PHARMACEUTICAL OPIOID PROBLEMS AND CHANGING TREATMENT NEEDS:
An Australian perspective

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Overview

• Pharmaceutical opioid use and definitions
• Characteristics of people who use pharmaceutical opioids (PO)
• The evidence base for treatment of pharmaceutical opioid dependence
• Treatment models
• Other at risk populations
Pharmaceutical Opioids

- Use of opioids for pain has increased dramatically over the past 10-20 years in many high income countries
- Opioids are an important and effective group of medications, especially for acute pain (which many countries have poor access to)
- Large increases in opioids don’t equate to problematic use HOWEVER there are strong correlations between increasing use and harms

PBS-subsidised opioid dispensings in Australia, 1992-2012

## National opioid utilisation

<table>
<thead>
<tr>
<th>Pack</th>
<th>Number</th>
<th>% of total packs sold</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong Prescribed Opioids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>859,518</td>
<td>2</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5,812,790</td>
<td>13.7</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>224,840</td>
<td>0.5</td>
</tr>
<tr>
<td>Methadone</td>
<td>541,701</td>
<td>1.3</td>
</tr>
<tr>
<td>Morphine</td>
<td>775,568</td>
<td>1.8</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1,881,695</td>
<td>4.4</td>
</tr>
<tr>
<td><strong>Total prescribed opioids</strong></td>
<td><strong>26,858,419</strong></td>
<td><strong>63.4</strong></td>
</tr>
<tr>
<td><strong>Other Prescribed Opioids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tapentadol</td>
<td>5,074</td>
<td>0</td>
</tr>
<tr>
<td>Tramadol</td>
<td>4,002,959</td>
<td>9.5</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>464,247</td>
<td>1.1</td>
</tr>
<tr>
<td>Codeine (Prescribed)</td>
<td>12,290,027</td>
<td>29</td>
</tr>
<tr>
<td><strong>Total prescribed opioids</strong></td>
<td><strong>15,490,207</strong></td>
<td><strong>36.6</strong></td>
</tr>
<tr>
<td><strong>Total opioids</strong></td>
<td><strong>42,348,626</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Degenhardt et al 2015 - Under review
Opioid utilisation by geographical area

Australia (2011 Statistical Local Areas)
Total opioid consumption (OME mg) per person
- 0-500
- 501-1,500
- 1,501-3,000
- 3,001-7,000
- 7,001-26,000

Degenhardt et al 2015 - Under review
Hospitalisations from opioids in Australia 1998 - 2009

Non-medical Pharmaceutical use in Australia

- Most drugs (alcohol, tobacco, heroin, ecstasy) decreasing
- Pharmaceuticals one of the few categories that increased from 2010-2013
  - 8% ‘ever’ used non-medically
  - 5% in the past 12 months
- Majority of opioid mortality and poisonings are now from pharmaceutical opioids

Who develops problems with pharmaceutical opioids and what do we know about treatment?
Who develops problems with pharmaceutical opioids?
Defining ‘non-medical’ or ‘problematic’ opioid use
Definitions

Addiction / Dependence

Physiological adaptation ≠ addiction
Withdrawal/tolerance ≠ addiction
How is ‘Substance Use Disorder’ defined

• Substance taken in larger amounts or over a longer period than was intended.
• Persistent desire or unsuccessful efforts to cut down or control the substance use.
• A great deal of time spent obtaining, using/recovering from substance use.
• Craving.
• Recurrent substance use resulting in a failure to fulfill responsibilities.
• Given up or reducing social, occupational, or recreational activities because of substance use.
• Recurrent hazardous substance use / use despite harm.

  *Loss of control over use of opioids*
People who use pharmaceutical opioids are a heterogeneous population.

“Addicted” (SUD)  “Substance abusers”  “Recreational users”  “Self-Treaters”  “Adherent”  “Chemical copers”  “Substance abusers”  “Addicted” (SUD)

Nonmedical Users  Pain Patients

Developing dependence to pain medications

"The headache would go temporarily and would return again ..I started off taking them four hourly ... It sort of got into a vicious cycle where I could take six Panadeine Forte and then two hours later take four Panadeine .. It was only when I swapped Dr’s and I went for a Panadeine Forte prescription and she said but I only gave you one three weeks ago and I said but they’re all gone that she actually picked up that I was addicted to them." (Female, 54 yrs)
Developing dependence to pain medications

- Cohort of treatment entrants \((n = 108)\) most \((66\%)\) initiated PO use for pain
Why do people keep taking them?

"by that stage, when I was having that many... when I started to feel really sick, trying to get them down, I got back down to 36 in one go and even that was pretty difficult because you’d retch trying to get them down but you just knew you needed to get them in there to make you feel OK again." (Female, 42yrs)
The Four “A’s” of Pain Treatment Outcomes

- Analgesia (pain relief)
- Activities of Daily Living (psychosocial functioning)
- Adverse effects (side effects)
- Aberrant drug taking (addiction-related outcomes)

Is the patient receiving benefits without being harmed by their medication? (C Stannard, UK)
Dependence with OTC codeine

- Increased dose (above daily maximum dose)
- Taking for reasons other than pain
- Difficulty going without codeine
- Codeine no longer effective
- Codeine no longer helps with pain
- Need higher doses/ exceeding maximum dose
Pharmaceutical opioid use amongst different populations
Use of Pharmaceutical Opioids by PWID (IDRS) (Annual AUS survey, people who regularly inject)

- Injecting use of morphine increased between 2001 and 2007 (from 40% to 50%), declined to 35% in 2013.
- Increase in oxycodone injecting use among IDRS participants, from 17% in 2005 to 31% in 2013.
- 6% reported injecting fentanyl (past six months in 2013)
- Heroin still main drug injected
- Oxycodone use weekly or less on average
- Summary: PO use usually opportunistic and occasional...

harm reduction, and existing treatments the focus
Mortality from pharmaceutical opioids

• Oxycodone (n = 465, 2001-2009)
  o Most deaths involved prescribed oxycodone (55%), non-injectors (54%) and chronic pain (52%)

• Fentanyl (n = 136, 2000-2011)
  o Minority (1/3) prescribed, most (55%) injecting, and 38% have chronic pain

• Codeine (n = 1200, 2000-2009) (In press)
  o High rates of comorbid mental health (53%), substance use (36%) and chronic pain (35%), history of injection (16%)
  o 49% accidental, 35% intentional
  o Source mostly (60%) not reported, 60% of coded cases are prescription codeine

Treatment demand in increasing

• USA increase from < 1.0% (1998) to 10 % (2011) of all treatment demand
  o Heroin treatment stable (14% -16%) for the past 15 years

• In 2011, 5% of all patients entering drug treatment programmes in Europe reported prescription opioids as their primary drug

• Increasing mortality in the UK

Treatment Episode Data Set : Admissions (TEDS) Substance Abuse and Mental Health Services Administration; 2014 (USA)
Treatment for opioids other than heroin (2015)

European drug report, 2015, EMCDDA
Australian PO Treatment samples

Explore existing sources:
• National Minimum Dataset – AOD Treatment
• Opioid pharmacotherapy data (NOPSAD)

Develop new studies:
• Retrospective case review
• Cohort studies
National Minimum Data on Drug Treatment

• Closed treatment episodes from the Alcohol and Other Drug Treatment Services National Minimum Data Set (AODTS-NMDS) for 2002–03 to 2010–11
  o Data on publicly funded alcohol and other drug treatment services
  o Most pharmacotherapy services and private services are outside the scope of AODTS-NMDS → a non-OST sample

Changing treatment demand in Australia

In 2010-11 PO represent one in five treatment episodes

Results: Changes in individual PO over time

Increases in codeine, oxycodone and fentanyl episodes

## Episode Characteristics by Opioid Type

<table>
<thead>
<tr>
<th></th>
<th>Heroin (n = 68517)</th>
<th>Strong Opioids (n=11458)</th>
<th>Codeine (n = 4424)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age (IQR)#</strong></td>
<td>30.0 (12.0)</td>
<td>35 (15.0) ↑</td>
<td>36.0 (14.0) ↑↑</td>
</tr>
<tr>
<td><strong>Gender (%Male)</strong></td>
<td>67.6</td>
<td>65.5 ↓</td>
<td>47.4 ↓</td>
</tr>
<tr>
<td><strong>Regional or remote location</strong></td>
<td>16.1</td>
<td>49.5 ↑</td>
<td>34.2 ↑</td>
</tr>
<tr>
<td><strong>Method of use of Principal DOC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injects</td>
<td>89.9</td>
<td>55.7 ↓</td>
<td>13.1 ↓</td>
</tr>
<tr>
<td>Swallow</td>
<td>1.1</td>
<td>35.7 ↑</td>
<td>82.6 ↑↑</td>
</tr>
<tr>
<td>Reports 'never injected'</td>
<td>4.4</td>
<td>16.6 ↑</td>
<td>52.5 ↑↑</td>
</tr>
<tr>
<td><strong>Other Drugs of Concern</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>12</td>
<td>16.2 ↑</td>
<td>14.5 ↑↑</td>
</tr>
<tr>
<td>Alcohol</td>
<td>10.3</td>
<td>10.8</td>
<td>14.6 ↑↑</td>
</tr>
<tr>
<td>Cannabis and related drugs</td>
<td>24.4</td>
<td>19.8 ↓</td>
<td>10.9 ↓↓</td>
</tr>
<tr>
<td>Meth/Amphetamines</td>
<td>16.8</td>
<td>13.3 ↓</td>
<td>6.0 ↓</td>
</tr>
</tbody>
</table>

↑p < .01 Compared to heroin  ↑↑p < .01Codeine compared to strong opioids

Results: Changes in gender over time

Increasing proportion of males for codeine and oxycodone, changing significantly faster for codeine
National Opioid Pharmacotherapy Statistics Annual Data (NOPSAD)
Pharmaceutical opioids: treatment populations

• International research has identified that there are important differences between people who use **pharmaceutical opioids** and **heroin**
  o Greater pain, more mental health comorbidity
  o Shorter opioid use histories, less treatment experience
  o More likely to be white, employed

Brands et al 2004; Moore et al 2007; Fischer et al 2008
## Consistent patterns across multiple studies

<table>
<thead>
<tr>
<th></th>
<th>Codeine web survey (n = 800)</th>
<th>Retrospective case series (n = 147)</th>
<th>POUT Cohort study (n = 108)</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>Most female</td>
<td>Codeine female/strong PO male</td>
<td>52% female</td>
<td>More females</td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td>Mainly employed</td>
<td>Higher amongst codeine</td>
<td>29% overall (higher for codeine)</td>
<td>Greater levels of employment</td>
</tr>
<tr>
<td><strong>Mental health</strong></td>
<td>Poor</td>
<td>High levels of co-morbidity</td>
<td>Most report depression, anxiety, trauma, highly medicated</td>
<td>Significant mental health problems</td>
</tr>
<tr>
<td><strong>Physical Health</strong></td>
<td>Poor physical functioning, Chronic pain</td>
<td>Most report pain as reason for initiation</td>
<td>85% report problematic pain in past year (41% current chronic pain)</td>
<td>Significant physical health problems</td>
</tr>
<tr>
<td><strong>Drug use history</strong></td>
<td>Around 60% ever used any illicit drugs (not different to non-dependent)</td>
<td>Varied by opioid type, multiple opioids and injection history for strong PO</td>
<td>58% ever injected, 17% used heroin in the past year</td>
<td>Significant minority have never injected/used heroin</td>
</tr>
</tbody>
</table>

Nielsen et al 2011 Journal of Opioid Management
Nielsen et al 2014 Drug and Alcohol Review
Nielsen et al 2015 In preparation – POUT cohort
Comparing codeine (n = 53) users to other pharmaceutical opioid users (n = 82) in treatment in NSW

Summary

• Increasing PO treatment presentations
• In comparison to heroin treatment
  o Non-injectors
  o More chronic pain
  o Over-represented at rural/regional treatment service
• Important differences between pharmaceutical opioids
• Some characteristics that might support good treatment outcomes (e.g. higher levels of employment)
• Some characteristics might complicate treatment (e.g. pain)
Treatment for pharmaceutical opioid dependence
Opioid agonist treatments

• Much of the focus of the rest of the talk
• Not all patients are ready or suitable for opioid agonist treatments (e.g. methadone, buprenorphine)
• These treatments have the strongest evidence
• To enter pharmacotherapy treatment ➔ met criteria for opioid dependence (most severe end of the spectrum) i.e. not all problematic use
Is treatment for PO dependence different?

Q: Can we just use the same old treatments?
A: ‘... it depends’

There are a number of important characteristics that might inform treatment needs

- Level of tolerance/opioid dependence
- Other comorbidities (mental and physical health – especially pain)
- History of injection? History of heroin use?
- Treatment access (e.g. supervised dosing, employment, families)
- What treatments do people want? (reluctance to enter `drug’ treatment)
Detoxification versus maintenance

Why detoxification for PO?

→ Shorter use histories, greater social support, employment, lower levels of neuroadaptation (i.e. lower doses of opioids)

→ Unwilling to enter long term treatment (stigma/employment)

Australian treatment research:

→ Codeine users are more likely to receive detox that strong opioid users (Nielsen et al 2014 Drug and Alcohol Review)

→ PO more likely to have shorter/less intensive treatment (e.g. assessment only) compared to heroin users (Nielsen et al 2015 Drug and Alcohol Dependence)
Long or short-term treatment?
Short term buprenorphine treatment

- **POATS study**: 653 treatment-seeking people dependent on prescription opioids 2 and 12 weeks of buprenorphine
  - Two weeks of buprenorphine – 93% relapsed
  - Twelve weeks of buprenorphine – 91% relapsed

*Short-term treatment is rarely enough*

Randomised trials comparing detox to maintenance

- Buprenorphine (1, 2 and 4 week) taper then naltrexone (n = 70)
- Buprenorphine taper (+ NTX) vs maintenance treatment (n = 113)
- Better retention and less substance use with maintenance/longer buprenorphine treatment

Sigmon et al 2013, Fiellin et al 2015
Which pharmacotherapy?

• Little evidence to compare pharmacotherapy
  ○ Four open label studies, two recruited buprenorphine injectors (previously opium/herion use)
• Neumann (2014) recruited PO with pain (n = 54)
  ○ Used low doses of OST (esp methadone)
  ○ Improved pain (no diff b/w MTD and BPN)
  ○ Less opioid use with MTD
  ○ No difference in retention, other drug use between groups
• Saxon (2013) n = 1269 (170 PO only) RCT comparing methadone with buprenorphine-naloxone
  ○ For PO there was NO difference in drug use OR retention between the groups (in contrast to heroin users)
Buprenorphine for pharmaceutical opioid dependence

Rationale for buprenorphine similar to other opioid dependent populations

- Less overdose risk
- Fewer supervision requirements compared with methadone (higher employment among PO)
- Less stigma
- May also have benefits in pain
Buprenorphine treatment for PO dependence

Induction for PO dependent people:

1) Rates of precipitated withdrawal were same or lower than with heroin users

2) Doses required are comparable

3) Few differences between PO

*Caution: specific protocol for methadone induction*

Predictors of treatment outcomes: Heroin use

Treatment outcomes for pharmaceutical opioid dependence compares favourably to those for heroin use

• Better retention
• Less substance use
• PO may have better outcomes with psychosocial adjunct treatments (e.g. CBT, contingency management)

Any heroin use predicts poorer outcomes (more opioid use, poorer retention)

Predictors of treatment outcomes: Pain

Mixed findings:
Weiss et al 2011 (POATS) – no difference in outcome by pain status at baseline

Potter et al – examined effect of pain on taper outcomes;
• Those with moderate to severe pain did better DURING treatment
• Those with pain had more self-reported use at follow-up (no difference in UDS)

**Note that most of these studies were specifically excluding patients with significant pain that needed opioids for management**
Buprenorphine for opioid dependence in pain patients

Open label with patients transferring from full opioid agonists (e.g. oxycodone) to buprenorphine (retrospective reports) – lower quality evidence

Malinoff et al. American Journal of Therapeutics. 2005

- Pain report less pain after transfer to buprenorphine
- Mean doses of 8–28 mg per day (dose frequency not reported)
- Patients on high opioid doses (> 200 mg OME a day) show comparable or greater improvements in pain and quality of life after transfer

Evidence is low quality but promising
Buprenorphine for codeine dependence

Isn’t codeine a weak opioid?

- People presenting with codeine dependence less likely to receive maintenance treatment
- Where maintenance offered doses required are comparable to other patients
  - Median buprenorphine dose was 12-16 mg (range 4-32 mg)
- Buprenorphine doses received markedly higher than estimated codeine doses based on standard dose conversion tables.

# Buprenorphine doses for codeine dependence

<table>
<thead>
<tr>
<th>Codeine Dose</th>
<th>Estimated BPN dose using conversion tables for pain treatment</th>
<th>Actual BPN dose day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.17</td>
<td>6</td>
</tr>
<tr>
<td>256 (20-32 tabs)</td>
<td>0.89</td>
<td>16</td>
</tr>
<tr>
<td>307</td>
<td>1.06</td>
<td>8</td>
</tr>
<tr>
<td>320</td>
<td>1.11</td>
<td>6</td>
</tr>
<tr>
<td>488</td>
<td>1.69</td>
<td>6</td>
</tr>
<tr>
<td>576</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>600</td>
<td>2.08</td>
<td>10</td>
</tr>
<tr>
<td>768</td>
<td>2.66</td>
<td>16</td>
</tr>
<tr>
<td>900 (70-100 tabs)</td>
<td>3.12</td>
<td>20</td>
</tr>
</tbody>
</table>
In summary: treatment for PO dependence

• We have treatments that work
• They work in similar ways
• The treatment system, rather than the treatments, may need tailoring
  o Higher levels of employment
  o More females
  o Pain
  o Non-injectors
  → Specific ‘PO Clinics’
The importance of treatment setting

“The only thing that concerns me sometimes is that I have to line up with the methadone people, or the other heroin users at the clinic”

(Male, 42 yrs)
Tailoring services for PO dependence

- Detailed assessment including pain history
- Separate physical location
- Transfer quickly to community pharmacy
Are we treating the at-risk patients?

- Existing research focus treating opioid dependence
- HOWEVER: Most ‘at-risk’ patients are nowhere near AOD treatment services

Pain and Opioids IN Treatment (POINT) cohort study

- 1500 patients with chronic pain prescribed opioids
  - 40% prescribed >90mg oral morphine equivalents daily, 15% >200mg OME daily
  - One third use benzodiazepines (most daily)
  - Median of 3-4 sedative medications (up to 32 medication in total)
  - High levels of depression/anxiety
  - 1 in 5 PO SUD, most (68%) report problems/concerns with opioids
Often we may be missing the point...

“it's a difficult balancing act to make sure the drug is accessible to those who need it, without making it too easy to get for those who might misuse it”

(Kos Sclavos – Pharmacy Guild)

- False dichotomy of good and bad patients
- Usually the patient with a pain condition develops dependence
- Earlier detection and intervention where problems are developing OR opioids not working
- Opioid dependence is a health problem – health response
Future work

• Helping pharmacists to talk to people about pain, and the role of opioids
• Universal precautions
• Evidence based medicine
• Public education about the role of opioids (and the role of other treatments) especially in chronic pain

*Is the patient receiving benefits without being harmed by their medication?*
Acknowledgements

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