National Addiction Centre

Institute of Psychiatry at The Maudsley

KING'S College LONDON

Take-Home naloxone: developments and futures

John Strang & Rebecca McDonald

National Addiction Centre, King's College London, UK

KING'S HEALTH PARTNERS

Pioneering better health for all

Overall message

- Proud of what we have achieved
- Humble about how much more we need to do

Declarations - JS (personal & institutional)

- NHS provider (community & in-patient); also Phoenix House, Lifeline, Clouds House, KCA (Kent Council on Addictions).
- Dept of Health, NTA, Home Office, NACD, EMCDDA, WHO, UNODC, NIDA.
- Dialogue and work with pharmaceutical companies re actual or potential development of new medicines for use in the addiction treatment field (incl re naloxone products), including (past 3 years) Martindale, Indivior, Mundipharma, Braeburn/Camurus and trial product supply from iGen and Braeburn.
- SSA (Society for the Study of Addiction); UKDPC (UK Drug Policy Commission), and two Masters degrees (taught MSc and IPAS) and an Addictions MOOC.
- Work also with several charities (and received support) including Action on Addiction, J Paul Getty Charitable Trust (JPGT) and Pilgrim Trust.
- The university (King's College London) has registered intellectual property on a buccal naloxone formulation, and JS has been named in a patent registration by a Pharma company as inventor of a novel concentrated naloxone nasal spray.
- Lecture includes data and analyses from collaboration with Pharma.

Declarations - RMcD

- RM has undertaken an unpaid student industry placement with Mundipharma Research Ltd., with focus on the analysis of naloxone nasal spray formulations.

- King's College London has separately applied to register intellectual property on a novel buccal naloxone formulation with which JS and RM are involved.

- RM & JS have worked as consultants for the United Nations (UNODC) and World Health Organization (WHO), supporting a naloxone study in Central Asia.

Structure of lecture

1. Lack of concept
2. Lack of easy product
3. Licencing of products?
4. Improvising nasal naloxone
5. Developing formal naloxone nasal sprays
6. Regulatory and price barriers
7. Attitude problems

Structure of lecture

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First serious consideration:
Strang J, Darke S, Hall W, Farrell M & Ali R (1996)
Heroin overdose: the case for take-home naloxone. *British Medical Journal*, 312: 1435.

(1996)

*** important achievements, but so slow, so very slow ***

Heroin overdose: the case for take-home naloxone

Home based supplies of naloxone would save lives

Non-fatal overdose is an occupational risk of heroin misuse[1] and fatal overdose is a common cause of premature death in heroin users.[2-4] One of the major contributors to a fatal outcome is the inadequacy of heroin users' responses to the overdoses of their peers. They may delay calling an ambulance for fear of the police arriving, and their efforts to revive comatose users are often ineffective. The distribution of naloxone to opiate users was first mooted in 1992[5] as an intervention that would be life saving in such situations.[6] With a rising toll of deaths from heroin overdose it is time to take the suggestion seriously.

Interviews with 320 heroin users in Sydney found that two thirds had had a drug overdose, a third within the past year, and that 80% had been present at the overdose of another user.[7] In Australia the incidence of deaths from heroin overdose has increased over the past decade while deaths from other drug related causes have fallen. In the United Kingdom a sharp increase in the numbers of deaths among opiate users has recently been reported from Glasgow.[8]

Naloxone has a long established use in emergency resuscitation of patients with opiate overdose.[9] Such a tried and tested

even greater risk if further opiates have been used in the interim).[15] A black market in naloxone might develop if opiate misusers wanted to protect themselves from overdoses: in such a case, however, the drug would be used for its intended purpose, and the black market would simply circumvent inequalities in access to the drug.

If naloxone were to be provided to opiate misusers for emergency resuscitation it would need some modification. The onset of many overdoses is too sudden to allow time for the victim to open an ampoule, draw up the contents, and inject himself or herself. The drug might be better provided in a disposable preloaded syringe, though such a form of delivery would increase its cost. Attention would also need to be paid to the shelf life of a product which would be kept for emergencies—though even reduced potency naloxone may still be life saving.

Further issues are raised by the possibility of naloxone being administered by third parties, such as friends or family members, or its use to resuscitate a person who had not been prescribed the drug. Lifesaving applications may include administration of home based emergency naloxone to a child

Two separate levels of naloxone advocacy

- The activist movement, civilian action, and assertion of legitimacy of take-home naloxone
- The adoption and incorporation by policymakers and health professionals of take-home naloxone as permitted and required action
- *Different decisions on way forward ??*

BMJ
British Medical Journal

Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes

Kerstin Dettmer, Bill Saunders, John Strang

(2001)

Doctors routinely give naloxone during emergency resuscitation after opiate overdose. The distribution of naloxone to opiate addicts has recently been addressed,[1–4] and a survey of drug users shows extensive support for the provision of supplies to take away.[4] We present the preliminary results of two pilot schemes to provide take home naloxone to opiate users.

Methods and results

The Berlin project

In January 1999 drug users in Berlin were given naloxone to take home. Opiate misusers attending a healthcare project (operating from a mobile van or ambulance) were offered training in emergency resuscitation after overdose, provided with naloxone (two 400 µg ampoules), needles, syringes, an emergency handbook, and information on naloxone. They were asked to report on any use of the drug. After 16 months, 124 opiate misusers had received training in resuscitation and were provided with supplies of naloxone to take away; 40 reported back, with 22 having given emergency naloxone (two on two occasions, one on three, and one on four).

The methods of administration were diverse.

Case 1 (Berlin)

"Three days ago, I was walking along the canal with a friend of mine. We saw a guy lying on the ground, with two people trying to help him—they were trying to help him breathe by mouth to mouth. When we ran over to them, we could tell it wasn't really working. The guy was blue in the face and hardly breathing any more. I could barely feel his pulse. Right away I gave him one ampoule of naloxone—I didn't think I could find a vein so I just shot it real slow into his upper arm. 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, he wanted to give me 50 Marks, but I wouldn't take it. 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." The ambulance staff then took the overdose victim to hospital for further observation.

The Jersey project

From October 1998 over the next 16 months naloxone (one minijet ready filled with 800 µg naloxone) was provided to 101 drug misusers in contact with local

(2009-11)

"Pilot sites trained the carers and relations of opiate misusers to respond to overdoses and use the antidote naloxone. This appears to have helped save lives..."

THE NTA OVERDOSE AND NALOXONE TRAINING PROGRAMME FOR FAMILIES AND CARERS

NHS
National Treatment Agency
for Substance Misuse

ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

REVIEW

doi:10.1111/add.13326

Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria

Rebecca McDonald & John Strang

National Addiction Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

ABSTRACT

Background and Aims Fatal outcome of opioid overdose, once detected, is preventable through timely administration of the antidote naloxone. Take-home naloxone provision directly to opioid users for emergency use has been implemented recently in more than 15 countries worldwide, albeit mainly as pilot schemes and without formal evaluation. This systematic review assesses the effectiveness of take-home naloxone, with two specific aims: (1) to study the impact of take-home naloxone distribution on overdose-related mortality; and (2) to assess the safety of take-home naloxone in terms of adverse events. **Methods** PubMed, MEDLINE and PsychINFO were searched for English-language peer-reviewed publications (randomized or observational trials) using the Boolean search query: (opioid OR opiate) AND overdose AND prevention. Evidence was evaluated using the nine Bradford Hill criteria for causation, devised to assess a potential causal relationship between public health interventions and clinical outcomes when only observational data are available. **Results** A total of 1397 records (1164 after removal of duplicates) were retrieved, with 22 observational studies meeting eligibility criteria. Due to variability in size and quality of the included studies, meta-analysis was dismissed in favour of narrative synthesis. From eligible studies, we found take-home naloxone met all nine Bradford Hill criteria. The additional five World Health Organization criteria were all either met partially (two) or fully (three). Even with take-home naloxone administration, fatal outcome was reported in one in 123 overdose cases (0.8%; 95% confidence interval = 0.4, 1.2). **Conclusions** Take-home naloxone programmes are found to reduce overdose mortality among programme participants and in the community and have a low rate of adverse events.

(2014)

Community management of opioid overdose

Recommendation

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.

World Health Organization

UNODC
United Nations Office on Drugs and Crime

World Health Organization

THE S-O-S-INITIATIVE

Stop Overdose Safely

UNODC-WHO Multi-site study on community management of opioid overdose, including emergency naloxone

AUTHORS: Gabriele Aiello (UNODC), Anja Busse (UNODC), Giovanna Campello (UNODC), Nicolas Clark (WHO), Christina Gamboa Riano (UNODC), Gilberto Gerra (UNODC), Wataru Kashino (UNODC), Dzmitry Krupchanka (WHO), Rebecca McDonald (King's College London), Vladimir Poznyak (WHO), Elizabeth Saenz (UNODC), John Strang (King's College London)

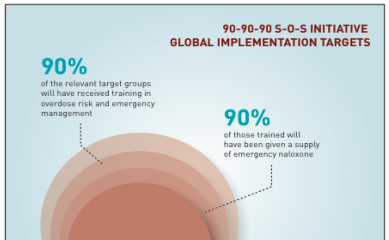
CONTACT: For further information on the S-O-S Initiative and for countries interested in joining the study with their own resources, please contact:

Vienna International Centre, P.O. Box 500, 1400 Vienna, Austria
Tel:+(43-1) 26060-0, Fax:+(43-1) 26060-5866, www.unodc.org,
Contact: treatnet@unodc.org

Department of Mental Health and Substance Abuse
20 Avenue Appia, CH-1211 Geneva 27, Switzerland
Contact: msb@who.int

The S-O-S Initiative, promoting the expanded community management of opioid overdose, was launched by the United Nations Office on Drugs and Crime (UNODC) and the World Health Organization (WHO) at the Commission of Narcotic Drugs (CND) 2017.[1] In line with the WHO (2014) guidelines on "Community Management of Opioid Overdose", this initiative aims to save lives by promoting access to naloxone and training of potential first responders (including peers and family members) in overdose management.

United Nations Member States and other stakeholders are encouraged to work towards universal coverage of opioid overdose management strategies including naloxone, as outlined in the following three targets:



The initiative was developed within the framework of the UNODC-WHO Programme on Drug Dependence Treatment and Care (UNODC project GLOK32), which aims to promote and support, with a particular focus on low- and middle-income countries, evidence-based and ethical treatment policies, strategies and interventions to reduce the health and social burden caused by drug use and dependence.

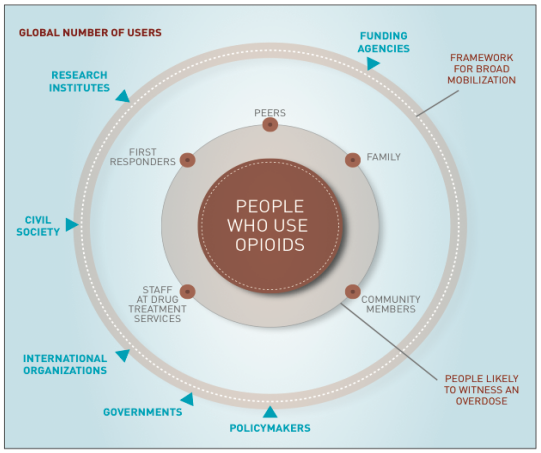
A number of high-level, international policy documents provide the global policy framework for this initiative:

- The Sustainable Development Goal (SDG) 3, Target 3.5: "Strengthen the prevention and treatment of substance abuse"
- Outcome Document of the 2016 United Nations General Assembly Special Session on the World Drug Problem (2016)
- Commission on Narcotic Drugs (CND) resolution 55/7 on "Promoting measures to prevent drug overdose, in particular opioid overdose" (2012)

The technical foundation for this initiative is defined by the following UNODC and WHO documents:

- WHO Guideline Community management of opioid overdose (2014)
- UNODC-WHO discussion paper "Opioid Overdose: Preventing and Reducing Opioid Overdose Mortality" (2013)
- UNODC-WHO International Standards for the Treatment of Drug Use Disorders (2016)
- WHO Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence (2009)

Under the umbrella of the UNODC-WHO Programme on Drug Dependence Treatment and Care and the S-O-S initiative, a UNODC-WHO Multi-site study on community management of opioid overdose, including emergency naloxone, is currently being developed and key elements of the study protocol are presented here.



This initiative aims to support Member States in their efforts to develop policy and legal frameworks for the community management of overdose approach. Moreover, it encourages broad partnerships between national governments, regional organizations, research institutes, civil society, interested funding agencies and other entities to work towards the 90-90-90 targets.

A further aim of this initiative is to mobilize and support people likely to witness an overdose in the community, with particular focus on people who use drugs, peers, as well as family members. The ultimate goal is to contribute towards reducing deaths due to preventable opioid overdose.

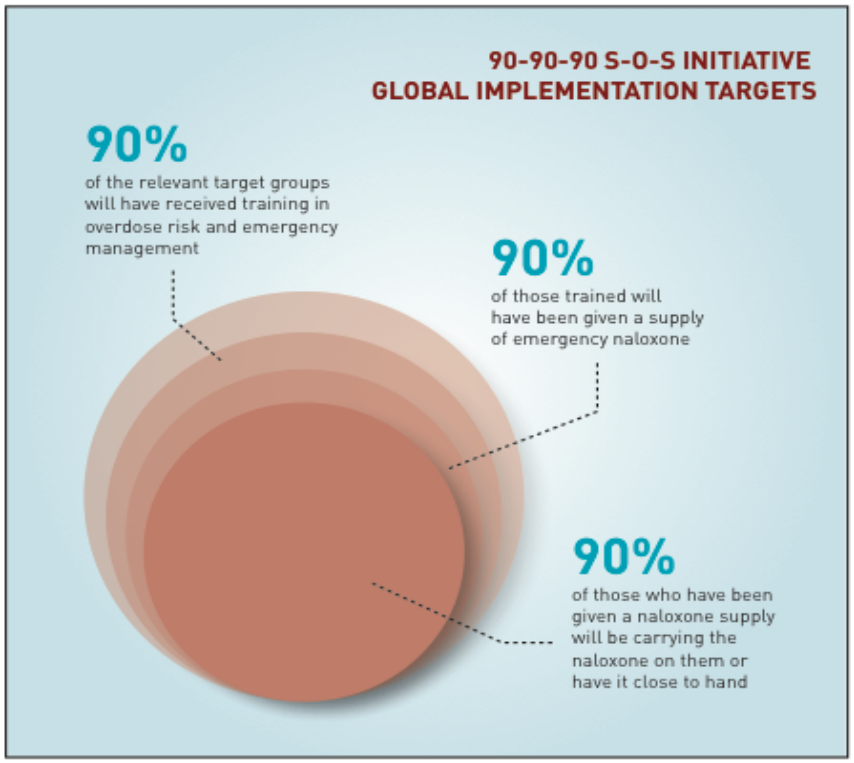
THE FACTS

Drug use and drug use disorders are a public health, developmental and security problem both in industrialized and developing countries. Drug disorders are associated with health problems, poverty, violence, criminal behaviour and social exclusion. Prevention and treatment of drug use disorders are essential demand reduction strategies of significant public health importance. Opioid use disorders and drug-related deaths, often from opioid overdose, are of concern in many parts of the world.

! With an estimated 207,400 drug-related deaths in 2014, corresponding to 43.5 deaths per million people aged 15-64, the number of drug-related deaths worldwide is unacceptably high, yet has remained relatively stable, although with significant variations in some jurisdictions.

! Preventable overdose deaths contribute to between roughly a third to a half of all drug-related deaths, which are attributable in most cases to opioids, even though it is known that treatment of opioid dependence especially with long acting opioid agonists reduces the risk of

following three targets:



- WHO Guidelines for the Psychosocially
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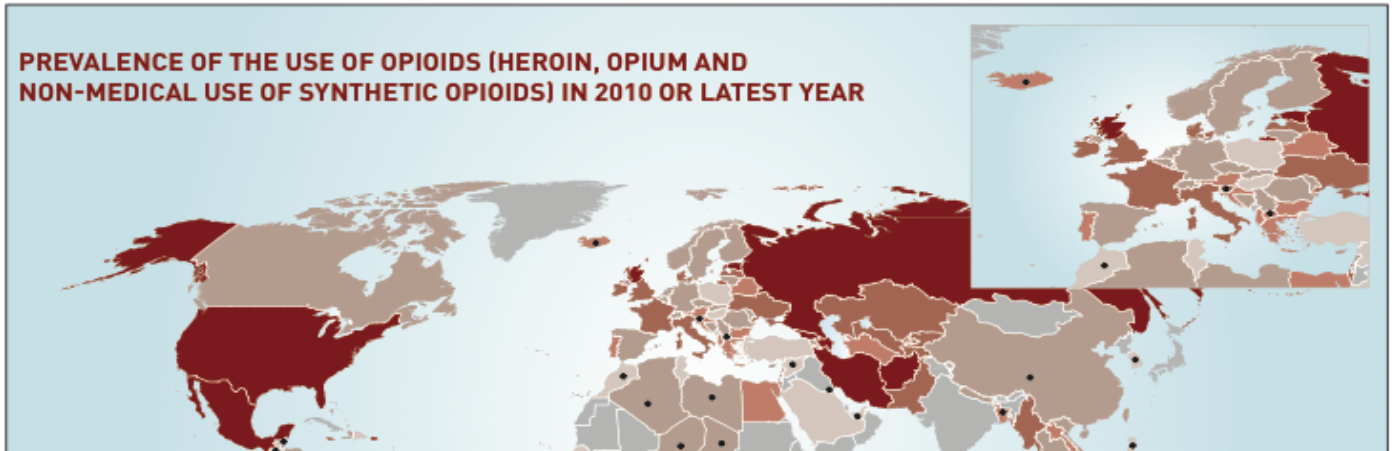

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- Different significance in different countries

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Population Pharmacokinetics of Intravenous, Intramuscular, and Intranasal Naloxone in Human Volunteers

Jonathonm Dowling, Geoffrey K. Isbister,†‡¶ Carl M. J. Kirkpatrick,‡ Daya Naidoo,§ and Andis Graudins*‖*

Abstract: To investigate the pharmacokinetics of naloxone in healthy volunteers, we undertook an open-label crossover study in which six male volunteers received naloxone on five occasions: intravenous (0.8 mg), intramuscular (0.8 mg), intranasal (0.8 mg), intravenous (2 mg), and intranasal (2 mg). Samples were collected for 4 hours after administration for 128 samples in total. A population pharmacokinetic analysis was undertaken using NONMEM. The data were best described by a three-compartment model with first-order absorption for intramuscular and intranasal administration, between-subject variability on clearance and central volume, lean body weight on clearance, and weight on central volume. Relative bioavailability of intramuscular and intranasal naloxone was 36% and 4%, respectively. The final parameter estimates were clearance, 91 L/hr; central volume, 2.87 L; first peripheral compartment volume, 1.49 L, second peripheral compartment volume, 33.6 L; first intercompartmental clearance, 5.66

with opioid poisoning requiring naloxone therapy are often difficult to cannulate as a result of previous intravenous substance abuse. This may delay the administration of antidote therapy. Intravenous drug abusers are also at increased risk of carrying bloodborne infections that could be transmitted to healthcare workers through needlestick injuries.[1] The half-life of naloxone is significantly shorter than most of the opioid agents, so its duration of action is shorter than that of most opioid agents. Patients may awaken from opioid toxicity and want to remove themselves from medical care when there is the risk of recurrence of opioid toxicity after the effects of naloxone wear off. This is a particular concern with long-acting opioids such as methadone and has prompted the use of a combination of intravenous and intramuscular naloxone in the field to prolong its duration of action. However, this approach is not evidence-based or based on an understanding

Drug and Alcohol REVIEW

APSAD

Drug and Alcohol Review (2017)
DOI: 10.1111/dar.12571

COMPREHENSIVE REVIEW

International patent applications for non-injectable naloxone for opioid overdose reversal: Exploratory search and retrieve analysis of the PatentScope database

REBECCA McDONALD[1]*, ØYVIND DANIELSSON GLENDE[2,3]*, OLA DALE[2,4] & JOHN STRANG[1,5]

[1]*National Addiction Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK,* [2]*Department of Circulation and Medical Imaging, NTNU-The Norwegian University of Science and Technology, Trondheim, Norway,* [3]*Apotek 1 Nardo, Trondheim, Norway,* [4]*St. Olav's Hospital, University Hospital of Trondheim, Trondheim, Norway, and* [5]*South London and Maudsley NHS Foundation Trust, London, UK*

Abstract

Issues. *Non-injectable naloxone formulations are being developed for opioid overdose reversal, but only limited data have been published in the peer-reviewed domain. Through examination of a hitherto-unsearched database, we expand public knowledge of non-injectable formulations, tracing their development and novelty, with the aim to describe and compare their pharmacokinetic properties.* ***Approach.*** *(i) The PatentScope database of the World Intellectual Property Organization was searched for relevant English-language patent applications; (ii) Pharmacokinetic data were extracted, collated and analysed; (iii) PubMed was searched using Boolean search query '(nasal OR intranasal OR nose OR buccal OR sublingual) AND naloxone AND pharmacokinetics'.* ***Key Findings.*** *Five hundred and twenty-two PatentScope and 56 PubMed records were identified: three published international patent applications and five peer-reviewed papers were eligible. Pharmacokinetic data were available for intranasal, sublingual, and reference routes. Highly concentrated formulations (10–40 mg mL^{-1}) had been developed and tested. Sublingual bioavailability was very low (1%; relative to intravenous). Non-concentrated intranasal spray (1 mg mL^{-1}; 1 mL per nostril) had low bioavailability (11%). Concentrated intranasal formulations (≥10 mg mL^{-1}) had bioavailability of 21–42% (relative to intravenous) and 26–57% (relative to intramuscular), with peak concentrations (dose-adjusted C_{max} = 0.8–1.7 ng mL^{-1}) reached in 19–30 min (t_{max}).* ***Implications.*** *Exploratory analysis identified intranasal bioavailability as associated positively with dose*

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Identification of non-injectable routes

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

Naloxone without the needle – systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal

John Strang[a,*,1], Rebecca McDonald[a,1], Abdulmalik Alqurshi[b], Paul Royall[b], David Taylor[b,c], Ben Forbes[b]

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Nasal
Buccal
Sublingual

ABSTRACT

Introduction: Deaths from opioid overdose can be prevented through administration of the antagonist naloxone, which has been licensed for injection since the 1970s. To support wider availability of naloxone in community settings, novel non-injectable naloxone formulations are being developed, suitable for emergency use by non-medical personnel.

Objectives: 1) Identify candidate routes of injection-free naloxone administration potentially suitable for emergency overdose reversal; 2) consider pathways for developing and evaluating novel naloxone formulations.

Methods: A three-stage analysis of candidate routes of administration was conducted: 1) assessment of all 112 routes of administration identified by FDA against exclusion criteria. 2) Scrutiny of empirical data for identified candidate routes, searching PubMed and WHO International Clinical Trials Registry Platform using search terms "naloxone AND [route of administration]". 3) Examination of routes for feasibility and against the inclusion criteria.

Results: Only three routes of administration met inclusion criteria: nasal, sublingual and buccal. Products are currently in development and being studied. Pharmacokinetic data exist only for nasal naloxone, for which product development is more advanced, and one concentrated nasal spray was granted licence in the US in 2015. However, buccal naloxone may also be viable and may have different characteristics.

Conclusion: After 40 years of injection-based naloxone treatment, non-injectable routes are finally being developed. Nasal naloxone has recently been approved and will soon be field-tested, buccal naloxone holds promise, and it is unclear what sublingual naloxone will contribute. Development and approval of reliable non-injectable formulations will facilitate wider naloxone provision across the community internationally.

Identification of non-injectable routes

- Review of 112 FDA-recognized routes of drug administration (FDA, 1992)

- Exclusion if the route…
  1. Involves injection or invasive procedure
  2. Requires medical training
  3. Is not acceptable in public (e.g., rectal)
  4. Does not produce adequate drug absorption
  5. Does not produce sufficiently rapid drug absorption relative to parenteral administration (Hertz, 2012)

Identification of non-injectable routes

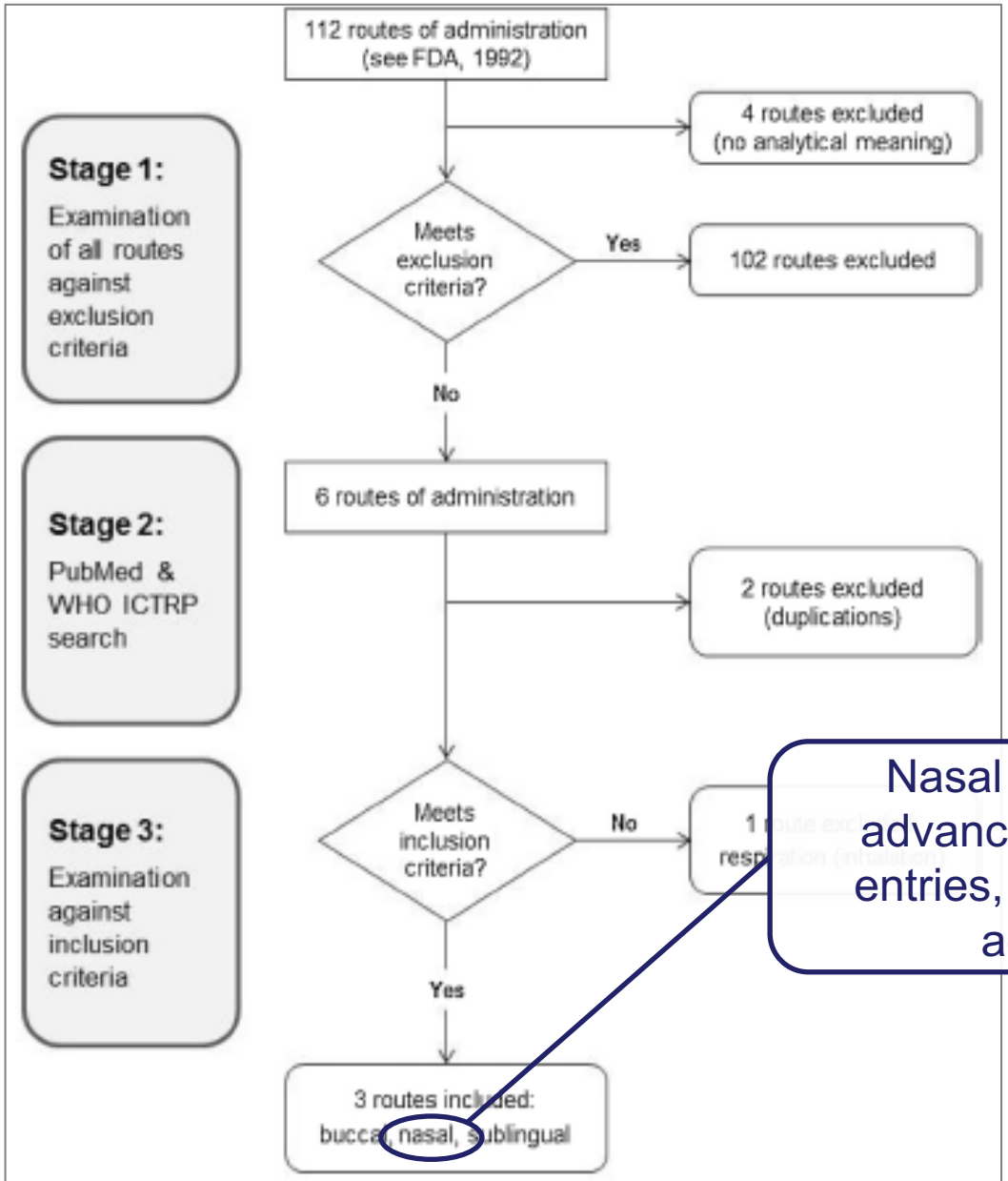

Fig. 1. Selection process of candidate routes of administration.

Nasal route most advanced (PubMed entries, clinical trials activity)

Exciting new developments: (all similar, but also different)

- Adapt (Lightlake) - ‘Narcan Nasal Spray’
- Indivior (Wermerling) - ‘Nalscue’
- Mundipharma - ‘Nyxoid’
- Norway

Exciting new developments: (all similar, but also different)

- Adapt (Lightlake) - ‘Narcan Nasal Spray’ - 4mg & 2mg - US, Canada (Europe?)
- Indivior (Wermerling) - ‘Nalscue’ - 0.9/1mg - France
- Mundipharma - ‘Nyxoid’ - 1.8/2mg - (Europe)
- Norway - ?? 1.6mg - (Norway)

Injection-free Alternatives

Pharmacokinetics

Pharmacokinetic Properties and Human Use Characteristics of an FDA-Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose

The Journal of Clinical Pharmacology
2016, 00(0) 1–11

DOI: 10.1002/jcph.759

(2016)

Philip Krieter, PhD[1], Nora Chiang, PhD[1], Shwe Gyaw, MD[1], Phil Skolnick, PhD, DSc (hon)[1], Roger Crystal, MD[2], Fintan Keegan, MSc[3], Julie Aker, MT (ASCP)[4], Melissa Beck, BA[4], and Jennifer Harris, BA[4]

Abstract

Parenteral naloxone has been approved to treat opiate overdose for over 4 decades. Intranasal naloxone, administered "off label" using improvised devices, has been widely used by both first responders and the lay public to treat overdose. However, these improvised devices require training for effective use, and the recommended volumes (2 to 4 mL) exceed those considered optimum for intranasal administration. The present study compared the pharmacokinetic properties of intranasal naloxone (2 to 8 mg) delivered in low volumes (0.1 to 0.2 mL) using an Aptar Unit-Dose device to an approved (0.4 mg) intramuscular dose. A parallel study assessed the ease of use of this device in a simulated overdose situation. All doses of intranasal naloxone resulted in plasma concentrations and areas under the curve greater than those observed following the intramuscular dose; the time to reach maximum plasma concentrations was not different following intranasal and intramuscular administration. Plasma concentrations of naloxone were dose proportional between 2 and 8 mg and independent of whether drug was administered to 1 or both nostrils. In a study using individuals representative of the general population, >90% were able to perform both critical tasks (inserting nozzle into a nostril and pressing plunger) needed to deliver a simulated dose of naloxone without prior training. Based on both pharmacokinetic and human use studies, a 4-mg dose delivered in a single device (0.1 mL) was selected as the final product. This product can be used by first responders and the lay public, providing an important and potentially life-saving intervention for victims of an opioid overdose.

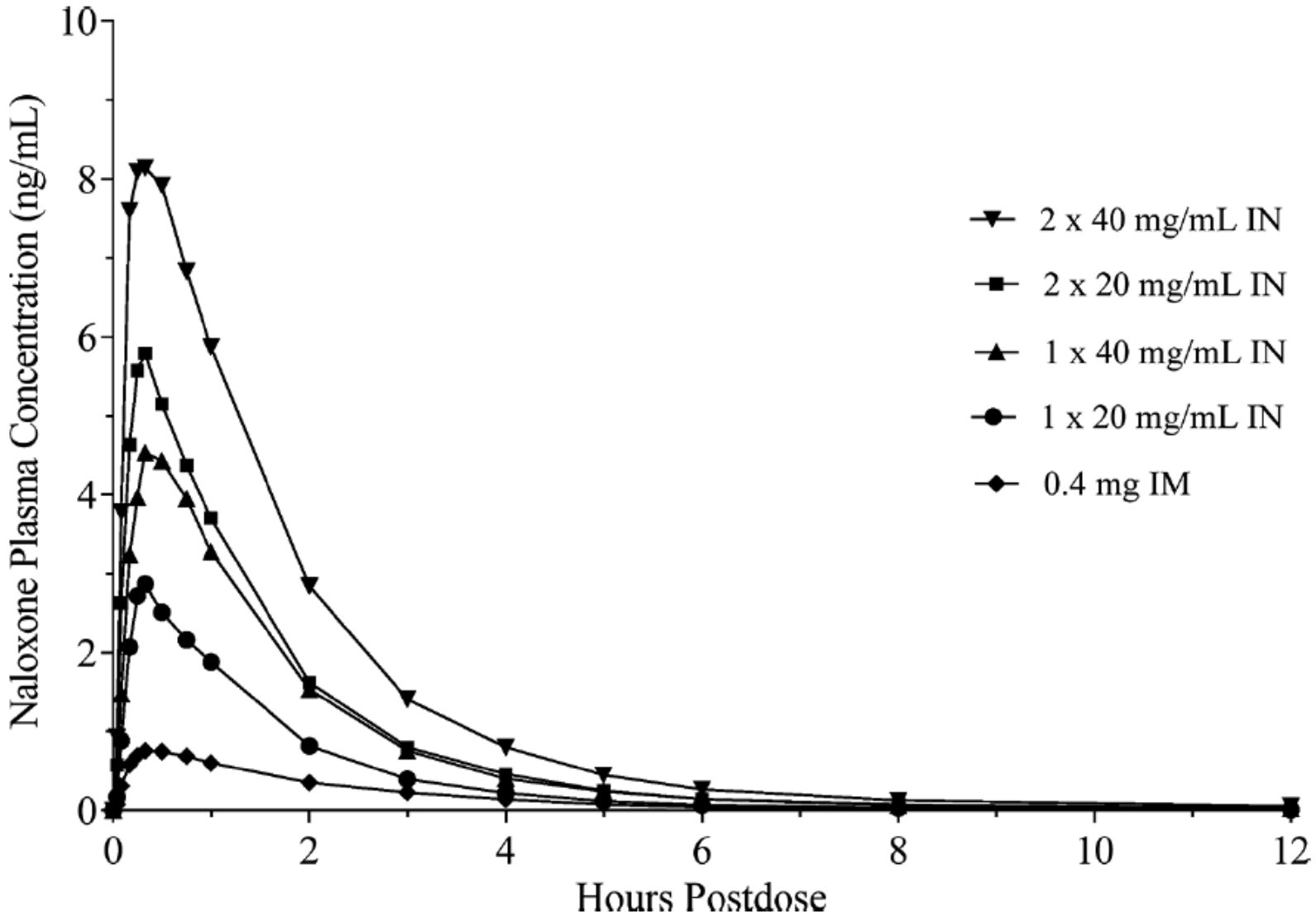

Figure 2. Plasma concentrations of naloxone following intranasal and intramuscular administration of naloxone HCl. Twenty-eight subjects were randomized in a 5-period, 5-treatment, 5-sequence crossover study, receiving 1 or 2 doses (0.1 mL per nostril) of a naloxone HCl formulation (20 and 40 mg/mL) or an intramuscular injection of 0.4 mg. IN, intranasal; IM, intramuscular.

Eur J Clin Pharmacol
DOI 10.1007/s00228-016-2191-1

PHARMACOKINETICS AND DISPOSITION

(2017)

Pharmacokinetics of a new, nasal formulation of naloxone

Ida Tylleskar[1] · Arne Kristian Skulberg[1,2] · Turid Nilsen[1] · Sissel Skarra[1] · Phatsawee Jansook[3] · Ola Dale[1,4]

Received: 28 September 2016 / Accepted: 28 December 2016

Abstract
Purpose Nasal naloxone is wanted for bystander administration in opioid overdose and as a needle-free alternative for emergency medical personnel. Epidemiologic studies have indicated a therapeutic effect of bystander administration of low-concentration/high-volume formulations. The objective for this study was to describe the nasal pharmacokinetics of 1.6 mg. Time to maximum concentrations (T_{max}) were reached at 17.9 min (11.4–24.5) and 18.6 min (14.4–22.9) for the 0.8 mg and the 1.6 mg doses, respectively.
Conclusion This nasal naloxone formulation had a rapid, systemic uptake and higher bioavailability than naloxone formulations not designed for IN use. This indicates that an optimized high-concentration/low-volume nasal spray formula-

Pharmacokinetics of a new, nasal formulation of naloxone

Authors
Ida Tylleskar[1], Arne Kristian Skulberg[1,2], Turid Nilsen[1], Sissel Skarra[1], Phatsawee Jansook[3], Ola Dale[1,4]
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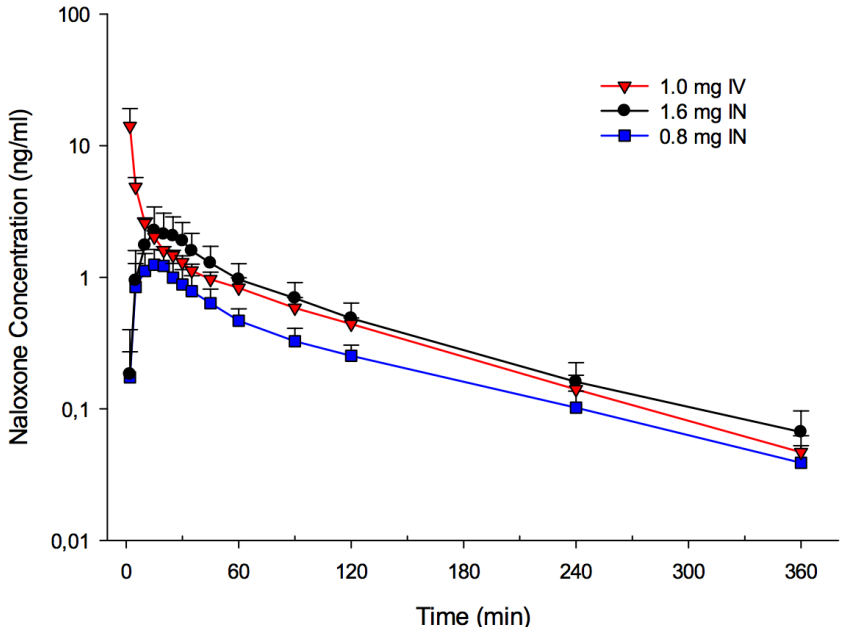
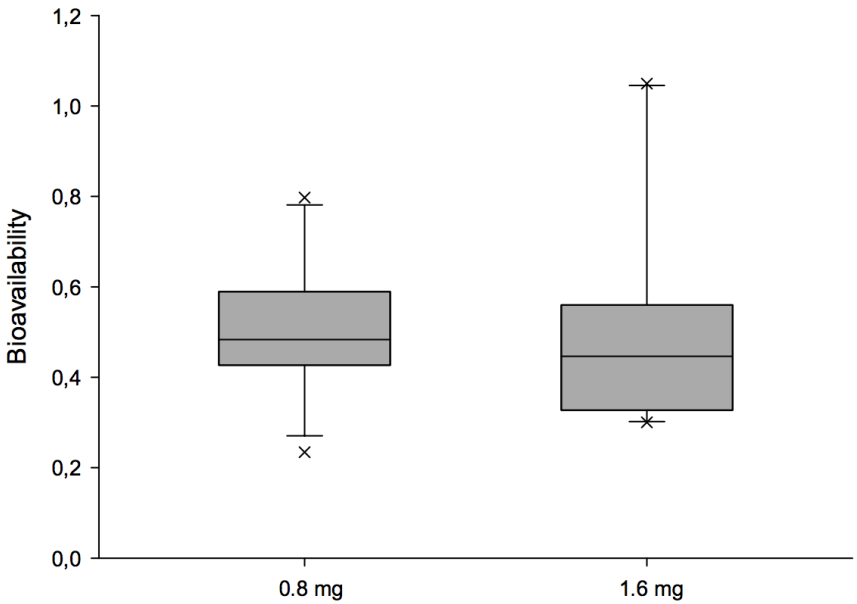
Abstract

Purpose

Time course for the serum concentrations of naloxone in healthy volunteers



Bioavailability of two doses nasal naloxone in healthy volunteers



ADDICTION

(2017)

RESEARCH REPORT

doi:10.1111/add.14033

Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study*

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ABSTRACT

Background and Aims Take-home naloxone can prevent death from heroin/opioid overdose, but pre-provision is difficult because naloxone is usually given by injection. Non-injectable alternatives, including naloxone nasal sprays, are currently being developed. To be effective, the intranasal (i.n.) spray dose must be adequate but not excessive, and early absorption must be comparable to intramuscular (i.m.) injection. We report on the pharmacokinetics (PK) of a specially produced concentrated novel nasal spray. The specific aims were to: (1) estimate PK profiles of i.n. naloxone, (2) compare early systemic exposure with i.n. versus i.m. naloxone and (3) estimate i.n. bioavailability. **Design** Open-label, randomized, five-way cross-over PK study. **Setting** Clinical trials facility (Croydon, UK). **Participants** Thirty-eight healthy volunteers (age 20–54 years; 11 female). **Intervention and comparator** Three doses of i.n. (1 mg/0.1 ml, 2 mg/0.1 ml,

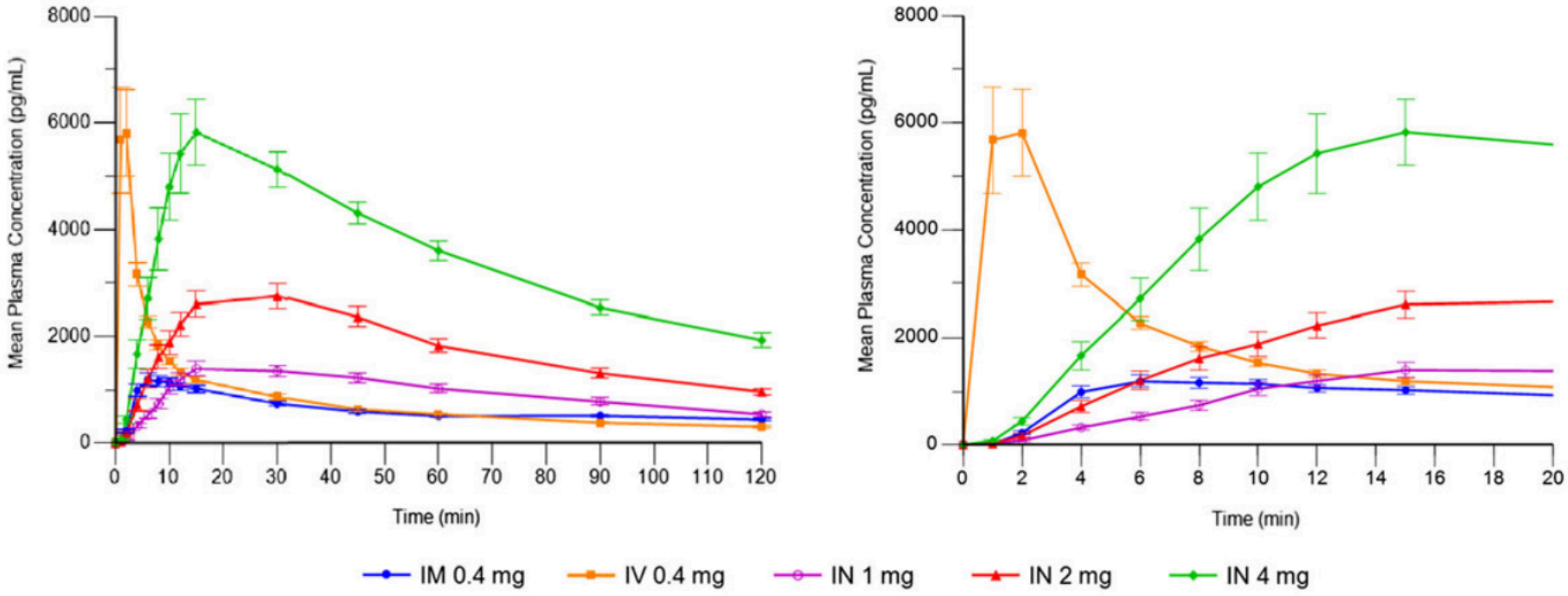

Figure 1 Mean plasma naloxone concentrations (observed values): dosing to 120 minutes (left) and dosing to 20 minutes (right)

Next generation: Buccal naloxone?

- Preclinical PK study in rats: good buccal bioavailability (F=71%) (Hussain et al., 1987, 1988)
- King's College London: instant-dissolving buccal naloxone tablet (Alqurshi et al., 2016)
  - Less affected by nasal damage, mucus, vomit?
  - Greater stability than nasal spray?
  - Greater easy of transport?
- _____
- Also Purdue Pharma & Klaria agreement (Aug 2017)

Injection-free Alternatives (cont'd)

molecular pharmaceutics

(2016)

Article

pubs.acs.org/molecularpharmaceutics

Amorphous Formulation and *in Vitro* Performance Testing of Instantly Disintegrating Buccal Tablets for the Emergency Delivery of Naloxone

Abdulmalik Alqurshi,[†] Zahrae Kumar,[†] Rebecca McDonald,[‡] John Strang,[‡] Asma Buanz,[§] Shagufta Ahmed,[∥] Elizabeth Allen,[∥] Peter Cameron,[⊥] James A. Rickard,[⊥] Verity Sandhu,[⊥] Chris Holt,[⊥] Rebecca Stansfield,[⊥] David Taylor,[†] Ben Forbes,[†] and Paul G. Royall*[,†]

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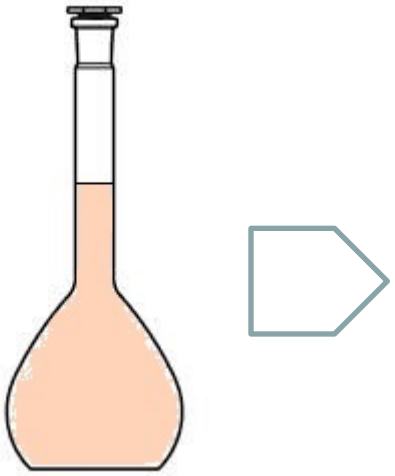
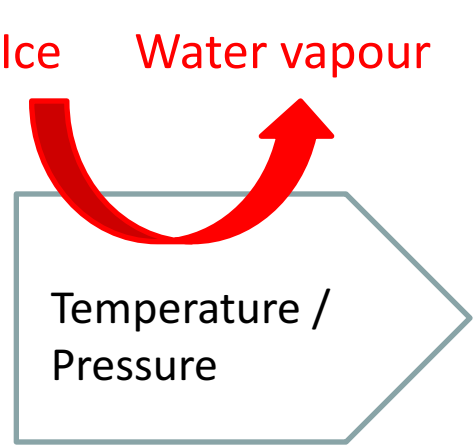
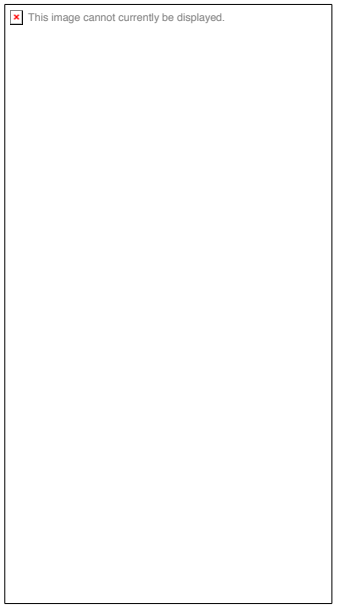
Naloxone Instant Melt Tablet Development

SOLUTION → FREEZE → DRY → TABLET







Stock solution
Naloxone and pharmaceutical grade excipients in water for injection

Solution pipetted into blister wells (top) and frozen (bottom) ready for lyophilisation

Frozen tablets lyophilised using tailored temperature and pressure cycle

Instant melt tablet

Structure of lecture

1. Lack of concept
2. Lack of easy product
3. Licencing of products?
4. Improvising nasal naloxone
5. Developing formal naloxone nasal sprays
6. **Regulatory and price barriers**
7. Attitude problems

Naloxone Monograph from EMCDDA (European Monitoring Centre on Drugs and Drug Addiction) (2016)

European Monitoring Centre for Drugs and Drug Addiction

INSIGHTS EN 20

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Preventing opioid overdose deaths with take-home naloxone

(2016)

Editors
John Strang and Rebecca McDonald
National Addiction Centre, Addictions Department, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom

EMCDDA project group
Dagmar Hedrich and Roland Simon

http://www.emcdda.europa.eu/news/2016/1/preventing-opioid-overdose-naloxone

- Clinical guidelines across the EU 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.

- In the UK, hepatitis-B vaccination already exists on an opt-out basis in prisons (NICE, 2012), and this could serve as model for future prison-based take-home naloxone-on-release schemes.

Structure of lecture

1. Lack of concept
2. Lack of easy product
3. Licencing of products?
4. Improvising nasal naloxone
5. Developing formal naloxone nasal sprays
6. Regulatory and price barriers
7. **Attitude problems**

Attitudes matter

- Covert discrimination
- Institutional inertia

Conclusions

- We have made great progress - feasibility of pre-provision
- Now three concentrated nasal spray products
  - Adapt: US, Canada; Europe?
  - Indivior: France
  - Mundipharma: Europe (as of early 2018)
- Over-the-counter status?
- ‘Standard of care’; expectation of provision?
- Remaining issues:
  - Possible field limitations of nasal? (Possible buccal future?)
  - Dose? And also dose titration?
  - Overcoming implementation inertia?

Overall message

- Proud of what we have achieved
- Humble about how much more we need to do

Thank you