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"Take home" naloxone: what does the evidence base tell us?

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Abstract

Purpose – *Opiod users are at high risk of suffering from drug overdoses. Naloxone has been used for decades in emergency treatment settings to reverse the symptoms of opioid overdose. Pilot studies and regional programmes have been rolled out to make naloxone more widely available. This review of user/carer administration of naloxone – so-called “take home naloxone” – aims to provide health professionals and interested readers with an up-to-date evidence base, clinical implications and practical concern considerations for such community management. The paper aims to discuss these issues.*

Design/methodology/approach – *A review and analysis of the recent literature on naloxone.*

Findings – *The evidence base suggests training and education is effective in preparing users for wider naloxone distribution. Furthermore, studies of varying quality indicate that naloxone may prove useful in reducing overdose-related deaths. However, even after implementation ineffective response techniques continued to be used at times and there remained a heistance to call medical services post overdose. Intranasal naloxone may reduce some of the risks associated with intramuscular naloxone. Ethical considerations, including provision of a needle and syringe kit to the community, should be considered. Studies suffered from a lack of follow-up data and methodological difficulties are associated with establishing opioid-related deaths post implementation. Two running trials in the UK might mitigate these concerns.*

Research limitations/implications – *Future research is needed to address wider context of an overdose and targeting associated risk factors.*

Originality/value – *Clinicians and other professionals will be informed on the most up-to-date evidence base and which areas are improtant to consider when take-home naloxone is introduced in their services.*

Keywords *Literature review, Intramuscular, Intranasal, Opioids, Overdose prevention programmes, Take-home naloxone*

Paper type *Literature review*

Introduction

In recent years there has been an increase in opioid-related deaths (Office of National Statistics (ONS), 2013; European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2015; Kim *et al.*, 2009), particularly in men between 25 and 39 years of age (Farrell and Marsden, 2005). Risk factors for opioid overdose include poly-drug use, a lack of available treatment options, including access to local drugs services and reduced tolerance after a period of abstinence (United Nations Office on Drugs and Crime (UNODC), 2013), which particularly occurs post-release from prison (Merrall *et al.*, 2010). Data indicate that the most recent rise in opioid-related deaths in the UK can be largely attributed to changes in heroin purity (ONS, 2013); indeed most overdose deaths include opioid use (European Monitoring Centre for Drugs and Drug Addiction, 2014).

An overdose can be recognised by the so-called “opioid overdose triad”, namely pinpoint pupils, unconsciousness and respiratory depression (UNODC, 2013). A person suffering from opioid overdose can die within minutes or experience a period of unresponsiveness that can last several

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hours (UNODC, 2013). Bystanders frequently report identifying a clear difference between what is often referred to as "gouching out" (a period of intermittent inattention and sedation) by users and actual overdoses (Bennett and Holloway, 2012), which are often unintentional (Heale *et al.*, 2003) and associated with depressive episodes (Bartoli *et al.*, 2013). An opioid overdose is seen as an expected and accepted risk associated with drug misuse by many users (Bennett and Holloway, 2012).

Qualitative studies have shown bystanders may be reluctant to use naloxone on users who have overdosed on opiods (Worthington *et al.*, 2006). Reasons include being subject to unwanted police, social work and medical surveillance (Worthington *et al.*, 2006). This may be further amplified by stigma and shame associated with the use of prohibited drugs and intravenous or intramuscular (IM) administration. These factors may make it more difficult for users to receive help and for bystanders to provide adequate support.

Naloxone is an opioid antagonist, which targets μ-opioid receptors and thus, upon use, rapidly reverses opioid binding (including overdosing) and induces withdrawal symptoms; it has no potential for abuse or overdose (Hoffman and Goldfrank, 1995). Naloxone has been routinely used for decades in emergency treatment to reverse the effects of an opioid overdose (Maxwell *et al.*, 2006). More recently, there have been advances in the development of "take-home kits" for heroin users that provide either nasal (called IN or intranasal) or injectable naloxone for self-administration/administration by another, with clear lifesaving potential in instances of overdose.

In the last years, there has been an increased interest in the USA, UK and elsewhere in administering naloxone via a needleless system, namely, the IN route. An added benefit of the use of IN is that it eliminates the risk of needle stick injuries and contracting blood-borne diseases among those administering naloxone using IM injection (Barton *et al.*, 2005).

In terms of efficacy, both IN and IM routes of administration have been shown to be effective in reversing an opioid overdose. However, a study has shown that the time from dose administration to clinical response for naloxone was longer for the IN route, but the overall time from patient contact to response was the same for the IV and IN routes (Robertson *et al.*, 2009). Given the difficulty and potential hazards in obtaining IV access in many patients with narcotic overdose, IN naloxone combined with training appears to be a useful and potentially safer alternative (Walley *et al.*, 2013; Doe-Simkins *et al.*, 2009; Robertson *et al.*, 2009; Kelly *et al.*, 2005).

Several pilot studies in the USA and Europe have evaluated wider access to naloxone; in light of nascent positive findings naloxone was added to the UK list of available injectable drugs (Article 7 of the Medicines Act) in 2005. This allowed naloxone administration by anyone – including those without medical training – in order to save a life in an emergency. However, naloxone continued to be a prescription drug only, which meant that it could only be prescribed directly to a named individual by a medical professional in IM form (Public Health England (PHE), 2015). Another option for naloxone prescription in non-medical settings is via Patient Group Direction, although this option is rarely used due to difficulties with establishing a full list of named individuals to whom to prescribe to (PHE, 2015; Advisory Council on the Misuse of Drugs, 2012). In 2011, legislative changes allowed naloxone to be prescribed by approved services without prescription in Scotland. From October 2015 further legislative changes will occur in England exempting it from prescription-only requirements when it is supplied by a drug service commissioned by a local authority or National Health Service (NHS) (PHE, 2015). As a result, naloxone is more likely to become a common place treatment in substance misuse services in England. However, it may take time before the effect of the legislative change will become evident. Even though studies support scale-up of access to naloxone, it may continue to be challenging to gain access to naloxone in the community (Wermeling, 2013), this would be largely attributable to the current prescription-only offering of naloxone.

This review aims to provide an overview for professionals and interested readers to consider the most recent evidence base on naloxone community programmes, the respective findings and impact of published studies for future implementation of programmes, and use of naloxone in the community. The review will commence by reviewing several aspects of the evidence base including reducing opioid overdose deaths, follow-up data and the effectiveness of training and education. Expected implications of wider availability of take-home naloxone in the community will be further evaluated thereafter.

Evidence base on take-home naloxone

The outcomes of the implementation of community naloxone prescription have been classified by the European Monitoring Centre for Drugs and Drug Addiction into the following categories: first, knowledge of opioid overdose and naloxone administration; second, attitudes towards naloxone; third, overdose management; fourth, naloxone administration; and fifth, reducing deaths due to overdose (EMCDDA, 2015). The following paragraphs will provide further detail on the evidence base classified by the EMCDDA (2015) from both the USA and UK. Other factors to consider are the differences in the nature of opioid use and overdose accross cultures, countries and regions. For instance, there is a difference between rural and urban overdoses. Heroin is most often associated with overdoses in large metropolitan cities. In rural regions, prescription medication is implicated in overdose (Westermeyer, 2004; Wermeling, 2013). Research on cross-country comparisons on patterns in opioid overdose is scant however it remains important to consider differences in prescribing practices and cultural differences in studies listed. Inherently, differences between regions would require differences in interventions.

Opioid overdose-related deaths: cause and effect?

There are various challenges associated with establishing the effectiveness of naloxone implementation and whether implementation leads to an actual reduction of opioid-related deaths or "lives saved". The majority of studies found a reduction in opioid-related deaths post naloxone programme implementation by evaluating opioid-related death records (Paone *et al.*, 2011; Enteen *et al.*, 2010). However, non-significant results after implementation of naloxone were found in the "National naloxone Programme" in Scotland (Watt *et al.*, 2014), which was carried out both in the community and in prisons. The baseline indicator of opioid overdose deaths was the time period 2006-2010; the supply of "take-home" naloxone kits was 1,461 from June 2011 until June 2013. The first results showed that there was no significant decrease in opioid-related deaths within four weeks of prison release in 2011 (8.4 per cent) compared to the 2006-2010 baseline indicator (9.8 per cent). However, there are inherent complexities associated with establishing cause and effect by monitoring pre-post death records (Clark *et al.*, 2014). Confounding variables such as other improvements in services or changes in population may affect the outcomes. Furthermore, the outcome measured, opioid-related deaths in the community can be a result of various factors hence it may not be possible to establish a direct cause and effect link.

A well-designed interrupted time series (ITS) study from the USA (Walley *et al.*, 2013), established a significant reduction in opioid deaths compared to comparison communities where no naloxone training and education programme was implemented. When a sample of over 2,900 individuals was trained across 19 communities and followed up over seven years, 327 rescues were reported. ITS can help control for secular trends, and thus strengthen outcome data. It was found that programmes associated with a higher cumulative rate of training and provision of opioid overdose education and nasal naloxone distribution are in turn further linked with a reduction in deaths. Currently, evaluating the best evidence, it cannot be unequivocally proved that the programme reduces opioid-related deaths; overall data are few in number, and, as noted methodologically hampered by the lack of a double blind randomised-controlled trial (RCT) to establish (or refute) causal associations (Clark *et al.*, 2014). Only Walley *et al.* (2013) has established a methodologically sound reduction.

Current trials

Two RCTs are currently rolled-out in England and Wales. The N-ALIVE trial, which was launched in early 2012 and operates in England and Wales will provide further information into the effectiveness of naloxone when distributed to prisoners on release (Strang *et al.*, 2013). The N-ALIVE project involves two phases; the first is a pilot that aims to demonstrate the feasibility of the project by recruiting 5,600 prisoners who have a history of injecting heroin and have served at least seven days in prison; a sub-study will collect additional qualitative information. The trial will assess heroin use and overdoses within four to 12 weeks of release. The second phase, with a

target participant pool of 56,000 will aim to test the effectiveness of giving naloxone-on-release and assessing whether naloxone will reduce overdose deaths. The study will follow participants over 12 weeks and consenting prisoners will be randomised to receive either a pack containing a single dose of naloxone or a control pack containing no naloxone. The large size of the study, and its robust methodology mean that its results are highly anticipated.

The Paramedic Administered Take Home Kits: feasible intervention for naloxone distribution in emergency response (PATHFINDER) study, a cluster randomised trial in Wales will provide further useful results on the feasibility of naloxone provision to opioid users by randomised groups (clusters) of paramedics (Moore *et al.*, 2014). Paramedics will be randomly allocated to specific training or practice as usual; patients who had an overdose and are treated by paramedics who have received the specific training will be issued take home naloxone kits and constitute the active intervention group. Participants will be followed-up at three months and death-records will be analysed with ITS analysis. The trial began in November 2012 and was initially due to last one year; the trial is now due to end in November 2015. It is not currently clear why the delay has occurred.

Community outcomes at follow-up

A second avenue to establish outcomes is to assess outcomes of naloxone kits at follow up. A return to services for another set of naloxone, which is also known as refill, provides a useful opportunity to establish follow-up data. The evidence base is limited by high attrition rates at follow-up in a majority of studies on naloxone (Clark *et al.*, 2014). Often drug users may disappear "off the radar", which makes it difficult to establish outcomes. The resulting response bias could lead to over or under reporting of community outcomes (Clark *et al.*, 2014).

Even though follow up figures from naloxone studies vary between 5 and 88 per cent (Clark *et al.*, 2014), reasons for refill are largely consistent across studies. The main reasons for refill, based on follow-up data are loss, use of naloxone kit, expiry and confiscation by the police. A study by Enteen *et al.* (2010) on 1,942 prescriptions found 24 per cent return for refill of which 12 per cent returned more than once. Reasons for refill were: use of naloxone to reverse overdose (40 per cent); loss of naloxone (49 per cent); and 12 per cent reported confiscation by police upon admission to jail. Of those participants who lost naloxone, 27 per cent reported that they also used naloxone in response to a subsequent overdose event. Overall, 11 per cent of all participants reported using naloxone during an overdose event, and 5 per cent reported using multiple prescriptions (refills) during more than one overdose event.

Similarly, Bennett *et al.* (2011) trained 426 individuals and 141 participants returned for refill between 2005 and 2008. The average time to return for a new kit of naloxone was 9.6 months. The majority, 63 per cent (89) reported to have administered naloxone in response to an overdose. These 89 individuals reported administrating naloxone in 249 separate overdoses, in 96 per cent of these situations, the overdose was reversed, in 3.2 per cent the outcome was unknown, and in two cases the person died. In addition, of the 52 others who returned for a refill but did not use it, reasons for returning were: naloxone being lost (48.1 per cent), confiscated by police (12 per cent), stolen (4 per cent), expired or other reasons (37 per cent). An interesting finding was that a small sample (3.4 per cent) of those who returned for refill did so ten to 24 times. This could imply that drug use communities have several well-connected members who could provide a future pivotal role in overdose education and naloxone provision programmes (Bennett *et al.*, 2011).

Structural reasons for a lack of refill returns may be a lack of funding and insufficient reporting systems (Yokell, 2011). A suggested evaluation framework by Clark *et al.* (2014) may prove useful in further establishing follow-up outcomes. For instance, this model noted the potential inclusion of the opioid overdose knowledge and attitudes scale for take home training evaluation, these are valid and reliable measures to assess knowledge and attitudes around opioid use, and have been used to measure the effectiveness of naloxone training (Williams *et al.*, 2013, 2014).

The wider impact of training and education

Various studies show that naloxone training can be beneficial in improving knowledge of effective techniques in overdose in varying population groups. This has recently been confirmed by two

systematic literature reviews on naloxone provision in the community (EMCDDA, 2015; Clark *et al.*, 2014). Clark *et al.* (2014) published the first systematic literature review on community-based opioid overdose prevention programmes (OOPS) including naloxone distribution. In this review of 19 studies the findings were largely positive with regards to the effectiveness of training; programmes in the community to manage opioid overdose were demonstrated to be effective in improving knowledge of prevention and risk factors of overdose. OOPS also improved overall capabilities to reverse opioid overdose with naloxone. One year later, the EMCDDA (2015) published a systematic review on 22 studies including one RCT. This found that there is consistent evidence that education and training is effective in improving knowledge and attitudes on the correct use of naloxone and management of witnessed overdose, but that the degree of change was often limited. In 2009 the National Treatment Agency for Substance Misuse (NTA, 2011) which became part of Public Health England in April 2013, launched a training programme in 16 pilot sites in the UK to train family and carers of opiate users ($n = 495$). Following training, carers used naloxone in 18 overdose events (although the naloxone was supplied to someone other than the individual listed on the prescription) and two applied basic life support. Many carers self-reported that the training clarified how to respond to an overdose and parents noted that they felt empowered and more confident. Parents also reported they felt a sense of control over their child's use and felt able to intervene in an overdose, whereas previously they felt powerless. The final conclusion indicated that training was effective but that training plus naloxone provision might yield a higher impact on overall fatal and non-fatal overdose rates.

Williams *et al.* (2014) published the first RCT on naloxone training in 2014. A non-blinded RCT with 123 participants comparing group-based training to an information only control group in the community found significant improvements on opioid overdose knowledge and attitudes towards overdose. At a three-month follow-up, naloxone was administered eights times. In sum, opioid overdose training was effective in enhancing skills and actions in case of an overdose compared to providing information only.

A promising avenue to further implement training may be to start with support groups for families of people using opioids, as research has found that members are motivated and willing to use naloxone training to save people when an overdose is witnessed (Bagley *et al.*, 2015). Training intensity can be brief if the audience has a high level of baseline knowledge with regards to opioid use and opioid overdoses. A study by Behar *et al.* (2015) found that a five to ten minute educational session combined with trial use of naloxone significantly improved outcomes for first-time recipients of IN naloxone. Wider provision of naloxone in England would need additional training, as baseline knowledge levels may be lower than levels of other opioid users.

A high variability in the use of techniques after training has been found in previous studies. For instance, even after training people may continue to use inappropriate strategies including pouring ice water on individuals who have overdosed (Clark *et al.*, 2014). This might be due to differences in effectiveness of training modules (Clark *et al.*, 2014). This raises the point that more adverse events are likely to occur when naloxone is administered by untrained people who may potentially be opioid intoxicated themselves. Byrne (2006) suggested that better training on resuscitation for family and friends of drug users may be more logical as early overdoses infrequently require naloxone. Furthermore, training evaluations including the trial by Williams *et al.* (2014) are pivotal in further establishing effective training methods for bystanders in the community.

Clinical implications: weighing cost and benefit

Although research has shown that naloxone provision can be effective in reducing opioid-related deaths and follow-up data shows promising results, various complications may occur when introducing take home naloxone to members of the community. There may be a small risk of serious cardiac complications after naloxone administration; the NHS in England has published an alert on inappropriate doses and risk of death by using naloxone in rare cases (PHE, 2015).

Furthermore, it has been reported that there is a level of stigma associated with carrying around a naloxone kit including a needle and syringe. Often users reported they would leave their kit at

home, which may limit the use in other life threatening situations outside of a home environment (Gaston *et al.*, 2009). Other administration methods, including IN naloxone, might mitigate the associated stigma related to carrying a needle and syringe kit.

UNODC (2013) highlighted various other risks associated with naloxone distribution in the community. This relates in particular to IM naloxone overdose kits, which include a needle and syringe. If given to people without training, this may lead to harm. Risks include unsterile injection or damage to skin (UNODC, 2013). Other substances, such as benzodiazepines may be added, to dilute or negate the effectiveness of naloxone (Gould, 2009). Inherently, providing a needle and syringe to families may yield concerns. Child protection may be another area to consider as the kit may form a potential risk and should always be stowed away from children (UNODC, 2013). IN provision would alleviate these risks and a RCT study has shown that there are minimal differences in the effectiveness of IN vs IM administration of naloxone (Kelly *et al.*, 2005). Currently, only IM take-home naloxone kits are available in England (PHE, 2015), thus if deemed feasible, introducing IN naloxone may be an area for future consideration.

A common criticism of naloxone distribution is that it will encourage injecting drug users to use more heroin to off-set the withdrawal (Maxwell *et al.*, 2006) and create a false sense of security and encourage users to use dangerous amounts (Gaston *et al.*, 2009). If naloxone is used in an overdose it can incite immediate opioid withdrawal symptoms seen in detoxification with some naloxone receivers citing it as "the worst feeling in the world" (Worthington *et al.*, 2006). McKegany (2011 cited in Travis, 2011) stated "There is a real possibility that some addicts will be prepared to use higher dosages of heroin, confident that they can reverse the effects if they need to". Although there is a lack of quantitative data to confirm this hypothesis, initial qualitative research shows that this proposition may hold true. Worthington *et al.* (2006) held focus groups with 13 opiate users to examine knowledge about overdose and its prevention, specifically naloxone. Participants affirmed that if naloxone was ever used on them they would have no option but to use more opiates in order to ease the discomfort. The authors note that, because naloxone only lasts for 30 minutes, using additional opiates increases the chance of a subsequent overdose when the naloxone wears off.

Many users remain reluctant to call for an ambulance. Seal *et al.* (2003) surveyed 82 street drug users to assess use and attitude towards naloxone. A majority of users were positive about receiving training and take-home naloxone and 51 per cent reported calling emergency assistance for the last overdose observed; however, 35 per cent expected that they might use higher dosages of heroin as a result, if they were given naloxone and training. Furthermore, 62 per cent of the sample predicted being less inclined to call an ambulance. One-third indicated that they might leave the victim after resuscitation with naloxone and nearly half (46 per cent) indicated that they might not be able to prevent the victim from using more heroin to alleviate symptoms.

Users have identified that naloxone should be part of a wider approach to reduce opioid-related deaths (Bennett and Holloway, 2012). Indeed, other approaches including provision of overdose education and teaching effective response techniques have been found effective and useful by users (Bennett and Holloway, 2012). Targeting specific risk factors associated with overdose can reduce the risk of non-fatal overdose. Kinner *et al.* (2012) found that more frequent drug use and more risky patterns of drug use are modifiable risk factors that can reduce the risk non-fatal overdose. For example, the suggestions of Farrell and Marsden (2005), which include timely identification and treatment, targeting of high risk individuals, provision of educational interventions and awareness training and providing opioid agonist maintenance alongside other therapeutic interventions may be equally important in reducing overdose-related deaths (Farrell and Marsden, 2005).

Besides administering naloxone and providing naloxone programmers other interventions that aim to reduce the risk of overdose should continue to be explored. Factors such as training, continuity of care (Leach and Oliver, 2011), multi-agency working (McMurran, 2007), and psycho-education for family and friends in appropriate response techniques (McMurran, 2007) may be similarly important. In order to reduce the number of overdoses on release it may also be necessary to assess the wider context of a client, including the factors which lead to drug use, and targeting these risk factors.

Future research should also look at how relevant aspects of aftercare differentially help prevent an overdose from recurring. The current research has focused to date on opiate users. However, there has recently been an increase in drug-related deaths among users of new psychoactive substances (Baumeister *et al.*, 2015). Attention should also be paid to the less common drugs implicated in overdose.

Conclusions

Although naloxone training and provision programmes are supported by a body of evidence and wider provision dominates and reflects the majority of the debate, the current literature incompletely accounts for the complexities surrounding naloxone prescription and administration. Treatment data shows consistent improvements in the knowledge and management of opioid overdoses. However, "hard" outcomes which include the number of lives saved are difficult to establish. Comparing data from the existing scientific literature is hindered by considerably differing programmes and methodology that vary widely with regard to the assessment of outcome measures, follow-up period, participant selection and training provided. Future administration methods, such as nasal administration of naloxone may prove useful in reducing some of the risks associated with IM naloxone.

Furthermore, non-specialist, user-led initiatives have shown to be highly effective in providing wider access to naloxone in the community. In order for such programmes to be fully effective, current barriers to wider access need to be resolved. This includes further training of non-medical professionals and training the public in overdose response techniques. Creating wider awareness of naloxone within the police, by providing training, would be useful in order to reduce confiscation of naloxone kits. This might improve efficacy of future trials. Further research is needed to assess which barriers are currently limiting access to naloxone and what the effects of the change in current legislation will be on the reduction in fatal opioid overdoses.

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