Identifying and treating codeine dependence: a systematic review

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Codeine is globally the most frequently used opiate,[1] and its consumption is increasing. In Australia, 27 780 234 packs of codeine-containing analgesics were supplied by community pharmacies during 2013, a rate of 1.24 packs per person.[2] In New Zealand, most of Canada, South Africa, Ireland, and the United Kingdom, codeine is available over the counter, usually combined with simple analgesics such as paracetamol or ibuprofen;[3] until recently, it was also available without prescription in Australia and France. Products containing greater amounts of codeine are generally only available on prescription.[3]

Codeine has low affinity for and intrinsic activity at μ-opioid receptors, and is considered a prodrug; its analgesic effects depend largely on its being converted to morphine by the polymorphic cytochrome P450 isoenzyme (CYP) 2D6.[4,5] Genetic variability in the activity of CYP2D6 underlie interperson differences in the analgesia achieved and the risk of opioid toxicity.[6] Tolerance can develop after a relatively short period of regular use.[7-9]

In view of the limited evidence that adding low dose codeine (< 30 mg) to simple analgesics increases pain relief,[10-15] the variability in its metabolism, and the availability of opioids with more predictable effects, the role of codeine in pain management is contentious.[16,17]

The liability of codeine to be misused has been shown in a randomised, double blind, placebo-controlled drug administration study,[18] and has been documented in several case series.[19,20] Although the prevalence of codeine dependence is unknown, the harms associated with overuse are well established, including serious morbidity causing great cost to the health care system.[21]

Some harms associated with codeine overuse are directly related to prolonged intake, but many serious consequences stem from concomitant overconsumption of ibuprofen or paracetamol in combination products.[19] Sequelae of supratherapeutic ibuprofen ingestion secondary to codeine dependence that require intensive care have been described, including several codeine-related deaths.[22] As a result, access to over-the-counter codeine has been restricted or removed in Manitoba (February 2016), France (July 2017), and Australia (February 2018).[23-25]

In order to respond appropriately, we need to identify people who are codeine-dependent. There has been greater awareness of dependence with the imminent rescheduling of codeine in Australia. Both in Australia and internationally, presentations to addiction treatment services have increased,[26-28] but treatment approaches for codeine dependence are poorly defined. The purpose of our systematic review was to identify the characteristics of people who are codeine-dependent, and to define approaches for identifying codeine dependence.

Abstract

Objectives: Codeine dependence is a significant public health problem, motivating the recent rescheduling of codeine in Australia (1 February 2018). To provide information for informing clinical responses, we undertook a systematic review of what is known about identifying and treating codeine dependence.

Study design: Articles published in English that described people who were codeine-dependent or a clinical approach to treating people who were codeine-dependent, without restriction on year of publication, were reviewed. Articles not including empirical data were excluded. One researcher screened each abstract; two researchers independently reviewed full text articles. Study quality was assessed, and data were extracted with standardised tools.

Data sources: MEDLINE and EMBASE were searched for relevant publications on 22 November 2016. The reference lists of eligible studies were searched to identify further relevant publications. 2150 articles were initially identified, of which 41 were eligible for inclusion in our analysis.

Data synthesis: Studies consistently reported specific characteristics associated with codeine dependence, including mental health comorbidity and escalation of codeine use attributed to psychiatric problems. Case reports and series described codeine dependence masked by complications associated with overusing simple analgesics and delayed detection. Ten studies described the treatment of codeine dependence. Three reports identified a role for behavioural therapy; the efficacy of CYP inhibitors in a small open label trial was not confirmed in a randomised controlled trial; four case series/chart reviews described opioid agonist therapy and medicated inpatient withdrawal; two qualitative studies identified barriers related to perceptions of codeine-dependent people and treatment providers, and confirmed positive perceptions and treatment outcomes achieved with opioid agonist treatments.

Conclusion: Strategies for identifying problematic codeine use are needed. Identifying codeine dependence in clinical settings is often delayed, contributing to serious morbidity. Commonly described approaches for managing codeine dependence include opioid taper, opioid agonist treatment, and psychological therapies. These approaches are consistent with published evidence for pharmaceutical opioid dependence treatment and with broader frameworks for treating opioid dependence.

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Methods

Search strategy

We searched MEDLINE and EMBASE on 22 November 2016 for the following terms: "codeine", "dependence", "substance-related disorders", "opioid-related disorders", "behaviour, addictive", and "substance withdrawal syndrome" (online Appendix, table 1). We restricted our search to human studies published in English;

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there was no restriction on year of publication. The reference lists of eligible studies were searched to identify further relevant publications.

One reviewer (SN, JJ or TM) independently examined the titles and abstracts of identified articles. The full text of relevant articles was independently assessed for inclusion by two authors, and reasons for exclusion documented as appropriate. Inter-reviewer disagreement about inclusion was resolved by consensus among all three authors.

Study inclusion criteria

We included studies that described people who were codeine-dependent (identification studies) or any clinical approach for treating people who were codeine-dependent (treatment studies).

Data extracted from identification studies included study characteristics (author, location, design, quality rating) and population characteristics (participant age, sex, employment, mental health, pain and substance use history, adverse effects related to codeine use, and management of adverse effects).

Treatment studies included randomised and non-randomised controlled trials, quasi-experimental, before-and-after studies, prospective and retrospective cohort studies, case–control studies, analytic cross-sectional studies, qualitative studies, and case reports and series. Treatment outcome measures included change in codeine use (days of use or amount used), retention in treatment, adverse events and other outcomes related to codeine use, opioid dependence, and pain.

Exclusion criteria

Reports limited to describing the clinical applications or pharmacology of codeine or other opioids, reports that did not separately report codeine-related data, and articles without empirical data (eg, letters, commentaries, reviews) were excluded (online Appendix, table 2).

Assessment of methodological quality (identification studies)

The quality of descriptive studies was assessed with a modified version of the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross Sectional Studies.[29] To enable application of a single tool to all study methodologies, the JBI tool was reduced from eight to five items, and an item from the Evidence-Based Librarianship (EBL) Critical Appraisal Tool for assessing sample bias was added[30] (online Appendix, table 3). The range for total scores was 0–6, higher scores reflecting higher quality.

Grading of evidence (treatment studies)

Studies examining treatment approaches were scored for quality according to GRADE criteria.[31]

Data collection

Data were extracted with a standardised data extraction tool into an Excel (Microsoft) spreadsheet. The tool was piloted and reviewed before being finalised.

Data synthesis

Findings were qualitatively and quantitatively synthesised when population characteristics were reported in a manner that enabled this approach. Meta-analysis of treatment studies was not possible because of the heterogeneity of study designs. When individual patient data were reported, details were extracted at the patient level to enable synthesis of patient characteristics.

Results

Of the 2150 articles initially identified, 41 were eligible for inclusion in our analysis (Box 1). The mean study quality score of the included articles was 3.0 (standard deviation [SD], 1.1).

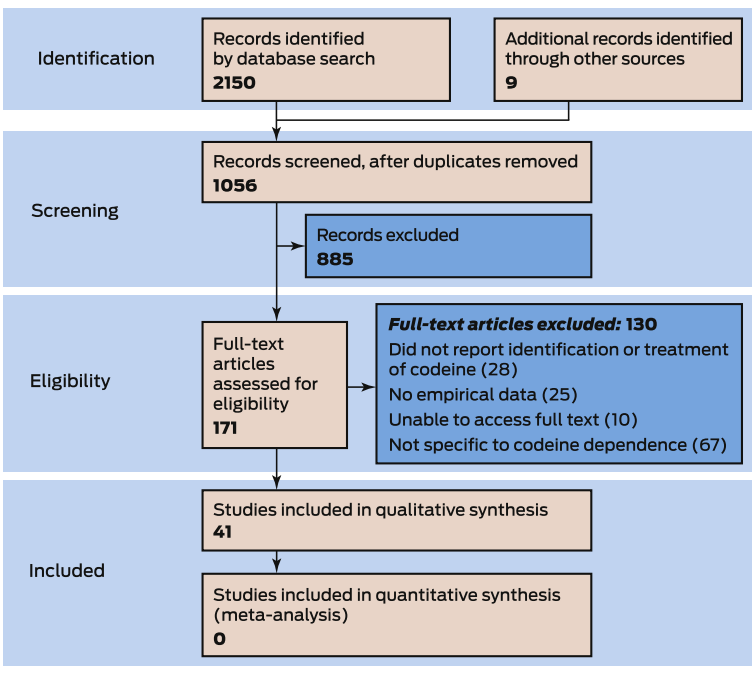
Identifying codeine dependence

Fourteen reports described samples of patients who were codeine-dependent (Box 2; online Appendix, table 4A); 22 described presentations by individual patients (Box 3, Box 4; online Appendix, tables 4B and C). No studies reported developing an approach for identifying people with codeine dependence as an aim, but two reported applying the Severity of Dependence Scale (SDS)[32] for defining codeine dependence (cut-off score, 5).[33,34]

Analyses of administrative data

Three studies examined data from administrative sources on the treatment of people for opioid dependence.[28,35,36] An Australian study compared codeine-related treatment episodes with those for patients for whom another prescribed opioid or heroin was the chief drug of concern. The proportion of women among those treated for codeine dependence declined from 70% in 2002 to 47% in 2011; people for whom codeine was the drug of concern were on average older and less likely to have a history of intravenous and illicit substance use than those treated for misuse of stronger prescription opioids or heroin.[28] A study of codeine prescriptions in Norway found that 0.5% of all codeine recipients in 2005 were likely to be using codeine problematically (annual prescription level exceeding twice the maximum daily dose for

1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of study selection



2 Studies describing characteristics of people who were codeine-dependent

Study	Design, location	Sample size, type	Sex (women)	Age (years)	Quality rating
Sproule 1999[20]	Survey, Canada	339 people who had used codeine 3 days/week for at least 6 months	51%	mean, 43.5 (range, 18–82)	5
Fredhein 2009[35]	National prescription database, Norway	385 190 people prescribed codeine during 2005	56%	mean, 52.3 (SD, 18.8)	5
Frei 2010[19]	Case series of patients who presented or were referred to hospital addiction medicine, Australia	27 treatment admissions for serious harms from over-the-counter ibuprofen–codeine products	48%	≥ 20	3
Thekiso 2010[42]	Retrospective chart review, Ireland*	20 inpatients admitted with over-the-counter codeine abuse or dependence	65%	mean, 49 (SD, 23)	4
McAvoy 2011[40]	Case series, New Zealand*	15 patients presenting for over-the-counter codeine detoxification	46%	mean, 44 (range, 30–60)	3
McDonough 2011[41]	Retrospective chart review, Victoria	32 people referred to hospital drug and alcohol services for excessive over-the-counter codeine use (Sept 2005 – Sept 2010)	72%	median, 38	2
Nielsen 2011[33]	Online survey, Australia	137 people who met criteria for codeine dependence (subset of 800 people reporting over-the-counter codeine use)	66%	mean, 37 (SD, 13)	3
Cooper 2013[38]	Qualitative interviews, United Kingdom*	25 participants recruited from internet support groups	52%	20–60s	3
Nielsen 2013[39]	Survey (qualitative research methodology), Australia	20 codeine-dependent people	60%	mean, 39 (SD, 11)	2
Dada 2015[36]	National administrative treatment dataset, South Africa	425 codeine-related admissions to alcohol and other drug treatment centres, 137 with codeine as drug of primary concern	25%	11–70 (20–39 years: 59%)	2
Nielsen 2015[28]	Cross-sectional study of national administrative datasets, Australia	4424 codeine treatment episodes	70% (2002) 47% (2011)	mean, 36	2
Nielsen 2015[27]	Retrospective chart review, Australia*	135 (53 codeine-dependent)	66%	mean, 38 (SD, 8)	4
Qiu 2015[37]	Case–control study mapping brain differences, China	60 (30 codeine-dependent people, 30 controls)	7%	mean, 25	2
Van Hout 2015[34]	Qualitative interviews, Ireland*	21 participants recruited through drug treatment centres (in treatment or in recovery for over-the-counter codeine use)	57%	mean, 39 (range, 26–62)	2

SD = standard deviation. * Study also included in Box 5 (treatment approaches). For further details, see online Appendix, table 4A. ◆

12 months); further, high dose prescribing of benzodiazepines was more prevalent in this group.[35] A South African study of national data on treatment for substance misuse (alcohol, pharmaceutical and illicit drugs) found that 2.5% of admissions involved codeine, and that codeine was recorded as the primary substance of concern for 0.8% of patients.[36]

Quantitative convenience samples

Two studies included convenience samples of people who reported using codeine. In an Australian web-based survey, 137 codeine-dependent participants were compared with 633 non-dependent participants; characteristics associated with dependence (assessed with the SDS) included taking higher than recommended doses, experiencing psychological distress, previous drug treatment, and chronic pain.[33] A 1999 Canadian postal survey on prescribed and over-the-counter codeine (participants recruited via newspaper advertisements) found that 37% of respondents met DSM-IV criteria for codeine dependence, most of whom reported chronic pain and family histories of substance use problems.[20]

Case–control study

A prospective case–control study described patients attending an addiction medicine clinic in China who were dependent on a codeine-containing cough syrup.[37] This imaging study found that the patients, who exhibited increased impulsivity, had cortical white matter microstructural abnormalities.[37]

Qualitative studies

Three qualitative studies have examined the perceptions of pharmacists and codeine-dependent people.[34,38,39] A British author[38] described the perception that dependence is not identified early, the challenges posed by the stigma attached to dependence, the fact that codeine-dependent people saw themselves as different to users of illicit opioids, and medical reasons for initiating codeine use.[38] A recent Irish study similarly described social stigma as a treatment barrier, and reported emotional distress as a driver for codeine use.[34]

Two typologies of codeine dependence have been proposed:[38,39] users who do not exceed therapeutic doses, and

3 Individual patient reports: acute description or management of codeine-related harms

Study	Location of patient (age, sex)	Harms from codeine use	Details of codeine dependence	Treatment
Faierman 1973[50]	USA (male, 30)	Hepatic injury with extensive fibrosis attributed to terpin hydrate component of cough syrup, as opposed to codeine	16–20 ounces codeine cough syrup daily	Not reported
Wylie 1994[64]	Scotland (female, 37)	Elevated liver enzyme levels	Up to 30 × 500 mg paracetamol/ 30 mg codeine phosphate per day	Treated for potential hepatotoxicity with acetylcysteine; discharged after 2 days
Dyer 2004[47]	United Kingdom (male, 49)	Perforated duodenal ulcer 3 years previously (inappropriate ibuprofen use), hypokalaemia	30 × 200 mg ibuprofen/12.8 mg codeine in the 3 days before admission. GP reported their taking 24 tablets at once previously	Serum potassium corrected with intravenous potassium therapy; advised that Nurofen Plus misuse caused his recurrent hypokalaemic episodes; offered assistance
Dutch 2008[46]	Australia (female, 39)	Anterior gastric antrum ulcer and 2.6 L of green turbid fluid in the peritoneal cavity	16–24 × 200 mg ibuprofen/12.8 mg codeine per day for 3 weeks	Transferred to intensive care in another hospital
	Australia (male, 41)	Gastric antrum ulcer with gross abdominal contamination	"A packet" of 200 mg ibuprofen/ 12.8 mg codeine per day for one year	Postoperatively, patient offered inpatient drug treatment, absconded before transfer arranged
Karamatic 2011[53]	Australia (male, 42)	Multiple jejunal ulcers with early structuring consistent with NSAID enteropathy	10 × 200 mg ibuprofen/12.8 mg codeine phosphate per day	40 mg omeprazole, 15 mg mirtazapine daily; 5 mg oxycodone every 4–6 h as needed
	Australia (female, 41)	Multiple web-like strictures with circumferential ulceration throughout small bowel consistent with NSAID enteropathy	20 × 200 mg ibuprofen/12.8 mg codeine phosphate per day, 5 years	Iron supplement
	Australia (male, 41)	Multiple jejunal ulcers	10–12 × 200 mg ibuprofen/12.8 mg codeine phosphate per day, > 5 years	Omeprazole and amitriptyline daily; hyoscine butylbromide, paracetamol and codeine and tramadol as needed
Ng 2011[58]	Australia (female, 32)	Oesophageal erosions, benign gastric ulcer, enlarged, oedematous kidneys without nephrocalcinosis	20 × 200 mg ibuprofen/12.8 mg codeine phosphate per day	Electrolyte replacement
	Australia (male, 37)	Progressive muscle weakness, low serum potassium level, biochemical features consistent with distal renal tubular acidosis	24 × 200 mg ibuprofen/12.8 mg codeine per day	Electrolyte replacement, buprenorphine maintenance therapy
	Australia (female, 45)	Microcytic anaemia, gastric antral ulceration with a peptic oesophageal stricture	50 × 200 mg ibuprofen/12.8 mg codeine phosphate per day	Electrolyte replacement
	Australia (male, 40)	Generalised weakness associated with hypokalaemia, with distal renal tubular acidosis	1.4–2.0 g ibuprofen in codeine combination product per day for 3 months	Electrolyte replacement
Page 2011[59]	Australia (females, 35, 39; males, 41, 55)	Renal tubular acidosis, normal anion gap metabolic acidosis	Longstanding misuse of ibuprofen (5–18 g/day) and codeine (320–1152 mg/day) in over-the-counter medications	Biochemical recovery of all patients; two patients required intensive care admission for central venous access and potassium replacement
Lake 2013[56]	Australia (male, 35)	Small bowel stricture secondary to NSAID, loss of partner and employment	Up to 90 × 200 mg ibuprofen/ 12.8 mg codeine phosphate per day, clear salience and neuroadaptation	Exploratory laparotomy and small bowel resection; patient controlled concomitant ketamine use; community drug treatment on discharge
Roussin 2013[61]	France (females, 38, 38, 42, 47; males, 42, 55)	Included depressive mood, and constipation and vertigo	120–200 mg codeine phosphate in combination product with paracetamol per day for 1–10 years	Not reported
Ammit 2016[44]	Australia (female, 39)	Gastric erosion and renal tubular acidosis	520 mg/day (over-the-counter ibuprofen combination) for past year; increased with physical and psychological stress	Symptomatic medication (diazepam, paracetamol, baclofen); balloon enteroscopy/dilation (small bowel obstruction); education about harms of ibuprofen. Following admission: opioid substitution therapy, counselling and 12-step program

NSAID = non-steroidal anti-inflammatory drug. For further details, see online Appendix, table 4B. ◆

4 Individual patient reports: treatment of codeine dependence, with or without management of acute harms

Study	Location (sex, age)	Harms from codeine use	Details of codeine dependence	Treatment and outcome
Gruber 1948[51]	USA (male, 57)	Neuroadaptation and decline in functioning, loss of weight, likely maintenance of chronic pain symptoms, suicide following withdrawal	Intravenous codeine up to 4.8 g daily in weeks before hospitalisation; 660 mg per day in previous months	Reducing doses of intravenous codeine over 12 days; 100 mg pethidine iv 4–6 times per day (days 3–11), acetylsalicylic acid injections (days 12–15) Withdrawal syndrome tolerated with some discomfort; committed suicide after discharge
Vaughan 1967[63]	New Zealand (male, 53)	Renal failure (fatal)	8–12 aspirin/phenacetin/codeine tablets daily, several years	Supportive therapy
	New Zealand (female, 39)	Renal failure (fatal)	50 aspirin/phenacetin/codeine tablets per week	Symptomatic treatment for renal failure
	New Zealand (female, 70)	Analgesic nephropathy	8 aspirin/phenacetin/codeine tablets per day, 20 years	
	New Zealand (male, 28)	Possible medication overuse headache	6–20 aspirin/phenacetin/codeine tablets per day, 20 years	Education on link between symptoms and analgesic use; patient ceased analgesics
Senjo 1989[62]	Japan (male, 34)	Suspected codeine use contributed to obsessive–compulsive disorder in both patients	10-year history of codeine use	Inpatient stay (2 months); withdrawal symptoms after 5 days codeine-free Obsessive–compulsive disorder improved after withdrawal
	Japan (male, 35)		10-year history of codeine use	Patient was violent after 2 days, transferred to another hospital Returned 2 months later with complete remission of symptoms
Bedi 1991[45]	India (male, 42)	Dependence and opioid withdrawal symptoms	Two bottles Phensedyl (total content: 450 mg codeine, 366 mg ephedrine, 180 mg promethazine) per day	Loperamide, diazepam, nitrazepam; supportive psychotherapy and family counselling advocated; drugs reduced over 10 days
Eng 1996[48]	USA (male, 54)	Medication overuse headache	6–15 × paracetamol/codeine tablets	Detoxification (methadone); referral to anxiety disorders program (diagnosed with GAD), CBT, taught relaxation Self-managed analgesic use (reduced analgesic use to paracetamol twice a week or less), developed alternative strategies for psychological symptoms
Lake 2008[55]	USA (female, 39)	Transformation of episodic to daily headache	10 butalbital with codeine and acetaminophen tablets per day for pain control for past year	Withdrawn from butalbital, codeine; coached in relaxation techniques. After multiple admissions: weekly psychotherapy, formal substance abuse program, observed urine drug screens). CBT, pain management.12-step program Ongoing relapse, eventually ceased substance use, diagnosed with fibromyalgia and prescribed opioids
Evans 2010[49]	New Zealand (male, 35)	Acute gastric ulcer, severe gastritis and post-bulbar duodenitis with active bleeding	More than 100 × 200 mg ibuprofen/12.8 mg codeine phosphate per day for back pain	Reducing codeine dose prescribed; counselling Gastrointestinal symptoms healed, but balloon dilation of pyloric stenosis required
Robinson 2010[60]	New Zealand (male, 53)	Gastric ulcer, gastric bleeding, hepatotoxicity	60–80 × 200 mg ibuprofen/12.8 mg codeine phosphate per day, 2 years	Treatment not reported Many patients reported significant opioid withdrawal symptoms despite treatment with ancillary medications
	New Zealand (female, 31)	Peptic ulcer and anaemia	48 × 200 mg ibuprofen/12.8 mg codeine phosphate per day, 2 years	
	New Zealand (female, 63)	Gastric ulcer	20 × 200 mg ibuprofen/12.8 mg codeine phosphate (and prescription codeine) per day, 3 years	
	New Zealand (female, 47)	"Inflammatory bowel disease"	Up to 72 × 200 mg ibuprofen/12.8 mg codeine phosphate per day, one year	

(continued)

4 Individual patient reports: treatment of codeine dependence, with or without management of acute harms (continued)

Study	Location (sex, age)	Harms from codeine use	Details of codeine dependence	Treatment and outcome
	New Zealand (male, 52)	Ileal resection	Up to 80 × 200 mg ibuprofen/ 12.8 mg codeine phosphate per day, one year	
	New Zealand (female, 31)	Gastric ulcer and bleeding (previous gastrectomy)	Up to 120 × 200 mg ibuprofen/12.8 mg codeine phosphate per day, 2 years	
	New Zealand (male, 35)		Up to 48 × 200 mg ibuprofen/12.8 mg codeine phosphate per day, 2 years	
Hard 2014[52]	United Kingdom (female, mid-20s)	Neuroadaptation, exclusion of other activities, financial	10-year history of codeine dependence (initially prescribed)	GP changed from codeine to dihydrocodeine as a harm minimisation strategy (approximately 2940 mg dihydrocodeine daily). Buprenorphine/ naloxone (maintenance: 10 mg buprenorphine/2.5 mg naloxone); engaged with recovery support services and psychosocial counselling; 12-step program Initially mild precipitated withdrawal; stabilised and returned to work
Marr 2015[57]	Scotland (female, 24)	Dependence	Initially self-medication for dental pain, escalated to prescribed and over-the-counter opioids	Stabilised on 16 mg buprenorphine/ 4 mg naloxone, transferred to mono-product for pregnancy Transferred to community prescriber, reported stigma and discomfort with drug treatment clinic environment
Kean 2016[54]	United Kingdom (male, mid-30s)	Neuroadaptation, relationship disharmony, rebound headaches, hypoalbuminaemia, ALT levels elevated	Codeine prescribed by GP for back pain, later supplemented with illicit codeine, escalating over years to 250 mg/day	Buprenorphine/naloxone induction (up to 8 mg/2 mg daily), tapered over 4 months. Anxiety/depression at end of taper responded to fluoxetine, counselling Abstinent, functioning and intact relationships
Van Hout 2016[65]	Ireland (female, 57)	Estranged from family, unable to work, episode of haematemesis	Use escalated from 12 to 24–48 tablets per day over 3 years after fracture	Stabilised on 4 mg buprenorphine/1 mg naloxone, counselling every 2 weeks Continues treatment in pharmacy setting; plan after 2 years to begin taper
	Ireland (female, 44)	Identified because of high volume of sick notes (impact on employment)	Escalated use of over-the-counter codeine (about 36 tablets per day) at time of traumatic event	Commenced buprenorphine–naloxone, venlafaxine for depression, propranolol for migraine and omeprazole for a peptic ulcer Stabilised on a 14 mg buprenorphine/ 3.5 mg naloxone, migraines largely resolved; soon after treatment, antidepressant treatment ended. Returned to work, planned reduction of buprenorphine
	Ireland (male, 45)	Perforated ulcer requiring surgical repair, three later ulcers, multiple surgical admissions for epigastric pain and gastrointestinal bleeding	Long history of over-the-counter codeine misuse causing life-threatening morbidity	Several failed detoxifications; attempts to stabilise on maintenance dose of codeine failed. Prescribed buprenorphine/naloxone Overdosed on benzodiazepines, hospitalised, buprenorphine withdrawn. After restabilisation, maintained on 12 mg buprenorphine/3 mg naloxone
	Ireland (male, 44)	Not specifically reported	Escalating amounts of over-the-counter codeine–ibuprofen (up to 72 tablets per day) over several years	Buprenorphine–naloxone, psychosocial interventions. Initial relapse (attempt to self-detoxify), recommenced on higher dose Initially stabilised on maintenance dose of 8 mg buprenorphine/2 mg naloxone daily; recommenced and stabilised on 12 mg buprenorphine/3 mg naloxone daily, ongoing counselling

ALT = alanine transaminase; CBT = cognitive behavioural therapy; iv = intravenous. For further details, see online Appendix, table 4C. ◆

codeine-dependent people who consume high doses of the drug. The second group is characterised by severe dependence and harms. Additional typologies include recreational users[39] and people who slightly exceed recommended doses.[38]

Retrospective chart reviews and case series

Five case series or retrospective chart reviews[19,40-43] identified common features of people with codeine dependence, including higher proportions of women than among those treated for misuse of other opioids, histories of problematic alcohol use, mental health comorbidity, and serious side effects resulting from using combination medicines containing codeine, including one death.[41] Prior heroin dependence was rare.

Reports on individual patients

Twenty-two reports described 49 individuals who were codeine-dependent[44-65] (Box 3, Box 4; online Appendix, tables 4B and 4C). Twenty-three were women (mean age, 42 years [SD, 9 years]). Of the 15 people for whom data on employment status were reported, nine were employed. Acute harms and information on treatment approaches were described. Inherent to cases of acute harm were complications attributable to the co-medications paracetamol and ibuprofen, including distal renal tubular acidosis, hypokalaemia, gastritis and other enteropathies, medication overuse headache, hepatic necrosis, hypoalbuminaemia, microcytic anaemia, and weight loss. In a case series of 27 patients,[19] most had initiated codeine to treat pain but later escalated their intake for other reasons; this was also reported in many case reports.

Acute management of harms was characterised by inpatient hospital management of serious problems (often requiring intensive care) to restore electrolyte balance,[47,58,59] manage gastrointestinal symptoms[44,53] (including bowel resection),[56] and to assess or treat hepatotoxicity.[50,64] Opioid withdrawal was managed with symptomatic medications and buprenorphine; potential hepatotoxicity was managed with acetylcysteine.[64]

Psychiatric comorbidity in people with codeine dependence was dominated by high prevalence conditions (depression and anxiety disorders).[20,27,44,48,53,58,60,61] Some reports described prior or comorbid addictions (benzodiazepines, opioids, alcohol),[34,35,40,42,60] and mental health conditions.[20,40-42,60] Bipolar disorder,[27,42] obsessive–compulsive disorder,[62] relationship breakdown,[47] suicide behaviour,[51,56] and bereavement or loss[47] were also described.

Individual patient reports described treatment approaches, including attempted self-management,[45,65] use of symptomatic medications,[60] prescribed codeine or dihydrocodeine[49,52] or buprenorphine and naloxone,[52,54,65] and detoxification with methadone.[48] Management of mental health symptoms with antidepressants and behavioural therapies was described.[48,54,55,65] One notable case combined methadone taper, cognitive behavioural therapy, and relaxation strategies, enabling codeine cessation and self-management of pain.[48] Resolution of presenting complaints (obsessive–compulsive disorder, medication overuse headache) after codeine cessation was described.[62,63]

Treatment studies

Ten studies described treatment approaches in detail (Box 5; online Appendix, table 4D). Common medication-based approaches included taper from codeine with symptomatic medications such as clonidine or benzodiazepines,[42,67] buprenorphine maintenance,[19,27] CYP inhibitors,[66,68] and gradual self-managed taper.[38] Positive outcomes for opioid agonist treatment (methadone and buprenorphine with or without naloxone) were described.[19,27,34,38,40,43,69] The role of internet support groups[38] and psychosocial treatments, including cognitive behavioural therapy, were highlighted in some studies.[42,67,69]

Two studies tested the hypothesis that preventing the *O*-demethylation of codeine to morphine with CYP inhibitors would reduce codeine use.[66,68] Initial promising results from an open label pilot study of fluoxetine (14 subjects)[66] were not replicated in a small randomised controlled trial that compared the effectiveness of fluoxetine or quinidine (two potent CYP2D6 inhibitors) with placebo.[68]

A retrospective review of inpatient admissions described taper with clonidine and benzodiazepines, combined with an intensive 4-week mental health treatment program.[42] Patients had a mean stay of 42 days (SD, 23 days), with withdrawal symptoms requiring treatment for a mean 16 days (SD, 10 days). Taper with buprenorphine was described by an Australian study which noted that codeine dependence was more likely to be treated with taper rather than maintenance.[27] Relapse after taper was not uncommon.[34,42]

A single arm study (11 patients) found that cognitive behavioural therapy could significantly reduce codeine use — six patients ceased using codeine altogether — and neuropsychological functioning was improved by codeine reduction or cessation without deterioration in pain or quality of life.[67] A mixed methods study also highlighted the role of psychological therapies.[69]

Seven studies described treatment with opioid agonists,[19,27,34,38,40,43,69] four of which did not report outcomes.[19,34,40,69] One small retrospective cohort study described high retention rates for patients treated with buprenorphine over 28 days (median daily dose, 12–16 mg); one patient described initial sedation that necessitated reducing the dose.[43]

Two qualitative studies described positive experiences and outcomes for treatment with methadone and buprenorphine, despite patient concerns about the treatment experience and the clinic environment.[34,38]

According to GRADE criteria, the quality of evidence from treatment studies was very low to low; most studies were retrospective and descriptive, and all had small sample sizes.

Discussion

Our review of codeine-dependent people indicates that approximately equal proportions of men and women are involved; their mean age is greater than for patients treated for problematic use of other opioids, the prevalence of mental health comorbidity is high, identification of dependence is often delayed, and patients experience serious complications associated with excessive consumption of combination products that include codeine. Problematic codeine use was associated with mental health problems. The quality and methodology of the studies we assessed varied considerably, but their depictions of the features associated with codeine dependence were consistent, describing a clinically challenging area in which under-reporting is highly likely. The reports highlight the importance of asking about the use of non-prescribed analgesics in a range of health care situations, particularly when gastrointestinal complications are identified. The diversity of those affected and the high level of morbidity suggest that population level interventions are required for screening and prevention wherever codeine is available over the counter. Careful questioning about recent patterns of use, the reasons for taking codeine, and withdrawal symptoms upon cessation may help identify when a patient should be comprehensively assessed for an opioid use disorder.

5 Treatment approaches for codeine dependence

Study	Design, location	Sample size (sex), age	Treatment approach and outcomes	Evidence quality (GRADE)
Romach 2000[66]	Open label pilot trial, Canada	14 (36% women); mean, 41 years (SD, 6.6 years)	20 mg fluoxetine per day as CYP2D6 inhibitor (began to taper opioids over 8 weeks of active treatment) All patients reduced opiate use (range, by 30 –100%). Depressive symptoms also reduced	Low
Fernandes 2002[68]	Double blind, randomised controlled trial, Canada	30 assessed, 17 started treatment (65% female), mean, 40 years (SD, 12 years)	All patients received brief behavioural therapy. Two weeks of baseline monitoring were followed by 8 weeks of daily treatment with fluoxetine or quinidine (two potent CYP2D6 inhibitors) or placebo No significant difference among the three groups in daily codeine intake or depression scores. By end of treatment, large decrease from baseline in mean daily codeine use in all groups: placebo by 57%, quinidine by 56%, and fluoxetine by 51%	Low
Frei 2010[19]	Case series, Australia	27 (48% female); 20 years or more	Opioid pharmacotherapy (16 patients), buprenorphine taper (3), buprenorphine maintenance (10), methadone (3). Outcomes not reported	Very low
Nilsen 2010[67]	CBT-based clinical trial with partial or complete codeine reduction, Norway	11 (82% women); mean, 43 years	Two specifically trained physicians delivered six CBT sessions (verbal reattribution, behavioural experiments), tapering codeine gradually within 8 weeks Codeine use significantly reduced from mean 237 mg to 45 mg; six ceased codeine	Very low
Thekiso 2010[42]	Retrospective chart review, Ireland	20 (65% female): mean, 49.2 years (SD, 23.4 years)	Treated for substance withdrawal with standard pharmacological protocol-driven regimes, underwent up to 4 weeks' comprehensive inpatient treatment. Withdrawal regime included tapering benzodiazepines and clonidine. Affective comorbidities also treated (pharmacological, "psycho-education" Mean length of stay, 42 days; mean length of treatment for withdrawal, 16 days	Very low
Cooper 2013[38]	Qualitative interviews, United Kingdom	25 (52% female); range, 20–60 years	One-quarter received drug treatment (methadone, buprenorphine) from treatment service or GP. Online support important for attempts to self-treat buprenorphine and methadone often achieved to positive outcomes — either on maintenance doses or opiate free — despite initial reservations	Very low
Nielsen 2015[27]	Retrospective chart review, Australia	135 (53 codeine-dependent, 66% women; mean, 38.6 years)	Codeine dependence more likely to be treated with buprenorphine than methadone, withdrawal management more common than longer term pharmacotherapy. Outcomes not reported	Very low
Nielsen 2015[43]	Retrospective chart review, Australia	19 (84% female); mean, 41 years (SD, 9 years)	Buprenorphine maintenance treatment by drug treatment services, five as inpatients,14 as outpatients Median dose, 12–16 mg buprenorphine, four patients continued to use opioids. buprenorphine doses higher than estimated based on codeine dose	Very low
Van Hout 2015[34]	Qualitative interviews, Ireland	21 (57% female): mean, 39 years (range 26–62 years)	Methadone (14 patients), buprenorphine (3). Supportive medical care and a slow tapering of codeine products or substitution. Buprenorphine viewed particularly positively in removing craving and withdrawal effects. Relapse with codeine tapering was common; attributed to lack of effect on cravings and use of over-the-counter codeine	Very low
Norman 2016[69]	Mixed methods (systematic review, qualitative interviews), Ireland, United Kingdom, South Africa	23 interviews with key experts	Buprenorphine and methadone in substitution therapy. Notes efficacy of CBT for treating opioid dependence Outlined "best practices" in treatment reported by stakeholders, suggested "innovations" for treatment. Did not assess treatments	Very low

CBT = cognitive behavioural therapy; CYP = cytochrome P450; SD = standard deviation. For further details, see online Appendix, table 4D. ◆

Treatment approaches include self-management with internet support, psychological treatments, symptomatic medications for opioid withdrawal, and opioid agonist treatments. In particular, buprenorphine treatment undertaken according to current guidelines was commonly described. Studies of opioid taper found that relapse was common (consistent with taper for opioid dependence in general). Taken together, the treatment studies and case reports provide evidence that opioid agonist treatments, combined with psychosocial adjuncts, may be suitable and acceptable to patients. The evidence, albeit low in quality, indicates that positive treatment outcomes could be achieved with these approaches.

In the absence of specific high quality evidence, judgements about approaches for treating people with codeine dependence must be based largely on studies of opioid dependence. The effectiveness of treatment with methadone and buprenorphine has been reported, and maintenance is more effective than withdrawal and detoxification for people who are dependent on pharmaceutical opioids[70] or opioids in general.[71] Research on selecting patients for treatment with opioid agonists is limited. According to the general principles of treatment, diagnosis of opioid dependence must first be confirmed.[72] A stepped care approach with less intensive treatment (eg, taper, counselling) for low severity dependence is recommended by national guidelines.[72] Patients who unsuccessfully attempt taper may be considered for maintenance opioid agonist treatment, which achieves better treatment outcomes than detoxification for pharmaceutical opioid dependence.[71] Because of wide variations in codeine metabolism, predicting opioid requirements with dose conversion tables is challenging;[43] for this reason their use is discouraged.

Psychological adjunct therapies can be beneficial,[73] but the role of psychosocial interventions as accompaniments to opioid agonist treatments requires further research.[74] The high prevalence of mental health comorbidities and the preference of patients for online support may indicate that online interventions for managing comorbidity may be useful. In general, the role of pharmacological treatments for depression or anxiety at the start of treatment is unclear. It is recommended that comorbidities are assessed after a period of abstinence because of the potential for diagnostic uncertainty caused by the acute effects of opioid toxicity and withdrawal.[75]

The treatment setting is also important. People consuming larger amounts of opioids together with sedatives (eg, benzodiazepines) are a population at greater risk, and referral to a specialist may be required.[72] Characteristics that may indicate that patients are appropriate for managing in primary care include being employed, having social support, and not having another substance use disorder or a history of illicit drug use.

Medication overuse headache

Headache is a common reason for initiating codeine use by patients who develop dependence.[19,61] Paradoxically, medication overuse headache — in this context, exacerbation of a pre-existing headache disorder by excessive intake of codeine — is another potential complication of codeine dependence.[48,55,63] Data that might guide the management of codeine overuse headache specifically have not been published. Management of opioid-related medication overuse headache usually consists of patient education, opioid withdrawal, and the initiation of prophylactic agents,[76-78] often in an inpatient setting.[76] Medication overuse headache that results from overusing analgesics, compared with overuse of triptans, is associated with a greater withdrawal headache duration (about 10 days),[79] with meaningful improvement only after 12 weeks or more,[80] and high relapse rates (eg, 71% at 4 years[81]).

Limitations of our analysis

Comparing codeine dependence in different groups of patients was made difficult by changing usage patterns over time, subgroup heterogeneity, and probable under-reporting of codeine use. Methodological constraints included low participant numbers, selection biases (admissions, help-seeking or co-medication sequelae as a proxy for neuroadaptation to codeine), and a lack of objective and standardised criteria for determining codeine dependence. Many studies employed internet-based recruitment or data collection,[33,38] potentially limiting the generalisability of findings to users without regular internet access, but this might be offset by the ability to reach users who are otherwise difficult to reach. Some studies did not specify whether codeine was prescribed or obtained over the counter, but most reports were concerned with over-the-counter codeine. Many studies that included codeine-dependent people were excluded from our analysis because they did not separately describe codeine dependence; this particularly applied to studies of medication overuse headache. Nevertheless, our review is the most comprehensive synthesis of data on the phenomena of codeine dependence, and we have described a range of potential treatment responses, including medication- and non-medication-based treatments.

Conclusion

Codeine dependence can be identified by screening patients who present with acute complications associated with taking combination analgesics, and by routine questioning about over-the-counter medication use. Common treatment approaches include detoxification and opioid agonist treatment. Clinical leadership in providing guidance about how to identify and treat individuals with codeine dependence is required as a matter of public health.

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1 International Narcotics Control Board. Narcotic drugs estimated world requirements for 2015 — statistics for 2013. New York: International Narcotics Control Board, 2015. https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2014/Narcotic_Drugs_Report_2014.pdf (viewed Apr 2017).

2 Gisev N, Nielsen S, Cama E, et al. An ecological study of the extent and factors associated with the use of prescription and over-the-counter codeine in Australia. *Eur J Clin Pharmacol* 2016; 72: 469-494.

3 Van Hout MC, Bergin M, Foley M, et al. A scoping review of codeine use, misuse and dependence; final report. Brussels: CODEMISUSED Project European Commission 7th Framework Programme, 2014. http://codemisused.org/uploads/files/Van_Hout_et_al_Scoping_Report_23-03-2015.pdf (viewed Apr 2017).

4 Coller JK, Christrup LL, Somogyi AA. Role of active metabolites in the use of opioids. *Eur J Clin Pharmacol* 2009; 65: 121-439.

5 Iedema J. Cautions with codeine. *Aust Prescr* 2011; 34: 133-135.

6 Somogyi AA, Barratt DT, Coller JK. Pharmacogenetics of opioids. *Clin Pharmacol Ther* 2007; 81: 429-444.

7 Mattoo SK, Basu D, Sharma A, et al. Abuse of codeine-containing cough syrups: a report from India. *Addiction* 1997; 92: 1783-1787.

8 Orriols L, Gaillard J, Lapeyre-Mestre M, Roussin A. Evaluation of abuse and dependence on drugs used for self-medication: a pharmacoepidemiological pilot study based on community pharmacies in France. *Drug Saf* 2009; 32: 859-873.

9 Nielsen S, Cameron J, Pahoki S. Over the counter codeine dependence [report]. Melbourne: Turning Point Alcohol and Drug Centre, 2010. http://atdc.org.au/wp-content/uploads/2011/02/OTC_CODEINE_REPORT.pdf (viewed Dec 2017).

10 Murnion BP. Combination analgesics in adults. *Aust Prescr* 2010; 33: 113-115.

11 McQuay HJ, Carroll D, Watts PG, et al. Does adding small doses of codeine increase pain relief after third molar surgery? *Clin J Pain* 1986; 2: 197-202.

12 Zhang WY, Po A. Do codeine and caffeine enhance the analgesic effect of aspirin? A systematic overview. *J Clin Pharm Ther* 1997; 22: 79-97.

13 Nielsen S, Tobin CL, Dobbin MDH. OTC codeine: examining the evidence for and against. *Aust Pharmacist* 2012; (Mar): 236-240.

14 Baratta JL, Gandhi K, Viscusi ER. Limited evidence that single-dose oral ibuprofen plus codeine is more effective than either drug alone. *Evid Based Nurs* 2014; 17: 51-52.

15 Derry S, Karlin SM, Moore R. Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2015; (2): CD01017.

16 MacDonald N, MacLeod SM. Has the time come to phase out codeine? *CMAJ* 2010; 182: 1825.

17 Anderson BJ. Is it farewell to codeine? *Arch Dis Child* 2013; 98: 986-988.

18 Babalonis S, Lofwall MR, Nuzzo PA, et al. Abuse liability and reinforcing efficacy of oral tramadol in humans. *Drug Alcohol Depend* 2013; 129: 116-124.

19 Frei MY, Nielsen S, Dobbin MD, Tobin CL. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases. *Med J Aust* 2010; 193: 294-296. https://www.mja.com.au/journal/2010/193/5/serious-morbidity-associated-misuse-over-counter-codeine-ibuprofen-analgesics

20 Sproule BA, Busto UE, Somer G, Romach MK. Characteristics of dependent and nondependent regular users of codeine. *J Clin Psychopharmacol* 1999; 19: 367-372.

21 Mill D, Johnson JL, Cock V, et al. Counting the cost of over-the-counter codeine containing analgesic misuse: a retrospective review of hospital admissions over a 5 year period. *Drug Alcohol Rev* 2017; doi: 10.1111/dar.12595 [Epub ahead of print].

22 Pilgrim JL, Dobbin M, Drummer OH. Fatal misuse of codeine—ibuprofen analgesics in Victoria, Australia. *Med J Aust* 2013; 199: 329-331. https://www.mja.com.au/journal/2013/199/5/fatal-misuse-codeine-ibuprofen-analgesics-victoria-australia

23 Australian Government Department of Health, Therapeutic Goods Administration. Scheduling delegate's final decision: codeine, December 2016. Updated Jan 2017. http://www.tga.gov.au/scheduling-decision-final/scheduling-delegates-final-decision-codeine-december-2016 (viewed Dec 2017).

24 Manitoba College of Pharmacists. Practice direction: exempted codeine preparations [effective Feb 2016]. http://mpha.in1touch.org/uploaded/web/Legislation/Practice%20Resources/Exempted%20Codeine%20Products%20Council%20Approved.pdf (viewed May 2017).

25 Cracknell C. Codeine now restricted to prescription-only. The Connexion [website] 13 July 2017. https://www.connexionfrance.com/French-news/Codeine-now-restricted-to-prescription-only (viewed July 2017).

26 Myers B, Siegfried N, Parry CD. Over-the-counter and prescription medicine misuse in Cape Town: findings from specialist treatment centres. *S Afr Med J* 2003; 93: 367-370.

27 Nielsen S, Murnion B, Dunlop A, et al. Comparing treatment-seeking codeine users and strong opioid users: findings from a novel case series. *Drug Alcohol Rev* 2015; 34: 304-311.

28 Nielsen S, Roxburgh A, Bruno R, et al. Changes in non-opioid substitution treatment episodes for pharmaceutical opioids and heroin from 2002 to 2011. *Drug Alcohol Depend* 2015; 149: 212-219.

29 Joanna Briggs Institute. Critical appraisal checklist for analytical cross sectional studies. Adelaide: Joanna Briggs Institute, 2016. http://joannabriggs-webdev.org/assets/docs/critical-appraisal-tools/JBI_Critical_Appraisal-Checklist_for_Analytical_Cross_Sectional_Studies.pdf (viewed Apr 2017).

30 Glynn L. A critical appraisal tool for library and information research. *Library Hi Tech* 2006; 24: 387-339.

31 Guyatt G, Oxman A, Akl E, et al. GRADE guidelines. Introduction: GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64: 383-394.

32 Gossop M, Darke S, Griffiths P, et al. The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction* 1995; 90: 607-614.

33 Nielsen S, Cameron J, Lee N. Characteristics of a nontreatment-seeking sample of over-the-counter codeine users: implications for intervention and prevention. *J Opioid Manag* 2011; 7: 363-370.

34 Van Hout MC, Horan A, Santlal K, et al. "Codeine is my companion": misuse and dependence on codeine containing medicines in Ireland. *Ir J Psychol Med* 2015; 9: 1-14.

35 Fredheim O, Skurtveit S, Moroz A, et al. Prescription pattern of codeine for non-malignant pain: a pharmacoepidemiological study from the Norwegian Prescription Database. *Acta Anaesthesiol Scand* 2009; 53: 627-633.

36 Dada S, Burnhams NH, Van Hout MC, Parry CDH. Codeine misuse and dependence in South Africa: learning from substance abuse treatment admissions. *S Afr Med J* 2015; 105: 776-779.

37 Qiu YW, Su HH, Lv XF, Jiang GH. Abnormal white matter integrity in chronic users of codeine-containing cough syrups: a tract-based spatial statistics study. *AJNR Am J Neuroradiol* 2015; 36: 50-56.

38 Cooper RJ. "I can' t be an addict. I am." Over-the-counter medicine abuse: a qualitative study. *BMJ Open* 2013; 3: e002913.

39 Nielsen S, Cameron J, Pahoki S. Opportunities and challenges: over-the-counter codeine supply from the codeine consumer's perspective. *Int J Pharm Pract* 2013; 21: 161-168.

40 McAvoy BR, Dobbin MD, Tobin CL. Over-the-counter codeine analgesic misuse and harm: characteristics of cases in Australia and New Zealand. *N Z Med J* 2011; 124: 29-33.

41 McDonough MA. Misuse of codeine-containing combination analgesics. *Med J Aust* 2011; 194: 486. https://www.mja.com.au/journal/2011/194/9/misuse-codeine-containing-combination-analgesics

42 Thekiso TB, Farren C. Over the counter (OTC) opiate abuse treatment. *Ir J Psychol Med* 2010; 27: 189-191.

43 Nielsen S, Bruno R, Murnion B, et al. Treating codeine dependence with buprenorphine: dose requirements and induction outcomes from a retrospective case series in New South Wales, Australia. *Drug Alcohol Rev* 2015; 35: 70-75.

44 Ammit M. Over-the-counter codeine dependency: a case analysis of an inpatient nursing intervention. *Aust Nurs Midwifery J* 2016; 23: 28-31.

45 Bedi RS. Dependence on a common cough linctus. *Indian J Chest Dis Allied Sci* 1991; 33: 227-228.

46 Dutch MJ. Nurofen Plus misuse: an emerging cause of perforated gastric ulcer. *Med J Aust* 2008; 188: 56-57. https://www.mja.com.au/journal/2008/188/1/nurofen-plus-misuse-emerging-cause-perforated-gastric-ulcer

47 Dyer BT, Martin JL, Mitchell JL, et al. Hypokalaemia in ibuprofen and codeine phosphate abuse. *Int J Clin Pract* 2004; 58: 1061-1062.

48 Eng EL, Lachenmeyer J. Codeine self-medication in a headache patient. *Headache* 1996; 36: 452-455.

49 Evans C, Chalmers-Watson TA, Gearry RB. Combination NSAID-codeine preparations and gastrointestinal toxicity. *N Z Med J* 2010; 123: 92-93.

50 Faierman D, Jacobs S. Liver injury from elixir of terpin hydrate with codeine. *Mt Sinai J Med* 1973; 40: 56-59.

51 Gruber CM, Nelson GM. Codeine addiction. *Ann Intern Med* 1948; 29: 151-153.

52 Hard B. Management of opioid painkiller dependence in primary care: ongoing recovery with buprenorphine/naloxone. *BMJ Case Rep* 2014; doi: 10.1136/bcr-2014-207308.

53 Karamatic R, Croese J, Roche E. Serious morbidity associated with misuse of over-the-counter codeine—ibuprofen analgesics. *Med J Aust* 2011; 195: 516. https://www.mja.com.au/journal/2011/195/9/serious-morbidity-associated-misuse-over-counter-codeine-ibuprofen-analgesics

54 Kean J. Illicit and over-the-counter codeine dependence after acute back pain-successful treatment and ongoing recovery after buprenorphine/naloxone taper. *Heroin Addict Relat Clin Probl* 2016; 18: 21-24.

55 Lake IAE. Screening and behavioral management: medication overuse headache — the complex case. *Headache* 2008; 48: 26-31.

56 Lake H. Ibuprofen belly: a case of small bowel stricture due to non-steroidal anti-inflammatory drug abuse in the setting of codeine dependence. *Aust N Z J Psychiatry* 2013; 47: 1210-1211.

57 Marr E, Hill D. Optimising service provision for prescribed opioid analgesic dependence. *Heroin Addict Relat Clin Probl* 2015; 17: 13-18.

58 Ng JL, Morgan DJR, Loh NKM, et al. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. *Med J Aust* 2011; 194: 313-316. https://www.mja.com.au/journal/2011/194/6/life-threatening-hypokalaemia-associated-ibuprofen-induced-renal-tubular

59 Page CB, Wilson PA, Foy A, et al. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. *Med J Aust* 2011; 194: 613-614. https://www.mja.com.au/journal/2011/194/11/life-threatening-hypokalaemia-associated-ibuprofen-induced-renal-tubular

60 Robinson GM, Robinson S, McCarthy P, Cameron C. Misuse of over-the-counter codeine-containing analgesics: dependence and other adverse effects. *N Z Med J* 2010; 123: 59-64.

61 Roussin A, Bouyssi A, Pouche L, et al. Misuse and dependence on non-prescription codeine analgesics or sedative H1 antihistamines by adults: a cross-sectional investigation in France. *PLoS One* 2013; 8: e76499.

62 Senjo M. Obsessive—compulsive disorder in people that abuse codeine. *Acta Psychiatr Scand* 1989; 79: 619-620.

63 Vaughan JV, Fleischl P, Nathan M, Taylor RC. Chronic renal disease and analgesic abuse. *N Z Med J* 1967; 66: 794-797.

64 Wylie AS, Fraser AA. Hazards of codeine plus paracetamol compounds. *Br J Gen Pract* 1994; 44: 376.

65 Van Hout MC, Delargy I, Ryan G, et al. Dependence on over the counter (OTC) codeine containing analgesics: treatment and recovery with buprenorphine naloxone. *Int J Ment Health Addict* 2016; 14: 873-883.

66 Romach MK, Otton SV, Somer G, et al. Cytochrome P450 2D6 and treatment of codeine dependence. *J Clin Psychopharmacol* 2000; 20: 43-45.

67 Nilsen HK, Stiles TC, Landro NI, et al. Patients with problematic opioid use can be weaned from codeine without pain escalation. *Acta Anaesthesiol Scand* 2010; 54: 571-579.

68 Fernandes LC, Kilicarslan T, Kaplan HL, et al. Treatment of codeine dependence with inhibitors of cytochrome P450 2D6. *J Clin Psychopharmacol* 2002; 22: 326-329.

69 Norman IJ, Bergin M, Parry CD, Van Hout MC. Best practices and innovations for managing codeine misuse and dependence. *J Pharm Pharm Sci* 2016; 19: 367-381.

70 Nielsen S, Larance B, Degenhardt L, et al. Opioid agonist treatment for pharmaceutical opioid dependent people. *Cochrane Database Syst Rev* 2016; (5): CD011117.

71 Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014; (2): CD002207.

72 Gowing L, Ali R, Dunlop A, et al. National guidelines for medication-assisted treatment of opioid dependence. Canberra: National Drug Strategy, 2014. http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/Publishing.nsf/content/AD14DA97D8EE00E8CA257CD1001E0E5D/$File/National_Guidelines_2014.pdf (viewed Dec 2017).

73 Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev* 2011; (9): CD005031.

74 Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst Rev* 2011; (10): CD004147.

75 Quello SB, Brady KT, Sonne SC. Mood disorders and substance use disorder: a complex comorbidity. *Sci Pract Perspect* 2005; 3: 13-21.

76 Evers S, Jensen R. Treatment of medication overuse headache: guideline of the EFNS headache panel. *Eur J Neurol* 2011; 18: 1115-1121.

77 Chiang C, Schwedt T, Wang S, Dodick D. Treatment of medication-overuse headache: a systematic review. *Cephalalgia* 2016; 36: 371-386.

78 Tassorelli C, Jensen R, Allena M, et al. A consensus protocol for the management of medication-overuse headache: evaluation in a multicentric, multinational study. *Cephalalgia* 2014; 34: 645-655.

79 Katsarava Z, Fritsche G, Muessig M, et al. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology* 2001; 57: 1694-1698.

80 Dodick DW, Silberstein SD. How clinicians can detect, prevent and treat medication overuse headache. *Cephalalgia* 2008; 28: 1207-1217.

81 Katsarava Z, Muessig M, Dzagnidze A, et al. Medication overuse headache: rates and predictors for relapse in a 4-year prospective study. *Cephalalgia* 2005; 25: 12-15. ■