Disclosures

I have received untied educational grants from Reckitt Benckiser, Mundipharma Australia and Seqirus for post-marketing studies of abuse-deterrent opioids.

- The NOMAD study was funded via an investigator-driven, untied educational grant from Mundipharma Australia.
- Studies of the diversion and injection of buprenorphine-naloxone were funded by Reckitt Benckiser.

I have also received untied educational grants from Indivior for work unrelated to this presentation.

Collaborators

Studies of the diversion and injection of buprenorphine-naloxone tablets and film

Louisa Degenhardt, Richard Mattick, Briony Larance, James Bell, Nicholas Lintzeris, Robert Ali, Adam Winstock, Nancy White, Paul Dietze, Rebecca Jenkinson

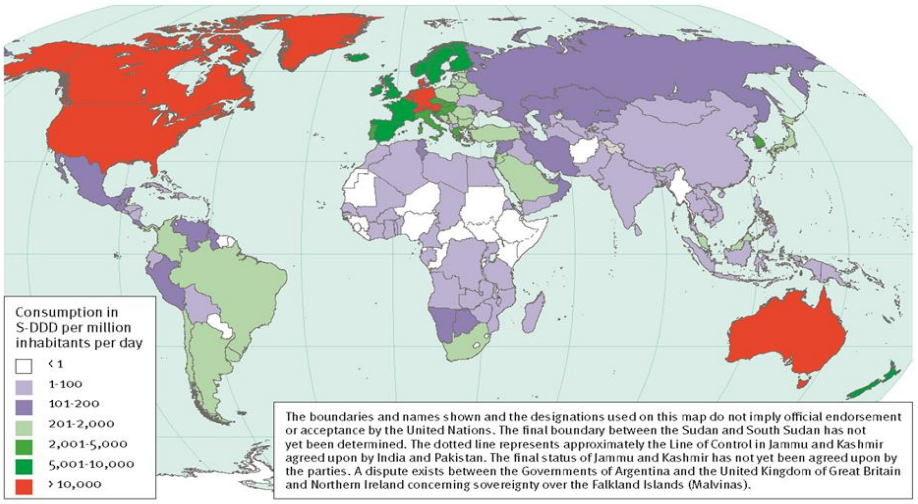
The impacts of a potentially tamper-resistant formulation of controlled-release oxycodone: The National Opioid Medications Abuse Deterrence (NOMAD) study

Louisa Degenhardt, Briony Larance, Nicholas Lintzeris, Raimondo Bruno, Robert Ali, Michael Farrell, Amy Peacock, Tim Dobbins.

Overview

1. Utilisation of opioids
2. Unintended consequences
3. The opioid crisis
4. Abuse deterrent formulations
5. Australian experience
   - Agonist-antagonist
   - Tamper-resistant
6. What have we learned?
7. Are ADFs effective in reducing opioid-related harm?

Availability of opioids for pain management (2011-13)



Note: Opioids defined as codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, ketobemidone, morphine, oxycodone, pethidine, tilidine and trimeperidine.
Source: International Narcotics Control Board.

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Source: Berterame et al (2016) Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *The Lancet*.

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Unintended consequences of opioid use

- **Non-adherent use**
  - Stockpiling
  - Doctor shopping
  - Tampering
- **Diversion**
  - Diversion to others
  - Use of someone else's medication
- **Dependence**
- **Overdose**

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Larance et al (2011) Definitions related to the use of pharmaceutical opioids: Extra-medical use, diversion, non-adherence and aberrant drug behaviours. *Drug and Alcohol Review*

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Not everyone is at similar risk for adverse outcomes…

Potential risk factors for poorer clinical outcomes:

- Mental health problems
- History of drug and alcohol use problems
- Experience of trauma
- More complex pain problems
- Other illnesses and disabilities
- Other medications

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The North American opioid crisis

- An unprecedented "epidemic" of opioid use and dependence (Fischer and Rehm, 2017)
- A "public health emergency" (Donald Trump, 2017)
- >90 Americans die of opioid overdose each day, including pharmaceutical opioids, heroin and illicit fentanyl.
- The CDC estimates total economic burden is $78.5 billion (USD) a year, including the costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement (Centres for Disease Control and Prevention, 2017).

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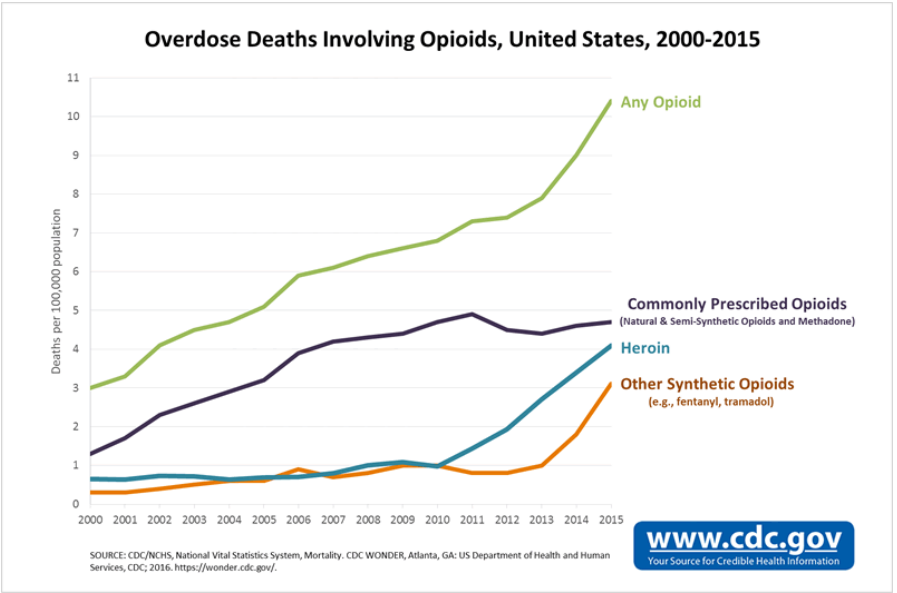

How did the opioid crisis develop in North America?

- Aggressive marketing of pharmaceutical opioids in the late 1990s.
- Increased prescribing of strong opioids such as oxycodone and fentanyl from early 2000s.
- Created a broad-base of opioid exposure in the general population and increasing problematic opioid use and demand.
- Complex interplay between pharmaceutical opioids, heroin and synthetic opioids, in response to dynamics of supply or price.
- Overwhelmed treatment system.

The Australian picture

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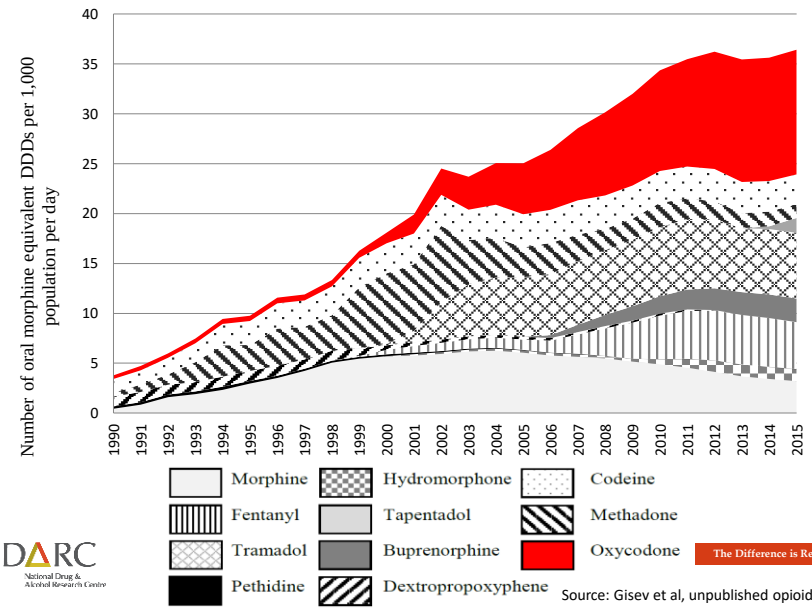
Opioid utilisation per 1,000 pop/day



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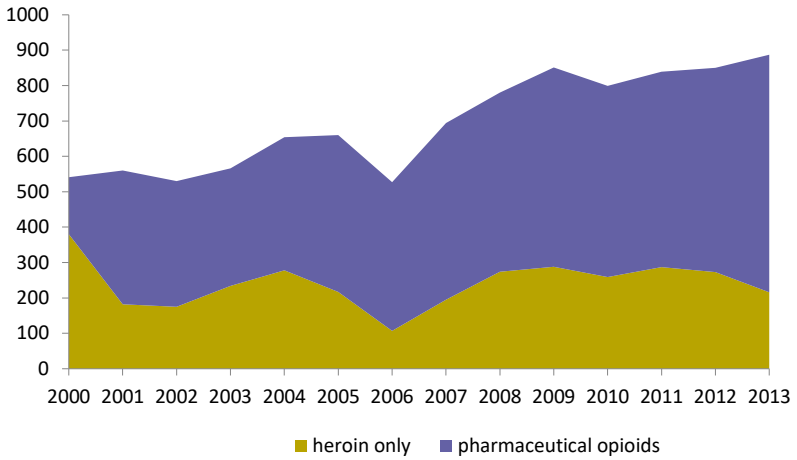
Source: Gisev et al, unpublished opioid sales data

Changing nature of opioid-related deaths



Source: National Coronial Information System (NCIS); Roxburgh et al (MJA, 2011); Roxburgh et al (2013); Roxburgh et al (2017)

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NIDIP National Illicit Drug Indicators Project

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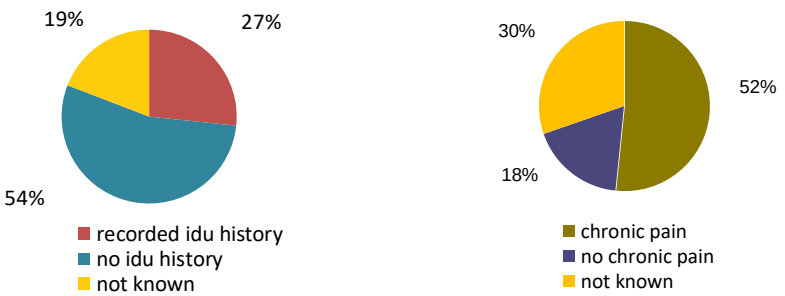
Opioid-related deaths, 2009



Source: National Coronial Information System (NCIS); Roxburgh et al (MJA, 2011); Roxburgh et al (2013)

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NIDIP National Illicit Drug Indicators Project

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The Australian picture

PO dispensings increased 15-fold in the last two decades (Blanch et al, 2014)

Marked shift from predominantly "weak" short-acting opioids to almost half of dispensings "strong" long-acting opioids (Karanges et al, 2016)

With increased opioid utilisation, we are seeing increases in

- Opioid-related hospital admissions (Roxburgh et al, 2011)
- Treatment-seeking (Nielsen et al, 2014)
- Overdose (Roxburgh et al, 2017).

PO collectively cause over 70% of opioid overdoses in Australia, mirroring rates observed in the US.

Abuse deterrent formulations (ADFs)

Abuse deterrent formulations (ADFs) of opioids

- Physical or chemical barriers ("tamper-resistant")
  - Physical barriers that prevent chewing, crushing, cutting etc.
  - Chemical barriers that resist extraction e.g. via dissolution
- Agonist-antagonist combinations
  - Antagonist released if manipulated and then injected/snorted
- Aversion
  - Combine drugs to produce an unpleasant effect e.g. if tampered with or too high a dose taken
- Delivery systems
  - Depot injectables, implants
- Prodrug
  - Lacks opioid activity until transformed in gastrointestinal tract

US Department of Health and Human Services (2013). *Guidance for Industry: Abuse-deterrent opioids – Evaluation and Labeling.* Rockville, MD: Food and Drug Administration.

Expectations of ADFs

Specific formulations target specific behaviours

- Agonist-antagonists – unintended injection
- Tamper-resistant – use via range of unintended ROAs
- Depot injections – non-adherence (missing doses, taking more than prescribed, etc)

But prescribers, policymakers and regulators also hope that ADFs will also reduce other harms, including opioid dependence and overdose.

Almost half US physicians believed ADFs are less "addictive" (Hwang et al, 2016)

Are ADFs effective?

How do ADFs impact upon

1. wider opioid utilisation?
2. the target behaviours/practices in high-risk populations?
3. other acute and chronic opioid-related harms (e.g., overdose, opioid dependence, etc)?

Buprenorphine-naloxone studies

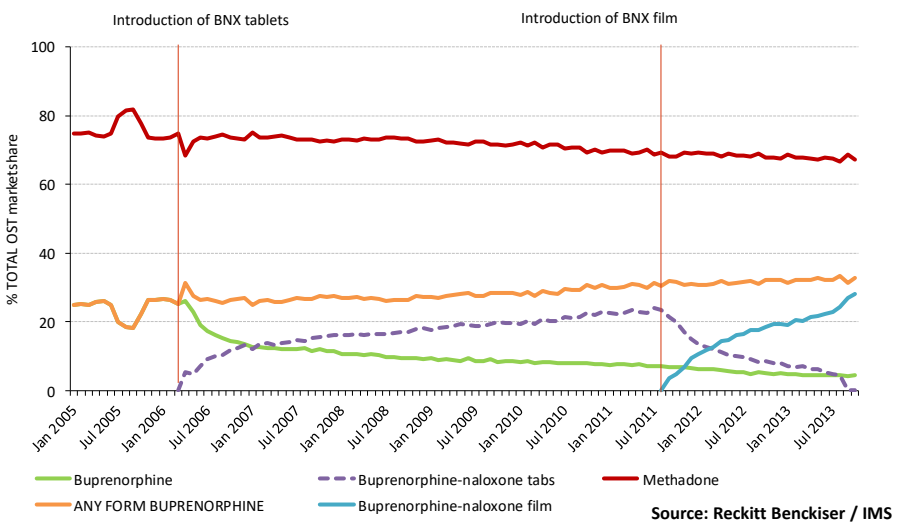
Buprenorphine-naloxone (Suboxone®)

Impact upon

1. OST marketshare?
2. Diversion and injection among OST clients (data not presented) and PWID?

Larance et al (2011) Post-marketing surveillance of buprenorphine-naloxone in Australia: diversion, injection and adherence with supervised administration. *Drug and Alcohol Dependence*
Larance et al (2014) The diversion and injection of a buprenorphine-naloxone soluble film formulation. *Drug and Alcohol Dependence*
Larance et al (2015) Diversion and injection of buprenorphine-naloxone film two years post-introduction in Australia. *Drug and Alcohol Review.*

Impact of buprenorphine-naloxone (BNX) on MAT marketshare, 2005-2013



Source: Reckitt Benckiser / IMS

Diversion and injection among (out of treatment) people who inject drugs

	2006	2007	2008	2009	2010	2011	2012	2013
Total IDRS sample (N)	914	909	909	881	902	868	923	887
Out-of-treatment PWID (n)	**448**	**453**	**444**	**495**	**453**	**419**	**541**	**444**

- Mostly male (64%)
- Mean age ~39 years
- 84% unemployed/receiving government benefits
- 50% in current treatment, mainly methadone
- 54% prison history

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Larance et al (2015) Diversion and injection of buprenorphine-naloxone film two years post-introduction in Australia. *Drug and Alcohol Review.*

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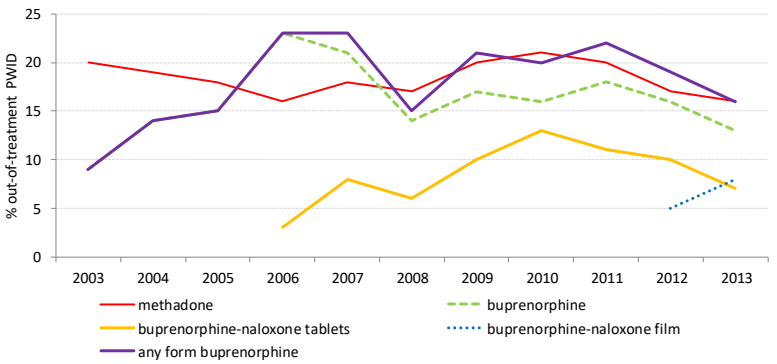
Recent* injection of MAT medication among (out-of-treatment) PWID, 2003-2013

*In the six months prior to interview



Source: IDRS interviews with PWID regularly, 2003-2013

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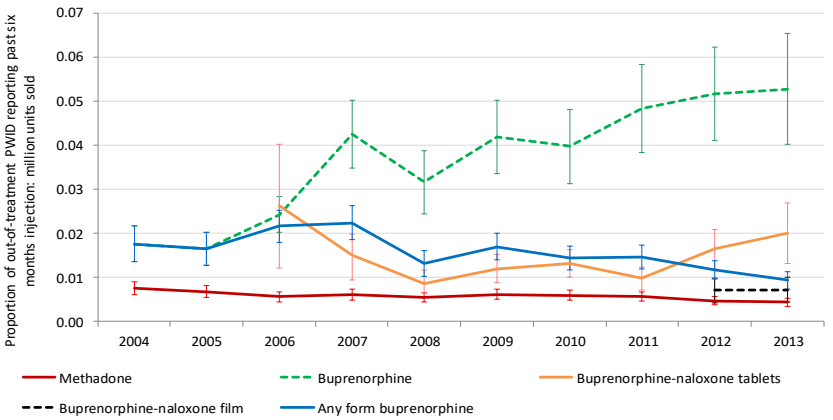
Any injection past six months, 2004-2013

Ratio of % injected in past six months: million standard units sold



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Larance et al (2015) Diversion and injection of buprenorphine-naloxone film two years post-introduction in Australia. *Drug and Alcohol Review.*

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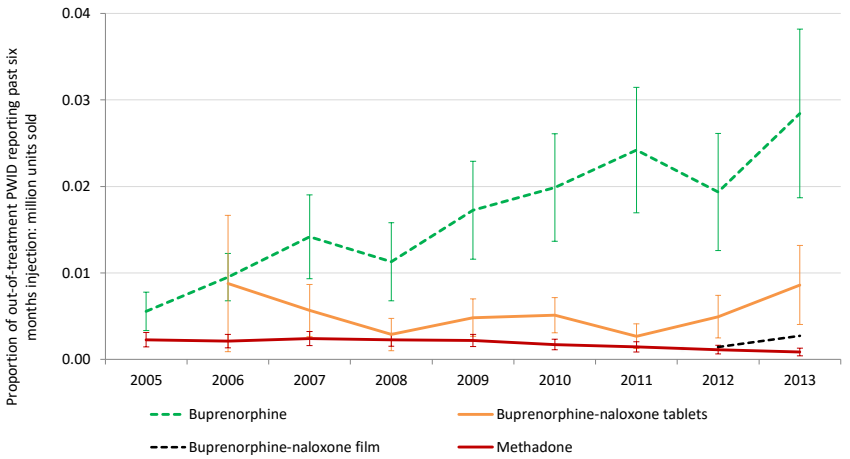
At least weekly injection past six months

Ratio of % injected weekly+: million standard units sold



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Larance et al (2015) Diversion and injection of buprenorphine-naloxone film two years post-introduction in Australia. *Drug and Alcohol Review.*

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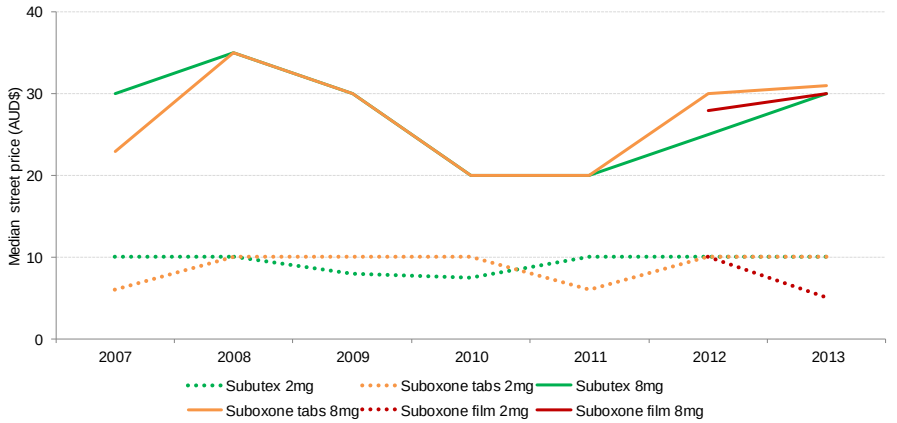
Median street price of buprenorphine

2007-2013 IDRS interviews



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Larance et al (2015) Diversion and injection of buprenorphine-naloxone film two years post-introduction in Australia. *Drug and Alcohol Review.*

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Summary: Out-of-treatment PWID

- ***Street price:*** From 2007-2013, buprenorphine-naloxone tablets and film had a similar street value to mono-buprenorphine.
- ***Injection:*** Buprenorphine-naloxone film injected by fewer PWID, less frequently, compared to mono-buprenorphine
  - particularly salient given differences in treatment availability and important differences in provision of takeaway doses
- Some PWID reported regularly injecting buprenorphine-naloxone formulations (both tablets and film).

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Larance et al (2015) Diversion and injection of buprenorphine-naloxone film two years post-introduction in Australia. *Drug and Alcohol Review.*

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Buprenorphine-naloxone

	Sublingual	Injected
Heroin user not in withdrawal	☹	☹☹
Current methadone treatment	☹	☹☹
Heroin user in withdrawal	☺	☹?
Current Subutex® treatment	☺	😐
Current Suboxone® treatment	☺	😐
Opioid-naive	☺	☺

Source: based on the National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence

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The impacts of a potentially tamper-resistant controlled-release oxycodone formulation

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NOMAD study

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OxyContin®/ Reformulated OxyContin®

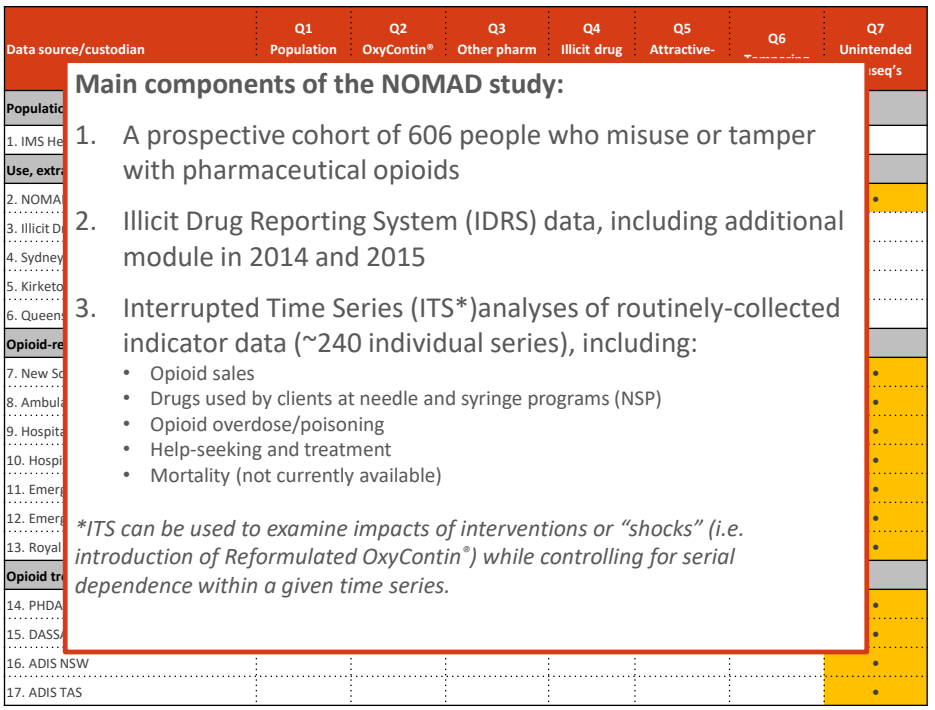
- OxyContin®= controlled release oxycodone
- One of the most widely prescribed opioids in Australia - concerns re: injection and harms; replaced with a *tamper-resistant* formulation
- **1st April 2014:** PBS listing of Reformulated OxyContin®

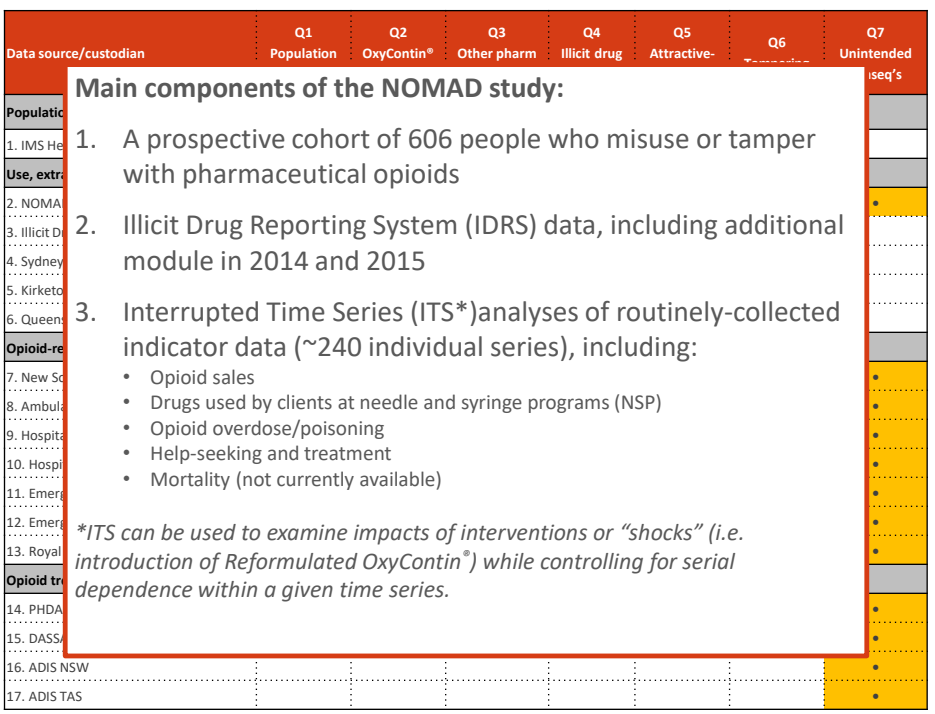
National Opioid Medication Abuse Deterrence (NOMAD) study:

Following the introduction of Reformulated OxyContin®…

1. Population-level utilisation of oxycodone and other opioids?
2. Extra-medical use of OxyContin®?
3. Extra-medical use of other forms of oxycodone or other pharmaceutical opioids?
4. Injection of other illicit drugs?
5. Attractiveness for tampering?
6. Methods of tampering with Reformulated OxyContin® evolve/become widespread?
7. Unintended consequences?

Degenhardt et al (2015). Evaluating the potential impact of a reformulated version of oxycodone upon tampering, non-adherence and diversion of opioids: The National Opioid Medications Abuse Deterrence (NOMAD) study protocol. *Addiction, 110,* 226-237


Data source/custodian
Q1 Population
Q2 OxyContin®
Q3 Other pharm
Q4 Illicit drug
Q5 Attractive-
Q6
Q7 Unintended
Main components of the NOMAD study:
1. A prospective cohort of 606 people who misuse or tamper with pharmaceutical opioids
2. Illicit Drug Reporting System (IDRS) data, including additional module in 2014 and 2015
3. Interrupted Time Series (ITS*)analyses of routinely-collected indicator data (~240 individual series), including:
• Opioid sales
• Drugs used by clients at needle and syringe programs (NSP)
• Opioid overdose/poisoning
• Help-seeking and treatment
• Mortality (not currently available)
*ITS can be used to examine impacts of interventions or "shocks" (i.e. introduction of Reformulated OxyContin®) while controlling for serial dependence within a given time series.
16. ADIS NSW
17. ADIS TAS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16. ADIS NSW
17. ADIS TAS

Reformulated OxyContin®

Impact upon

1. Wider opioid utilisation?
2. Tampering and injection among PWID?
3. Other opioid-related harms?

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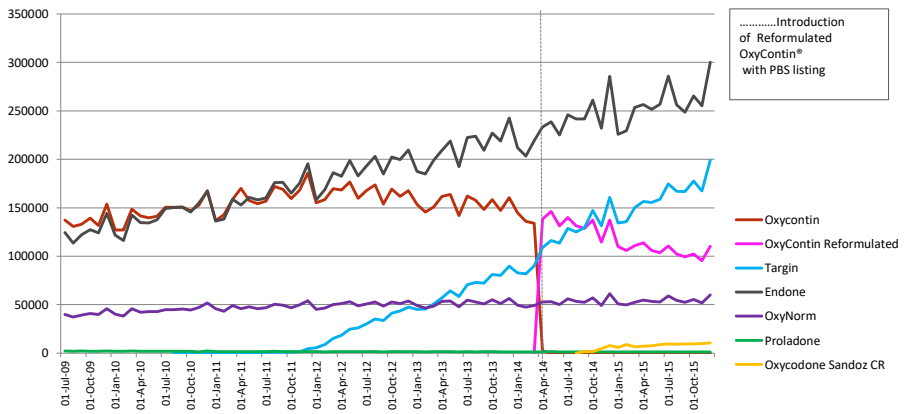
Unit sales of Endone®, Oxycontin®, Targin®, OxyNorm®, generic controlled-release oxycodone and Proladone®, 2009-2015



Note: The above data refer to sales of pack units of pharmaceutical opioids.
Source: IMS Health

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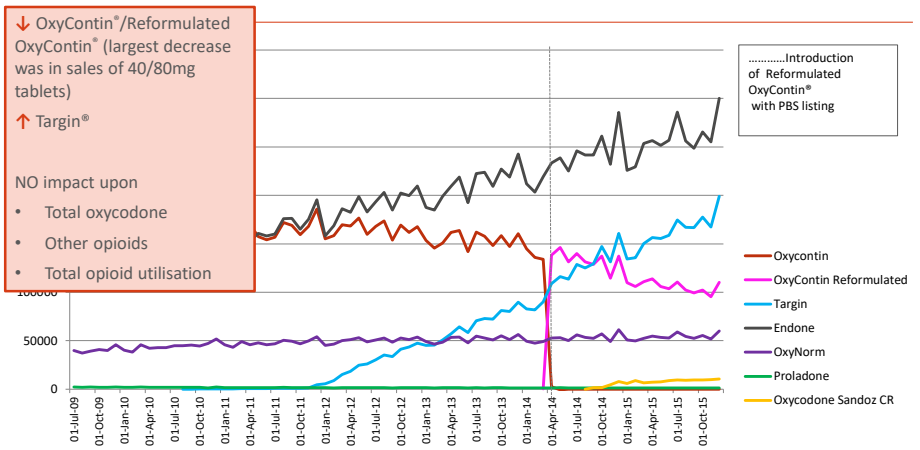
The Difference is Research

Unit sales of Endone®, Oxycontin®, Targin®, OxyNorm®, generic controlled-release oxycodone and Proladone®, 2009-2015



Note: The above data refer to sales of pack units of pharmaceutical opioids.
Source: IMS Health

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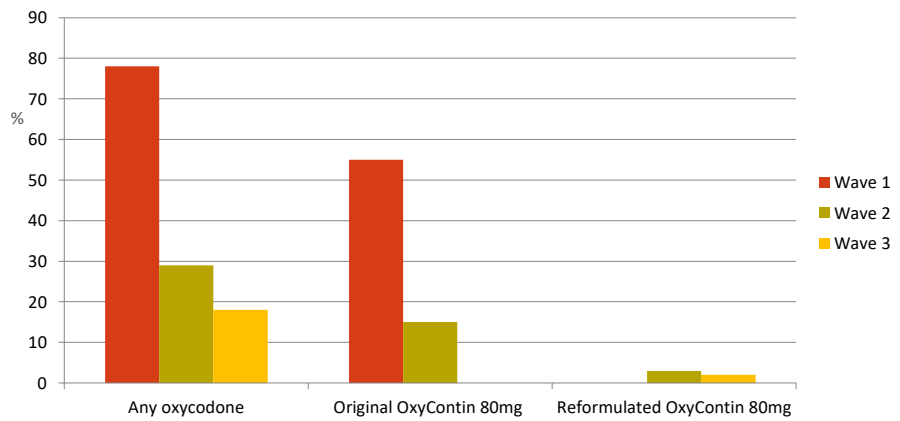
NOMAD cohort: OxyContin® injection (past month)



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NOMAD study

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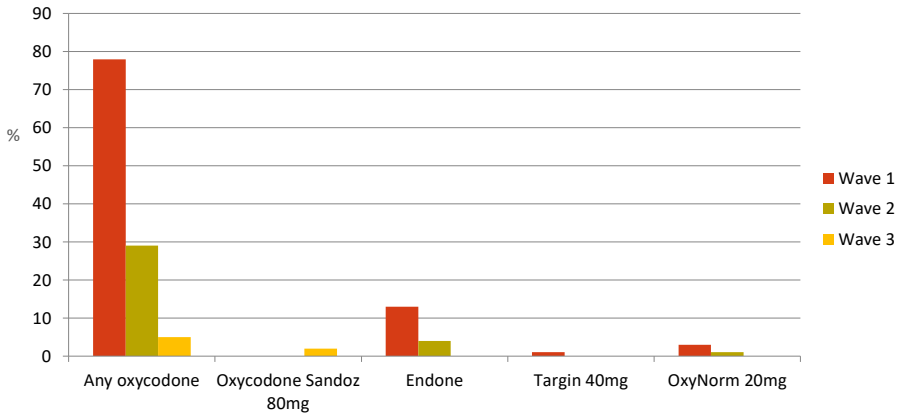
NOMAD cohort: other oxycodone injection(past mth)



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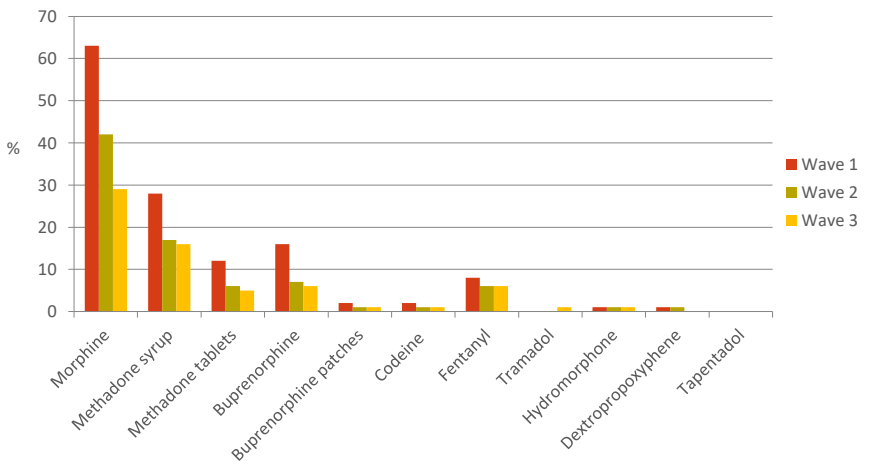
NOMAD cohort: Injection of other opioids(past mth)



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NOMAD study

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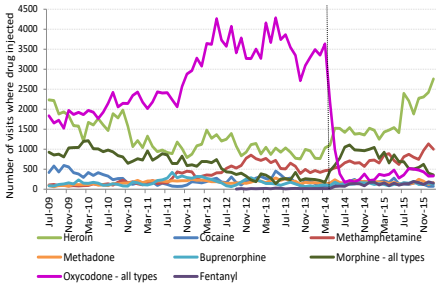
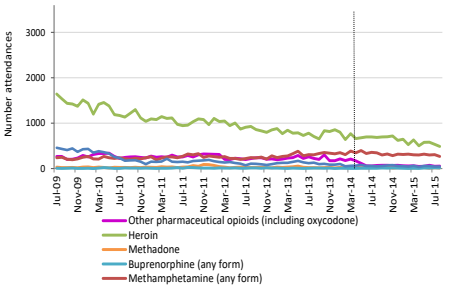
Injection of oxycodone and other drugs among PWID

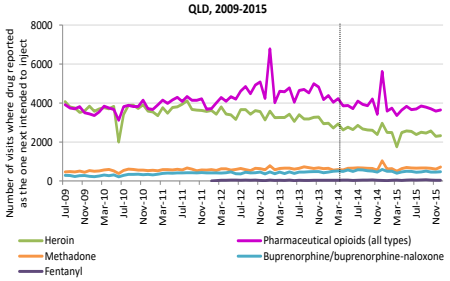
2a: Number of client visits per month by drug injected, Sydney Medically Supervised Injecting Centre (MSIC), King's Cross, New South Wales (NSW), 2009-2015



2b: Number of attendances at two needle-syringe programmes (NSPs) by 'last drug injected', King's Cross, NSW, 2009-2015



2c: Number of attendances at Queensland (QLD) Health NSPs, by 'drug intending to inject', QLD, 2009-2015



Injection of oxycodone and other drugs among PWID

2a: Number of client visits per month by drug injected, Sydney Medically Supervised Injecting Centre (MSIC), King's Cross, New South Wales (NSW), 2009-2015

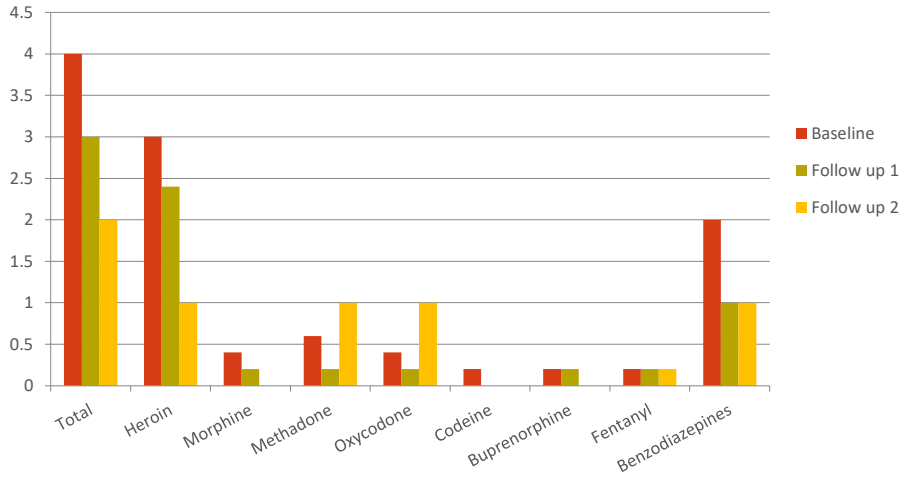
2b: Number of attendances at two needle-syringe programmes (NSPs) by 'last drug injected', King's Cross, NSW, 2009-2015

2c: Number of attendances at Queensland (QLD) Health NSPs, by 'drug intending to inject', QLD, 2009-2015

↓ pharmaceutical opioids (NOMAD cohort and available NSP data)
↓ oxycodone injection (NOMAD and MSIC data)

No change heroin or methamphetamine (NOMAD and available NSP data)

Overdose (past month)



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Baseline n=25; Follow-up 1 n=17; Follow-up 2 n=11

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Opioid-related harms: population-level data

Key study outcome	Nature of population included	Summary of impact	Data sources informing pooled estimates
Drug overdose (all drugs)	Total population	No change	Available health service data
Opioid overdose/poisoning	Total population	No change	NSW health service data
Other drug overdose/poisoning	Total population	No change	NSW health service data
Medication-assisted treatment (total patients)	Total population	No change	Available MAT data
Total new treatment entrants	Total population	No change	NSW PHDAS only
Treatment entry – oxycodone	Total population	↓	NSW PHDAS only

- ***'Available health service data'***: pooled z-scores across drug overdose/poisonings data from Tasmania EDDC, Tasmania hospital, NSW EDDC, NSW APDC and Royal Adelaide Hospital emergency department data.
- ***'NSW health service data'*** includes: pooled z-scores on opioid overdose from NSW ambulance data, NSW EDDC and NSW APDC.
- ***'NSW health service data'*** includes: pooled z-scores on other (non-opioid) drug overdose from NSW ambulance data, NSW EDDC and NSW APDC.
- ***'Available MAT data' includes:*** pooled z-scores across total number of OST patients in NSW (PHDAS) and South Australia (DASSA).

Other opioid-related harms

Key study outcome	Nature of population included	Summary of impact	Data sources informing pooled estimates
Drug overdose (all drugs)	Total population	No change	Available health service data
Opioid overdose/poisoning	Total population	No change	NSW health service data
Other drug overdose/poisoning	Total population	No change	NSW health service data
Opioid substitution therapy (total patients)	Total population	No change	Available OST data
Total new treatment entrants	Total population	No change	NSW PHDAS only
Treatment entry – oxycodone	Total population	↓	NSW PHDAS only

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Other opioid-related harms

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Reformulated OxyContin® tampering attempts
(not all attempts successful)

	Wave 2	Wave 3
	% (N=522)	% (N=499)
Tampering (any method)		
Ever tried tampering	18	27 ↑
Ever successfully tampered	12	22 ↑
Past month tampering	8	8
Of those who tried to tamper (past month): Spent >24 hours tampering	33	4 ↓
Injecting		
Ever tried injecting	15	25 ↑
Ever successfully inject	9	20 ↑
Successful inject past month	6	7 ↑

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Chewing, snorting and smoking reported by <1%.
↑ = statistically significant increase from previous timepoint
↓ = statistically significant decrease from previous timepoint

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Key findings

NOMAD study

- Clear impacts among PWID, with reductions in injection of OxyContin®/Reformulated OxyContin®, no switch to other oxycodone, and no clear evidence of a shift to other opioids or drugs.
- PWID developed methods to circumvent the tamper-resistant formulation, but this practice was not widespread.
- Did not appear to impact at population-level upon overall opioid utilisation or harms.

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Larance et al (under review) Impacts of a potentially tamper-resistant oxycodone formulation on opioid use and harms in Australia: Main findings from the National Opioids Abuse Deterrence (NOMAD) study. *Lancet Psychiatry*

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What have we learned?

- ~93,000 people who inject drugs in Australia vs. 2.9 million Australians prescribed an opioid.
- As a population-wide strategy to reduce harms of overuse or overprescribing, the introduction of this TRF alone was not be sufficient to have an impact on these outcomes.
- The introduction of the TRF product did result in lower levels of oxycodone use and injection in high risk groups of PWID.
- TRFs are only one part of a multi-faceted response.

Multi-faceted responses are required to address unintended consequences

- Abuse-deterrent formulations
- Government permits for long-term prescribing
- "Real time" reporting systems
- Supervised opioid dosing in medication-assisted treatment
- Clinical review of patient progress/adherence
- Treatment of substance use disorders among pain patients
- Enhancing reach and attractiveness of medication-assisted treatment for opioid dependence
- Adjunctive psychosocial treatment (for pain or opioid dependence)
- Harm reduction e.g. naloxone provision

Degenhardt. Larance et al (2015) Reducing extra-medical use and harms of pharmaceutical opioids: The potential role of abuse-deterrent formulations. *The Lancet Psychiatry*

Why hasn't Australia seen the same rapid escalation in opioid-related harm?

- Our universal healthcare system likely provides some protection
- Restricted direct-to-consumer advertising
- Medication-assisted treatment and needle and syringe programme coverage are far higher in Australia (relative to the US)

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Larance et al (2017) Pharmaceutical opioid use and harm in Australia: The need for proactive and preventative responses. *Drug and Alcohol Review*

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We can't afford to be complacent

Two recent policy developments:

- Upscheduling of OTC codeine (Feb 2018)
- Legislation for real time prescription monitoring introduced into the Victorian Parliament (Aug 2017)

Additional strategies include

- enhancing approaches to pain management and comorbidity,
- more attractive and accessible treatments for opioid dependence, and
- scaling-up the provision of take-home naloxone for people using prescribed and illicit opioids.

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Larance et al (2017) Pharmaceutical opioid use and harm in Australia: The need for proactive and preventative responses. *Drug and Alcohol Review*

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Are ADFs effective in reducing opioid-related harm?

Yes	No
They may be effective in reducing the specific harmful practices they are designed to deter (e.g., buprenorphine-naloxone and TRF-CRO)	They are unlikely to result in a net reduction in opioid utilisation. They are unlikely to impact on opioid dependence or opioid overdose at a population-level (e.g., TRF-CRO)

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NOMAD:

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