Progression of Rx Drug Abuse

Filling the Balloon

- Person in Pain
- Guidelines
- Susceptible Person
- Recreational Abuser
- Abuse of Other Drugs

States:
- Intact
- Chewed
- Crushed

Outcomes:
- Addiction
- Overdose
- Death

Process:
- Guidelines
  - Susceptible Person
    - Recreational Abuser
      - Abuse of Other Drugs
- Filling the Balloon
  - States: Intact, Chewed, Crushed
  - Outcomes: Addiction, Overdose, Death
- Treatment
Who Cares About Chewing?

RADARS SKIP: Adults meeting DSM-IV criteria for substance abuse with a primary drug that is an opioid

Route among past month abuse (%)


- Chewed
- Smoked
- Snorted
- Injected

- IR
- Non-ADF ER
- Other ADF ER
- OxyContin
• Question: What is the evidence that opioid analgesics with abuse deterrent labeling improve outcomes (abuse, misuse, overdose, death)?

• 44 reports on opioids with abuse deterrent labeling
  – Hydrocodone (n=7)
  – Morphine (n=5)
  – Oxycodone (n=32)*

• Hill Criteria

• Also assessed confounding factors and bias

# Bradford Hill Criteria

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
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<tr>
<td><strong>Strength</strong> <em>(effect size)</em></td>
<td>The larger the association, the more likely that it is causal.</td>
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<tr>
<td><strong>Consistency</strong> <em>(reproducibility)</em></td>
<td>“Has it been repeatedly observed by different persons, in different places, circumstances and times?”</td>
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<tr>
<td><strong>Specificity</strong></td>
<td>Causal relationship is supported by a very specific population at a specific site and disease with no other likely explanation</td>
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<td><strong>Temporality</strong></td>
<td>The effect has to occur after the cause and after expected delay</td>
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<td><strong>Biological gradient</strong></td>
<td>Greater exposure should generally lead to greater incidence.</td>
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<td><strong>Plausibility</strong></td>
<td>A plausible mechanism between cause and effect</td>
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<tr>
<td><strong>Coherence</strong></td>
<td>Coherence between epidemiological and laboratory findings</td>
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<tr>
<td><strong>Experiment</strong></td>
<td>&quot;... some preventive action is taken. Does it in fact prevent?&quot;</td>
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<tr>
<td><strong>Analogy</strong></td>
<td>The effect of similar factors may be considered.</td>
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<tr>
<td><strong>Additional Criteria</strong></td>
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<tr>
<td><strong>Confounding</strong></td>
<td>Alternative explanations for the observed associations</td>
</tr>
<tr>
<td><strong>Bias</strong></td>
<td>Systematic artifacts of data collection or study design</td>
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Cases Involving Intentional Abuse, Poison Center Program

- Effect Size
- Temporality
- Specificity
Investigations Opened, Drug Diversion Program

- Effect Size
- Temporality
- Specificity
Drugs Used in Past 30 Days, Opioid Treatment Program

- Effect Size
- Temporality
- Specificity
Drugs Used in Past 30 Days, Survey of Key Informants’ Patients Program

- Effect Size
- Temporality
- Specificity
- Consistency

Reformulation

Change from baseline average (%)

Year and Quarter

- OxyContin®
- Hydrocodone
- Hydromorphone
- IR oxycodone
- Morphine
- Other opioids group
Figure 2. Reported Change in Treatment Measures of Abuse After Reformulation of Oxycodone ER

- **Severtson 2016**: 24,049
- **Cicero 2012**: 2,566
- **Severtson 2016**: 12,438
- **Sankey 2016**: 365
- **Cicero 2015**: 10,784
- **Butler 2012**: 140,496
- **Cassidy 2014**: 232,874

**Rate Ratio, Change in Abuse after Reformulation**

- **Months**: 3, 4, 47, 20, 17
Studying abuse deterrent opioid formulations in Australia
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?
4. Extra-medical use of other pharmaceutical opioids and heroin?
5. Attractiveness for tampering?
6. Methods of tampering/oxycodone extraction evolve/become widespread?
7. Unintended consequences?

NOMAD prospective cohort

Methods

• N=606 people who tamper with pharmaceutical opioids
  Eligibility: Reported (a) past month injecting, snorting, chewing or smoking of pharmaceutical opioid(s) and (b) engaged in this practice at least monthly in the past six months.

• 3 study jurisdictions: NSW, TAS and SA

• 3 waves of data collection
  • Wave 1: Nov 2013 – Mar 2014
  • Wave 2: May 2014 – Aug 2014
  • Wave 3: May 2015 – Sep 2015

• Excellent cohort retention
  • 92% of eligible participants at Wave 2
  • 90% of eligible participants at Wave 3

Baseline cohort characteristics

• Majority (96%) injected a drug (past 6 months)

• Demographically similar to other studies of PWID
  Predominantly male (69%); High levels of unemployment (82%); homelessness (17%); prison history (62%).

• Significant comorbidity
  61% current mod-severe depression; 54% chronic pain or disability past 6 months.

• Half (54%) in OST (past 6 months).
Participants referred into the study (n=1321)

Participants assessed for eligibility (n=1176)

Eligible participants n=692

Completed baseline n=606

Completed follow-up 1, n=547 (90%), (92% of eligible participants)

Completed follow-up 2, n=499, (82%) (90% of eligible participants)

Baseline interviews: November 2013-March 2014 (prior to reformulation)

Follow-up 1- May-August 2014

Loss after eligibility n=86
- Withdrew consent n=1
- Could not contact n=4
- Did not complete n=81

Not interviewed at follow-up 1 n=59
- In prison n=9
- Withdrew consent n=4
- Inpatient facility n=2
- Could not contact n=44

Not interviewed at follow-up 2 n=107
- In prison n=31
- Excluded n=3
- Deceased n=8
- Withdrew consent n=8
- Inpatient facility n=3
- Could not contact n=54

Ineligible n=484
- In prison past month n=11
- Did not use or tamper with pharmaceutical opioids n=283
- Only used OST medication n=146
- Did not use opioid medication for long enough n=42
- Not living in jurisdictions n=2

Could not contact n=123
- No longer interested n=22
Oxycodone injection (past month)

- Any oxycodone
- OxyContin OC 80mg
- OxyContin OP 80mg
- Oxycodone Sandoz 80mg
- Endone
- Targin 40mg (/20mg naloxone)
- OxyNorm 20mg tablet

Baseline
Follow-up 1
Follow-up 2

The Difference is Research
Fig. 4. Client visits per month where oxycodone, morphine, fentanyl and heroin were injected, Sydney Medically Supervised Injecting Centre (MSIC), July 2009–August 2014.

Degenhardt et al., Drug Alc Dependence 2015; 151: 56-57.
NOMAD study summary

- Prior to reformulation, 80mg OxyContin® were most frequently diverted/injected
- Observed declines in OxyContin®/oxycodone use and injection following introduction of reformulation among the NOMAD cohort and NSP/MSIC data
  - Heroin and methamphetamine remain primary drugs of injection among NOMAD cohort and NSP/MSIC clients.
  - Some tampering with Reformulated OxyContin has persisted at follow-up 2 (27% attempted in past month), but overall, Reformulated OxyContin® was viewed as less attractive for tampering/injection
Negative Data – NSDUH past 30 day Nonmedical Use

Novak S. FDA-2013-D-0045, 2013

[Graph showing the past year nonmedical use estimate numbers in thousands from 2004 to 2014 with a peak in 2010 indicated by a red box labeled "Reformulation".]
Summary

• Introduction of oxycodone ER was followed by improved outcomes related to oxycodone ER

• Other opioids have increased over the same time period (heroin)

• The results are similar in 3 different countries with different baseline conditions, different measurement instruments and timeframes.

• The early initial decrease in oxycodone ER contrasted with increases for most other opioids during the first year or more, but was then followed by decreases for almost all opioids.

• Multiple sources of bias and confounding are present, however, we conclude that none of these accounts for the observed decrease.