National Addiction Centre

Institute of Psychiatry at The Maudsley

KING'S College LONDON

Naloxone without the needle: non-injectable options

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Declarations

- 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 is a consultant for the United Nations (UNODC), supporting a naloxone study in Central Asia.

Overview

1. **Background: Why is non-injectable naloxone needed**
2. Method: Criteria for non-injectable routes
3. Non-injectable naloxone: products in development

Community management of opioid overdose

World Health Organization

WHO (2014). *Community Management of Opioid Overdose.* Geneva: WHO.

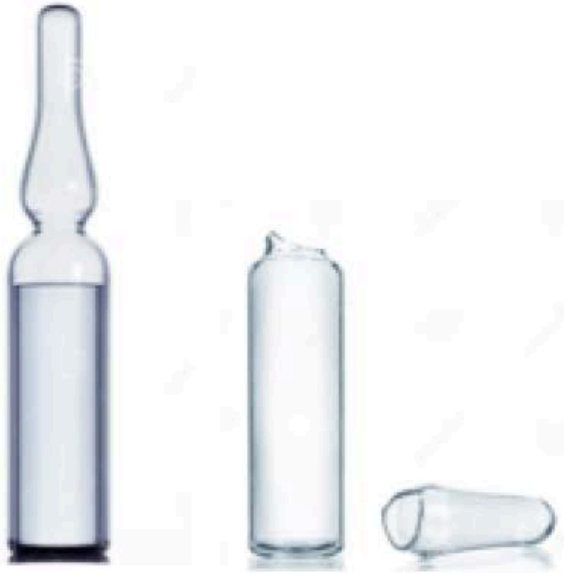
Community management of opioid overdose

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.

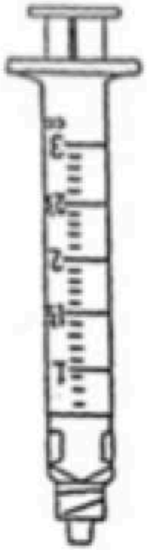
World Health Organization

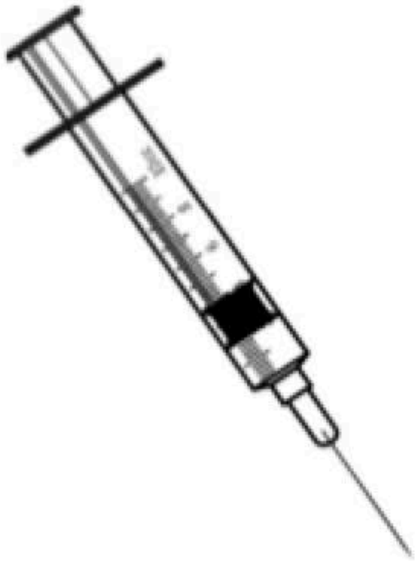
WHO (2014). *Community Management of Opioid Overdose.* Geneva: WHO.



All work

None perfect





1 | Why is non-injectable naloxone needed?

- Training required
- Risk of needle-stick-injury
- Prescription-only medication status
  (Article 71, EU Medicinal Products Directive, 2001/83)

2.1 | Identification of non-injectable routes

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Review

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

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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.

Strang, J., McDonald, R., Alqurshi, A., Royall, P., Taylor, D., & Forbes, B. (2016). Naloxone without the needle− systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal. *Drug and Alcohol Dependence*, *163*, 16-23.

2.2 | Identification of non-injectable routes

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

- Inclusion if the route…
  1. Suitable for OD emergency situation
  2. No major risk of compromise from OD complication

- 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)

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2.3 | Identification of non-injectable routes

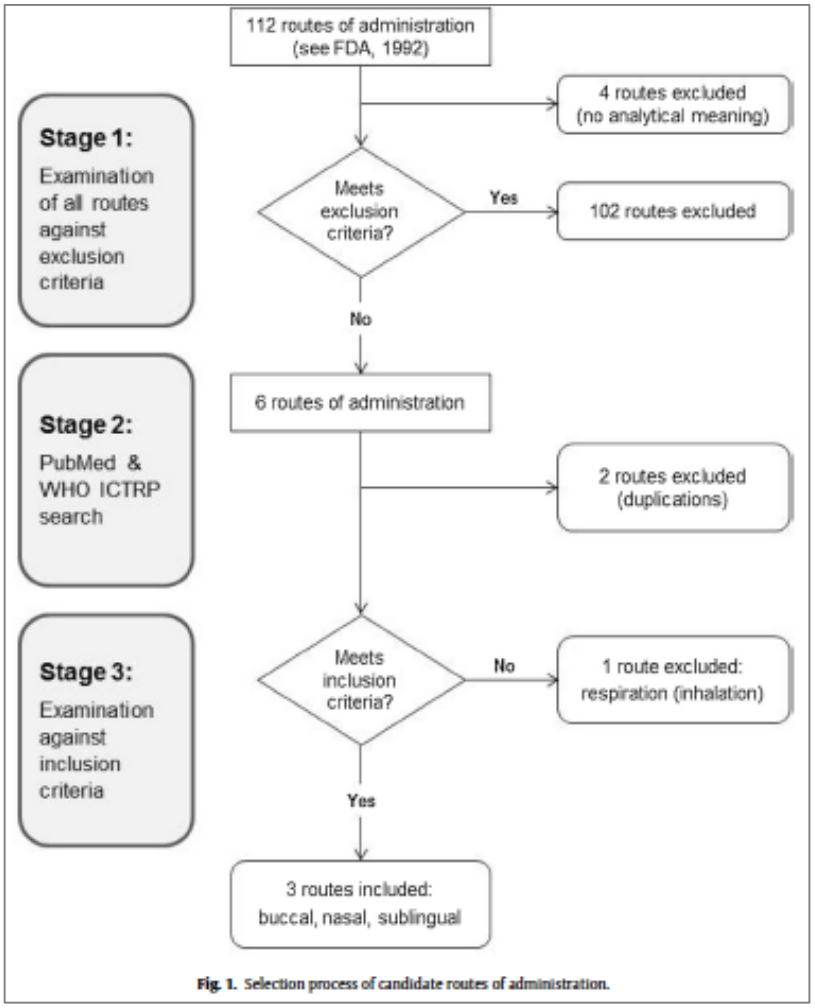

Fig. 1. Selection process of candidate routes of administration.

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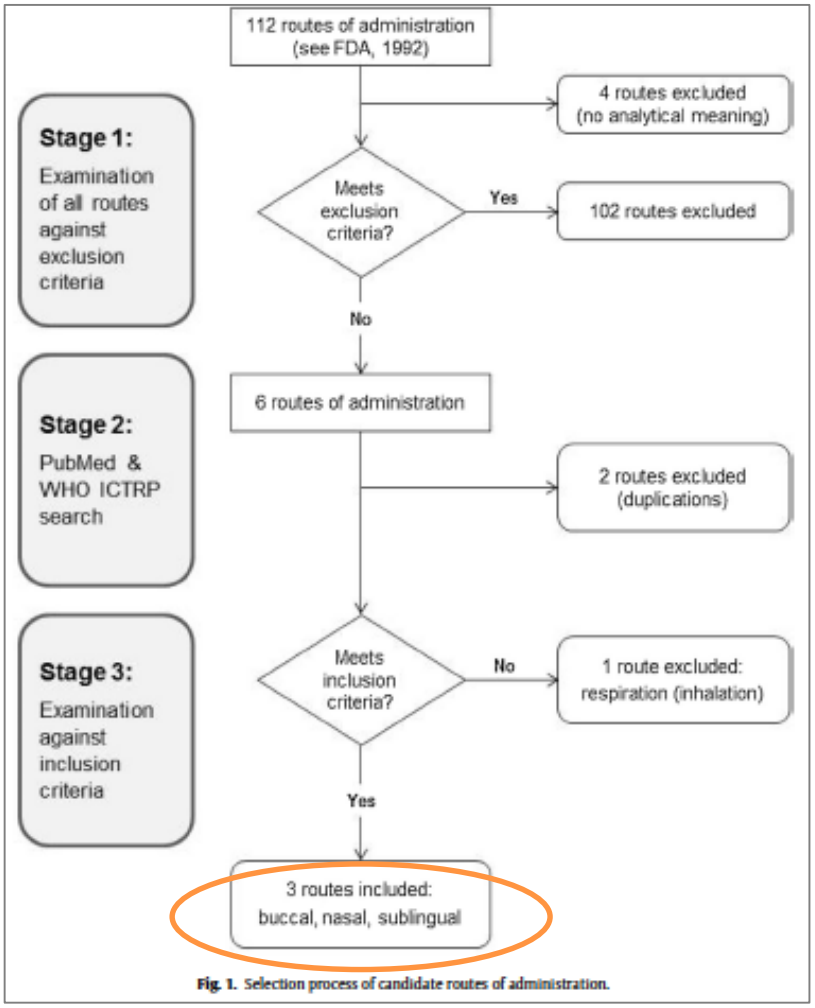

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3.1 | Results: Research activity (PubMed)

- Sublingual:
  - 1 pharmacodynamic study: mixed results (Preston et al., 1990)
- Nasal:
  - 18 in vivo studies (across species)
- Buccal:
  - 2 preclinical pharmacokinetic studies: good bioavailability (F≦71%) (Hussain et al., 1987, 1988)

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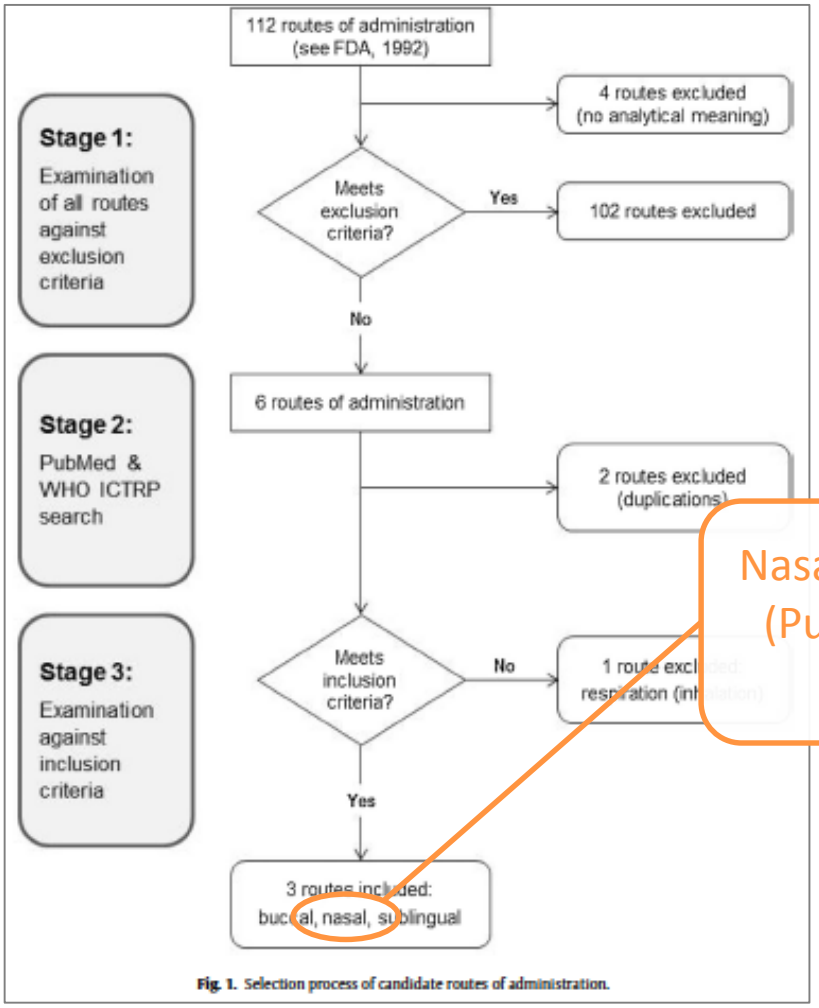

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Nasal route most advanced (PubMed entries, clinical trials activity)

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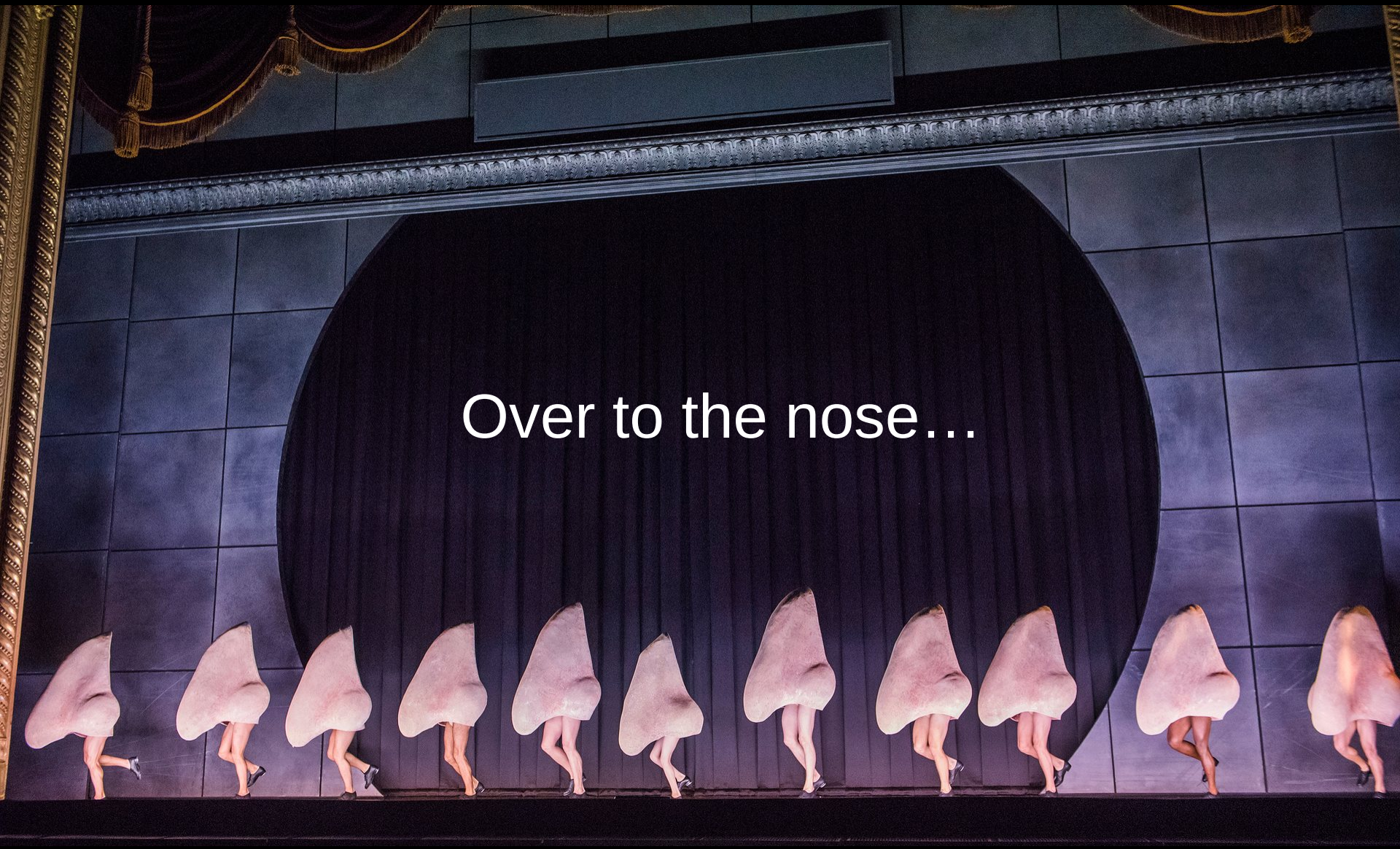
Naloxone nasal spray: what is required?

1. Easy to use
2. Small volume → concentrated solution
3. Good early absorption (similar to IM)
4. Dose adequate, but not excessive



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