

NDARC

National Drug &
Alcohol Research Centre

The Difference is Research

Codeine: The facts

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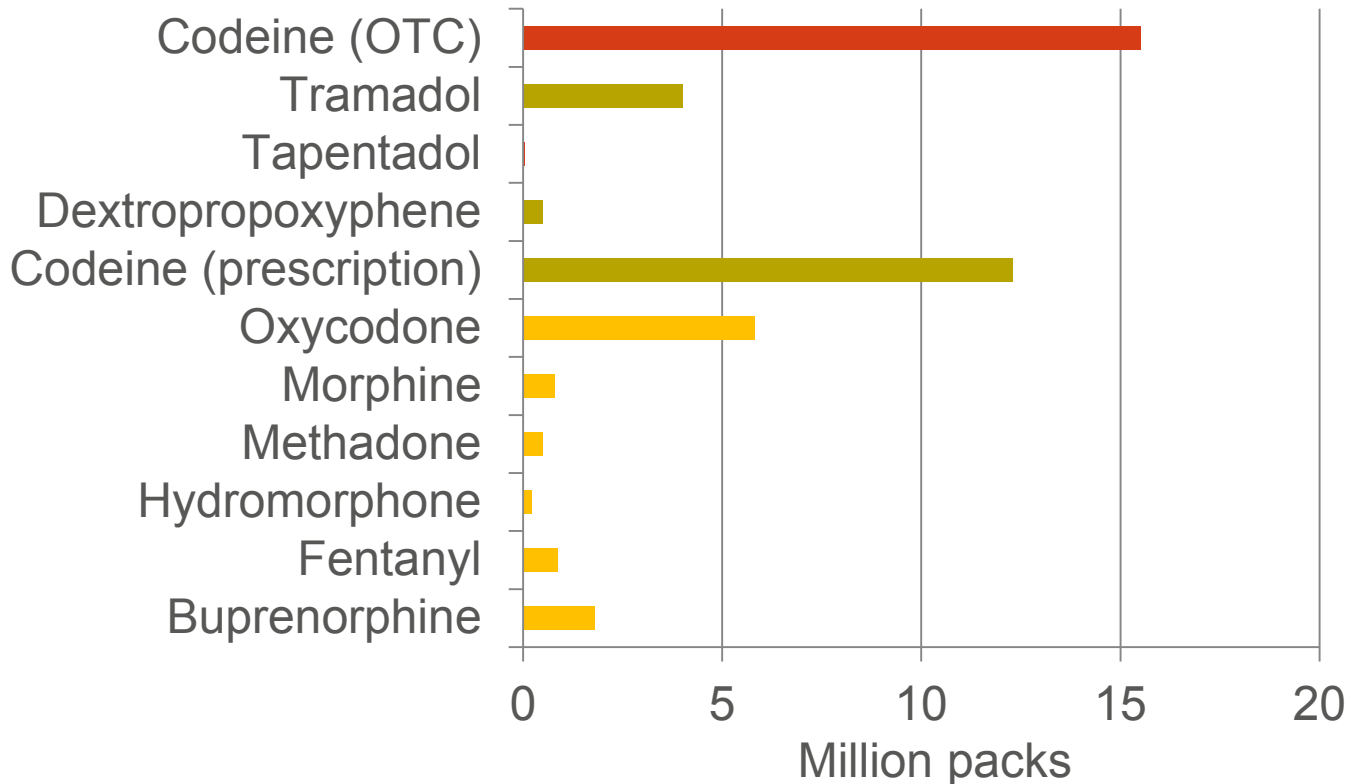
Australia's
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Codeine: overview

1. Codeine use in Australia
2. Characteristics of codeine dependence
3. Identifying codeine dependence
4. Treatment approaches (focus on primary care)

Codeine use in Australia



Opioid pack sales (in millions) from: Degenhardt, Gisev, Cama, Nielsen, Larence and Bruno. The extent and predictors of pharmaceutical opioid utilisation in Australia. *Pharmacoepidemiology and Drug Safety*. (2016)

Codeine use in Australia

- > 15 million packs OTC and 12 million prescribed
- Highest codeine use in remote areas and low income areas

Eur J Clin Pharmacol
DOI 10.1007/s00228-015-1995-8



PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

An ecological study of the extent and factors associated with the use of prescription and over-the-counter codeine in Australia

Natasa Gisev¹ • Suzanne Nielsen¹ • Elena Cama¹ • Briony Larance¹ •
Raimondo Bruno^{1,2} • Louisa Degenhardt¹

Codeine as an analgesic

- Weak mu-opioid agonist
- Analgesic effect predominantly through its metabolism to morphine via CYP2D6 enzyme
- Considerable variable in metabolism between individuals (from poor to ultra-rapid metabolism)
- Ultra-rapid metabolism → opioid toxicity
- Poor metabolism → no analgesic effect

Kirchheiner J et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J. 2007

Codeine-related harm

- Codeine-related deaths increased from 3.5 per million in 2000 to 8.7 per million in 2009
 - Trebling of non-OST drug treatment presentations for codeine between 2002-2011
 - Among people entering methadone and buprenorphine increasing numbers report codeine as the main drug
 - 2014 – 2.7% of cases (1287 people)
 - 2015 – 3.5% of cases (1676 people)
 - 2016 – 4.6% of cases (1562 people*)
- * missing data from Vic and ACT means actual number likely to be higher (>2000)

Characteristics of codeine dependence

Over-the-counter codeine dependence

- Different studies (convenience samples) find approximately one in five people using OTC codeine meet dependence criteria
- No difference on demographic characteristics (age, gender, employment, education)
- Those meeting dependence criteria *more* likely to report:
 - chronic pain (OR 2.3, 95%CI 1.2 -4.4)
 - psychological distress (OR 1.1, 95%CI 1.0-1.1)
 - previous AOD treatment (OR 2.3. 95%CI 1.2 – 4.4)
 - exceeding recommended dose (OR 8.7, 95%CI 4.7-16.3)
- Most (58%) ‘dependent’ people did not have an AOD history
- Most (75%) with dependence had never sought any help

Use patterns: codeine dependence

- Typically 8 – 100 tablets per day
 - ‘Therapeutic dose dependence’
 - ‘High-dose dependence’

“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)

Illustrations of codeine dependence

"I was getting cluster migraines, one after the other, as one went away another one would start, that's what I thought but ... what was actually happening was my body had become used to such a level of codeine that once that level started to drop I started to get a withdrawal headache and of course I would think oh god, my migraine is back. ... I didn't realise that it was a vicious cycle because by that stage the headache was part of the codeine addiction." (Female, 54 yrs)

Identifying codeine dependence in pharmacy / primary care

Open ended questions: Codeine use

- Current use: *“How often do you take codeine?”*
“How long have you been taking codeine in that way”
- Dose escalation: *“do you ever need to take more than two tablets to relieve your pain?”* (*“Can you tell me about that?”*)
- Withdrawal: *“What happens when you don’t take codeine?”* (*ask about timing of last dose and emerging symptoms*)

Opioid withdrawal: signs and symptoms



Opioid withdrawal symptoms

EYES

Pupillary dilation

Lacrimation

NOSE

Rhinorrhea

SKIN

Piloerection

GI

Nausea

Vomiting

Diarrhea/cramps

VITAL SIGNS

Tachycardia

Hypertension

CNS

Restlessness

Irritability

Insomnia

Craving

MUSCULOSKELETAL

Aches/pains

- Most patients are unfamiliar with opioid withdrawal
- Not all patients have all symptoms
- Some patients have not gone without codeine to experience withdrawal

Screening Tool: OTC Codeine Assessment

1a How often do you take OTC codeine? (Choose one of the following)

Every day Most Days

Proceed to question 1b

Once a week or more About once a month Every few months Once or twice a year

Proceed to question 2

1b How long have you been using OTC codeine with this frequency?

Last week Last four weeks

Last year Longer than one year Longer than three years

2 What was the main reason OTC codeine was taken the last occasion it was used? (Choose one of the following)

Headache Back pain Dental pain Migraine Period pain Any other physical pain

To relax To feel better To sleep Other _____

3 In the past 12 months, how difficult did you find it to stop or go without OTC codeine? (Choose one of the following)

Not difficult

Quite difficult

Very difficult

Impossible

Screening Tool: OTC Codeine Assessment

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Every day Most Days

Proceed to question 1b

Once a week or more About once a month Every few months Once or twice a year

Proceed to question 2

1b How long have you been using OTC codeine with this frequency?

Last week Last four weeks

1 Point

Last year Longer than one year Longer than three years

2 Points

2 What was the main reason OTC codeine was taken the last occasion it was used? (Choose one of the following)

Headache Back pain Dental pain Migraine Period pain Any other physical pain

0 Points

To relax To feel better To sleep Other _____

1 Point

3 In the past 12 months, how difficult did you find it to stop or go without OTC codeine? (Choose one of the following)

Not difficult

0 Points

Quite difficult

1 Point

Very difficult

1 Point

Impossible

1 Point

Assessing dependence

Screening \neq diagnosis

Tolerance and withdrawal \neq 'addiction'

- Goal is to identify those that may need help ceasing codeine

Scoring 2 or more = need for a more detailed assessment

ICD-10 definition of dependence

3 or more in 12 months

- A strong desire to take codeine
- Difficulties in controlling codeine use
- Physiological withdrawal on cessation
- Evidence of tolerance
- Progressive neglect of alternative pleasures/ interests due to codeine use
- Persisting with codeine use despite clear evidence of harm

Managing codeine dependence in primary care

Evidence summary: Treating dependence

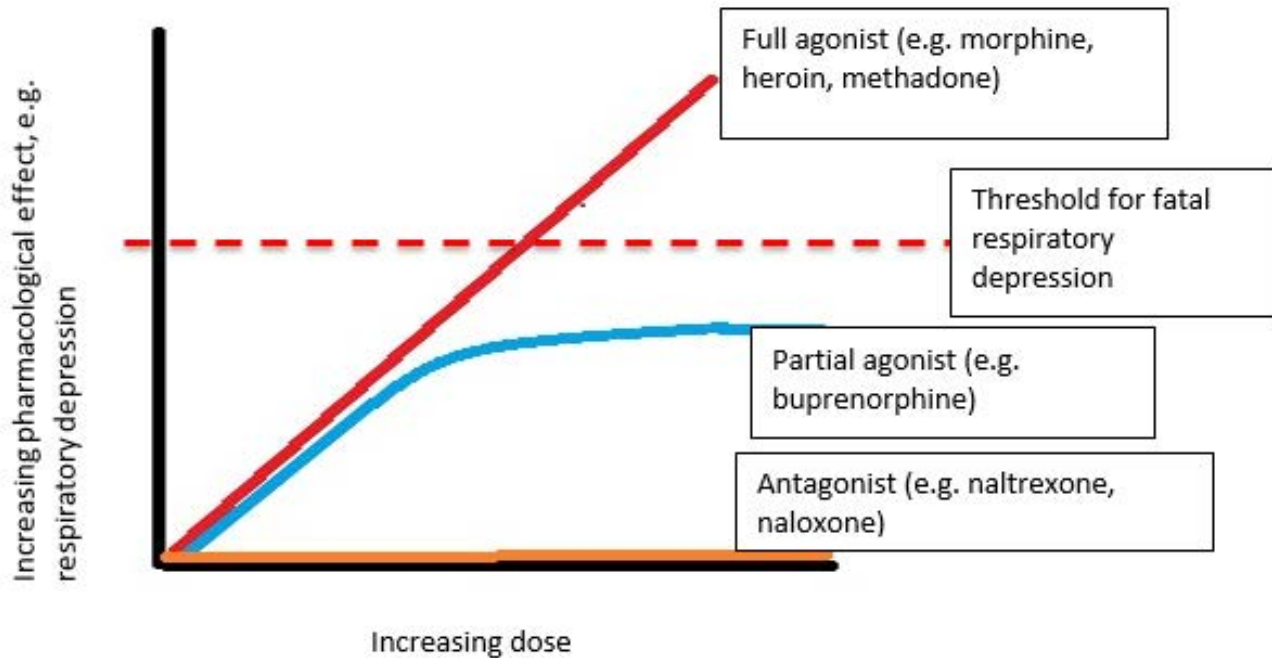
- Choice of pharmacotherapy
- Taper versus maintenance
- Dose requirements

Buprenorphine or methadone?

- Cochrane review: For *pharmaceutical opioid* dependence, the evidence supports methadone AND buprenorphine(+naloxone)
- For codeine dependence...
 - Most experience is with buprenorphine
 - Greater flexibility in treatment (i.e. takeaways)
 - Safety profile important with unclear level of neuroadaptation
 - Ceiling on respiratory depression
 - Unaccredited GPs can prescribe in many states



Full and partial agonists



Taper versus maintenance?

- Cochrane review - better outcomes with maintenance compared with taper/short term treatment
- Consistent with systematic review that found frequent relapse after taper

Buprenorphine dose

- Codeine is considered a ‘low potency’ or ‘weak’ opioid, generally used orally
- Considerable variation in metabolism (and therefore opioid effect) between patients
- How does this impact on dose requirements with buprenorphine?

Treating codeine dependence with buprenorphine: Dose requirements and induction outcomes from a retrospective case series in New South Wales, Australia

SUZANNE NIELSEN^{1,2,3}, RAIMONDO BRUNO^{1,4}, BRIDIN MURNION², ADRIAN DUNLOP^{5,6}, LOUISA DEGENHARDT^{1,7,8,9}, APO DEMIRKOL^{3,10}, PETER MUHLEISEN³ & NICHOLAS LINTZERIS^{2,3}

Drug and Alcohol REVIEW

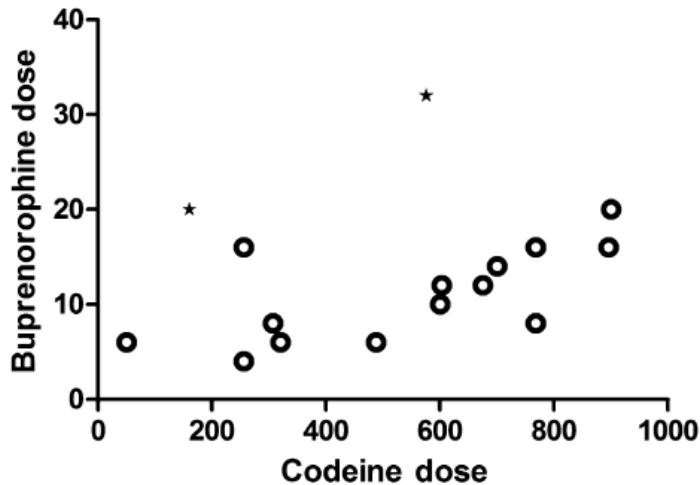
Drug and Alcohol Review (2015)
DOI: 10.1111/dar.12315

Retrospective case series (n = 19)

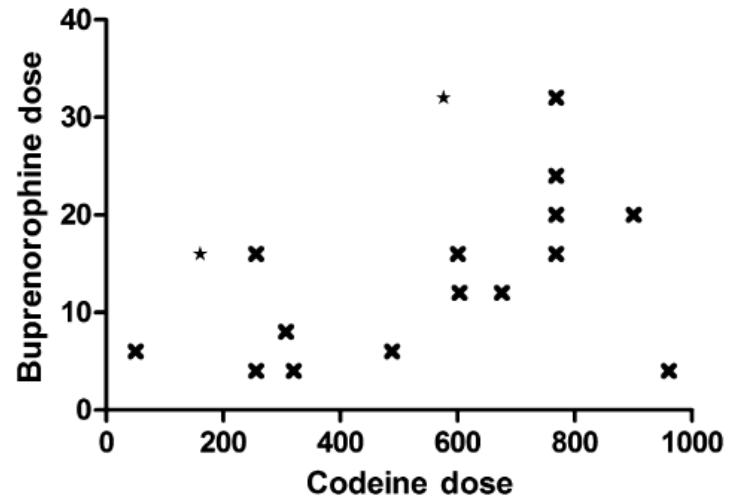
- Most (n = 16, 84%) female, mean age 41.2 (SD 9.3)
- Mean 8 years (95%CI 4-11) codeine use; no other opioids
- 42% benzodiazepines, 32% problematic alcohol use
- Few (4/19) reported heroin use history, most (63%) commenced for pain
- Mean baseline codeine dose 564mg (95%CI 431 – 696mg) (~ 2 packets per day OTC codeine)
- Median buprenorphine dose received was 12 mg at Day 7 and 16 mg at day 28
- **This dose is much greater than provided by buprenorphine patches, and much greater than estimated using dose conversion tables**

Buprenorphine dose - codeine dependence

Lots of individual variation = dose titration



a Buprenorphine dose day 7



b Buprenorphine dose day 28 of treatment

Treatment setting

- Perceptions of ‘drug treatment’ services consistently identified as a treatment barrier
- Stepped-care approach
 - Less complex presentations (e.g. employed, no history of injection, no history of illicit drug use, ++ social supports) → consider primary care setting
 - More complex presentations (e.g. multiple substances, more severe dependence, unmanaged/unstable comorbidities, complex chronic pain, pregnancy) → D&A service or pain service

Assessing codeine dependence in primary care settings

Unlikely dependence (Group 1)

- Unlikely to be dependent, or tolerant.
- Use codeine less frequently, or have used for a shorter period

Management:

- brief advice on changes in codeine availability
- alternative options for acute pain

Group 1: unlikely dependence

Limited role for low-dose codeine products (or any opioids in chronic pain)

- Caution in transferring from OTC to prescribed opioids (dose conversation estimates are limited with variations in metabolism).
- Education for patients on limited efficacy of low dose codeine

Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department

A Randomized Clinical Trial

Andrew K. Chang, MD, MS; Polly E. Bijur, PhD; David Esses, MD; Douglas P. Barnaby, MD, MS; Jesse Baer, MD

“no statistically significant or clinically important differences in pain reduction at 2 hours among single-dose treatment with ibuprofen and acetaminophen or with 3 different opioid and acetaminophen combination analgesics”

Uncertain dependence, probable tolerance (Group 2)

- Codeine use most days, only for pain
- May not have tried to cease
- Unclear dependence

Management: support attempt at ceasing codeine where no clear diagnosis of opioid dependence.

Pain management plan → limited role for low-dose codeine (or long-term opioids) in chronic pain

Group 2: Uncertain dependence

Trial of cessation/taper

- can patient stop on own – what happens?
- Advise on opioid withdrawal symptoms
- Prescribe weak opioid/buprenorphine taper if familiar with how to do this
- Refer to, or consult with AOD / pain specialists/ experienced GP if need support

Probable dependence, including significant tolerance to opioids (Group 3)

Taking regular, maximum or greater than-maximum doses codeine (i.e. daily or multiple times a day for months to years).
Use for pain, or non-pain reasons including sleep and to help manage psychological distress.

Other possible characteristics:

- other mental health conditions/substance use to consider
- difficulty stopping or unable to imagine stopping codeine
- withdrawal symptoms 6-12 hours after last dose (may confused with re-emergence of pain e.g. rebound headaches)

Assess against opioid dependence criteria

Probable dependence, including significant tolerance to opioids (Group 3)

Management:

- consider maintenance treatment with buprenorphine+naloxone (or methadone)
- Attempted detoxification is also an option, if unsuccessful, maintenance treatment is indicated.
- Patients with complex needs (polysubstance dependence, unstable mental health, higher doses, previous complications etc.) → refer to /liaise with AOD specialists/pain specialists

Opioid agonist treatment (OAT, buprenorphine or methadone)

OAT will not be appropriate for all patients that experience problems with codeine.

OAT may be appropriate where:

- Confirmed opioid dependence (e.g. ICD-10)
- Attempts to manage opioids with other strategies failed (+/- taper unsuccessful)
- Risk of overdose / relapse
- Patient willing to consider OST

Summary: as we approach Feb 1

Screen for likely dependence / education for patients that use codeine

Detailed assessment where indicated

Attempt taper if unclear opioid dependence

Buprenorphine+naloxone (or methadone) appropriate if opioid dependent

- Usual induction and dose ranges for buprenorphine
- Dose titration critical due to individual variability ++

Consider treatment setting (primary care with support from AOD where appropriate)

Resources

Resources - pain

Pain assessment

<https://www.aci.health.nsw.gov.au/chronic-pain/health-professionals/assessment-beta>

Pain management

<https://www.aci.health.nsw.gov.au/chronic-pain/health-professionals/management-of-chronic-pain>

<https://www.racgp.org.au/afp/2014/august/gp-pain-management/>

Codeine hub – talking to patients

<https://www.tga.gov.au/tips-talking-about-codeine-guidance-health-professionals-prescribing-authority>

<https://www.tga.gov.au/codeine-info-hub>

Resources: opioid dependence

Assessment/treatment overview:

http://medicinetoday.com.au/sites/default/files/cpd/3-MT2015-06SUPPL-PRESCRIPTION_OPIOID_MISUSE-LINTZERIS.pdf

In Western Australia, all GPs can initiate and prescribe buprenorphine/naloxone for up to five patients once they complete a two-hour online course.

Alcohol and Drug Information Service (ADIS)

Perth 08 9442 5000

http://ww2.health.wa.gov.au/Articles/A_E/Community-Program-for-Opioid-Pharmacotherapy-CPOP

Regional WA: 1800 198 024

24 hour hotline for health professionals:

WA Clinical Advisory Service 08 9442 5042

Evidence for opioid agonist treatment

FAQ:

<https://ndarc.med.unsw.edu.au/resource/frequently-asked-questions-opioid-agonist-treatment-pharmaceutical-opioid-dependence>

Webinar:

<https://ndarc.med.unsw.edu.au/resource/using-opioid-agonist-treatment-pharmaceutical-opioid-dependence>

Frequently asked questions on opioid agonist treatment for pharmaceutical opioid dependence: An evidence summary

Author: Dr Suzanne Nielsen

Resource Type: AOD Worker Resources,
Fact Sheets, General

 [FAQ Pharmaceutical Opioid
Dependence Treatment.pdf](#)

