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## Opioid overdose prevention and response: key implementation challenges (or 'Why have we failed to solve the problem of opioid overdose?')

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## Disclosure of interest statement

- Professor Dietze has received investigator-driven funding from Gilead Sciences Inc for work related to hepatitis C treatment and an untied educational grant from Indivior for work related to the introduction of buprenorphine/naloxone formulations into Australia
- Professor Dietze has served as an unpaid adviser on an Advisory Board for Mundipharma related to an intranasal naloxone product

# What is an opioid overdose

- Opioids bind to receptor sites in the central nervous system, including respiratory control centres
- Lose the body's ability to detect carbon dioxide levels
- Raised CO<sub>2</sub> levels and low O<sub>2</sub> levels
- Systemic acidosis affecting the brain, heart, lungs and kidneys
- Lowered blood pressure
- Low or absent consciousness (eg measured through GCS)
- Lowered or loss of gag and cough reflex which increases the aspiration risk
- Key effect is compromised respiration

# Prevention and intervention is possible

*Opioid overdoses need not occur and need not be fatal!*

*Risk of occurrence is increased in events by:*

- *Concomitant use of CNS depressants*
- *Shifting from private to public injecting locations*
- *Injecting as opposed to smoking drugs*

*Clear opportunity for intervention:*

- *Estimated that in 60% of cases person not alone*
- *Estimated that >50% of people die >20-30 minutes after use*
- *Supported breathing can allow survival*
- *Opioid effects can be reversed by naloxone*

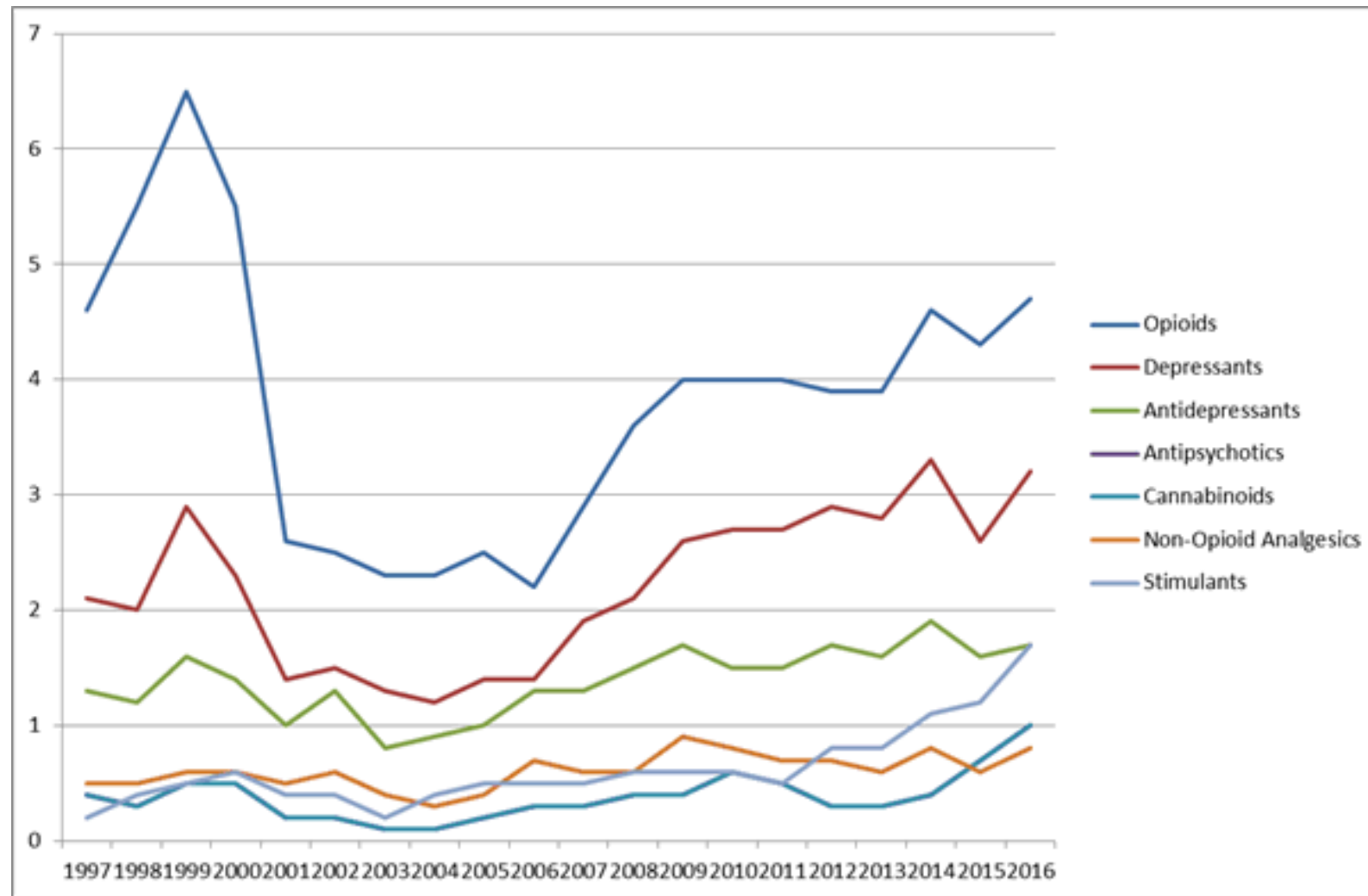
*Dietze et al, Addiction 2005; Brugal et al, Addiction 2002; Darke & Hall, J Urban Health, 2003; Darke & Duflou, Addiction, 2016*

# Overdose prevention – available interventions

- Drug & other treatment options (OST)
- First responders (e.g. ambulance paramedics and fire brigade)
  - Direct response
  - Discretionary law enforcement
- Education – overdose recognition and response
- **Take-home naloxone**
- **Supervised injecting facilities**

*Adapted from Darke & Hall, J Urban Health, 2003*

# Rate of drug related deaths in Australia



Australian Bureau of Statistics - 2017

## Response 1: Take-home naloxone

- Take-home naloxone = providing naloxone to people likely to witness an overdose (usually with training in overdose recognition and response)
- First mooted in Melbourne in 1992 by John Strang
- Berlin, Jersey programs published, Chicago from 1996
- Evidence naloxone can be used safely by trained non-medical peers with many thousands of such overdose reversals having been reported
- Observational evidence that THN programs can reduce overdose death rates at a community level
- Walley et al (2013) found a significant difference in death rates between cities and towns where THN programs have, or have not been implemented
- Modelling suggests naloxone distribution to opioid users is likely to reduce overdose deaths, would increase QALYs and be highly cost effective

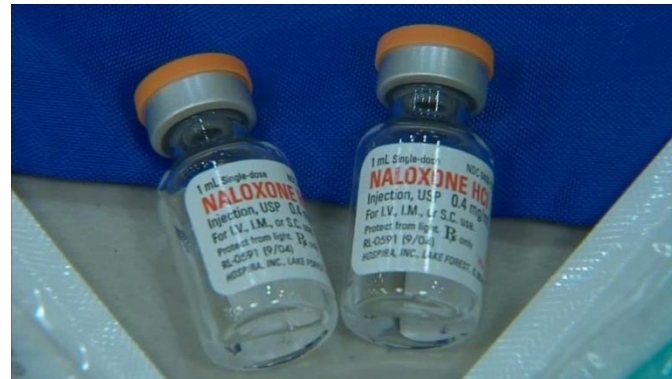
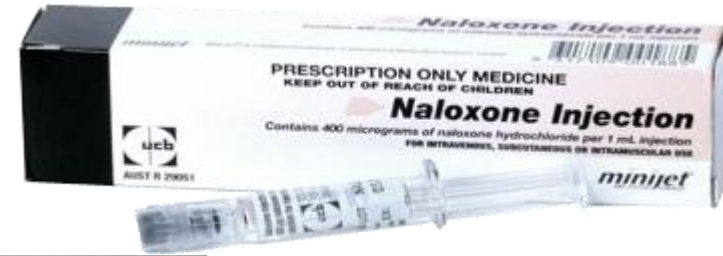
*e.g. Dettmer et al, Addiction 1999; Walley et al, BMJ 2013, Mueller et al, 2015; Coffin & Sullivan, Ann Internal Med 2013*



# What is naloxone?

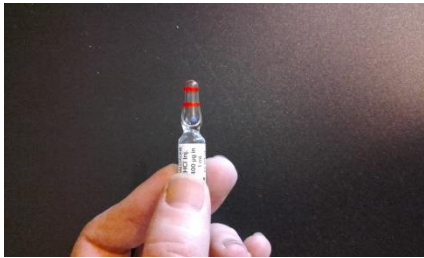
- Naloxone is an opioid antagonist that reverses the acute effects of opioids
- Over four decades of use in emergency medicine
- Has no other effects - safe, reliable and effective
- Key response to opioid overdose in hospitals and ambulance services
- Can be administered IV, IM, IN
- 2014 WHO endorsed making naloxone available to people likely to witness an overdose
- In Australia it has been a prescription only medication (S4), but after TGA rescheduling in March 2016 it can now also be purchased over-the-counter in pharmacies (S3) [dual listing]





# Take-home naloxone – key recent findings

- Bradford-Hill analyses conclude THN is effective
- Australian uptake:
  - NSW: from July 2012 - 83 followed up, 30 reversals (now >1000 trained)
  - SA: from November 2012 – aim for 100 trained
  - WA: from Jan 2013 – 153 trained, 32 reversals (now >280 trained)
  - VIC: from Jan 2013 – 99 followed up, 27 reversals (now >1000 trained by HRV alone)
  - QLD: from Jan 2014 – 50 trained, 5 reversals



See Chronister et al, *Drug Alcohol Rev* 2018; Dwyer et al, *Drug Alcohol Rev* 2018; McDonald et al, *Addiction* 2016, Olsen et al, *Drug Alcohol Rev* 2018

# Taking stock of take-home naloxone in Australia

- No consistent legislation (e.g. Good Samaritan provision)
- No national coordination (left to states)
- No distribution targets
- No standard/universal access through all key health services (what about Ambulance, Emergency Department, Needle/Syringe Programs, Drug Treatment Services?)
- Incomplete first responder access
- Very limited point-of-custodial-release distribution
- No consistent programs for pharmacists or primary care
- ***No national overdose strategy since 2001***

# THN implementation challenges

1. Knowledge within at-risk populations
2. Knowledge amongst service providers
3. Support systems and resources
4. Dose and form across settings

# 1. Client knowledge

- Most work with PWID or recreational use
- In chronic non-cancer pain limited overdose knowledge, limited knowledge of naloxone as response<sup>1</sup>
- Requirements:
  - Educational resources
  - Campaigns
  - Co-prescription<sup>2</sup>

<sup>1</sup>Nielsen et al, *Pain Med* 2018, <sup>2</sup> Coffin et al, *Ann Internal Med* 2016

## 2. Provider knowledge

- Most work with drug user service system
- In pharmacy, limited knowledge of naloxone as response<sup>1</sup>
- Requirements:
  - Educational resources
  - Campaigns
  - Co-prescription<sup>2</sup>

<sup>1</sup>Nielsen et al, *Addiction* 2016; Ontario model: <https://www.ontario.ca/page/get-naloxone-kits-free>

### 3. Support systems, sites and resources

- Almost no over-the-counter pharmacy access in Australia since 2016
- Pharmacy access laws associated with overdose fatalities<sup>1</sup>
- Requirements:
  - Peak bodies engagement needed for THN success
  - Incentives for provision
  - Resources developed for PWID & recreational use, but only fledgling development and research for chronic non-cancer pain
  - More research on THN in Emergency Department<sup>2</sup>, other hospital<sup>3</sup>, primary care<sup>4</sup>

<sup>1</sup>Abouk et al *JAMA Intern Med.* 2019, <sup>2</sup>Samuels et al. *J Subst Abus Treat.* 2018;94:29-34.

<sup>3</sup>Jakubowski et al. *Subst Abus.* 2019;40(1):61-65. <sup>4</sup>Behar et al. *Prev Med.* 2018;114:79-87.



## 4. Dose and form: Intranasal naloxone

- Queries as to dose needed in synthetic opioid era<sup>1</sup>
- Case series and trial evidence suggests intranasal efficacy<sup>2, 3</sup>
- Unblinded trials suggest less efficacy than intramuscular when given at same dose<sup>4</sup>
- New, more concentrated formulations developed, tested and marketed<sup>5</sup>
- No blinded trial data

<sup>1</sup>Moss & Carlo, *Subs Abuse Treat Prev Policy*, 2019. <sup>2</sup>Barton, 2002; <sup>3</sup>Kerr et al, *Addiction* 2008; <sup>4</sup>Kerr et al, *Addiction* 2009; <sup>5</sup>McDonald et al, *Addiction* 2017

# Intranasal naloxone: efficacy

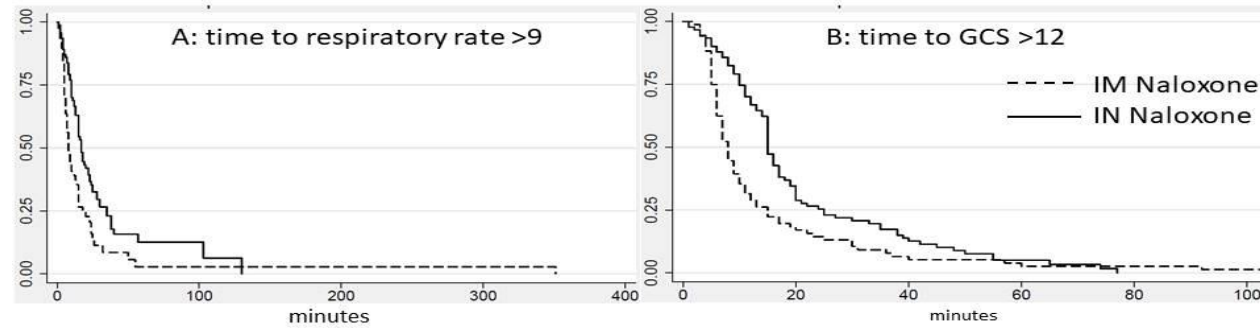


Figure 2: Kaplan-Meier survival curves for time to respiratory rate >9 (Panel a) and time to GCS>12 (Panel B) for intranasal (solid line) and intramuscular (dashed line) naloxone treatment arms

- 800 mcg Intranasal naloxone is not as effective as 800 mcg intramuscular naloxone for reversing opioid overdose
- *BUT – positive response to intranasal within 10 minutes for 77% of cases*
- *Implications for intranasal naloxone used in clinical practice*
- *Where does this leave us?*

# PK data

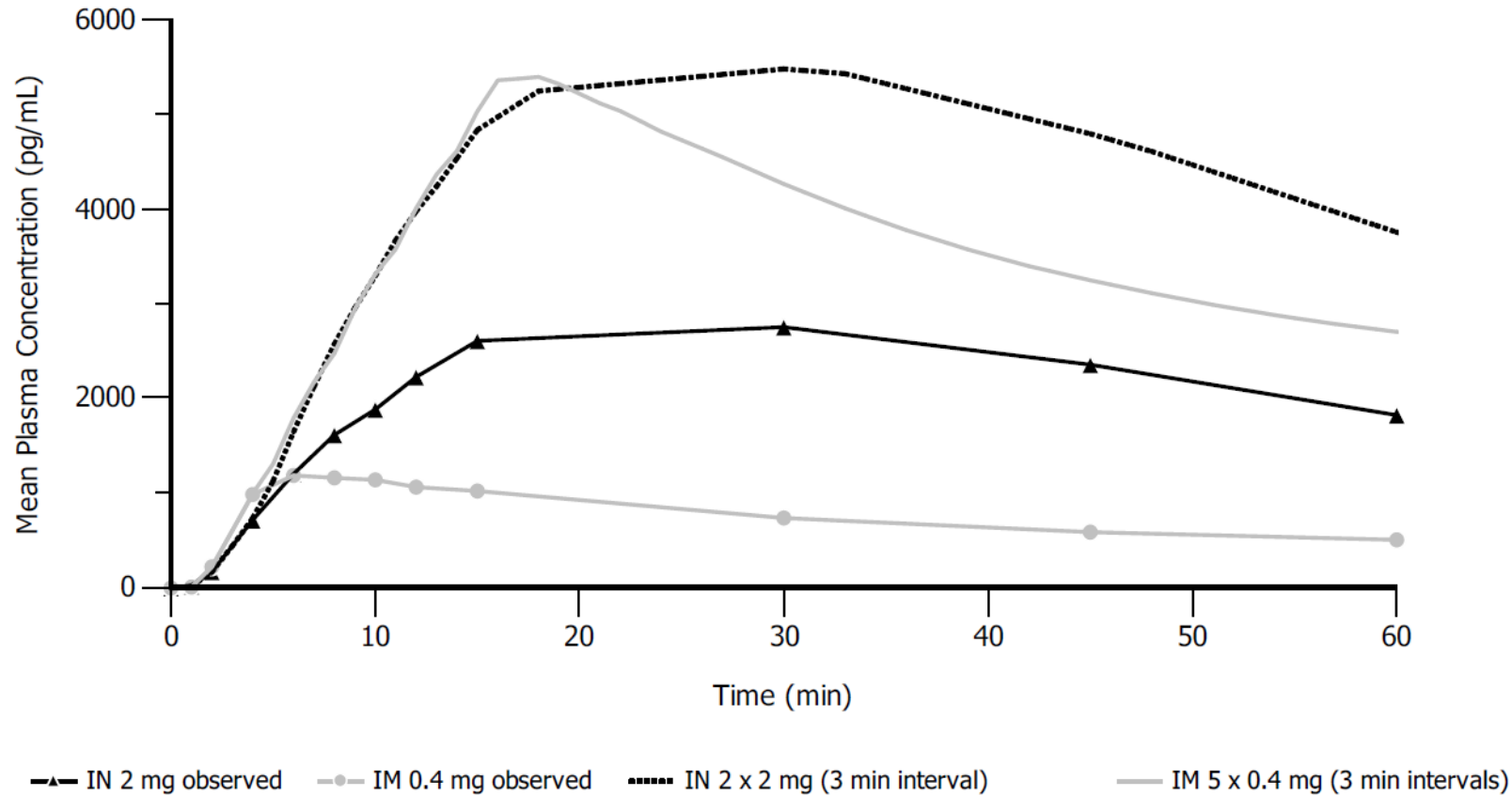
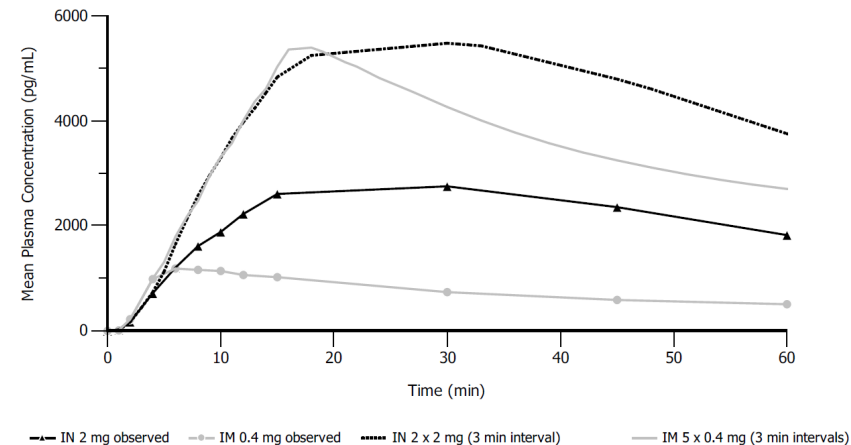


Figure 3: Scaled mean plasma naloxone concentrations after repeat administration at 3-minute intervals (vs mean observed profiles of 0.4 mg IM and 2 mg IN doses)

McDonald et al, 2017

# What dose of naloxone should be used?

- 800 mcg Intranasal naloxone used in study
- *WHO – 400-800mcg IM standard*
- *FDA – 2mg since 2016*
- *MSIC – 800 mcg (but heavily obtunded)*
- *Ambulance Victoria – 1.6 mg (despite using 400 mcg ampules)*
- *Narcan (4mg) and Nyxoid (2mg)*



McDonald et al, Addiction 2017

Figure 3: Scaled mean plasma naloxone concentrations after repeat administration at 3-minute intervals (vs mean observed profiles of 0.4 mg IM and 2 mg IN doses)

# Implications of naloxone dosing

- Too much?
- Too little?

## Response 2: Supervised injecting facilities

- Injecting room, safe injecting room, safe house, safety clinic, tolerance room, NOT 'shooting galleries'
- Legally sanctioned indoor facility, supervision by trained staff, safe and sterile conditions, access to sterile injecting equipment
- Single or multi function (cafes / lounges, counseling, primary medical care, laundry etc)
- Referral to appropriate services (treatment, material aid, advocacy, employment)
- Opioid overdose strategy aimed at PWID

# Medically Supervised Injecting Centre (Kings Cross) 1



Photo: Dr Ingrid van Beek

## Medically Supervised Injecting Centre (Kings Cross) 2



Photo: Dr Ingrid van Beek



## Medically Supervised Injecting Centre (Kings Cross) 5



Photo: Dr Ingrid van Beek

## Medically Supervised Injecting Centre (Kings Cross) 7



Photo: Dr Ingrid van Beek

# Sydney MSIC



# Sydney MSIC

- No increase in drug use (or honey-pot)
- Reduction in ambulance callouts
- Reduction in deaths due to overdose (4-9 depending on assumptions)
- Increase in referrals
- Clear cost-effectiveness
- Reduction in public injecting and associated discarded injecting equipment



*MSIC Evaluation Committee, 2003 Salmon et al, 2010*

# Why only one Sydney MSIC

- Trial status
- Emergency dissipated (but didn't go away)
- Continued vocal opposition (sustained campaign in tabloid newspapers)
- Poor planning?
- Government changes
- What is the scope for Melbourne?



# The Melbourne MSIR



# The Melbourne MSIR



# The Melbourne MSIR

**Melbourne safe injecting room hailed a success by director after thousands of visits in first two months**

By state political reporter [Richard Willingham](#)  
Updated 31 Aug 2018, 1:18pm

**Patten says safe injecting room 'not working as well as we'd hoped'**

**By Melissa Cunningham and AAP**  
February 22, 2019 — 4.04pm

**Public heroin use spurs calls for change at Richmond injecting room**

By [Paul Sakkal](#)  
April 10, 2019 — 8.18pm

[Three arrested, one suspected overdose near \*\*Richmond injecting ...\*\*](#)

**Herald Sun**-11 Apr 2019



# THN & SIFs – problem solved?

- Urgent scale up needed
  - *of all interventions*
- Deaths in the home among people who use alone (see Stam et al, 2019)
- Deaths among people who don't inject

# What do we need?

1. Scaled responses
2. Targets and models for all interventions and the mix of interventions
3. National and international leadership (including strategy)
4. Improved interventions
5. New interventions (focus on non-injecting and private use)

# New understandings

- Never overdose?
  - Behavioural & biological factors
- What naloxone dose is needed?
  - Why do all the formulations seem to work?

# New interventions

- Overdose = compromised respiration
  - Lowered oxygen saturation
- What is normal
- Wearable mo



# Acknowledgments

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