



Naloxone in Europe: a focus report

Introduction

The 15th annual 'Improving Outcomes in the Treatment of Opioid Dependence' (IOTOD) meeting took place at the H4 Hotel Berlin Alexanderplatz on 17–18 May 2017. The meeting succeeded in bringing together clinicians from around the world, prompting informative and honest discussions on several key issues in the field of opioid dependence.

Reducing opioid overdoses is one such key issue and IOTOD 2017 dedicated an entire session to discussing the distribution of naloxone, an opioid overdose-reversal medication, along with overdose training through take-home naloxone (THN) programmes. With the aim of expanding on this topic, this 'Naloxone in Europe' focus report summarises the current landscape of naloxone and THN programmes across Europe, detailing the case of Scotland as an example of good THN practice.

The life-saving potential of naloxone

Overdose deaths remain a major health concern across Europe and opioids account for the majority of the 6,300–8,000 drug-induced fatalities that occur each year.^{1,2} In the UK, opioid-related deaths are on the rise (figure 1) and in 2016 over 50% of all overdose deaths in England and Wales were opioid-related.³

There are several interventions used to reduce opioid-related deaths; a subset of these aim to prevent overdoses from occurring, such as maintaining patients on opioid substitution treatment (OST) and implementing good treatment practice.⁴ Other strategies are designed to stop an overdose in the event of one, and distribution of the opioid antagonist naloxone is a prime example of this.⁴ The life-saving potential of timely naloxone administration is due to the antagonist's strong affinity for μ -opioid receptors over which it competes with other opioids. By binding to these receptors, naloxone prevents opioid metabolites from activating them (figure 2) and is therefore able to counteract opioid-induced respiratory depression, a key feature of an opioid overdose which can result in low oxygen blood levels, organ failure, unconsciousness and death.^{2,4,5} In some cases, naloxone can trigger the loss of opioid analgesia and, in opioid-dependent individuals, the competitive antagonist may induce sudden withdrawal symptoms.⁶ However, serious adverse events are extremely rare and it has no potential for direct misuse.^{2,6,7}

Naloxone's favourable risk–benefit profile and life-saving potential has motivated several organisations to support and encourage increasing its availability,

Naloxone formulations^{2,8}

- Naloxone injection is a liquid formulation and is available for intravenous, intramuscular and subcutaneous routes of administration. It is supplied in glass ampoules and pre-filled syringes
- Naloxone nasal spray formulations exist but are not currently licensed in Europe
- Injectable naloxone liquid formulations are available in concentrations of 0.4 mg/ml to 1 mg/ml

Signs of an opioid overdose are:^{2,5,9}

- Unconsciousness and unresponsiveness to noise or touch
- Shallow or no breathing (respiratory depression)
- Snore-like gurgling noise
- Pinpoint pupils
- Pale or clammy face
- Blue or grey tinges to skin and fingernails, and lips turn blue or purplish black

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and it is listed as an ‘essential medicine’ by the World Health Organization (WHO).^{7,10} Provision of access to naloxone is also included in the EU Action Plan 2017–2020 as a strategy to prevent drug-related deaths.¹¹ Furthermore, the S-O-S (Stopping Overdose Safely) Initiative was recently launched and aims to provide overdose training to potential witnesses of overdoses, to increase their access to naloxone and to ensure potential overdose witnesses either carry naloxone or have the product in proximity.¹²

What makes a THN programme?

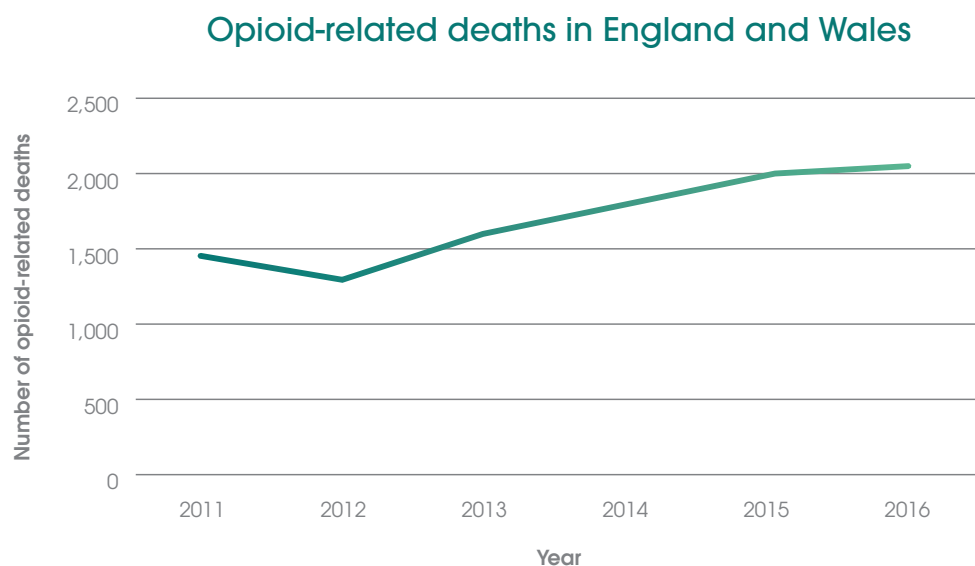
THN programmes provide naloxone supplies and overdose awareness education to users and potential overdose witnesses with the goal of reducing opioid fatalities and improving patient outcomes.^{2,6} They can be delivered through a wide range of settings, such as clinics, prisons and outreach services and overdose training can be delivered in many different formats, including lecture-type sessions or one-on-one conversations.²

It is important that THN programmes engage individuals at risk of an opioid overdose, including

people who use opioids, heroin users exiting prison, individuals initiating medication-assisted treatment and previous opioid users discharged from treatment clinics.² It is crucial to empower these individuals with naloxone and training because, not only are they at risk of an overdose themselves, but they may have increased chances of being present during an opioid overdose event.² Furthermore, THN programmes should be available to opioid users’ peers (e.g. family members and carers) and people who work closely with opioid users (e.g. hostel staff members, workers at needle and syringe programmes, law enforcement staff, etc.) as these individuals are likely to witness overdose events.^{2,6}

Overdose training is a key component of THN programmes as they educate individuals on several aspects of overdoses, while dispelling myths surrounding opioid intoxication reversal that prevail among drug users (e.g. bathing an intoxicated individual in cold water, injecting salt solutions, administering stimulants, etc.).⁶ While delivery and intensity of the educational interventions employed

Figure 1 Number of deaths in England and Wales that are related to opioid poisoning from the Office for National Statistics.³



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may differ in each programme, they generally cover several important topics. These include overdose risk factors, identification of an opioid overdose, how to act in the event of an overdose (with an emphasis on calling an ambulance), how to use naloxone, the potential benefits and limitations of naloxone, and how to reacquire naloxone following its use and expiration.^{2,5,6} Training people on how to identify an opioid overdose is also covered in THN programmes² and is emphasised by Kirsten Horsburgh, national naloxone coordinator of the THN programme in Scotland: 'Making sure people are able to recognise an overdose is absolutely crucial'.¹³

Some programmes do not provide full cardiopulmonary resuscitation (CPR) training as it can be considered to be too time-consuming for a brief overdose education session.² However, other programmes do,^{2,14} and the WHO Community Management of Opioid Overdose guidelines are strongly in favour of providing training due to the

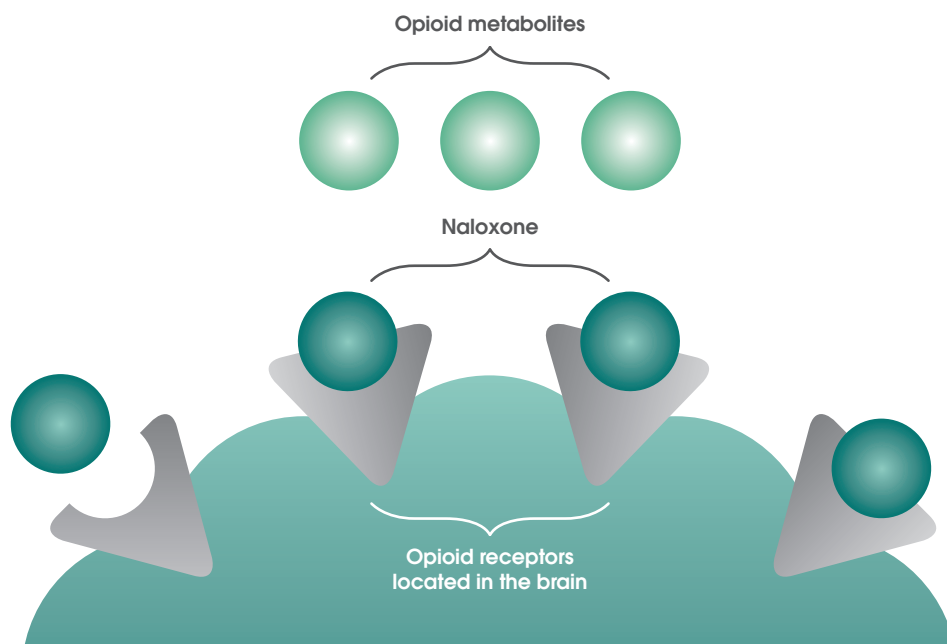
ability of CPR (including rescue breathing) to save lives and its low likelihood to cause harm during opioid overdose events.¹⁰

Finally, improvement of individuals' knowledge should be assessed and systematic follow-ups should be used to evaluate the quality and effectiveness of THN programmes in improving patient outcomes.²

The evolution of naloxone distribution

Historically, naloxone use was restricted to medical care and, following its approval in the 1970s, the product was principally administered intravenously by emergency service staff. However, the emergence of subcutaneous and intramuscular routes of administration, and the recognition that overdoses are usually witnessed by others, led to calls in many countries for governments to increase naloxone's accessibility to opioid users and to potential bystanders.^{2,15}

Figure 2 A diagram of naloxone binding to μ -opioid receptors in the brain, preventing opioid metabolites from activating them. (adapted from EMCDDA, 2016).²



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Provision of THN was originally debated in the early 1990s and, in Europe, the first THN schemes were set up in Berlin, Jersey, Turin, Bologna and Padua in the late 1990s.² In 2016, naloxone was available in only a third of EU member states,¹⁶ despite it being listed as an essential medicine by the WHO.⁷ Indeed, implementation of THN programmes in Europe has been relatively slow with 10 countries* reporting to have set up THN programmes.⁴ Of these, Scotland and Wales have implemented nationwide schemes and promising results have shown a reduction in opioid-related deaths following their introduction in prisons (see Success in Scotland for more).^{4,17} The number of European THN programmes has increased in recent years and there is growing support for naloxone distribution in guidelines and

governmental documents, such as the 2017 UK Drug Strategy.¹⁸ As previously mentioned, the EU Action Plan 2017–2020 has also included providing access to naloxone ‘specifically certified to treat opioid overdose symptoms by trained laypersons in the absence of medical professionals’ as a strategy to prevent drug-related deaths.¹¹

Contributing to the strong endorsement of naloxone provision is the S-O-S Initiative, which launched in 2017 by the United Nations Office on Drugs and Crime (UNODC) and WHO. The detailed strategy aims to prevent opioid overdose deaths around the world by increasing naloxone availability and training to all individuals likely to witness an overdose. The S-O-S Initiative has set global 90-

The game-changing evidence

Evaluating the impact of THN programmes on overdose mortality is significantly challenging and, until recently, compelling evidence for programmes’ efficacy was lacking. This was partly due to the methodological and ethical limitations of conducting randomised controlled trials, and, importantly, because of early pilot studies failing to quantify the reduction of mortality rates.^{2,19}

In recent years, the publication of well-designed studies and systematic reviews has transformed the naloxone landscape by providing robust evidence for the association of THN programmes with a reduction in opioid-related deaths.^{8,19,20} Results suggested that in communities running THN programmes the rate of opioid-related mortality was significantly lower than in communities without THN programmes. Furthermore, these schemes were associated with a significant improvement in knowledge of

overdose, patient management and naloxone administration, and were reported to be cost-effective and have reduced rates of adverse outcomes.^{8,19,20} Results from one meta-analysis suggested that naloxone administration by non-clinical individuals who had received overdose training was associated with superior recovery outcomes compared with naloxone administration by non-medical individuals who had not received the training.²¹

The results suggesting that THN programmes reduce opioid-related mortality represent a significant advancement, as it was challenging to achieve policy change and introduce these projects without compelling evidence. This highlights the importance of continuing to monitor THN programmes, ideally by systematically following-up all participants, in order to determine their quality and overall impact on the community.²

*Denmark, Estonia, France, Germany, Italy, Ireland, Lithuania, Norway, Spain and the United Kingdom

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'Making sure people are able to recognise an overdose is absolutely crucial'

Kirsten Horsburgh

90-90 targets: 90% of the target groups will receive overdose training, 90% of trained individuals will obtain emergency naloxone and 90% of individuals with a naloxone supply will either have the product in proximity or carry it with them. In order to reach these targets, the strategy will encourage countries to change policy and laws to facilitate overdose management, promote collaboration between governments and organisations striving towards preventing overdose fatalities, and to support drug users, peers of drug users and all other individuals who are likely to witness an overdose event.¹²

At present, there remains room for improvement in naloxone distribution, yet the number of European THN programmes has increased in recent years and support for naloxone distribution in clinical guidelines, governmental documents and international strategy plans might see this trend continue in the future.⁴

Considerations for implementing THN programmes

There are many important elements of setting up and running a THN programme to consider. While these considerations will vary nationally and even locally, valuable recommendations that might facilitate the process have been made based on existing THN programmes, which to date are reported in 10 European countries.⁴

An important matter to consider is legislation and policy, which can differ greatly between countries and even within a country, and will massively influence the introduction and running of THN programmes. In some European countries, there are laws in place that might deem administration or possession of naloxone an offence, and access to

naloxone is reduced when the product is restricted by law to prescription-only by hospital clinicians.² However, several countries have successfully overcome these systematic challenges with laws to ensure people who administer naloxone in the event of an overdose are not held liable, and in Italy naloxone is available without a prescription, greatly increasing access to the product.² Furthermore, endorsement from governmental bodies is not only a huge facilitator in terms of legality, but can also provide vital funding, such as is the case in Denmark.²

Another important matter to consider is the opioid users themselves. Some may be reluctant to possess naloxone and many are unwilling to seek medical help in the event of an overdose due to potential police involvement.² Thus, including users, their families and their peers in the programmes massively helps in tackling these patient-level barriers as it increases outreach and acceptability.²

According to Stephen Malloy, independent consultant and former national coordinator for the national naloxone programme in Scotland, programmes should not only involve people who use drugs, but should put them at the very centre of the project. 'Unequivocally, [this] is the only way to achieve the outcomes we want to see.'²² It is also useful to provide overdose training to police, firefighters and ambulance workers as they are likely to be present during an overdose event.²

Other recommended actions include enrolling prisoners on release in THN programmes (see Success in Scotland) and not depending on a single naloxone product or manufacturer for the scheme.² Finally, in Norway, integrating THN programmes into standard care at healthcare facilities supported the sustainability of the project.²

The increase in THN programmes being set up will most likely be accompanied by the emergence of

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'Unequivocally, [this] is the only way to achieve the outcomes we want to see'

Stephen Malloy

more guidance on the matters to consider for this process. While it is key to take into account national and local circumstances before following these recommendations, much can be learnt from others' 'trial and error' and it is important for healthcare providers, policymakers and anyone advocating better patient outcomes for opioid users to actively work together towards the implementation of THN schemes where they are needed.

Success in Scotland

In 2011, a nationwide THN programme was introduced in Scotland with one clear objective: to minimise the rising number of opioid-related deaths in Scotland; the primary outcome being a reduction in opioid-related deaths following prison release.^{2,17,23} Known as the Scottish National Naloxone Programme (NNP), the project organises provision of naloxone kits from prisons, specialist drug centres and other community-based services to individuals at risk of overdose.^{2,17} This includes previous opioid users that are discharged or released from hospitals and prisons,¹⁷ as they commonly undergo a loss of opioid tolerance that increases their likelihood of experiencing an overdose.²³ Furthermore, community services include peers of patients at risk of opioid overdose and staff members as recipients of naloxone kits. Originally funded by the Scottish Government, the distributed kits are now locally funded by NHS boards.¹⁷

Since its introduction, several pieces of promising results evaluating the NNP's impact have been published. Firstly, kit distribution among individuals at risk of overdose has markedly increased in Scotland, with double the amount of kits supplied in 2015/2016 compared with 2011/2012. Additionally, there has been a rise in the proportion of repeat

kits distributed from 12% in 2011/2012 to 38% in 2015/2016. This is a positive result considering that many times providing repeat kits indicates the original kit has been used to reverse an overdose.¹⁷

Importantly, the NNP's efficiency has been evaluated based on its impact on the number of opioid fatalities following release from prison or discharge from hospitals. Analysis has shown that rates of opioid-related deaths during the first four weeks of hospital discharge have not been significantly lower following the introduction of NNP and figures have varied from year to year with no consistent trend emerging.¹⁷ According to Kirsten Horsburgh, national naloxone coordinator of the THN programme in Scotland, there is a suboptimal level of naloxone supply per health board basis via hospitals, where the provision of naloxone to people when they are discharged is limited. These findings greatly contrast with the findings that show a significant reduction in opioid-related deaths four weeks following prison release when comparing before and after NNP implementation.¹⁷ Indeed, during the period prior to NNP's implementation (2006–2010), the percentage of opioid-related deaths four weeks upon prison release was 9.6%, while this decreased to 6.3% during 2011–2013.²³ By 2015, the percentage had further decreased to 4.7%, and all years from 2012 to 2015 have seen significantly lower opioid-related deaths four weeks after prison release compared with the pre-implementation period.¹⁷

While work remains to be done, the significant reduction in opioid-related deaths after prison release highlights the importance of the Scottish NNP and suggests the project has directly contributed to the prevention of these avoidable deaths.¹⁷ As mentioned, the Scottish NNP is considered an example of good naloxone distribution practice and these promising results are expected to encourage countries elsewhere to implement nationwide THN programmes.^{2,23}

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Conclusion

Since the 1970s when naloxone was first introduced, there has been progress made to provide wider access to naloxone across Europe.² At present, THN programmes exist in 10 EU member states and several guidelines encourage the provision of naloxone and overdose education to opioid users and others who may witness overdoses.² Monitoring of these projects has allowed researchers to evaluate their overall impact and, indeed, results continue to reaffirm the hypothesis that THN programmes increase overdose knowledge and reduce opioid-related deaths in communities where they are introduced.²

In Europe, overdose deaths rates are extremely high and opioid-related fatalities are on the rise in the UK.⁶ An immediate response to this major health concern is much needed so it is critical for opioid users, clinicians, policymakers and governmental bodies to actively work together to provide wider access to naloxone and to overcome any remaining barriers that prevent THN programmes from being implemented.⁶ Success in this respect will be key to reducing the number of avoidable drug-related deaths that occur across Europe, thereby improving patient outcomes and quality of life.

References

1. European Monitoring Centre for Drugs and Drug Addiction. Mortality among drug users in Europe: new and old challenges for public health. 2015. Available at: <http://www.emcdda.europa.eu/system/files/publications/961/TDAU14010ENN.pdf> [last accessed July 2017]
2. European Monitoring Centre for Drugs and Drug Addiction. Preventing opioid overdose deaths with take-home naloxone. 2016. Available at: <http://www.emcdda.europa.eu/system/files/publications/2089/TDXD15020ENN.pdf> [last accessed July 2017]
3. Office for National Statistics (ONS). Dataset: Deaths Related to Drug Poisoning, England and Wales. 2017. Table 6a. Available at: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsrelatedtodrugpoisoningenglandandwalesreferencetable> [last accessed July 2017]
4. European Monitoring Centre for Drugs and Drug Addiction. Preventing overdose deaths in Europe. Available at: <http://www.emcdda.europa.eu/topics/pods/preventing-overdose-deaths> [last accessed July 2017]
5. World Health Organization (WHO). Information sheet on opioid overdose. Available at: http://www.who.int/substance_abuse/information-sheet/en/ [last accessed July 2017]
6. Public Health England (PHE). Take-home naloxone for opioid overdose in people who use drugs. Available at: <http://www.nta.nhs.uk/uploads/phetake-homenaloxoneforopioidoverdosefeb2015rev.pdf> [last accessed July 2017]
7. New EMCDDA insights into naloxone, the overdose antidote that can help save lives. 2016. Available at: <http://www.emcdda.europa.eu/news/2015/naloxone> [last accessed July 2017]
8. European Monitoring Centre for Drugs and Drug Addiction. Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone. 2015. Available at: http://www.emcdda.europa.eu/system/files/publications/932/TDAU14009ENN_web_.pdf [last accessed July 2017]
9. Harm reduction coalition. Recognizing Opioid Overdose. Available at: <http://harmreduction.org/issues/overdose-prevention/overview/overdose-basics/recognizing-opioid-overdose/> [last accessed August 2017]

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- 10.** World Health Organization (WHO). Community management of opioid overdose. 2014. Available at: http://apps.who.int/iris/bitstream/10665/137462/1/9789241548816_eng.pdf?ua=1&ua=1
- 11.** EU action plan on drugs 2017–2020. Available at: [http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52017XG0705\(01\)](http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52017XG0705(01)) [last accessed August 2017]
- 12.** United Nations Office on Drugs and Crime (UNODC) and World Health Organization (WHO). The S-O-S Initiative—Stop Overdose Safely. Available at: https://www.unodc.org/documents/commissions/CND/The_S-O-S_InitiativeStop_Overdose_Safely_-_UNODC-WHO_multi-site_study_on_community_management_of_opioid_overdose_including_emergency_naloxone.pdf [last accessed August 2017]
- 13.** Personal communication, Kirsten Horsburgh (National Naloxone Coordinator, Scottish Drug Forum, UK).
- 14.** Naloxone.org.uk. CPR and naloxone. Clarification of basic life support for the naloxone programme. Available at: <http://naloxone.org.uk/index.php/naloxoneseparator/naloxoneinformation/bls> [last accessed July 2017]
- 15.** European Harm Reduction Network. Harm Reduction in Europe: mapping coverage and civil society advocacy. Available at: http://www.eurohrn.eu/images/stories/pdf/publications/EuroHRN_CivilSociety.pdf [last accessed July 2017]
- 16.** New EMCDDA insights into naloxone, the overdose antidote that can help save lives. News release. 2016. Available at: <http://www.emcdda.europa.eu/news/2016/1/preventing-opioid-overdose-naloxone> [last accessed July 2017]
- 17.** Information Services Division. Publication Report. National Naloxone Programme Scotland. Monitoring Report 2015/16. 2016. Available at: <http://www.isdscotland.org/Health-Topics/Drugs-and-Alcohol-Misuse/Publications/2016-10-25/2016-10-25-Naloxone-Report.pdf> [last accessed July 2017]
- 18.** HM Government. 2017 Drug Strategy. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/628148/Drug_strategy_2017.PDF [last accessed July 2017]
- 19.** Clarke AK, et al. A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med* 2014;8:153-63.
- 20.** McDonald R and Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction* 2016;111:1177-1187.
- 21.** Giglio RE, et al. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. *Injury Epidemiology* 2015;2(10).
- 22.** Personal communication, Stephen Malloy (Previous Scottish National Coordinator for Take Home Naloxone, Scottish drug forum, UK)
- 23.** Bird SM, et al. Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: a before (2006–10) versus after (2011–13) comparison. *Addiction* 2016; 111:883–891.