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Codeine dependence: characteristics and treatment with buprenorphine

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Medicine | National Drug and Alcohol Research Centre

Disclosures

- I am a pharmacist
- I have been an investigator on projects unrelated to this work that were funded by Reckitt-Benckiser
- I am a current investigator an untied educational grant from Indivior
- I have not received salary funding from any either of these grants (salary funding from NHMRC)
- I have not received payment for this presentation today

Overview

1. Background on codeine use in Australia
2. Characteristics of people who develop codeine dependence
3. Treating codeine dependence with buprenorphine

Brief history of codeine in Australia

- Codeine is widely available in Australia
- Stronger products introduced in 2002 onwards
- In 2015 it was foreshadowed that the S3 would be deleted (i.e. only prescription only)
- Still awaiting a final decision from the TGA

Codeine use in Australia

- OTC sales represent ~1 pack/adult Australian/year
- > 15 million packs OTC and 12 million prescribed
- Highest 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 Gisev[1] · Suzanne Nielsen[1] · Elena Cama[1] · Briony Larance[1] · Raimondo Bruno[1,2] · Louisa Degenhardt[1]

"Although codeine is widely used, its place in therapy is uncertain"

(eTherapeutic guidelines: analgesic)

MJA 2010 (Cases from 2005-2008)

MEDICINE AND THE COMMUNITY

Serious morbidity associated with misuse of over-the-counter codeine–ibuprofen analgesics: a series of 27 cases

Matthew Y Frei, Suzanne Nielsen, Malcolm D H Dobbin and Claire L Tobin

While extensive overseas evidence is accumulating about the non-medical use of prescription opioids[1-5] and the serious consequences of such use,[1-4,6,7] literature on non-prescribed or over-the-counter (OTC) opioids is mainly confined to case descriptions.[8-11] This is despite indications, such as in the 2007 Australian National Drug Strategy Household Survey, that over half a million Australians used pain killers for non-medical purposes,[12] the third most common category of substance use in Australia after cannabis and ecstasy.

Although codeine is often described as a weak opioid analgesic, codeine dependence is a well recognised complication of long-term use.[13-15] Codeine-containing medications are

ABSTRACT

Objective: To investigate morbidity related to misuse of over-the-counter (OTC) codeine–ibuprofen analgesics.

Design and setting: Prospective case series collected from Victorian hospital-based addiction medicine specialists between May 2005 and December 2008.

Main outcome measures: Morbidity associated with codeine–ibuprofen misuse.

Results: Twenty-seven patients with serious morbidity were included, mainly with gastrointestinal haemorrhage and opioid dependence. The patients were taking mean daily doses of 435–602 mg of codeine phosphate and 6800–9400 mg ibuprofen. Most patients had no previous history of substance use disorder. The main treatment was opioid substitution treatment with buprenorphine–naloxone or methadone.

Conclusions: Although codeine can be considered a relatively weak opioid analgesic, it is nevertheless addictive, and the significant morbidity and specific patient characteristics associated with overuse of codeine–ibuprofen analgesics support further awareness, investigation and monitoring of OTC codeine–ibuprofen analgesic use.

MJA 2010; 193: 294–296

Evidence of harms

Harm	Description	Main products	Examples in the Australian and NZ literature
Dependence	Features of dependence include escalating doses, withdrawal symptoms on discontinuation, and continued use of codeine despite experiencing harms. A number of cases of dependence to OTC codeine products have been successfully treated with Opioid Agonist Treatments such as methadone or buprenorphine	OTC codeine combination products	Frei et al 2010, McDonough 2011, Evans et al 2010, Robinson et al 2010
GI Harm	Gastric and peptic ulcers, examples of perforation, haemorrhage, pyloric stenosis, gastrectomy and other bowel surgery	OTC codeine-ibuprofen	Dutch 2008, Frei et al 2010, McDonough 2011, Evans et al 2010, Robinson et al 2010
Anaemia	Resulting from blood loss, often secondary to gastric ulcers	OTC codeine-ibuprofen	Frei et al 2010, Evans et al 2010, Robinson et al 2010
Renal Effects	Renal tubular acidosis due to prolonged high doses of ibuprofen, renal failure	OTC codeine-ibuprofen	Frei et al 2010,
Hypokalaemia	Low potassium leading to muscle weakness and respiratory difficulties, one case of rhabdomyolysis and quadriparesis. Some needed ICU admission for life support.	OTC codeine-ibuprofen	Ernest et al 2010, Page et al 2011, Frei 2010, Ng et al 2011

Recent trends

- Trebling of non-OST drug treatment presentations between 2002-2011 (Nielsen et al 2015, DAD)
- Rate of codeine-related deaths increased from 3.5 per million in 2000 to 8.7 per million in 2009 (Roxburgh 2015)

Who develops dependence to codeine?

Characteristics of non-treatment seeking people with codeine dependence

- Web survey of 800 people who use codeine, 138 met criteria for dependence
- No difference on demographic characteristics (age, gender, employment, education) between those that met criteria for dependence and those that did not

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ORIGINAL ARTICLE

Characteristics of a nontreatment-seeking sample of over-the-counter codeine users: Implications for intervention and prevention

Suzanne Nielsen, BPharm, BPharmSc (Hons), PhD; Jacqui Cameron, BA, BSW, MPhil (Social Science Research); Nicole Lee, BSc (Hons), GradCertEd (Tertiary), PhD, MAPS

Characteristics associated with developing dependence

- Chronic pain, psychological distress, previous AOD problems associated with dependence
- Note that most people meeting criteria for dependence did not have AOD history (58%)
- Most had not sought help (75%)

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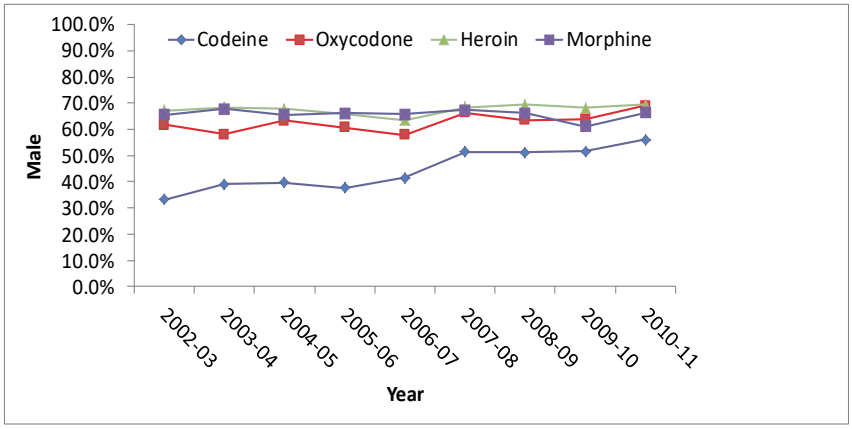
	p	OR	95% confidence interval for OR	
			Lower	Upper
Age	0.927	0.999	0.972	1.027
Reported health as good to excellent	0.249	1.570	0.729	3.379
Mental Health Score (SF12)	0.134	0.968	0.928	1.010
Physical Health Score (SF12)	0.366	0.979	0.934	1.025
K10 Score	0.007	1.076	1.021	1.134
Was person employed	0.717	1.158	0.524	2.559
Complete tertiary education	0.556	1.194	0.661	2.159
Previous AOD treatment	0.015	2.332	1.176	4.624
Person self-reports chronic pain	0.011	2.319	1.214	4.430
Used doses greater than recommended	0.000	8.702	4.655	16.268

Codeine dependence differs from other pharmaceutical opioid dependence: Gender



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Increasing proportion of males for codeine and oxycodone, changing significantly faster for codeine

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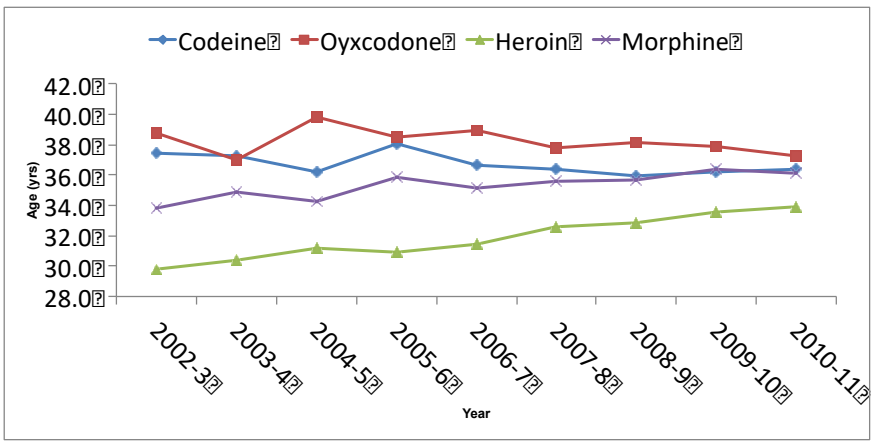
Codeine dependence differs from other pharmaceutical opioid dependence: Age



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Increasing age for heroin and morphine. Trend for declining age with codeine.

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Characteristics by opioid type (NMDS)

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

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

Illustrations of codeine dependence

"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)

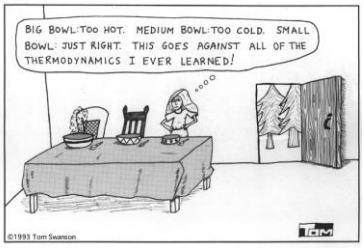
"by that stage, when I was having that many… when I started to feel really sick, trying to get them down, I got back down to 36 in one go and even that was pretty difficult because you'd retch trying to get them down but you just knew you needed to get them in there to make you feel OK again." (Female, 42yrs)

Treating codeine dependence with buprenorphine

Why BPN for codeine be any different?

- Codeine dependent people have different characteristics to other opioid dependent people
- Codeine is considered a 'low potency' or 'weak' opioid
- Codeine generally used orally

TOO HIGH → Potential sedation/ overdose ☹
TOO LOW → Low starting doses and slow induction is associated with poorer retention and more opioid use ☹



Characteristics: retrospective case series

- Most (n = 16, 84%) female
- Mean age 41.2 (SD 9.3)
- Mean 8 years codeine use (95%CI 4-11ys)
- All only using codeine, 42% benzodiazepines, 32% problematic alcohol use
- Minority (4/19) reported any heroin use history
- Most (63%) reported commencing codeine for a pain condition

Opioid doses

- Mean baseline codeine dose 564mg (95%CI 431 – 696mg) (~ 2 packets per day OTC codeine)
- Median buprenorphine dose received was 12mg at Day 7 and 16mg at day 28

Codeine dose is associated with BPN dose

- Lots of individual variation = dose titration

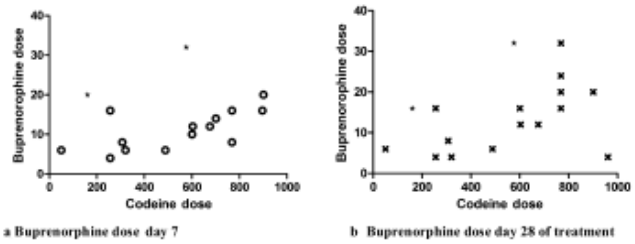


Figure 1. *Plot of baseline codeine dose and buprenorphine dose at Day 7 of treatment Day 28 of treatment.*

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

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 MURNION[2], ADRIAN DUNLOP[5,6], LOUISA DEGENHARDT[1,7,8,9], APO DEMIRKOL[3,10], PETER MUHLEISEN[5] & NICHOLAS LINTZERIS[2,3]

Codeine Dose Conversion examples

Codeine Dose	Estimated BPN dose using conversion tables for pain treatment^	Actual BPN dose day 7
50	0.17	6
256	0.89	16
307	1.06	8
320	1.11	6
488	1.69	6
576	2	32
600	2.08	10
768	2.66	16
900	3.12	20

Treatment outcomes

- All in the case series in treatment at 28 days
- One case where sedation was documented, responded to a 20% reduction in dose
- Most cases reported no additional opioid use
  - over-the-counter codeine and/or oxycodone was documented in four cases.

Summary: Buprenorphine dose requirements

- Small retrospective sample in a specialist service
- Enormous inter-patient variation → always titrate the dose to the individual patient
- Although codeine dependent people differ in a number of important ways, on average, *this did not equate to a difference in dose requirements*

Buprenorphine doses were:

- *Consistently higher than the doses that may be estimated from dose conversion tables*
- *Comparable to the dose ranges observed in the treatment of opioid dependence more generally*

Other treatment considerations for codeine dependence

Comparing codeine dependence to strong (prescription) opioid dependence (n = 135)

People seeking treatment for codeine dependence:

- More likely to be employed
- More likely to be female
- Taking only codeine
- Using codeine orally
- No history of heroin use

Good candidates to consider low supervision or unsupervised treatment

Drug and Alcohol Review (May 2015), 34, 304-311
DOI: 10.1111/dar.12224

Comparing treatment-seeking codeine users and strong opioid users: Findings from a novel case series

SUZANNE NIELSEN[1,2,3], BRIDIN MURNION[2], ADRIAN DUNLOP[4,5], LOUISA DEGENHARDT[1,6,7,8], APO DEMIRKOL[1,9], PETER MUHLEISEN[4] & NICHOLAS LINTZERIS[2,3]

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Treatment received

- Those seeking treatment for codeine dependence were:
  - More likely to receive buprenorphine than methadone
  - Less likely to receive any form on long-term OST
- Could reflect patient or provider preference, or treatment availability (some geographical locations could only offer withdrawal)
- Relapse common post detox, with return to codeine use is reported by experienced clinicians

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Treatment research for pharmaceutical opioids

Opioid agonist treatment for pharmaceutical opioid dependent people (Review)

Nielsen S, Larance B, Degenhardt L, Gowing L, Kehler C, Lintzeris N

Summary of findings: Cochrane review

- No differences in retention or substance use outcomes for pharmaceutical opioid dependent people (comparing MTD and BPN)
- Buprenorphine maintenance had better outcomes for retention and substance use compared with taper/TAU
- Findings are consistent with Weiss et al 2011
  - Most PO dependent people 'relapse' following either short (2 week) or longer (12 week) BPN treatment with taper = maintenance treatment often needed

Treatment perceptions

Perceptions of opioid substitution treatment were generally negative, and in some cases were informed by inpatient withdrawal experiences:

'I didn't want to have to go through it again. I was in there with all these hardened drug users.'
(Female, 42 yrs)

'I just couldn't face going to a methadone clinic... lining up to get my daily dose of methadone or buprenorphine' (Male, 25 yrs)

Treatment delivery models

Tailoring services for PO dependence

- Detailed assessment including pain history
- Separate physical location
- Begin dosing or transfer quickly to community pharmacy

OTP Clinic

PO Clinic

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In summary

- Codeine dependence is increasing and the harms are serious/fatal
- Those with codeine dependence are a unique population that differ from other pharmaceutical opioid dependent people and those that use heroin
- Despite this, buprenorphine dose requirements appear broadly similar (individual variation ++)
- Treatment delivery could take into account patient stability and options for less supervised treatment