Pacini Editore & AU CNS

Expert Opinion

Heroin Addict Relat Clin Probl 2019; 21(1): 5-14

HEROIN ADDICTION & RELATED CLINICAL PROBLEMS

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Improving response capacities in opioid overdose management

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Summary

Background: The recreational use of opioids is increasing in Italy as elsewhere in Europe and so the prevention of opioid overdose (OD) deaths remains a major challenge for addiction services. In Italy, the availability of the opiate antagonist naloxone, the standard treatment for OD, is limited to the emergency and first aid system with an uneven distribution of Take Home Naloxone programmes (THN). **Aim:** To review the current status of naloxone use for OD in Italy and to consider whether a new intranasal formulation of naloxone may offer an easier and safer administration compared with previous injectable formulations. **Methods:** The authors met on two occasions to discuss as experts in the field, based on their real-world practice. **Results:** This formulation has a rapid onset of effect and its pharmacokinetic profile is similar to intramuscular formulations. It may be more acceptable due to the elimination of needles for administration. **Conclusions**: The advent of intranasal naloxone can help to simplify the delivery process by providing a more effective and appropriate solution to OD. In turn, this may also facilitate the implementation of THN programmes that reach more affected individuals and help to save more lives. More extensive distribution of naloxone (including the intranasal spray formulation) to target groups and populations has the potential to reduce mortality and other consequences of OD.

Key Words: Opioid overdose; mortality; naloxone intranasal; harm reduction; THN/take home

1. Introduction

In Italy in the last two years there has been a slight increase in heroin use, particularly among young people aged 15–19 years. The prevention of opioid overdose (OD) deaths therefore continues to be a major challenge for addiction services, and the analysis of new consumers and their consumption patterns can help this aim [10].

The standard treatment for opioid overdose is naloxone. Although it is a life-saving drug and the Italian legislation allows its purchase without a prescription, its availability remains limited, excluding the emergency and first aid system and a limited number of Take Home Naloxone programmes (THN; i.e., the distribution of naloxone to consumers and their affiliated networks). THN programmes have been operational since 1991 but they are currently unevenly distributed across Italy [22]. The availability of the new intranasal formulation of naloxone, with an easier and safer administration compared with previous formulations, [7] offers a new solution for the prevention and management of overdose. To facilitate access, the primary objective is to create a network between stakeholders involved in the mechanism of prevention and management of OD, strengthening the role of those who are already actively participating in the process and involving new professionals and methods of action.

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2. Opiate overdose

2.1. Epidemiological data

The use of psychotropic drugs is a known preventable cause of death in European adults. Cohort studies on high-risk consumers of psychotropic drugs show total mortality rates ranging from 1–2% per year. Overall, opioid users in Europe have a death risk 5–10 times higher than that of their peers. In Europe, overdose continues to be the leading cause of death among drug users, and more than three quarters of overdose victims are men (78%). However, caution should be exercised in interpreting overdose data, especially the cumulative European total, primarily due to systematic omissions of reports in some countries and delays caused by registration procedures. Annual estimates therefore stand as a provisional minimum value [6].

The Italian data on overdose mortality is also underestimated. Focusing on the analysis of the Special Mortality Registry of the Ministry of the Interior, there were 266 drug-induced deaths in 2016 in Italy. Of these, 89.8% were men, 5.6% were foreigners and 51.8% were people over the age of 39. Substances were not specified in 44% of cases but opiates were involved in 73% of cases (mainly heroin). The regions of Piedmont (36 deaths), Tuscany (28 deaths), Emilia Romagna and Veneto (25), Lazio and Lombardy (20) had more events in 2016, whereas no drug-related deaths were seen in Molise [1].

2.2. Treatment of overdose

Opiate overdose can be recognised based on certain signs and symptoms such as pinpoint pupils and respiratory depression, while mydriasis is a sign of opiate abstinence [20, 34]. Patients with suspected opioid overdose should be treated if the respiratory rate is <12 breaths per minute or if they are hypoxic to pulse oximetry (oxygen saturation <90%) [3]. The initial treatment of hypoxic patients is to provide oxygen and assisted ventilation as necessary. In general, this procedure involves the release of airways and the application of ventilation with a breathing bag and a mask for the delivery of oxygen [3].

Naloxone is a non-selective, short-acting opioid receptor antagonist with established success for the treatment of overdose of short-acting opiates, such as heroin, and overdose of prescription opiates [21]. Priority should be given to breathing and oxygenation in the treatment of opiate overdose. Any respiratory arrest should be treated with assisted ventilation and oxygen, pending the administration of naloxone or the effect of the drug. In most cases, the availability of naloxone in the shortest possible time is directly linked to patient survival.

Generally, the recovery of adequate respiration occurs within 30 seconds of administration of naloxone. The ideal dose of naloxone is the one that improves breathing without inducing withdrawal, but an excessive dose is better than too low a dose. A standard dose for the treatment of suspected heroin overdose corresponds to 400 µg intramuscularly, 800 µg subcutaneously or 1.8 mg as nasal spray, repeated 2 minutes later, if necessary. However, an initial too high dose of naloxone (with respect to the patient's tolerance level and amount of opioid taken), can induce severe withdrawal, increasing the risk of vomiting and aspiration pneumonia [31].

The management of overdose of an opiate with a long-half-life is more complicated. In this situation, the duration of opioid sedation is higher than the naloxone effect. The safest method to treat long-acting opioid overdose is probably ventilation, if available. Although patients may also be treated with repeated doses of naloxone or naloxone infusions, death may occur if naloxone infusions are inadvertently interrupted or if the patient wakes up and suspends medical attention by themselves.

Before stopping treatment, patients should be ideally kept under surveillance for several hours after naloxone administration. Although in practice this may be difficult to achieve, it is extremely important in patients suspected of overdose associated with long half-life opiates. Overdose may be due to the intake of street opiates or opiates prescribed by a doctor.

1. Most overdose deaths occur in the presence of another person. In cases of overdose involving illicit drugs, people may be reluctant to call an ambulance because of the fear of police involvement. Consequently, availability of naloxone among those who use and inject illegal drugs and their friends and family can be lifesaving.
2. Approximately half of overdoses caused by prescription opioids involve patients with chronic pain. These patients often have little understanding of the risks of overdose, especially the risks associated with the concomitant use of substances acting on the central nervous system (CNS), such as alcohol and benzodiazepines. For this situation, the patient, their friends and families need train-

ing, and the role of general practitioners and pharmacists is critical to facilitate this. The training should include an explanation of overdose risks and the best acting countermeasures. Therefore, access to naloxone is a good opportunity for an early pre-hospital intervention for this group of patients [14].

3. Naloxone

Naloxone can rapidly counteract opiate overdose. As an opiate antagonist it binds to opioid receptors and can reverse and block the effects of opioids. Its action can quickly restore normal breathing in a person whose breathing has slowed or stopped as a result of the overdose of heroin or opiate drugs prescribed for severe pain [24].

Naloxone is non-addictive and considered to be generally safe with no side effects and no secondary pharmacological effects or safety pharmacology effects except for possible opioid withdrawal symptom. In an emergency, such as an OD event, the choice of administration route can be critical: naloxone is generally administered by intravenous injection in the hospital setting, or intramuscular (IM) injection in the pre-hospital setting. Nasal administration is an interesting option for non-healthcare professionals, for example witnesses on the scene, who are worried by possible injuries that can be caused by needles [19].

It can be argued that, in some respects, prescription naloxone is a loss of opportunity. The need for a prescription itself selects only a portion of the population at risk (i.e., individuals who are in touch with health services; those who have no problem in discussing drug abuse with their physician). As many as 60-70% of the people at risk don't have a stable relationship with health services. Within this context, it should also be considered that naloxone is used not just to treat, but also to prevent ODs. Therefore, expanding the availability of naloxone to potential overdose witnesses, including emergency services staff, drug users, their friends and families, and other potential witnesses may reduce the impact of opiate-related overdoses. Death associated with opiate overdoses typically occurs within 1–3 hours of taking the drug [15]. Respiratory crisis may put people at risk of brain damage due to hypoxia. As a result, the administration of naloxone in the shortest possible time is of utmost importance to avoid death or brain damages due to overdose.

There are three naloxone formulations currently approved by the Food and Drug Administration (FDA) in the United States of America (USA).

3.1. Injectable naloxone (professional training required)

Professional training is required for the use of naloxone in the USA. The use of improvised emergency kits combining an injectable naloxone formulation with an atomizer capable of delivering naloxone intranasally has become widespread. These improvised intranasal devices may not provide equivalent naloxone levels to products that are FDA approved. Furthermore, their use is considered to be dangerous and therefore not recommended.

3.2. Self-injectable naloxone

This is a ready-to-use self-injection device that makes it easy to use for families or emergency staff to inject naloxone quickly into the outer part of the thigh. Once activated, the device provides users with verbal instructions describing how to administer the drug, similar to automated defibrillators [29].

3.3. Pre-packed nasal spray

Naloxone intranasal spray (Nyxoid®) is a prefilled needle-free device requiring no assembly that is sprayed into a nostril with the patient lying on their back. It is relatively easy to use and is suitable for home use or "on the road" use in emergency situations. The intranasal formulation avoids the risks potentially related to injections by unskilled personnel [30].

3.4. Who can administer naloxone to someone who has overdosed?

Injection fluid is commonly used by paramedics, emergency room physicians, and other specially trained first aid personnel. Naloxone intranasal spray is designed facilitate the administration of naloxone to anyone in an emergency situation as it allows naloxone to be sprayed into the nose safely at precise administered doses [7]. In contrast, improvised atomisers that were used in the past to convert syringes to be used as a nasal spray, and which may not provide appropriate drug dosing, should be avoided.

3.5. What precautions are necessary to administer naloxone?

Persons who receive naloxone should be monitored continuously until they arrive in the emergency room and for a few hours after being administered the last dose of naloxone to ensure that their respiratory rate does not slow down or stop [7].

3.6. What are the side effects of naloxone?

Naloxone is considered to be safe as its only effects are on opioids in the CNS. Naloxone can (but not always) cause withdrawal symptoms that can be bothersome but not life-threatening. In contrast, opioid overdose may seriously affect survival. Withdrawal symptoms may include headaches, changes in blood pressure, tachycardia, sweating, nausea, vomiting and tremors [7].

In "Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence", [34], the World Health Organization recommends the use of naloxone in opiate overdose. The WHO states that the use of naloxone is indicated to eliminate the effects of intoxication and opiate overdose. It is specifically stated that: "Each healthcare facility with medical staff must ensure that opiate antagonist can be administered to treat opiate overdose. This includes stockpiling procedures and appropriate tools for administration. It has been shown that the distribution of naloxone, with appropriate training on its use in overdose cases for opiate-dependent patients and their families, is a viable approach for reducing drug overdose deaths in the community." [11, 25, 26]. This approach is comparable to the distribution of adrenaline to patients with severe allergic reactions and their families.

The EU Action plan on drugs 2017–2020 [8] refers to the need to promote and extend plans aimed at improving the prompt availability of naloxone. Addressing the need to help prevent opioid-related mortality, the EU Action plan calls for increased availability of naloxone-containing medicinal products suitable for the treatment of opiate overdose by non-professional users in the absence of medical personnel.

Such programs can be highly successful. For example, in 2018, 152,000 naloxone kits were distributed or prescribed in Australia, resulting in successful outcome of 26,000 opiate overdose cases [14].

The 15th annual Improving Outcomes in the Treatment of Opioid Dependence (IOTOD) meeting underlined that the need to reduce opiate overdose is one of the key problems in Europe today. IOTOD 2017 dedicated an entire session to discuss naloxone distribution programs to take home (THN) alongside overdose management training courses [13].

3.7. Misconceptions about naloxone

Research findings indicate that expanding the supply of naloxone is not associated with increased risk-taking by patients or any increases in drug use. The reverse is true. Studies that specifically examined the use of opioids among those who were trained in the use of naloxone reported a reduction in drug use [2]. Additionally, naloxone also works with more powerful opioids, such as fentanyl, albeit at higher dose levels [4, 12].

3.8. Accessibility to naloxone

In the Italian legal framework, naloxone can be distributed to people who may need to make it available to qualified personnel as needed. The administration of naloxone by non-professional subjects in cases of emergency is still covered by article 54 of the Italian Criminal Code ("No one shall be punished for acts committed under the constraint of necessity to preserve himself/herself or others from the present danger or a serious personal harm, which is not caused voluntarily nor otherwise avoidable, and provided that the acts committed are proportionate to the threatened harm") [22].

Today, naloxone is mostly distributed by low-threshold services [22]. The number of SerDs (Servizi per le Dipendenze - Drug Addiction Centers) in Italy distributing naloxone to patients is not documented, whereas it is often lacking in pharmacies, as reported by numerous surveys [9, 32].

4. New opportunities: intranasal Naloxone

4.1. Characteristics

The parenteral administration route is preferred in the acute hospital setting but the IM route is preferable in other settings because finding a venous access requires time and qualified personnel may not be available. In these scenarios, the formulation of intranasal spray has attracted considerable interest based on its ease-of-use and rapid onset of effect relative to the IM route [18]. In an open-label, randomized, five-way cross-over pharmacokinetic study, 38

Table 1. Key points for the use of Naloxone as prevention of OD

• Take-home naloxone (THN) can prevent death from heroin/opioid overdose, but pre-provision is difficult because naloxone is usually given by injection.
• THN programs have overcome legal barriers in many countries. However, a successful THN program is not just a clinical matter, it involves the coordinated actions of several stakeholders including governmental decisions, a supportive legal framework, police support, medical structures, patient groups, patient families, emergency services, distribution programs (e.g. to users who are leaving prison).
• Non-injectable alternatives, including naloxone nasal sprays, are available to meet this need.
• To be effective, the delivered intranasal spray dose of naloxone must be adequate but not excessive, and early absorption must be comparable to intramuscular injection.
• More extensive distribution of naloxone (including of the intranasal spray formulation) to target groups and populations has the potential to reduce mortality and other consequences of OD.
• Societal and scientific misconceptions and/or misinformation and/or behaviour based on outdated information must be overcome in order to achieve the aim of more widespread naloxone distribution.
• Naloxone distribution should be accompanied by information on the risks of OD along with user-friendly information on the correct use of the spray.
• Intranasal spray is inherently safer than injection (no risks associated with needles) and everybody can administer naloxone in case of a suspected OD.
• Within the legal and regulatory framework, naloxone nasal sprays simplify the delivery of naloxone, increasing the chances of favourable outcomes.

healthy volunteers (age 20–54 years; 11 female) received either three doses of intranasal spray naloxone (1 mg/0.1 ml; 2 mg/0.1 ml; 4 mg/0.2 ml) or either 0.4 mg IM or IV naloxone as reference. Mean peak concentration (Cmax) values for 1 mg (1.51 ng/ml), 2 mg (2.87 ng/ml) and 4 mg (6.02 ng/ml) intranasal naloxone exceeded 0.4 mg IM (1.27 ng/ml) naloxone. All three intranasal naloxone doses rapidly achieved plasma levels >50% of peak concentrations by 10 minutes, peaking at 15-30 minutes (Tmax). By comparison, the IM reference reached Tmax at 10 minutes. The 0.4 mg IM curve was followed closely in the first 10 minutes post-dosing and maintaining blood levels were maintained above twice the IM reference for the next 2 hours. The mean bioavailability was 47-51% for intranasal relative to IM naloxone. Simulation of repeat dosing (2 × 2 mg intranasal versus 5 × 0.4 mg IM doses) at 3-minute intervals demonstrated that comparable plasma naloxone concentrations are anticipated by either route. Overall, these robust findings demonstrate that concentrated 2 mg intranasal naloxone is well-absorbed and provides early exposure comparable to 0.4 mg IM naloxone [18].

As naloxone is a lipophilic compound that has no pre-systemic hepatic metabolism/elimination, nasal administration achieves good bioavailability, reported to be between 10% and 40%, depending on the concentration of drug used, that is sufficient to reverse respiratory depression resulting from overdose [28].

Studies have demonstrated that the safety and tolerability of the naloxone intranasal spray product are comparable to naloxone IV or IM, which are considered generally as well tolerated [7, 21]. Mechanism of action/dosing: the naloxone intranasal spray is part of a resuscitation action in suspected opioid ODs. If the first intranasal spray is unsuccessful, or if the first dose is insufficient, administration can be repeated with a further spray with no significant additional risks.

4.2. Operating advantages

The naloxone intranasal spray product can be administered by health professionals or by witnesses unfamiliar with the field, avoiding the use of needles [7]. The current Italian legislation, which allows the dispensing of naloxone without a prescription (the only non-prescription opiate antagonist drug – SOP [27]), and its administration by non-medical staff makes the spray formulation a suitable approach to help reduce mortality due to OD. The availability of such a non-prescription option to use in cases of OD therefore provides a valuable low-risk option for emergency treatment. The key points of Naloxone use are summarised in Table 1. In appendix 1 key information for a training course of 10-15 minutes on the use of naloxone is reported.

Appendix 1. Key information for a training course of 10-15 minutes on the use of naloxone
Overdose signs include:
• Reduction of respiratory rate and breathing depth (until the extreme condition of breathing absence and cyanotic colour
• Reduced reactivity, unconsciousness
• Small pupils until becoming as large as a pinprick
When opioid overdose is suspected:
• Position the person in a way to keep patient's airways unobstructed
• If you are able to do it, practice mouth-to-mouth resuscitation
• Call an ambulance and immediately give a dose of Nyxoid® (naloxone intranasal spray)
• If the comatose state persists or resumes, the mouth-to-mouth resuscitation should be continued and the administration of Nyxoid® (naloxone intranasal spray) should be repeated until the person begins to wake up

5. OD prevention system

The two cornerstones for the prevention of OD and opioid OD deaths in the Italian system are the SerDs and the Damage Reduction Services (RdD, Riduzione del Danno). The latter implement the prevention of OD mainly by carrying out THN programmes. Conversely, SerDs administer treatments with agonist drugs (methadone and buprenorphine) with the purpose of reducing risks, increasing and stabilizing the patients' opioid tolerance; [23] to a lesser extent they are involved in the distribution of naloxone. Within this framework, THN is part of the actions within the public and private services with which there are special arrangements, whereas pharmacies can still carry out private sale services.

5.1. Why expand naloxone access?

An erroneous assumption is that subjects who use heroin do so when surrounded by people and that overdose events are generally witnessed and shared by other people. In reality the event often occurs at home, and frequently any witnesses present put basic resuscitation techniques into practice, with variable degrees of success. Furthermore, they reluctantly call rescue services as they are worried of being reported for personal drug use or prosecuted for more serious offences.

As naloxone is a potentially life-saving element it can be argued that it should be available, reachable and accessible in all its administration routes, both injected and intranasally, and most importantly when an OD episode occurs. The classification of naloxone as an over-the-counter drug that does not require a prescription is therefore an essential factor, which allows any operators, even non-healthcare professionals, as well as all customers and citizens to have access to this drug and become an active player in the strategy for preventing deaths due to OD. The intranasal formulation further simplifies the process.

Naloxone distribution is instrumental both in reducing damage and in facilitating contact with the users: for example, through Nyxoid® distribution programs it might be possible to initiate a relationship with the users. The overall management of ODs will enable a management of the whole opiate addiction problem, that goes far beyond preventing deaths from ODs. One of the main reasons for the need to have intranasal naloxone available over the counter is that we should not select the patients who can have access to this opportunity.

This proposition is also support for the proposition that its usefulness becomes decisive when associated with information on the effect of the decrease in tolerance after periods of voluntary or forced abstinence and on how to practice resuscitation. Several studies have shown that THN programmes are associated with a local reduction in overdose mortality rates. An American study showed that the training of over 150 people per 100,000 of the population reduced fatal overdoses by about 25% compared to a geographical area where training and distribution programmes were not planned [33]. The availability of THN programmes is also associated with increased access to drug addiction treatment programs [16].

It has been 20 years since the THN provision was first proposed and yet they have only recently overcome legal barriers in many countries and provision remains low compared to evident growing clini-

cal need. The 'opt-out' model of required pre-provision may achieve wider naloxone coverage [17].

Young consumers require special attention. Usage trends in this population are mostly characterized by poly-drug use and injection route is not the first choice. In this population, the OD risk has been highly underestimated. The trends of an increase in the use of opiates even in younger populations of poly-consumers, reported in many countries, suggests the urgent need to implement information and distribution measures for naloxone in new natural consumption settings and according to new ways of outreach. Furthermore, it would be useful to inform this population about the availability of naloxone in pharmacies or services via the Internet. The necessary training can also be provided online. As this population mostly includes non-injectors, the availability of intranasal naloxone could be critical.

Objections related to naloxone distribution: Information that has been disseminated for decades has been proven to be groundless and outdated. For example:

- People who use heroin and have naloxone available to combat any overdose would be willing to use it at a riskier level. However, this objection does not take into account the refusal by those who use heroin, and especially drug addicts, to take naloxone. Many users think that naloxone not only suppresses the euphoric and narcotic effect of heroin but also triggers opioid withdrawal symptoms.
- The distribution of naloxone sends a message of endorsement of heroin use. Objections about other harm reduction measures (e.g., "distributing sterile syringes encourages drug use") are well-known but never proven to be true. Naloxone vials are distributed to individuals who already use heroin, and not as an indiscriminate approach to young people at risk of use. Furthermore, naloxone distribution is invariably accompanied with information and educational materials aimed at raising awareness of overdose risk and never condoning or legitimizing drug use.

5.2. Operational proposal: a network for OD prevention delivered through THN programs

Although Italy is at the forefront of European Community countries with respect to naloxone access, we need to focus on different areas of improvement. It is desirable to create a continuum of action among all stakeholders involved in the prevention and management of OD events by strengthening the action of those already actively participating in the process and adding new subjects. In addition to naloxone distribution, the common base must be the dissemination of THN programmes aimed at raising awareness of the risk and consequences of OD along with how it can be managed. Everyone involved, including non-healthcare professionals, must be able to share information and act at the scene of an OD. The expansion of THN programmes is also at root of the EU Drug action plan 2017–2020 currently available and in the draft phase for consultation. The document proposes, among other actions, to increase and share best practices related to harm reduction programmes which necessarily include THN programmes [5].

5.2.1. Encourage addiction Services to develop THN programmes

SerDs play a fundamental role in preventing deaths due to OD and in the THN model. One of the key outcomes of replacement therapies is the reduction of mortality due to OD. In this respect, healthcare services must act alongside RdD services. SerDs are widespread on the territory, covering a significant proportion of consumers (57%), and may therefore have a risk assessment task regarding OD throughout the therapeutic path. They also stand as a naloxone distribution point as well as an information and advice point on its use. Staff who work in these services have the necessary skills to identify subjects most at risk of OD and help them with targeted prevention actions, including providing naloxone. People who are most at risk are for example:

- Poly-consumers (e.g., heroin associated with alcohol and benzodiazepines);
- Subjects who resume heroin use after an abstinence period, particularly after a detoxification therapy or a period in prison.

Consumers' families are an important target group. A primary objective is to take relatives with a drug problem to addiction services. However, family members must also be aware of the OD risk for their loved ones. SerDs have more possibilities than those under RdD to implement educational programmes and deliver naloxone as needed.

The use of therapeutic communities or other residential treatment centres exposes users to the risk of OD due to substantially reduced tolerance at time of discharge. As a result, it is important that service pro-

viders have the necessary skills and tools to deliver impactful information and also provide naloxone as needed.

Prisoners with drug addiction have a high risk of OD events immediately after being released from prison. A targeted action for information and distribution of naloxone when the consumer is at the end of a period of detention is therefore absolutely necessary.

5.2.2. Increase RdD services (the strategic promoters of THN)

Data from the most recent monitoring (i.e., from 2015 [22]) revealed a total of 115 RdD services (35 road units for RdD; 34 outreach actions to limit the risks in the recreational field; 23 drop-ins; the remaining are services of another type). This SBS (Servizi a Bassa Soglia) network is widespread throughout the country but in a very unstructured way, with entire areas of the country where there are no RdD services, including THN. RdD services act close to the drug scene and the natural consumer settings. They also access consumers who are not in contact with the services. As they are completely absorbed in the consumers' world, they are a key figure in promoting and supporting the distribution of naloxone among consumers. The service network should therefore be extended to further increase the chances of favourable OD outcomes.

5.2.3. New players to be involved

Primary care physicians. This network is potentially widespread and with a high level of professional skills. Primary care physicians may be involved either in the prevention of OD through information and counselling or in the distribution of naloxone when their patients (or family members) use opiates.

Pharmacies. As naloxone is included in the 11th official pharmacopoeia table all pharmacies should have it available. Furthermore, as naloxone is an SOP drug, anyone can freely purchase it without a prescription despite being for intravenous administration. Although this was often documented by the media, the non-availability of naloxone in pharmacies stands as an unclear attitude of pharmacists regarding purchase without a prescription. Increased awareness of operators of local pharmacies is therefore necessary. The availability of the intranasal formulation can help to overcome misunderstandings regarding purchase without prescription of naloxone.

The police force. As the police are often at the place where an overdose event has occurred, it would be advisable to provide officers with naloxone and give them the necessary information for appropriate and timely use.

6. Conclusions

It is clear that the epidemic of opioid overdose in Italy is fought not only by distributing naloxone, but also through complex strategies such as education/information campaigns among heroin users, distribution of materials, promotion of behavioural-normalization treatment programmes, etc. It is important to be clear that none of these programmes works against naloxone distribution programmes. Naloxone training programmes could easily be integrated into pre-existing education programmes on overdose or other awareness-raising programmes. Furthermore, the potential benefits from increasing the use of naloxone for OD are significant in terms of lives saved, while the potential social or economic costs are low. In the Italian framework, where the concept of THN is already structured, the nasal spray formulation of naloxone represents an advance in providing a safe and life-saving intervention. Due to its ease of administration and absence of complex or risky medical procedures, the nasal spray formulation represents an opportunity to make existing strategies more effective and to identify new action settings and new stakeholders for inclusion in the operational framework for OD prevention.

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Acknowledgements

None

Role of the funding source

The article was completed independently with no funding. We thank Martin Guppy, an independent medical writer, who helped with English-language editing and journal styling prior to submission, on behalf of Argon Healthcare International. This assistance was funded by Mundipharma Pharmaceuticals Srl, Milano, Italy.

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Conflict of interest

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Received and Accepted December 18, 2018