone spray product was denied FDA approval on 24 November 2015, due to insufficiently rapid absorption of the nasal spray relative to the injectable naloxone reference (Reuters, 2015). As of late September 2015, some pharmacies in 15 US states, including California and Pennsylvania, have special practice agreements which allow pharmacists to sell naloxone without a prescription. These practice agreements will also cover the newly approved nasal spray product.

([7]) Off label: when a medicine is prescribed for an indication that is not described in its licence (e.g. a different dose, indication, age group or route of administration).

Massachusetts and other parts of the United States, in Denmark and Norway, and in the Highland region of Scotland, where naloxone nasal spray kits were distributed to at-risk patients who had received overdose response training. While the ease of administration may make the nasal spray particularly suitable for administration by layperson responders without medical training, the non-response rate to the nasal spray is a major concern in a community-based environment, where no backup naloxone injection is available to lay responders (i.e. until an ambulance arrives) (Strang, McDonald et al., in press). The Danish take-home naloxone programme gives out naloxone kits with both the mucosal atomiser device for nasal administration and a needle for intramuscular injection. According to a 2013 survey of 136 US-based take-home naloxone programmes, 51 % of programmes provided only injectable naloxone, 37 % provided only nasal kits and 12 % provided both injectable and intranasal naloxone (CDC, 2015).

The nasal spray is typically distributed as a 2-mg/2 ml formulation. It remains unclear whether using a more concentrated naloxone formulation could reduce the nasal naloxone non-response rate or the non-response rate reflects a subgroup of opioid users with severe damage to their nasal mucosa from snorting drugs. Dose-ranging studies with dependent volunteers could provide an answer to this question.

Clinical trials investigating the pharmacokinetics of intranasal formulations are under way in Norway and the United States, but no results have been published to date. Two companies have separately filed FDA applications for new intranasal naloxone products, on which they gave presentations at an FDA-convened naloxone meeting in the United States in July 2015 (Hebert, 2015; Mulligan, 2015). At the earliest, these products would enter the market in late 2015.

A further complication with naloxone nasal spray kits is that they are currently more expensive than standard naloxone injections, and there are reports of pharmaceutical companies increasing the price of the naloxone nasal kits as demand increases (Clausen, 2014; Fiore, 2014; see also Chapter 4).

Other non-injectable routes

Among possible alternative routes, rectal suppositories can be excluded because of poor acceptability to family and peers. Oral ingestion is not possible, as much of the active naloxone dose is lost when metabolised by the liver. Sublingual delivery appears to lead to unreliable naloxone blood levels, as a study assessing pharmacodynamic response to sublingual naloxone in an opioid-using sample (Preston et al., 1990) found high inter-subject variability. In contrast, buccal naloxone administration was found to produce good bioavailability in rodents (Hussain et al., 1987), and a first clinical trial investigating the pharmacokinetics of buccal naloxone is currently being carried out in the United Kingdom (EudraCT: 2014-001802-16). The buccal route is already used for other emergency medications; for instance, buccal midazolam has largely replaced rectal suppositories in the emergency management of seizures or status epilepticus (MHRA, 2011).

What criteria should a novel naloxone product fulfil?

The benchmark for any non-injectable naloxone product, if considered for wider community use, should be that it is as effective and reliable as the licensed injection.

According to guidelines presented at a 2012 meeting convened by the US FDA, a novel naloxone formulation would need to demonstrate bioequivalence to the licensed injection in order to obtain regulatory approval (FDA, 2012). Bioequivalence between a novel naloxone product and the licensed injection can be assumed if the administration of one or more standardised doses of the new product results in at least as much drug exposure as a parenteral dose of at least 0.4 mg. If the relative bioavailability of the new product compared with the approved injection is low, then it is unclear if adequate efficacy can be reached. Vice versa, if the relative bioavailability is unexpectedly high, then this may have implications for the safety profile of the novel formulation. Furthermore, the relative bioavailability compared with injection would need to be reasonably constant between different individuals. Absorption will need to be at least as rapid as intramuscular injection, whereby onset of effect starts within 3 to 7 minutes of administration (see Chapter 1).

To be considered for registration by the European national medicines regulatory bodies, any novel naloxone product will need to fulfil similar quality standards to those defined in the United States (Table 6.1). A novel naloxone formulation will also need to be reviewed for safety ([8]) and usability ([9]). The FDA advises that the amount of safety data required will

([8]) Drug safety evaluation (also known as pharmacovigilance) is the assessment of side effects (harm information) based on the results of animal testing and clinical trials. How a drug is manufactured is also considered as part of the safety evaluation.

([9]) 'Usability' refers to the interaction between human factors and the device of drug delivery, with focus on user safety and potential risks and errors.

TABLE 6.1
Product criteria for novel naloxone formulation

Key criterion	Question
Bioavailability	How much naloxone is absorbed in the bloodstream, compared with naloxone injection?
	If low bioavailability, is product effective?
	If high bioavailability, is product safe?
Speed of onset	How quickly is naloxone absorbed?
Duration of action	How long is naloxone available in the bloodstream?
Reliability	Is variability between subjects sufficiently low?
Usability	Ease of administration: suitable for layperson?
Storage	Is storage in home environment possible? Does active ingredient remain sufficiently stable?

NB: Adapted from FDA, 2012. These criteria refer to the US FDA approval process for novel naloxone products. EU criteria may differ. Reference product: Licensed naloxone injection.

depend on how much the pharmacokinetic profile of the novel formulation differs from the licensed injection (Hertz, 2012). A crucial step is to test whether or not the novel naloxone product is suitable for layperson administration (Compton et al., 2013; FDA, 2012; Volkow et al., 2014): can laypersons without medical training correctly diagnose an overdose and administer the formulation? Vice versa, is the novel naloxone formulation safe if it ends up in the hands of a non-intended population, for example children?

In addition, standard requirements for product manufacturing and quality apply, and stability controls, excipient controls and batch controls will need to be conducted to ensure that different samples of the novel naloxone product are sufficiently similar in drug content and that the active ingredient, naloxone, does not diminish significantly over time.

Provided these criteria are fulfilled, the development of an injection-free formulation may enable re-classification of naloxone from prescription-only medicine to over-the-counter medication by the national medicine regulatory bodies or at a European level under the European Medicines Agency, which would promote wider access to the antidote. Critics warn that this regulatory process may be lengthy and cost-intensive (Burris et al., 2001).

Creating a legal framework for take-home naloxone

Positive examples

Two distinct legal changes in the United Kingdom made the Scottish National Naloxone Programme, which mainly uses an injectable naloxone formulation (with the exception of NHS Highland, which uses intranasal naloxone; see 'Conclusion' below), possible and allowed the widespread implementation of take-home naloxone in community centres. Firstly, in June 2005, national legislation was changed to add naloxone to the list of injectable medicines that can be given 'by anyone for the purpose of saving life in an emergency' (Medicines for Human Use Order, 2005). An emergency dose of naloxone could now be given to reverse heroin overdose without specific medical instruction. This legal change opened the doors to take-home naloxone provision and to training family members and peers in naloxone administration. The first Scottish pilots were launched in 2007 (McAuley et al., 2012).

Secondly, in 2011, the Scottish Lord Advocate passed guidelines that allowed naloxone to be provided to opioid users without prescription for use in an emergency (ACMD, 2012) and to be stored in non-medical facilities. The new guidelines allowed the placement of naloxone in locations with high overdose risk (e.g. shelters and hostels) and allowed the distribution of take-home naloxone from community centres without a physician on site, which significantly reduced the staffing burden of take-home naloxone prescribing. New legislation along similar lines is expected for England in late 2015.

In the United States, Good Samaritan laws granting legal immunity to bystanders summoning aid in the event of an overdose are increasingly common. By 2014, at least 14 states had passed such laws to allow take-home naloxone administration (NPHL, 2014), and 18 states and the District of Columbia had amended their laws to promote wider access to naloxone by relieving prescribers of the risk of prosecution when prescribing take-home naloxone (Alcorn, 2014). In Europe, such legislation exists in Luxembourg (see also Chapter 4).

Sharing models of legal approaches across the European Union

Most EU Member States currently do not have legal provisions for take-home naloxone in place, but a number of individual communities and countries in Europe have clarified the legal status of take-home naloxone prescribing and administration.

At least two levels of facilitating naloxone laws exist in the European Union: in Member States where naloxone is a prescription-only medication, the legal status of naloxone can be matched to the status of other injectable antidotes with life-saving potential that can be administered by bystanders, such as adrenaline for the

treatment of severe allergic reactions (anaphylactic shock). In Italy, naloxone has over-the-counter status; that is, pharmacists can dispense the antidote without a prescription.

The roll-out of take-home naloxone implementation in Europe can be accelerated by the sharing of model legislation, lessons learnt and best practices, which can then be adapted to the situation in different countries.

Increasing healthcare provider awareness

Provider awareness of take-home naloxone can be augmented by offering accreditable continuing medical education courses on overdose prevention. Provider education initiatives should include clarification of the legal status of take-home naloxone and particularly focus on medical services that constitute points of first access for opioid users: general practitioners, emergency care and drug-treatment services.

Take-home naloxone coverage among at-risk patients can be increased through the introduction of clinical guidelines that require providers to implement take-home naloxone on an opt-out basis, whereby all at-risk patients are prescribed naloxone unless patients specifically decline. This proactive approach to naloxone prescribing is considered to generate higher naloxone coverage among patients than a more passive approach, whereby patients are asked if they would like to receive a take-home naloxone prescription (and are then offered a prescription only if they opt in).

Policymakers can also support the implementation of take-home naloxone programmes by requiring insurers to cover individual naloxone kits (Beletsky et al., 2012).

Wider target groups to become involved in take-home naloxone programmes

How can the 2014 WHO guidelines be more fully implemented throughout the European Union? To answer this question, we need to define the groups of people in the community who are likely to witness an opioid overdose. Obvious target groups include opioid users themselves and their partners, families and peers, as well as ambulance staff.

However, it is also important to consider professionals whose workplaces bear a high risk of witnessing opioid overdose: naloxone should be available to trained health professionals, to people working with people who use drugs, including staff at drug-treatment centres and hostels and shelters for the homeless, to outreach workers and to those working in prisons.

In addition, non-medical first responders such as police officers and firefighters can be instructed in overdose management and naloxone administration, as has already been successfully implemented in several states in the United States.

Scaling up: examples of good practice

Best practice: national programmes (Scotland, Wales)

Scotland and Wales currently operate the only national take-home naloxone programmes in the world (see Chapter 4). Both started off as local pilots in 2007 and expanded to national scope in 2011. Both programmes are fully government funded and use central databases to track the number of naloxone kits issued and project impact.

Between 1 July 2009 and 31 March 2014, 4 579 take-home naloxone kits were issued in Wales, and use of the kits was reported in 375 opioid overdose events. In an effort to increase the volume of take-home naloxone kits in circulation, 1 802 kits were issued in Wales in 2013/14 alone; 150 recorded overdose reversals were recorded in the same period. Two deaths were reported (not further specified). The Welsh take-home naloxone programme tracks overdose prevention training and the provision of take-home naloxone kits in a national Harm Reduction Database, which subsumes local data from 37 registries across Wales (Public Health Wales, 2014).

Scotland has its own registry for drug-related deaths, which enables the Scottish National Naloxone Programme to track the number of opioid overdose deaths in relation to the number of take-home naloxone kits in circulation. In 2013/14, the programme issued 6 472 naloxone kits, of which 5 395 were in the community and 1 077 to prisoners on release. Analysis of the drug-related deaths data from the Scottish registry was able to show that, since the programme's start in 2011, the number of heroin-related deaths within 4 weeks of release from prison decreased gradually every year,

coinciding with a steady increase in the number of take-home naloxone kits provided.

The Scottish National Take-home Naloxone Programme has managed to raise public awareness around overdose risk factors, symptoms and emergency response through a resourceful project website (www.naloxone.org.uk), which includes instructional videos, a 'naloxone finder' tool and a free overdose app for download.

With regard to best practice, the Welsh naloxone programme makes several recommendations: firstly, to ensure optimal data quality, take-home naloxone programme evaluations should also enquire about non-fatal overdose history, housing status, ethnicity and risk behaviour; secondly, treatment agencies should offer take-home naloxone to all patients enrolled in opioid substitution treatment; and, thirdly, all take-home naloxone recipients (regardless of treatment status) should be contacted before the expiry of their naloxone kit for re-supply. The Scottish protocol for data analysis has recently been published (Bird et al., 2014).

Best practice: prison-release schemes

New take-home naloxone programmes should pay special attention to providing naloxone when prisoners with a history of opioid use are released. The period following release from prison is characterised by a high concentration of heroin overdose deaths: among prisoners with a history of injection drug use, one in 200 will die of an opioid overdose within the first 4 weeks after release from prison (Strang et al., 2013). Providing training in overdose risk and crisis management plus take-home naloxone at the time of prison release could significantly improve the survival rate of imprisoned (former) opioid users.

The UK-based N-ALIVE randomised controlled trial (duration: May 2012 to December 2014) was the first trial to provide naloxone to former heroin-injecting prisoners on their release, and the results are due to be published in late 2015 (see also Chapter 4). Prison-based or post-prison release take-home naloxone distribution has since been introduced in the United States, in San Francisco, Rhode Island and New York (Clear, 2015), as well as in Tomsk, Russia (OSF, 2013).

A recent example of a healthcare intervention that has been successfully integrated into prison-based routine care is hepatitis-B vaccinations in the United Kingdom. Prisoners in the United Kingdom are now all offered hepatitis-B vaccination on an opt-out basis (NICE, 2012). This could serve as an implementation model for future prison-based take-home naloxone schemes targeting (former) opioid users at release.

New pilots

Recent community-based take-home naloxone programmes have been launched in Denmark, Estonia (both 2013) and Norway (2014; see Chapter 4). While Estonia relies on the licensed pre-filled naloxone syringe for intramuscular injection, the Norwegian take-home naloxone kit contains a spray device (mucosal atomiser) for nasal administration and the Danish kit contains both. Preliminary data from all three programmes are reported in Chapter 4. As part of the Norwegian programme it is also planned to expand take-home naloxone provision to released former prisoners who have a history of opioid use.

New pilots are planned in France (likely to use intranasal naloxone) and in Ireland. The Irish government has released plans to provide 600 take-home naloxone kits for intramuscular injection to active opioid users and (former) users upon release from prison. The Irish naloxone website can be accessed at www.drugs.ie/resources/naloxone/. Poland is currently considering the introduction of a take-home naloxone scheme.

Stronger research designs

For better methodological quality, future studies could use time-series analyses, stepped-wedge randomised trial designs or prospective controlled cohort designs, comparing communities where take-home naloxone is implemented with communities where it is not implemented or only partial roll-out has taken place. Self-report data should be complemented with verifiable

data sources, for example hospital admissions data and mortality registry data (EMCDDA, 2015b).

In recent years, evaluation studies with more powerful study designs have been conducted: time-series analysis (Walley et al., 2013), cost-effectiveness analyses (Coffin and Sullivan, 2013) and randomised controlled trials (Strang et al., 2013). With increasing evidence on the benefits of take-home naloxone, wider implementation of take-home naloxone can be expected.

Conclusion

International guidelines and an increasing body of evidence support naloxone training and education, combined with provision of take-home kits as an effective measure to reduce opioid overdose deaths (WHO, 2014; EMCDDA, 2015b). More specifically, the introduction of an overdose education and naloxone distribution programme in several local communities in the United States has been associated with a reduction in overdose fatalities (Walley et al., 2013); the cost-effectiveness of naloxone provision was determined through modelling studies for the US health system (Coffin and Sullivan, 2013); and low wastage rates have been reported (Kan et al., 2014). Experiences with training in overdose management plus provision of take-home naloxone are currently accumulated in projects in several European countries, and best-practice examples have been identified. This provides a better knowledge basis for policymakers and practitioners who are considering the introduction and delivery of the intervention.

The 2014 WHO guidelines recognise the effectiveness of take-home naloxone in the prevention of opioid-overdose fatalities and recommend that opioid users as well as non-users likely to witness an overdose should receive training in overdose management and naloxone administration. This includes drug users in the community as well as those in treatment; risk of overdose is particularly high at the start and end of opioid substitution treatment, on release from prison and on discharge from hospital, detox or residential care (Davoli et al., 2007; Ravndal and Amundsen, 2010). For all of these active or former opioid users, take-home naloxone provision should be part of standard medical care.

Family members, partners and peers, as well as professionals in frequent contact with opioid users, may also witness an overdose and hence are also important target populations.

From a harm-reduction perspective, the guidelines represent a significant and necessary step towards the prevention of overdose deaths. Take-home naloxone has been well received by drug users and carers — groups that demonstrate enthusiasm, commitment, trainability qualities and insight into potential risks — and the intervention has been piloted with great commitment by early adopters.

Take-home naloxone is currently available in fewer than 10 of the 28 EU Member States. Overdose deaths across the European Union remain at a remarkably high level, and action is urgently needed to improve take-home naloxone availability.

Member States without existing take-home naloxone programmes should move quickly to clarify the legal status of the harm-reduction intervention in their countries. Moreover, clinical guidelines across the European Union should be adapted to establish take-home naloxone provision as a care standard (e.g. on an opt-out basis), where (former) opioid users are routinely offered a take-home naloxone kit and can choose to refuse the naloxone supply based on their personal preference (opt out).

Finally, take-home naloxone programmes should carefully document and monitor national data on take-home naloxone provision and associated overdose mortality as a basis for programme evaluation and sustainability.

References

ACMD (Advisory Council on the Misuse of Drugs) (2012), *Consideration of naloxone*, Home Office, London.

Alcorn, T. (2014), 'America embraces treatment for opioid drug overdose', *The Lancet* 383(9933), pp. 1957–1958.

AMA (American Medical Association) (2012), *AMA adopts new policies at annual meeting* (https://www.ama-assn.org/ama/pub/news/news/2012-06-19-ama-adopts-new-policies.page).

ASAM (American Society of Addiction Medicine) (2013), *Public policy statement on the use of naloxone for the prevention of drug overdose deaths* (http://prescribetoprevent.org/wp2015/wp-content/uploads/1naloxone-rev-8-14.pdf).

Barton, E. D., Colwell, C. B., Wolfe, T., Fosnocht, D., Gravitz, C., Bryan, T. et al. (2005), 'Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting', *Journal of Emergency Medicine* 29, pp. 265–271.

Beletsky, L., Ruthazer, R., Macalino, G. E., Rich, J. D., Tan, L. and Burris, S. (2007), "Physicians' knowledge of and willingness to prescribe naloxone to reverse accidental opiate

overdose: challenges and opportunities", *Journal of Urban Health* 84, pp. 126–136.

Beletsky, L., Rich, J. D. and Walley, A. Y. (2012), 'Prevention of fatal opioid overdose', *JAMA* 308, pp. 1863–1864.

Binswanger, I. A., Koester, S., Mueller, S. R., Gardner, E. M., Goddard, K. and Glanz, J. M. (2015), 'Overdose education and naloxone for patients prescribed opioids in primary care: a qualitative study of primary care staff', *Journal of General Internal Medicine* 30, pp. 1837–1844.

Bird, S. M., Parmar, M. K. and Strang, J. (2014), 'Take-home naloxone to prevent fatalities from opiate-overdose: protocol for Scotland's public health policy evaluation, and a new measure to assess impact', *Drugs: Education, Prevention and Policy* 22, pp. 66–76.

Burris, S., Norland, J. and Edlin, B. R. (2001), 'Legal aspects of providing naloxone to heroin users in the United States', *International Journal of Drug Policy* 12, pp. 237–248.

Cassels, C. (2015), *Fentanyl: DEA sounds nationwide alarm on drug's dangers* (available at http://www.medscape.com/viewarticle/841683).

CDC (Centers for Disease Control and Prevention) (2015), *Opioid overdose prevention programs providing naloxone to laypersons: United States, 2014* (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6423a2.htm).

Clark, A. K., Wilder, C. M. and Winstanley, E. L. (2014), 'A systematic review of community opioid overdose prevention and naloxone distribution programs', *Journal of Addiction Medicine* 8, pp. 153–163.

Clausen, T. (2014), *Nasal naloxone, as take-home provision for users and relatives in Norway: first experiences* (available at http://www.emcdda.europa.eu/events/2014/meetings/naloxone).

Clear, A. (2015), *Overdose prevention in a New York City prison: start of a groundbreaking new initiative* (http://www.huffingtonpost.com/allan-clear/overdose-prevention-new-york-city-jail-_b_6625424.html).

Coffin, P. O. and Sullivan, S. D. (2013), 'Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal', *Annals of Internal Medicine* 158, pp. 1–9.

Compton, W. M. and Volkow, N. D. (2006), 'Major increases in opioid analgesic abuse in the United States: concerns and strategies', *Drug and Alcohol Dependence* 81, pp. 103–107.

Compton, W. M., Volkow, N. D., Throckmorton, D. C. and Lurie, P. (2013), 'Expanded access to opioid overdose intervention: research, practice, and policy needs', *Annals of Internal Medicine* 158, pp. 65–66.

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

Dowling, J., Isbister, G. K., Kirkpatrick, C. M., Naidoo, D. and Graudins, A. (2008), 'Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers', *Therapeutic Drug Monitoring* 30, pp. 490–496.

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) (2014), *European drug report 2014: Trends and developments*, Publications Office of the European Union, Luxembourg.

EMCDDA (2015a), *European drug report 2015: Trends and developments*, Publications Office of the European Union, Luxembourg.

EMCDDA (2015b), *Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone*, EMCDDA Papers (available at http://www.emcdda.europa.eu/publications/emcdda-papers/naloxone-effectiveness).

FDA (Food and Drugs Administration) (2012), *Role of naloxone in opioid overdose fatality prevention* (http://www.fda.gov/downloads/Drugs/NewsEvents/UCM318909.pdf).

FDA (2015), *FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose*, FDA news release (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473505.htm).

Fiore, K. (2014), *Nasal naloxone price set to jump* (http://www.medpagetoday.com/Psychiatry/Addictions/48829).

Galea, S., Worthington, N., Piper, T. M., Nandi, V. V., Curtis, M. and Rosenthal, D. M. (2006), 'Provision of naloxone to injection drug users as an overdose prevention strategy: early evidence from a pilot study in New York City', *Addictive Behaviors* 31, pp. 907–912.

Green, T. C., Bowman, S. E., Zaller, N. D., Ray, M., Case, P. and Heimer, R. (2013), 'Barriers to medical provider support for prescription naloxone as overdose antidote for lay responders', *Substance Use & Misuse* 48 (7), pp. 558–567.

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P. and Schünemann, H. J. (2008), 'GRADE: an emerging consensus on rating quality of evidence and strength of recommendations', *BMJ* 336(7650), pp. 924–926.

Guyatt, G., Oxman, A. D., Akl, E. A., Kunz, R., Vist, G., Brozek, J. et al. (2011), 'GRADE guidelines: 1. Introduction: GRADE evidence profiles and summary of findings tables', *Journal of Clinical Epidemiology* 64, pp. 383–394.

Hebert, S. (2015), *Indivior's intranasal naloxone* (http://www.fda.gov/downloads/Drugs/NewsEvents/UCM454814.pdf).

Hertz, S. (2012), *Naloxone for outpatient use: data required to support an NDA* (http://www.fda.gov/downloads/Drugs/NewsEvents/UCM300874.pdf).

Hussain, M. A., Aungst, B. J., Kearney, A., and Shefter, E. (1987), 'Buccal and oral bioavailability of naloxone and naltrexone in rats', *International Journal of Pharmaceutics* 36, pp. 127–130.

Hughes, B. (2014), *Distribution and use of naloxone: legal issues* (available at http://www.emcdda.europa.eu/events/2014/meetings/naloxone).

Kan, M., Gall, J. A., Latypov, A., Gray, R., Bakpayev, M., Alisheva, D. et al. (2014), 'Effective use of naloxone among people who

inject drugs in Kyrgyzstan and Tajikistan using pharmacy- and community-based distribution approaches', *International Journal of Drug Policy* 25, pp. 1221–1226.

Kelly, A. M., Kerr, D., Dietze, P., Patrick, I., Walker, T. and Koutsogiannis, Z. (2005), 'Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose', *Medical Journal of Australia* 182, pp. 24–27.

Kerr, D., Kelly, A. M., Dietze, P., Jolley, D. and Barger, B. (2009), 'Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose', *Addiction* 104, pp. 2067–2074.

McAuley, A., Best, D., Taylor, A., Hunter, C. and Robertson, R. (2012), 'From evidence to policy: the Scottish national naloxone programme', *Drugs: Education, Prevention and Policy* 19, pp. 309–319.

Maxwell, S., Bigg, D., Stanczykiewicz, K. and Carlberg-Racich, S. (2006), 'Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths', *Journal of Addictive Diseases* 25, pp. 89–96.

Mayet, S., Manning, V., Williams, A., Loaring, J. and Strang, J. (2011), 'Impact of training for healthcare professionals on how to manage an opioid overdose with naloxone: effective, but dissemination is challenging', *International Journal of Drug Policy* 22, pp. 9–15.

Medicines for Human Use (Prescribing) (Miscellaneous Amendments) Order 2005 (available at www.opsi.gov.uk/si/si2005/20051507.htm).

MHRA (Medicines & Healthcare products Regulatory Agency) (2011), *Buccal midazolam (Buccolam): new authorised medicine for paediatric use—care needed when transferring from unlicensed formulations* (http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON131931).

Mounteney, J., Giraudon, I., Denissov, G. and Griffiths, P. (2015), 'Fentanyls: are we missing the signs? Highly potent and on the rise in Europe', *International Journal of Drug Policy* 26, pp. 626–631.

Mulligan, S. (2015), *Intranasal naloxone: characteristics of a new formulation* (http://www.fda.gov/downloads/Drugs/NewsEvents/UCM454813.pdf).

Neale, J. and Strang, J. (2015), 'Naloxone: does over-antagonism matter? Evidence of iatrogenic harm after emergency treatment of heroin/opioid overdose', *Addiction* 110, pp. 1644–1652.

NHS (National Health Service) England (2014), *Patient safety alert: risk of distress and death from inappropriate doses of naloxone in patients on long-term opioid/opiate treatment* (http://www.england.nhs.uk/wp-content/uploads/2014/11/psa-inappropriate-doses-naloxone.pdf).

NICE (National Institute for Health and Care Excellence) (2012) *Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection* (http://www.nice.org.uk/guidance/ph43/chapter/recommendations#recommendation-5-testing-for-hepatitis-b-and-c-in-prisons-and-immigration-removal-centres)

NPHL (Network for Public Health Law) (2014), *Legal interventions to reduce overdose mortality: naloxone access and overdose Good Samaritan laws* (https://www.networkforphl.org/_asset/qz5pvn/network-naloxone-10-4.pdf).

OSF (Open Society Foundation) (2013), *Inside information: overdose trainings in prisons and jails* (available at http://naloxoneinfo.org/case-studies/prisons-and-jails#sthash.cccfEGeE.dpuf).

Preston, K. L., Bigelow, G. E. and Liebson, I. A. (1990), 'Effects of sublingually given naloxone in opioid-dependent human volunteers', *Drug and Alcohol Dependence* 25, pp. 27–34.

Public Health Wales (2014), *Harm reduction database Wales: take home naloxone 2013–14* (available at http://www.wales.nhs.uk/sitesplus/888/page/56567).

Ravndal, E. and Amundsen, E. J. (2010), 'Mortality among drug users after discharge from inpatient treatment: an 8-year prospective study', *Drug and Alcohol Dependence* 108, pp. 65–69.

Reuters (2015), *FDA rejects Indivior's nasal spray for opioid overdose* (http://www.reuters.com/article/us-indivior-fda-idUSKBN0TD2CS20151124#IkRFIvzs7gHsXeqF.99).

Richert, T. (2015), 'Wasted, overdosed, or beyond saving: to act or not to act? Heroin users' views, assessments, and responses to witnessed overdoses in Malmo, Sweden', *International Journal of Drug Policy* 26, pp. 92–99.

Seal, K. H., Thawley, M. R., Gee, M. L., Bamberger, J., Kral, A. H., Ciccarone, D. et al. (2005), 'Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study', *Journal of Urban Health* 82, pp. 303–311.

Strang, J., Bird, S. M. and Parmar, M. K. (2013), '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* 90, pp. 983–996.

Strang, J., Bird, S. M., Dietze, P., Gerra, G. and McLellan, A. T. (2014), 'Take-home emergency naloxone to prevent deaths from heroin overdose', *BMJ* 349, g6580.

Strang, J.*, McDonald, R.*, Tas, B., and Day, E. (in press), 'Clinical provision of nasal naloxone without experimental testing and without regulatory approval: imaginative shortcut or dangerous bypass of essential safety procedures?', *Addiction*.

Tobin, K. E., Gaasch, W. R., Clarke, M. C., MacKenzie, E. and Latkin, C. A. (2005), 'Attitudes of emergency medical service providers toward naloxone distribution programs', *Journal of Urban Health* 82, pp. 296–302.

UNODC (2012), 'Resolution 55/7: Promoting measures to prevent drug overdose, in particular opioid overdose', in *Drug-related resolutions and decisions adopted by the*

* Joint first author.

General Assembly, the Economic and Social Council (ECOSOC) and the Commission on Narcotic Drugs (CND), United Nations Office on Drugs and Crime, Vienna (https://www.unodc.org/documents/commissions/CND/Drug_Resolutions/2010-2019/2012/CND_Res-55-7.pdf).

Volkow, N. D., Frieden, T. R., Hyde, P. S. and Cha, S. S. (2014), 'Medication-assisted therapies: tackling the opioid-overdose epidemic', *New England Journal of Medicine* 370, pp. 2063–2066.

Walley, A. Y., Xuan, Z., Hackman, H. H., Quinn, E., Doe-Simkins, M., Sorensen-Alawad, A. et al. (2013), 'Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis', *BMJ* 346, pp. f174.

Wermeling, D. P. (2013), 'A response to the opioid overdose epidemic: naloxone nasal spray', *Drug Delivery and Translational Research* 3, pp. 63–74.

WHO (World Health Organization) (2014), *Community management of opioid overdose* (available at http://www.who.int/substance_abuse/publications/management_opioid_overdose/en/).

Appendix

Opioid Overdose Attitudes Scale (OOAS): Instructions

The Opioid Overdose Attitudes Scale (OOAS)

The OOAS is a self-administered questionnaire which aims to evaluate attitudes towards managing an opioid overdose among addiction professionals, patients and their family members. It takes approximately 15 minutes to complete.

The OOAS has 28 items grouped into three sub-scales relating to overdose management: *Competence* (self-perceived ability to manage an overdose), *Concerns* (concerns on dealing with an overdose) and *Readiness* (willingness to intervene in an overdose situation).

- Competence 10 items: 1, 2, 3, 11, 12, 14, 20, 21, 24, 26
- Concerns 8 items: 4, 6, 7, 15, 16, 18, 23, 25
- Readiness 10 items: 5, 8, 9,10, 13, 17, 19, 22, 27, 28

Psychometric properties

The OOAS was adapted from the structure of the Drug and Drug Problem Perception Questionnaire (Watson et al., 2007). Its psychometric properties are described in Williams et al. 2013. The scale has proved to be internally reliable (alpha coefficient 0.90) and robust over time (Intra-Class Correlations = 0.82). Competence, concerns and readiness items' scores fall in the fair-to-excellent range for test–retest reliability (ICC = 0.92, 0.55 and 0.65, respectively).

The scale has also proven to have face, content and construct validity. Content validity was tested by comparing the scores of addiction professionals and family members of opioid users. Professionals reported significantly higher scores than family members. Concurrent validity was tested by correlating the OOAS score and the General Self-efficacy Scale, but no association was found.

Scoring

The OOAS is scored continuously using a 5-point Likert scale: completely disagree (1 point), disagree (2 points), unsure (3 points), agree (4 points) and completely agree (5 points).

Reverse negative items:

The following negative items need to be reversed before computing the total of scale points: 4, 6, 7, 9, 11, 15, 16, 17, 18, 23, 24, 25. You can use the 'record into same variables' function of SPSS. Recode these items as: completely disagree (5 point), disagree (4 points), unsure (3 points), agree (2 points) and completely agree (1 point).

Totals scores:

Once negative items have been reversed, add all items' points. The total scale points can range from 28 to 140 points.

Sub-scores

- Competence: add the points of the following items: 1, 2, 3, 11, 12, 14, 20, 21, 24, 26
- Concerns items: add the points of the following items: 4, 6, 7, 15, 16, 18, 23, 25
- Readiness items: add the points of the following items: 5, 8, 9,10, 13, 17, 19, 22, 27, 28

SPSS data-base and syntaxes can be obtained from the author (please see contact details below).

Data

The table below presents OOAS values that have been recorded for drug users and family members:

	Family members (*n* = 73)			Drug Users (*n* = 89)		
	Mean (SD)			Mean (SD)		
	Pre-training	Immediately post-training	3-months post-training	Pre-training	Immediately post-training	3-months post-training
Total OOAS	97.99 (± 12.7)	118.06 (± 12.8)	116.25 (± 9.7)	102.63 (± 10.4)	118.80 (± 13.9)	113.44 (± 9.9)
Competence	28.28 (± 7.1)	41.61 (± 4.4)	40.83 (± 3.4)	31.46 (± 5.8)	42.48 (± 5.4)	40.60 (± 3.6)
Concerns	28.51 (± 6.2)	32.71 (± 6.5)	32.08 (± 3.7)	28.87 (± 4.7)	31.98 (± 5.5)	30.44 (± 3.9)
Readiness	41.21 (± 4.9)	43.73 (± 4.7)	43.34 (± 4.1)	42.29 (± 4.4)	44.34 (± 5.1)	42.39 (± 3.8)

The data are available in Anna Williams' PhD thesis (2011) and were published in Williams et al. (2013, 2014):

Williams AV (2011). Training on overdose management and naloxone administration for family members and carers of opioid users: an evaluation of the short-term benefits using validated measures. PhD Thesis. King's College London: UK.

Williams AV, Marsden J & Strang J (2014), Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes. Addiction, 109: 250–259.

Williams AV, Strang J & Marsden J (2013). Development of Opioid Overdose Knowledge (OOKS) and Attitudes (OOAS) Scales for take-home naloxone training evaluation. Drug Alcohol Dependence, 132(1–2):383–6.

Further information can be found at: http://www.kcl.ac.uk/ioppn/depts/addictions/research/drugs/Naloxone/Resources.aspx

Opioid Overdose Attitudes Scale

Please, answer the following questions thinking about how you would deal with an opioid overdose (opioids such as: heroin, methadone, morphine, oxycodone, tramadol, fentanyl or codeine).

Before you start answering the questions please read the following definitions:

Opioid overdose: difficulty breathing, turning blue, lost consciousness unable to be roused, collapsing occurring in conjunction with opioid use (opioids such as: heroin, methadone, morphine, oxycodone, tramadol, fentanyl or codeine).

Naloxone: is a medicine (a kind of 'opioid antidote') commonly used by ambulance services to reverse the effects of an opioid overdose and bring the person back into consciousness.

Please, mark how much you agree with each statement:	Completely Disagree	Disagree	Unsure	Agree	Completely Agree
1. I already have enough information about how to manage an overdose	O	O	O	O	O
2. I am already able to inject naloxone into someone who had overdosed	O	O	O	O	O
3. I would be able to check that someone who had an overdose was breathing properly	O	O	O	O	O
4. I would be afraid of giving naloxone in case the person becomes aggressive afterwards	O	O	O	O	O
5. If someone overdoses, I want to be able to help them	O	O	O	O	O
6. I would be afraid of doing something wrong in an overdose situation	O	O	O	O	O
7. I would be reluctant to use naloxone for fear of precipitating withdrawal symptoms	O	O	O	O	O
8. Everyone at risk of witnessing an overdose should be given a naloxone supply	O	O	O	O	O
9. I couldn't just watch someone overdose, I would have to do something to help	O	O	O	O	O
10. If someone overdoses, I would call an ambulance but I wouldn't be willing to do anything else	O	O	O	O	O
11. I am going to need more training before I would feel confident to help someone who had overdosed	O	O	O	O	O
12. I would be able to perform mouth to mouth resuscitation to someone who had overdosed	O	O	O	O	O
13. Family and friends of drug users should be prepared to deal with an overdose	O	O	O	O	O
14. I would be able to perform chest compressions to someone who had overdosed	O	O	O	O	O
15. I would be concerned about calling emergency services in case the police come around	O	O	O	O	O
16. If I tried to help someone who had overdosed, I might accidently hurt them	O	O	O	O	O
17. If I witnessed an overdose, I would call an ambulance straight away	O	O	O	O	O
18. I would be afraid of suffering a needle stick injury if I had to give someone a naloxone injection	O	O	O	O	O
19. If I saw an overdose, I would panic and not be able to help	O	O	O	O	O
20. If someone overdoses, I would know what to do to help them	O	O	O	O	O
21. I would be able to place someone who had overdosed in the recovery position	O	O	O	O	O
22. I would stay with the overdose victim until help arrives	O	O	O	O	O
23. I would prefer not to help someone who has overdosed, because I'd feel responsible if they died	O	O	O	O	O
24. I know very little about how to help someone who has overdosed	O	O	O	O	O
25. Needles frighten me and I wouldn't be able to give someone an injection of naloxone	O	O	O	O	O

Please, mark how much you agree with each statement:	Completely Disagree	Disagree	Unsure	Agree	Completely Agree
26. I would be able to deal effectively with an overdose	O	O	O	O	O
27. If I saw an overdose, I would feel nervous, but I would still take the necessary actions	O	O	O	O	O
28. I will do whatever is necessary to save someone's life in an overdose situation	O	O	O	O	O

The Opioid Overdose Attitudes Scale (OOAS): Scoring instructions

The OOAS is a self-administered questionnaire which aims to evaluate attitudes towards managing an opioid overdose among addiction professionals, patients and their family members. It takes approximately 15 minutes to complete.

The OOAS has 28 items grouped into three sub-scales relating to overdose management: *Competence* (self-perceived ability to manage an overdose), *Concerns* (concerns on dealing with an overdose) and *Readiness* (willingness to intervene in an overdose situation).

- Competence 10 items: 1, 2, 3, 11, 12, 14, 20, 21, 24, 26
- Concerns 8 items: 4, 6, 7, 15, 16, 18, 23, 25
- Readiness 10 items: 5, 8, 9,10, 13, 17, 19, 22, 27, 28

Scoring

The OOAS is scored continuously using a 5-point Likert scale: completely disagree (1 point), disagree (2 points), unsure (3 points), agree (4 points) and completely agree (5 points).

Reverse negative items:

The following negative items need to be reversed before computing the total of scale points: 4, 6, 7, 9, 11, 15, 16, 17, 18, 23, 24, 25. You can use the 'record into same variables' function of SPSS. Recode these items as: completely disagree (5 point), disagree (4 points), unsure (3 points), agree (2 points) and completely agree (1 point).

Totals scores:

Once negative items have been reversed, add all items' points. The total scale points can range from 28 to 140 points.

Sub-scores

- Competence: add the points of the following items: 1, 2, 3, 11, 12, 14, 20, 21, 24, 26
- Concerns items: add the points of the following items: 4, 6, 7, 15, 16, 18, 23, 25
- Readiness items: add the points of the following items: 5, 8, 9,10, 13, 17, 19, 22, 27, 28

Opioid Overdose Knowledge Scale

The OOKS aims to assess the level of knowledge of opioid overdose management among addiction professionals, patients and family members. It records knowledge about risk factors for having an opioid overdose, signs of an opioid overdose, actions to be taken in an overdose situation, naloxone effects and administration, adverse effects and aftercare procedures. The scale also identifies misinformation and myths about opioid overdose.

The OOKS has scores on four domains:

- *Risk*: risk factors for an overdose
- *Signs*: signs of an overdose
- *Action:* actions to be taken in an overdose
- *Naloxone use*: naloxone effects, administration and aftercare procedures

It is a self-administered structured questionnaire which takes approximately 10 minutes to complete. The scale is formed of 4 multiple-choice questions, 4 forced-choice questions and 6 true/false statements.

Psychometric Properties

The psychometric properties of the OOKS are described in Williams et al (2013). The scale has proved to be internally reliable (alpha coefficient 0.83) and robust over time (Intra-Class Correlations = 0.90). The domains' reliability (ICC) are as follow: risks 0.87, signs 0.69, actions 0.53 and naloxone use 0.83.

The scale has also proven to have face, content and construct validity. Content validity was tested by comparing the scores of addiction professionals and family members of opioid users. Professionals reported significantly higher scores than family members. Concurrent validity was tested by correlating OOKS score and the Brief Overdose Recognition and Response Assessment (BORRA). The OOKS total score was positively correlated with the BORRA's Overdose Recognition ($r = 0.5$, $P < 0.01$) and BORRA's Naloxone Indication sub-scales ($r = 0.44$, $P < 0.05$).

Scoring

The OOKS items use a 'yes/no or don't know'; or 'true/false or don't know' response format. Each correct answer scores one point. 'Don't know' and incorrectly marked responses (mistakes) are scored zero. Total score range: 0–45 points.

Total Score (45 items):

- One point if marked (33 Correct/True items): 1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1i, 2b, 2c, 2d, 2e, 2g, 2h, 3a, 3b, 3d, 3f, 3g, 3i, 3j, 4a, 5a, 5b, 5c, 6a, 7a, 8b, 9T, 11T, 12T, 14T
- One point if NOT marked (12 Incorrect/False items): 2a, 2f, 2i, 2j, 3c, 3e, 3h, 3k, 5d, 5e, 10F, 13F. You might choose to use the 'record into same variables' function of SPSS and inverse the values of these items.

Risk (9 items):

- One point if marked: 1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1i

Signs (10 items):

- One point if marked: 2b, 2c, 2d, 2e, 2g, 2h
- One point if NOT marked: 2a, 2f, 2i, 2j

Action (11 items):

- One point if marked: 3a, 3b, 3d, 3f, 3g, 3i, 3j
- One point if NOT marked: 3c, 3e, 3h, 3k

Naloxone Use (15 items):

- One point if marked: 4a, 5a, 5b, 5c, 6a, 7a, 8b, 9T, 11T, 12T, 14T
- One point if NOT marked: 5d, 5e, 10F, 13F

SPSS data-base and syntaxes can be obtained from the author (please see contact details below).

Data

The table below presents OOAS values that have been recorded for drug users and family members:

	Family members (*n* = 73)			Drug users (*n* = 89)		
	Mean (SD)			Mean (SD)		
	Pre-training	Immediately post-training	3-months post-training	Pre-training	Immediately post-training	3-months post-training
Total OOKS	30.41 (± 7.1)	39.20 (± 3.1)	37.30 (± 4.5)	33.14 (± 4.6)	39.43 (± 3.5)	39.05 (± 3.5)
Risks	6.79 (± 2.27)	8.41 (± 1.4)	7.45 (± 1.7)	7.18 (± 1.8)	8.25 (± 1.1)	7.85 (± 1.4)
Signs	6.38 (± 1.9)	7.89 (± 1.5)	7.48 (± 1.4)	7.24 (± 1.5)	8.42 (± 1.4)	8.08 (± 1.2)
Action	9.46 (± 1.6)	10.10 (± 1.48)	10.25 (± 1.1)	9.86 (± 0.8)	10.42 (± 0.9)	10.64 (± 0.5)
Naloxone	7.77 (± 3.7)	12.79 (± 1.4)	12.21 (± 1.8)	8.83 (± 2.8)	12.33 (± 1.7)	12.48 (± 1.7)

The data are available in Anna Williams (2011) PhD thesis and it was published in Williams et al. (2013, 2014):

Williams AV (2011). Training on overdose management and naloxone administration for family members and carers of opioid users: an evaluation of the short-term benefits using validated measures. PhD Thesis. King's College London: UK.

Williams AV, Marsden J & Strang J (2014), Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes. Addiction, 109: 250–259.

Williams AV, Strang J & Marsden J (2013). Development of Opioid Overdose Knowledge (OOKS) and Attitudes (OOAS) Scales for take-home naloxone training evaluation. Drug Alcohol Dependence, 132(1–2):383–6

Author contact details

Both the OOKS and OOAS scales are currently available in English, Portuguese and Italian and can be translated to other languages. Please contact the author for other versions of the instrument.

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Further information can be found on: http://www.kcl.ac.uk/ioppn/depts/addictions/research/drugs/Naloxone/Resources.aspx

Opioid Overdose Knowledge Scale

Please answer the following questions about heroin overdose (or an overdose from other opioids such as: methadone, morphine, oxycodone, tramadol, fentanyl or codeine):

1. Which of the following factors increase the risk of a heroin (opioid) overdose? (Tick all that apply)

- ☐ Taking larger than usual doses of heroin
- ☐ Switching from smoking to injecting heroin
- ☐ Using heroin with other substances, such as alcohol or sleeping pills
- ☐ Increase in heroin purity
- ☐ Using heroin again after not having used for a while
- ☐ Using heroin when no one else is present around
- ☐ A long history of heroin use
- ☐ Using heroin again soon after release from prison
- ☐ Using heroin again after a detox treatment

2. Which of the following are indicators of an opioid overdose? (Tick all that apply)

- ☐ Having blood-shot eyes
- ☐ Slow/shallow breathing
- ☐ Lips, hands or feet turning blue
- ☐ Loss of consciousness
- ☐ Unresponsive
- ☐ Fitting
- ☐ Deep snoring
- ☐ Very small pupils
- ☐ Agitated behaviour
- ☐ Rapid heartbeat

3. Which of the following should be done when managing an opioid overdose? (Tick all that apply)

- ☐ Call an ambulance
- ☐ Stay with the person until an ambulance arrives
- ☐ Inject the person with salt solution or milk
- ☐ Mouth to mouth resuscitation
- ☐ Give stimulants (e.g. cocaine or black coffee)
- ☐ Place the person in the recovery position (on their side with mouth clear)
- ☐ Give Naloxone (opioid antidote)
- ☐ Put the person in a bath of cold water
- ☐ Check for breathing
- ☐ Check for blocked airways (nose and mouth)
- ☐ Put the person in bed to sleep it off

4. What is naloxone used for?

- ☐ To reverse the effects of an opioid overdose (e.g. heroin, methadone)
- ☐ To reverse the effects of an amphetamine overdose
- ☐ To reverse the effects of a cocaine overdose
- ☐ To reverse the effects of any overdose
- ☐ Don't know

5. How can naloxone be administered? (Tick all that apply)

- ☐ Into a muscle (intramuscular)
- ☐ Into a vein (intravenous)
- ☐ Under the skin (subcutaneous)
- ☐ Swallowing — liquid
- ☐ Swallowing — tablet
- ☐ Don't know

6. Where is the most recommended place for non-expert to administer naloxone?

- ☐ Outside of thighs or upper arms
- ☐ Any vein
- ☐ Heart
- ☐ By mouth
- ☐ Don't know

7. How long does naloxone take to start having effect?

- ☐ 2–5 minutes
- ☐ 5–10 minutes
- ☐ 10–20 minutes
- ☐ 20–40 minutes
- ☐ Don't know

8. How long do the effects of naloxone last for?

- ☐ Less than 20 minutes
- ☐ About one hour
- ☐ 1 to 6 hours
- ☐ 6 to 12 hours
- ☐ Don't know

Please mark "true", "false" or "don't know"	True	False	Don't know
9. If the first dose of naloxone has no effect a second dose can be given	☐	☐	☐
10. There is no need to call for an ambulance if I know how to manage an overdose	☐	☐	☐
11. Someone can overdose again even after having received naloxone	☐	☐	☐
12. The effect of naloxone is shorter than the effect of heroin and methadone	☐	☐	☐
13. After recovering from an opioid overdose, the person must not take any heroin, but it is ok for them to drink alcohol or take sleeping tablets	☐	☐	☐
14. Naloxone can provoke withdrawal symptoms	☐	☐	☐

Opioid Overdose Knowledge Scale (OOKS): Scoring instructions

The OOKS aims to assess the level of knowledge of opioid overdose management among addiction professionals, patients and family members. It records knowledge about risk factors for having an opioid overdose, signs of an opioid overdose, actions to be taken in an overdose situation, naloxone effects and administration, adverse effects and aftercare procedures. The scale also identifies misinformation and myths about opioid overdose.

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- One point if NOT marked (12 Incorrect/False items): 2a, 2f, 2i, 2j, 3c, 3e, 3h, 3k, 5d, 5e, 10F, 13F. You might choose to use the 'record into same variables' function of SPSS and inverse the values of these items.

Risk (9 items):

- One point if marked: 1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1i

Signs (10 items):

- One point if marked: 2b, 2c, 2d, 2e, 2g, 2h
- One point if NOT marked: 2a, 2f, 2i, 2j

Action (11 items):

- One point if marked: 3a, 3b, 3d, 3f, 3g, 3i, 3j
- One point if NOT marked: 3c, 3e, 3h, 3k

Naloxone use (15 items):

- One point if marked: 4a, 5a, 5b, 5c, 6a, 7a, 8b, 9T, 11T, 12T, 14T
- One point if NOT marked: 5d, 5e, 10F, 13F

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About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 20 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

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EMCDDA Insights are topic-based reports that bring together current research and study findings on a particular issue in the drugs field.

Preventing opioid overdose deaths with take-home naloxone examines the case for distributing naloxone, an emergency medication, to people who inject opioids such as heroin and to others who might witness an opioid overdose. Through its capacity to reverse opioid overdose, naloxone can save lives if administered in time. This comprehensive review begins by looking at the pharmacology of naloxone and the opioids it counteracts, and the physiological mechanisms involved. The chapters that follow look at the circumstances of opioid overdose deaths and the use of naloxone in regular clinical practice. The historical development and spread of take-home naloxone programmes and the practical side of their implementation — focusing on training recipients in how to recognise and respond to an overdose — are each the subject of a chapter. The study closes by considering the prospects for the future, in the context of the development of new products, new legislation and new initiatives.

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