



Appendix

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Identification and treatment of codeine dependence: a systematic review

Online appendix

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Table 1. Sample search, Medline

Search number	Search term	Details	Hits
1	codeine	MeSH heading, used for: Ardinex codeine phosphate codeine isocodeine n methylmorphine n-methylmorphine	4334
2	dependence	Not MeSH heading	217921
3	Substance-related disorders	MeSH heading, used for: abuse, drug abuse, substance abuses, substance addiction, drug addiction, substance dependence, drug dependence, substance disorder, drug use disorder, substance use drug abuse drug addiction drug dependence drug habituation drug use disorder drug use disorders habituation, drug organic mental disorders, substance induced organic mental disorders, substance-induced substance abuse substance abuses substance addiction substance dependence substance use disorder substance use disorders substance-related disorders	95278
4	Opioid-related disorders	MeSH heading, used for: abuse, narcotic abuses, narcotic addiction, narcotic addiction, opiate dependence, narcotic dependence, opiate disorder, opioid-related narcotic abuse narcotic abuses	11698

		narcotic addiction narcotic dependence opiate addiction opiate dependence opioid-related disorders	
5	Behavior, Addictive	MeSH heading, used for: addictive behavior addictive behaviors behavior, addictive behaviors, addictive	
6	Substance Withdrawal Syndrome	MeSH heading, used for: drug withdrawal symptom drug withdrawal symptoms substance withdrawal syndrome substance withdrawal syndromes symptom, drug withdrawal symptom, withdrawal symptoms, drug withdrawal symptoms, withdrawal syndrome, substance withdrawal syndromes, substance withdrawal withdrawal symptom, drug withdrawal symptom withdrawal symptoms, drug withdrawal symptoms withdrawal syndrome, substance withdrawal syndromes, substance	21918
7	2 OR 3 OR 4 OR 5 OR 6		327009
8	1 AND 7		589
9	Limit 8 to Humans AND English		465

Table 2. Summary of excluded studies

First author	Date	Reason for exclusion
Agnich	2013	Not specific to codeine dependence
Agyapong	2012	No full text
Allen	2015	No full text
Alvarez	2009	No full text
Anonymous	2013	Letter/commentary (no empirical data)
Anonymous	2010	Not specific to codeine dependence
Arora	2013	Not specific to codeine dependence
Basu	2012	Does not inform identification or treatment
Bateman	2013	Letter/commentary (no empirical data)
Bergin	2015	No empirical data
Boe	2009	Not specific to codeine dependence
Buckley	1986	Not specific to codeine dependence
Burton	2012	Letter/commentary (no empirical data)
Busto	1998	Not specific to codeine dependence
Butler	2010	Not specific to codeine dependence
Cevoli	2006	Not specific to codeine dependence
Chiang	2005	Not specific to codeine dependence
Cohen	2010	Not specific to codeine dependence
Cooper	2013b	Not specific to codeine dependence
Corbelli	2012	Not specific to codeine dependence
Couch	2006	Not specific to codeine dependence
Diener	2006	No empirical data
Downie	2000	Not specific to codeine dependence
Dowson	2005	No empirical data
Dowson	2015	No empirical data
Dunkley	2007	Letter/commentary (no empirical data)
Elander	2014	Not specific to codeine dependence
Ernest	2010	Not specific to codeine dependence
Foster	2011	No full text
Frazier	1994	Letter/commentary (no empirical data)
Gerostamoulos	2010	Not specific to codeine dependence
Gisev	2016	Does not inform identification or treatment
Green	2014	No full text
Green	2011	Not specific to codeine dependence
Gupte	2012	Letter/commentary (no empirical data)
Gupte	2013	Letter/commentary (no empirical data)
Haag	2007	Letter/commentary (no empirical data)
Hackman	2014	Not specific to codeine dependence
Hamer	2014	Does not inform identification or treatment
Hard	2014	Not specific to codeine dependence
Hebbert	1951	Does not inform identification or treatment

Henricson	1999	Does not inform identification or treatment
Herrera	2016	No full text
Holliday	2015	Does not inform identification or treatment
Hollingworth	2015	Does not inform identification or treatment
Hou	2011	Does not inform identification or treatment
Howe	2013	Not specific to codeine dependence
Huffman	1975	Does not inform identification or treatment
Isaac	1993	Letter/commentary (no empirical data)
Ishigooka	1991	Does not inform identification or treatment
Jensen	1992	Does not inform identification or treatment
Juska	2013	Not specific to codeine dependence
Kalapatapu	2010	Not specific to codeine dependence
Kardachi	2013	Letter/commentary (no empirical data)
Kathiramalainathan	2000	Not specific to codeine dependence
Kelly	2012	Does not inform identification or treatment
Knisely	2008	Not specific to codeine dependence
Krausz	1996	Not specific to codeine dependence
Kristoffersen	2014	Not specific to codeine dependence
Lader	1984	Not specific to codeine dependence
Lake	2016	Not specific to codeine dependence
Larance	2015	Does not inform identification or treatment
Lessenger	2008	Does not inform identification or treatment
Lobmaier	2010	Not specific to codeine dependence
Manchikanti	2008	Not specific to codeine dependence
Manubay	2014	Does not inform identification or treatment
Martell	2007	Not specific to codeine dependence
Martin	2009	Letter/commentary (no empirical data)
Mauskop	2002	Not specific to codeine dependence
McAvoy	2014	Letter/commentary (no empirical data)
McDonald	2013	Not specific to codeine dependence
McRae	2008	Does not inform identification or treatment
Mercadante	2004	Does not inform identification or treatment
Mitchell	2009	Does not inform identification or treatment
Moeller	2009	Does not inform identification or treatment
Moorekite	2008	Not specific to codeine dependence
Murnion	2010	Not specific to codeine dependence
Opheim	2015	No full text
Paterson	1990	Letter/commentary (no empirical data)
Peters	2003	Does not inform identification or treatment
Peters	2007b	Does not inform identification or treatment
Peters	2007	Not specific to codeine dependence
Pilgrim	2013	Not specific to codeine dependence
Qiu	2016	Does not inform identification or treatment

Rapoport	2008	No empirical data
Romach	1999	Not specific to codeine dependence
Rappolt	1979	Does not inform identification or treatment
Roberts	2005	Letter/commentary (no empirical data)
Romach	1999	Not specific to codeine dependence
Roussin	2011	No full text
Roxburgh	2015	Does not inform identification or treatment
Sellers	2000	No empirical data
Sheu	2008	Not specific to codeine dependence
Sim	2004	Letter/commentary (no empirical data)
Smith	2005	Not specific to codeine dependence
Soyka	1999	Not specific to codeine dependence
Stefanidou	2010	Does not inform identification or treatment
Talbott	2006	Not specific to codeine dependence
Tang	2012	Not specific to codeine dependence
Torrens	2014	No full text
Touzeau	2014	No full text
Tretter	1998	Does not inform identification or treatment
Tsang	2012	Not specific to codeine dependence
Turaeva	2013	Does not inform identification or treatment
Tyndale	1997	Not specific to codeine dependence
Van Hout	2016	No empirical data
Van Hout	2016c	No empirical data
Van Hout	2016b	No empirical data
Van Schoor	2015	Not specific to codeine dependence
Vest	2016	Not specific to codeine dependence
Vignau	2001	Not specific to codeine dependence
Vukmir	2004	Not specific to codeine dependence
Wang	2013	Does not inform identification or treatment
Wasaify	2006	Not specific to codeine dependence
Wasan	2009	Not specific to codeine dependence
Weaver	1999	Not specific to codeine dependence
Webster	2010	Not specific to codeine dependence
Weich	2008	Not specific to codeine dependence
West	2009	Not specific to codeine dependence
Widlitz	2002	Not specific to codeine dependence
Woods	2010	Not specific to codeine dependence
Wu	2008	Not specific to codeine dependence
Wu	2009	Not specific to codeine dependence
Wu	2010	Not specific to codeine dependence
Wu	2016	Not specific to codeine dependence
Wunsch	2007	Not specific to codeine dependence
Ytterberg	1998	Not specific to codeine dependence

Zanyk	1988	Letter/commentary (no empirical data)
Zedler	2014	Not specific to codeine dependence
Zinkernagel	2001	Not specific to codeine dependence

Table 3. Modified JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
5. Was appropriate statistical analysis used?	☐	☐	☐	☐
6. (EBL item) Is the choice of population bias-free?	☐	☐	☐	☐

Abbreviations: EBL = Evidence-based Librarianship, JBI = Joanna Briggs Institute.

Tables 4A-D. Summary of included studies

Table 4A: Studies describing characteristics of codeine dependence.

Study ID	Study Design	Study location	No. of participants	Age (years)	Gender	Other study population details	Current pain condition	Mental health	Employment status	Other drug use	Other relevant characteristics	Details of codeine dependence	Quality rating
Cooper 2013* (1)	Qualitative interviews	United Kingdom	25	20-60	13/25 Female	Recruited from internet support groups, specific to OTC codeine.	Pain conditions included headaches /migraine, abdominal and period pain and hangover treatments.	NR	2 retired, 1 unemployed 1 student, 1 housewife, 3 not reported, remainder (17) employed/ self-employed.	NR	Genuine medical reasons were almost always associated with initial use of OTC codeine, participants considered themselves 'addicted'.	Three groups; those who never exceeded the dose, those who slightly exceeded it and those who considerably exceeded maximum doses.	3
Dada 2015 (2)	National treatment administrative data set from South Africa	South Africa	425 total codeine-related admissions 137 had codeine as primary substance of abuse	Range 11-70; Highest proportion aged 20-29 (36.3%), 30-39 (23.1%)	25% Female	Admissions to alcohol and other drug treatment centres for codeine misuse or dependence, predominantly OTC codeine.	NR	5% reported mental health problems	46% employed	63% reported other substances as primary drug of abuse (alcohol, cannabis, heroin).	Most (60%) had high school education or higher. Few (37%) had previously received treatment for dependence.	Codeine almost exclusively (97%) used orally.	2
Fredheim 2009 (3)	Examination of national prescription database	Norway	385 190 who were supplied codeine in 2005	Mean (whole sample) 52.3 (SD 18.8)	56% Female	All users of prescription codeine compounds during the years 2004, 2005 and 2006.	~90% for acute/ intermittent pain.	NR	NR	Co-medication with benzodiazepine more frequent among codeine-experienced people.	10% of the Norwegian adult population use codeine annually.	1787 (0.5%) exceeded 730 defined daily doses in one year, taking at least double the recommended dose.	5
Frei 2010* (4)	Case series	Victoria, Australia	27	20 and above	13/27 Female	Patients were inpatients referred to hospital addiction medicine, specifically examined OTC codeine.	NR	NR	NR	Three patients had history or alcohol use disorder, ten patients had a history of drug injection, 15/27 reported only using OTC codeine.	Opioid dependence and gastrointestinal complications were the most common morbidities.	Mean daily dose of 435–602 mg of codeine phosphate	3

Study ID	Study Design	Study location	No. of participants	Age (years)	Gender	Other study population details	Current pain condition	Mental health	Employment status	Other drug use	Other relevant characteristics	Details of codeine dependence	Quality rating
McAvoy 2011* (5)	Case series	New Zealand	15	44 (range 30-60)	7/15 Female	Compared to populations in two other published reports (n = 7 and n = 77). Specifically examined OTC codeine use.	NR – many recently hospitalised due to problems with codeine.	93% had comorbid mental health conditions.	NR	53% had alcohol or other drug use disorders.	53% had gastrointestinal bleeding or dyspepsia.	Taking mean of 49 tablets per day	3
McDonough 2011 (6)	Retrospective chart review	Victoria, Australia	32	Median 38	23/32 Female	Referred to hospital drug and alcohol services for excessive OTC codeine use (Sep 2005 - Sep 2010).	All started in the context of acute pain, and all had chronic pain ultimately.	All had psychiatric problems associated with codeine use.	NR	NR	One case of surgical intervention and eventual opioid replacement treatment.	All diagnosed as opioid dependent. One death related to gastric ulceration, in the context of relapse.	2
Nielsen 2011 (7)	Online survey	Australia	137 who met criteria for codeine dependence	37 (SD 13)	66% Female	OTC Codeine dependent people subset of 800 people who self-reported OTC codeine use.	47% reported current chronic pain	Mean K10 score of 24.5 (SD 9.5) indicates high psychological distress. .	38% completed tertiary degree, 73% employed or full-time student.	62% reported ever using illicit drugs, 42% had ever sought help for an alcohol or other drug problem, 26% had ever sought help for their codeine use.	Psychological distress, chronic pain history, alcohol or other drug treatment history.	Age of first use 24 years, two thirds exceeded recommended dose and used for non-medical purposes.	3
Nielsen 2013 (8)	Qualitative exploration of OTC codeine dependence	Melbourne, Victoria, Australia	20	39 (SD 11)	12/20 Female	OTC codeine dependent	Chronic pain conditions including medication overuse headache.	NR	NR	25% reported history of illicit drug use, 55% previous treatment for alcohol or drug dependence (including codeine dependence).	Identification of dependence challenging in pharmacy settings. Increased questioning by pharmacists was related to help-seeking.	All assessed to meet DSM IV criteria for codeine dependence. Three use patterns described; therapeutic, recreational and high dose.	2

Study ID	Study Design	Study location	No. of participants	Age (years)	Gender	Other study population details	Current pain condition	Mental health	Employment status	Other drug use	Other relevant characteristics	Details of codeine dependence	Quality rating
Nielsen 2015a (9)	Cross-sectional study of administrative data sets	Australia, national data set	4424 codeine treatment episodes	Mean 36	70% Female in 2002; 47% female in 2011	Among codeine-related treatment episodes injection was less common (13% vs. 56% for strong opioids and 90% for heroin). Codeine source not known (i.e. OTC or prescribed).	NR	NR	NR	Other drugs of concern reported in treatment episode: benzodiazepines (15%), alcohol (15%), cannabis (11%), stimulants (6%)	One in three treatment episodes (34%) provided in regional/remote location.	NR	2
Nielsen 2015b* (10)	Retrospective chart review	New South Wales, Australia	135 (53 dependent on codeine)	38 (SD 8)	35/53 Female	Most (89%) reported codeine was OTC	62% reported a pain condition, 66% initiated codeine for pain.	79% psychiatric comorbidity, 59% depression, 26% anxiety disorder.	43% employed	45% nicotine, 9% cannabis, 26% history of problematic alcohol use, 32% current benzodiazepine use.	Seven (13%) reported any history of heroin use.	Codeine use for median of 5 years; 83% reported codeine was the only opioid they used.	4
Qiu 2015 (11)	Case control study mapping brain differences	China	60 (30 codeine dependent people and 30 controls)	Ave 25	2 Female 28 Male	Age of first codeine use 20 years. Not stated if codeine syrup requires prescription.	NR	Ave Barratt Impulsiveness Scale 72.	NR	Naïve for illicit drug use, no regular alcohol use. Ave 16.5 cigarettes/day.	Codeine dependence was associated with differences in white brain matter that may be linked to impulsivity.	Average 487 mL cough syrup /day. Average duration chronic codeine use 5 years.	2
Sproule 1999 (12)	Survey	Toronto, Canada	339	Ave 43.5 (range 18-82) (40 +/- 10 for dependent patients)	51% Female	Included if codeine use 3 days/week, minimum 6 months. Completed high school (65%), currently married/sig relationship (46%). OTC and prescribed codeine.	81% reported chronic pain: Headaches (41%), back pain (22%), other including muscle/ joint pain (25%).	Depression (23%), anxiety (21%)	Unemployed (27%)	27% of dependent had sought help for substance disorder, especially alcohol (15%) and stimulants (14%).	Smaller proportion of >60 years of age dependent (15%) vs younger (47%) 65% in dependence group had family history of substance problems.	37% met DSM IV criteria for codeine dep. Ave use 179 mg/day Mean first use 26 +/- 13 years. mean number codeine use 12 +/-	5

Study ID	Study Design	Study location	No. of participants	Age (years)	Gender	Other study population details	Current pain condition	Mental health	Employment status	Other drug use	Other relevant characteristics	Details of codeine dependence	Quality rating
Thekiso 2010* (13)	Retrospective chart review	Dublin, Ireland	20	49.2 (SD 23.4)	13/20 Female	Study specific to OTC codeine use	4/20 patients reported chronic pain.	95% had significant psychiatric morbidity.	NR	65% reported either harmful alcohol use or dependence.	Specifically noted over-the-counter codeine use	6 diagnosed with 'harmful opioid use', 14 diagnosed with opioid dependence	4
Van Hout 2015* (14)	Qualitative interviews	Dublin, Ireland	21	Ave 39 (range 26-62)	12/21 Female	Participants reported OTC and prescribed codeine use, preference for OTC ibuprofen-codeine	NR	NR	52% unemployed	Many combined with alcohol, particularly at nighttime.	NR	15 pts had a SDS score of 10 or more. Maximum daily doses between 24 - 115 tablets.	2

Ave Average; DSM IV Diagnostic and Statistical Manual of Mental Disorders; JBI Joanna Briggs Institute; NR Not Report; OTC over the counter; SD Standard Deviation *details from study also presented in Table 3 (treatment approaches).

Table 4B: Individual patient reports - Acute description and/or management of codeine-related harms.

Study	Location	Age	Gender	Pain conditions	Mental health	Employment	Other drug use	Other notes	Presenting symptoms	Harms from codeine use	Details of codeine dependence	Treatment approach	Details of outcome
Ammit 2016 (15)	Sydney, Australia	39	Female	Abdominal pain (constipation for 3 days). Started for back pain.	Anxious	Part-time employed	Alcohol, heroin in 20s	OTC codeine	Abdominal and back pain	Gastric erosion and renal tubular acidosis.	520 mg daily codeine (OTC ibuprofen combination) for past year. Use increased with physical and psychological distress.	Symptomatic medication (diazepam, paracetamol and baclofen) Balloon enteroscopy and dilation for small bowel obstruction. Education; patient knew of harms with paracetamol but not ibuprofen.	After admission started on opioid substitution therapy, counselling and re-attending 12 step program.
Dutch 2008 (16)	Melbourne, Australia	39	Female	24 h history of acute epigastric pain.	NR	NR	History of alcohol	History of pancreatitis, OTC codeine use	Epigastric pain, pallor, mild diaphoresis, rapid heart rate, severe abdominal pain	Anterior gastric antrum ulcer and 2.6 L of green turbid fluid in the peritoneal cavity.	16-24 Nurofen Plus® tablets daily for 3 weeks.	Transferred to intensive care in another hospital.	NR
		41	Male	Severe abdominal pain past 12 h.	NR	NR	NR	Initially attempted to self-manage abdominal pain with laxatives	Abdominal pain and tenderness	Gastric antrum ulcer with gross abdominal contamination.	Had been taking one 'pack' of Nurofen Plus® tablets daily for one year.	Postoperatively, patient offered inpatient drug treatment, absconded before transfer arranged.	NR
Dyer 2004 (17)	London, United Kingdom	49	Male	NR	History of depression, recent bereavement and divorce	NR	Previous IV drug and alcohol use. GP confirmed non-medical OTC codeine use.	Denied 'drug abuse', cause of hypokalaemia was not detected initially.	Low serum potassium (first presentation), discharged 10 days later. Represented 3 days later with GCS of 6, which responded to naloxone. Later self-discharged. Readmitted 2 weeks later with lethargy and vomiting, low serum sodium and potassium.	Perforated duodenal ulcer 3 years previously (inappropriate ibuprofen use), hypokalaemia	30 Nurofen Plus® tablets in the 3 days prior to admission. GP reported taking 24 tablets at a time previously.	Serum potassium was corrected with IV potassium therapy. Advised that the Nurofen Plus® use was the cause of his recurrent hypokalaemic episodes, advised to cease and offered assistance.	NR
Faierman 1973 (18)	New York, United States of America	30	Male	NR	NR	Employed (delivery man)	NR	Codeine cough mixture (not noted if prescribed)	Generalised seizure	Hepatic injury with extensive fibrosis attributed to terpin hydrate component of cough syrup, as opposed to codeine.	NR	NR	NR
Karamatic 2011 (19)	Townsville, Australia	42	Male	Chronic ankle pain	Depression	NR	Alcohol use	All presentations of OTC codeine dependence associated with NSAID enteropathy.	Recurrent severe hypokalaemia; vomiting, abdominal pain and weight loss; iron deficiency and hypoalbuminaemia; vitamin B12 deficiency.	Multiple jejunal ulcers with early stricturing consistent with NSAID enteropathy.	Ibuprofen 200 mg/ codeine phosphate 12.8 mg, 10 tablets per day.	Omeprazole 40 mg daily; mirtazapine 15 mg daily; oxycodone 5 mg 4-6 h as needed.	NR

Study	Location	Age	Gender	Pain conditions	Mental health	Employment	Other drug use	Other notes	Presenting symptoms	Harms from codeine use	Details of codeine dependence	Treatment approach	Details of outcome
Karamatic 2011 (cont.)		41	Female	Misdiagnosed as Crohn's disease	NR	NR	NR		Abdominal pain, diarrhoea and vomiting; iron deficiency anaemia; hypoalbuminaemia.	Multiple web-like strictures with circumferential ulceration throughout the small bowel consistent with NSAID enteropathy	Ibuprofen 200 mg/codeine phosphate 12.8 mg: 20 tablets per day for 5 years.	Iron supplement	NR
		41	Male	Chronic back pain	Depression	NR	Excessive alcohol use		Iron deficiency anaemia; hypoalbuminaemia.	Multiple jejunal ulcers	Ibuprofen 200 mg /codeine phosphate 12.8 mg: 10–12 tablets per day for >5 years.	Omeprazole and amitriptyline daily; Buscopan® paracetamol& codeine and tramadol as needed	NR
Lake 2013 (20)	Hobart, Australia	35	Male	Codeine use initiated in the context of dental pain 10 years ago.	History of suicide behaviour	Unemployed	Nil	Use of OTC codeine. Initially unaware of codeine addiction risk.	3-month history of abdominal pain, acutely worse over 24 h, associated with nausea and vomiting, and with chronic constipation and anorexia	Small bowel stricture secondary to NSAID, loss of partner and occupation.	Up to 90 tablets of codeine/ibuprofen per day, clear salience and neuroadaptation.	Exploratory laparotomy and small bowel resection, patient controlled ketamine use, community drug treatment on discharge from hospital.	Post-operative delirium, which started on day 3 and fluctuated over 4 days.
Ng 2011 (21)	Perth, Australia	32	Female	Migraine	Depression	NR	Previous use of drugs by injection	Focus on renal aspects of presentations, specifically OTC codeine	Paralysis associated with profound hypokalaemia, distal renal tubular acidosis, epigastric pain.	Oesophageal erosions, benign gastric ulcer, enlarged, oedematous kidneys without nephrocalcinosis.	20 tablets per day of ibuprofen 200 mg / codeine phosphate 12.8 mg	Electrolyte replacement.	NR
		37	Male	NR	NR	NR	Tobacco		Progressive muscle weakness, hypokalaemia, distal renal tubular acidosis.		24 tablets ibuprofen 200 mg / codeine phosphate 12.8 mg daily	Electrolyte replacement and buprenorphine maintenance therapy.	NR
		45	Female	Dental caries	NR	NR	Previous use of drugs by injection		7 days of lethargy and anorexia, hypokalaemia, distal renal tubular acidosis.	Microcytic anaemia, gastric antral ulceration with a peptic oesophageal stricture.	Approximately 50 tablets per day of ibuprofen 200 mg / codeine phosphate 12.8 mg	Electrolyte replacement	NR
		40	Male	Back pain	NR	NR	Tobacco		Profound generalised weakness, hypokalaemia, distal renal tubular acidosis.		1.4–2.0 g/day of ibuprofen for 3 months in codeine combination product.	Electrolyte replacement	NR
Page 2011 (22)	NSW, Australia	35	Female	NR	NR	NR	NR	OTC codeine	All patients presented with biochemical signs of renal tubular acidosis with severe hypokalaemia and a normal anion gap metabolic acidosis from long-standing misuse of ibuprofen taken in combination with codeine from OTC medications.	Renal tubular acidosis, Normal anion gap metabolic acidosis.	All patients presented with long-standing misuse of ibuprofen (5-18 g/day)+ codeine (320 - 1152 mg /day) from OTC medications.		Biochemical recovery in all 4 patients
		55	Male	NR	NR	NR	NR						

Study	Location	Age	Gender	Pain conditions	Mental health	Employment	Other drug use	Other notes	Presenting symptoms	Harms from codeine use	Details of codeine dependence	Treatment approach	Details of outcome
Page 2011 (cont.)		41	Male	NR	NR	NR	NR					Both patients required intensive care admission for central venous access and potassium replacement.	
		39	Female	NR	NR	NR	NR						
Roussin 2013 (23)	France	38	Female	Migraine	Depressive mood	NR	NR	Study examined OTC codeine	Withdrawal causes rebound pain and 'feeling bad'	Depressive mood	120 mg of codeine phosphate daily for 3 years in combination product with paracetamol. GP not aware of use.	NR	NR
		42	Female	'Pain'	NR	NR	NR		Withdrawal causes rebound pain and 'feeling bad'	NR	160 mg of codeine phosphate daily for 10 years in combination product with paracetamol. GP aware of use.	NR	NR
		47	Female	Back pain	NR	NR	NR	Reports use for 'well being'	Withdrawal causes rebound pain and nervousness	Constipation and vertigo	160 mg of codeine phosphate daily for 1 year in combination product with paracetamol. GP not aware of use.	NR	NR
		55	Male	Cervicalgia	NR	NR	NR		NR	NR	120 mg of codeine phosphate daily for 3 years in combination product with paracetamol. GP aware of use.	NR	NR
		38	Female	None	Anxiety	NR	NR		Withdrawal causes sweating and 'feeling bad'	NR	200 mg of codeine phosphate daily for 3 years in combination product with paracetamol. GP aware of use.	NR	NR
		42	Male	Migraine	NR	NR	NR		NR	NR	120 mg of codeine phosphate daily for greater than 1 year in combination product with paracetamol. GP aware of use.	NR	NR
Wylie 1994 (24)	Glasgow, Scotland	37	Female	Sciatica	Patient reported codeine improves her mood.	NR	NR	Prescribed codeine reported	Elevated ALT, GGT, normal coagulation tests.	NR	Using paracetamol 500 mg/codeine phosphate 30 mg, up to 30 tablets per day.	Treated for potential hepatotoxicity with acetylcysteine, discharged after 2 days.	NR

Key: ALT Alanine Transaminase; GCS Glasgow Coma Scale; GGT Gamma-Glutamyl Transferase; GP General Practitioner; IV Intravenous; NR Not Recorded; NSAID Non-Steroidal Anti-Inflammatory Drug; OTC Over The Counter.

Table 4C: Individual patient reports - Treatment of codeine dependence with or without management of acute harms.

Study	Location	Age	Gender	Pain conditions	Mental health	Employment	Other drug use	Other notes	Presenting symptoms	Harms from codeine use	Details of codeine dependence	Treatment approach	Details of outcome
Bedi 1991 (25)	Punjab, India	42	Male	Nil	Nil	Self-employed (farmer)	Nil	Tried unsuccessfully to self-manage withdrawal. OTC codeine			2 bottles of Phensydeyl® (450 mg of codeine, 366 mg of ephedrine and 180 mg of promethazine) daily.	Treated with loperamide, diazepam and. nitrazepam. Supportive psychotherapy and family counselling were advocated for. Drugs reduced over ten days.	Loose motions, sleep disturbance (first 48 h). Symptoms not severe and subsided. 7 month follow up uneventful.
Eng 1996 (26)	Manhasset, United States of America	54	Male	Severe headaches, 10 year history of obtaining medications for headaches	Generalized anxiety disorder	Employed, anxious about his job	Reported obtaining 'pills' from the black market, no other substance use outside medication for headache described	Hypertension, peptic ulcer, skin allergies. Reports prescribed codeine use.	"Stinging" and localized headache in the forehead. No aura or accompanying visual, gastrointestinal, or neurological symptoms.	Medication overuse headache	6-15 tablets containing paracetamol with codeine.	Detoxification with methadone, referral to an Anxiety Disorders Program (due to significant anxiety and stress). Assessed to have GAD, patient did not relate headaches to stress initially. Began CBT, taught relaxation.	Self-manage analgesic use, developed alternative strategies for psychological symptoms. Was able to reduce analgesic use to paracetamol alone twice a week or less.
Evans 2010 (27)	Christchurch, New Zealand	35	Male	Previously fit, reported codeine use for back pain.	NR	NR	NR	1-year history of daily epigastric pain; worse on eating. OTC codeine	Haemoglobin concentration of 67 g/L, albumin 31 g/L, exertional dyspnoea, lower leg oedema.	Acute gastric ulcer, severe gastritis and post-bulbar duodenitis with active bleeding.	Taking > 100 Nurofen Plus® per day for back pain.	Prescribed a reducing codeine dose as an opiate substitute for the Nurofen Plus® and received counselling for his addiction.	Ulcer, gastritis and duodenitis healed, however balloon dilation of the subsequent pyloric stenosis was required.
Gruber 1948 (28)	Philadelphia, United States of America	57	Male	Chronic abdominal pain	NR, although patient ultimately suicided.	Employed (Physician)	Paraldehyde, alcohol, morphine	Past history of appendectomy, cholecystectomy, inguinal herniotomy, ureteric calculus, acute toxic hepatitis. Unclear if codeine prescribed.	8-year history of epigastric pain and loss of weight.	Neuroadaptation and decline in functioning, loss of weight, likely maintenance of chronic pain symptoms, suicide following withdrawal.	IV use of codeine in the form of Pantopon®, up to 4.8 g daily in the weeks antedating hospitalisation but otherwise 660 mg daily for months prior.	IV codeine in reducing doses over 12 days, IV Demerol® 100 mg 4-6 times per day from day 3-11, followed by acetylsalicylic acid and sterile water injections days 12-15.	Withdrawal syndrome tolerated with some discomfort; characterised by haemodynamic, autonomic, sensory, muscular excitability, mental state and weight changes. Returned home and suicided by undisclosed means.
Hard 2014 (29)	Newport, United Kingdom	Mid-20's	Female	Generalised aches and pains, putative diagnosis was "myalgic encephalopathy"	Low mood	Employed	Diazepam	Reported prescribed codeine.	Generalised pain	Neuroadaptation, exclusion of other activities, financial,	10-year history of codeine dependence (initially prescribed).	Harm minimisation with dihydrocodeine 600 tablets /week. Commenced on buprenorphine/naloxone over 2 days (4/0.5 mg twice on day 1, 16/4 mg day 2), engaged with recovery support services and psychosocial counselling. Maintained on buprenorphine 10 mg/naloxone 2.5 mg. 12-step program.	Initially mild precipitated withdrawal (patient was not in withdrawal when buprenorphine commenced). Stabilised and returned to work.

Study	Location	Age	Gender	Pain conditions	Mental health	Employment	Other drug use	Other notes	Presenting symptoms	Harms from codeine use	Details of codeine dependence	Treatment approach	Details of outcome
Kean 2016 (30)	Bradford, United Kingdom	Mid-30's	Male	Non-specific low back pain	Stress secondary to employment and family	Full time employed	Tobacco, occasional alcohol only	Illicit and OTC codeine	Escalating codeine use lethargy, low mood, weight loss, constipation, abdominal pain, and cramps.	Neuroadaptation, relationship disharmony, rebound headaches, hypoalbuminaemia, ALT elevation.	Initiated on codeine by GP for back pain, later supplemented with illicit codeine, escalating over years, 250 mg/day	Buprenorphine/naloxone induction up to 8 mg buprenorphine daily, tapered over 4 months. Emergent symptoms of anxiety and depression at the end of the taper responded to fluoxetine and counselling.	Depressive and anxiety symptoms following buprenorphine/naloxone taper. Abstinent, functioning and intact relationships
Lake 2008 (31)	AnnArbor, United States of America	39	Female	Daily headache (4 year), episodic headache since age 18.	One episode of major depression, insomnia, histrionic, relying on passive coping techniques.	Home schooled her 4 daughters for religious reasons	10 butalbital tablets daily, a history of recreational drug use in adolescence (in sustained remission). Unclear if prescribed.	Marital disharmony and invalidation of pain.	Medication overuse headache	Transformation of episodic to daily headache.	10 butalbital with codeine and acetaminophen tablets per day for pain control for the past year, prior to first admission.	Initially withdrawn from butalbital and codeine. coached in relaxation techniques. After multiple admissions, more punitive treatment contract (weekly psychotherapy, formal substance abuse program, observed urine drug screens). CBT, pain management and 12-step program.	Ongoing relapse, eventually ceased substance use, diagnosed with fibromyalgia and prescribed opioids.
Marr 2015 (32)	Lanarkshire, Scotland	24	Female	Dental pain initially	None	Shop assistant	None noted	Working and socialising normally. Taking prescribed and OTC codeine.	Escalating prescribed tramadol with co-codamol, withdrawal emerging on cessation	Dependence	Initially self-medication for dental pain, escalated to prescribed and OTC opioids	Stabilised on buprenorphine-naloxone 16/4 mg, transferred to mono-product for pregnancy	Transferred to community prescriber, reported stigma and discomfort with drug treatment clinic environment
Robinson 2010 (33)	New Zealand	53	Male			NR	Alcoholism	All cases of OTC codeine.	NR	Gastric ulcer, gastric bleeding, hepatotoxicity	60-80 Nurofen Plus® tablets per day for 2 years	NR	Many patients reported significant opioid withdrawal symptoms despite treatment with ancillary medications.
		31	Female		Depression	NR			NR	Peptic ulcer and anaemia	48 Nurofen Plus® tablets daily for 2 years		
		63	Female		Depression	NR	Alcoholism		NR	Gastric ulcer	Nurofen Plus® (and prescription codeine) 20 tablets daily for 3 years		
		47	Female	Headache	Depression, anxiety, psychosis	NR	Alcoholism	Previous gastric bypass and partial colectomy	NR	"inflammatory bowel disease"	Nurofen Plus® up to 72 tablets daily for 1 year		
		52	Male			NR	Alcoholism and opioid dependence		NR	Ileal resection	Nurofen Plus® up to 80 tablets daily for 1 year		
		31	Female	Chronic pelvic pain	Depression	NR	Alcoholism and cannabis		NR	Gastric ulcer and bleeding (previous gastrectomy)	Nurofen Plus® up to 120 tablets daily for 2 years		

Study	Location	Age	Gender	Pain conditions	Mental health	Employment	Other drug use	Other notes	Presenting symptoms	Harms from codeine use	Details of codeine dependence	Treatment approach	Details of outcome
Robinson 2010 (cont.)		35	Male			NR	Alcoholism and benzodiazepine dependence		NR		Nurofen Plus® up to 48 tablets daily for 2 years		
Senjo 1989 (34)	Hokkaido, Japan	34	Male	NR	OCD, anxiety, dysphoric mood	NR	NR	Neurological exams on both yielded negative results. Unclear if codeine prescribed	Unkempt, dehydrated, with stereotypy	Suspected codeine use contributed to OCD in both patients.	10 year history of codeine use	Inpatient stay (2 months). Symptoms of withdrawal after 5 days codeine-free as inpatient.	OCD improved following codeine withdrawal.
		35	Male	NR	Social withdrawal, OCD	Unemployed			Unkempt, dehydrated and in opioid withdrawal		10-year history of codeine use.	Patient became violent after 2 days and was transferred to another hospital.	Returned 2 months later with complete remission of symptoms.
Van Hout 2016 (35)	Dublin and Waterford, Ireland	57	Female	Broken wrist 3 years earlier and had taken codeine-ibuprofen at the time for pain.	NR	Became unable to work due to codeine use	NR	OTC Codeine gave her a 'high' as well as experiencing dissociation from herself.	Single episode of haematemesis, related to high consumption of ibuprofen.	Estranged from family, unable to work, and episode of haematemesis.	Use escalated from 12 tablets per day to 24–48 tablets a day over a three-year period since the fracture.	Stabilised on a 4 mg/1 mg dose of buprenorphine-naloxone, counselling every two weeks.	Continues treatment in pharmacy setting, with plan after 2 years of treatment to begin taper.
		44	Female		10-year history of migraines and depression.	Yes	NR	After traumatic personal event (end of marriage) was diagnosed with depression and prescribed antidepressants.	Pharmacist noted high volume of OTC codeine use, combined with employer query.	Identified due to high volume of sick notes (impact on employment) .	Began to escalate her use of OTC codeine (~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/3.5 mg dose, her migraines largely resolved and soon after treatment, was able to cease antidepressant treatment. Returned to work, planned reduction of buprenorphine
		45	Male	Nil noted	Severe personality difficulties	NR	Past history of alcohol dependence and on-going benzodiazepine use.	OTC codeine		Perforated ulcer which required surgical repair, three later ulcers, Multiple surgical admissions due to the severity of his epigastric pain and gastrointestinal bleeding	A long history of OTC codeine misuse that was causing life-threatening morbidity.	Attempted several detoxifications but quickly relapsed on each occasion. Attempts to stabilise on a maintenance dose of codeine failed. Prescribed buprenorphine naloxone.	Overdosed on benzodiazepines, was hospitalised and buprenorphine treatment was initially withdrawn. Re-stabilised, on 12 mg/3 mg buprenorphine-naloxone
		44	Male	Originally prescribed codeine for back pain	Depression	Depression following job loss contributed to codeine escalation	Alcohol use lead to family breakdown, ongoing with cannabis and benzodiazepine s use.	Pre-existing heart condition exacerbated by OTC codeine-ibuprofen consumption.	Presented to his community drug service in a poor physical health.	Not specifically reported	Over several years he began using escalating amounts of OTC codeine-ibuprofen up to 72 tablets per day.	Buprenorphine-naloxone in conjunction with psychosocial interventions. Initial relapse with attempt to self-detoxify, recommenced on higher dose.	Initially stabilised on a maintenance dose of 8 mg/2 mg daily, recommenced and stabilised on 12mg daily, on-going counselling.

Study	Location	Age	Gender	Pain conditions	Mental health	Employment	Other drug use	Other notes	Presenting symptoms	Harms from codeine use	Details of codeine dependence	Treatment approach	Details of outcome
Vaughan 1967 (36)	Napier, NZ	53	Male	Osteoarthritis in the hips	NR	Employed (carpenter)	NR	Not noted if codeine was OTC or prescribed	Drowsiness, confusion	Renal failure (fatal)	All used aspirin/phenacetin/codeine tablets 8-12 codeine tablets daily for 'years'	Supportive therapy	
		39	Female	Headache	NR	Housewife	NR		Nausea/vomiting, oliguria	Renal failure (fatal)	50 codeine tablets per week	Symptomatic treatment for renal failure	
		70	Female	Rheumatoid arthritis	NR	NR	NR		Anaemia	Analgesic nephropathy	8 tablets per day over 20 years		
		28	Male	Migraines	NR	Employed (agricultural worker)	NR		Renal colic	Possible medication overuse headache	6-20 tablets per day for 20 years	Education about link between symptoms and analgesic use, patient ceased analgesics.	Headaches resolved, still slight ache in loin.

Key: CBT Cognitive Behavioural Therapy; GAD Generalised Anxiety Disorder; GP General Practitioner; IV Intravenous; NR Not Recorded; OTC Over The Counter.

Table 4D: Treatment approaches for codeine dependence

Study ID	Study Design	Study location	Sample size	Mean age (years)	Gender	Other population details	Treatment approach	Details of treatment outcomes including adverse events	Treatment duration and retention	Other notes / Evidence quality (GRADE)
Cooper 2013 (1)	Qualitative interviews	United Kingdom	25	20-60	13/25 Female	Recruited from internet support groups, OTC codeine	One quarter had drug treatment incl. MTD or BPN from a treatment service or GP. Participants described either stopping completely or reducing the dose gradually. Online support important in attempts to self-treat.	The use of BPN and MTD often led to positive outcomes—either on maintenance doses or opiate free. Some concerns initially about treatments being inappropriate and suited only for illicit substance misusers.	NR	Perceptions that services were not set up to accommodate OTC addiction; barriers included the mixing of clients with different addictions, a perception that staff viewed OTC addiction as a lesser problem, and a lack of staff experience. (VL)
Fernandes 2002 (37)	Double blind randomised controlled trial	Toronto, Canada	30 assessed, 17 started treatment	40 (SD 12)	11/17 Female	Eligible subjects were chronic users of codeine-containing prescription or OTC medications (> 56 mg/day) for at least 6 months.	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 three groups in daily codeine intake or depression scores. At end of treatment, there was a large decrease in mean daily codeine use from baseline in all three groups: placebo by 57%, quinidine by 56%, and fluoxetine by 51%.	18 enrolled, 8 in treatment at 8 weeks (total duration 10 weeks)	Reduction in depression attributed to decrease in codeine use along with the support and counselling given during treatment. (L)
Frei 2010 (4)	Case series	Victoria, Australia	27	20 and above	13/27 Female	Patients presented or were inpatients referred to hospital addiction medicine reporting OTC ibuprofen-codeine use	Most patients (n=16) treated with opioid pharmacotherapy; BPN taper (n = 3), BPN maintenance (n = 10) or MTD (n = 3)	No further information on treatment outcomes		(VL)
Nielsen 2015b (10)	Retrospective chart review	New South Wales, Australia	135 (53 codeine)	38.6	35/53 Female	Codeine group more likely to be female, employed and use only one pharmaceutical opioid. No difference in age between the codeine group and the strong opioid group. Most (47/53) reported OTC codeine use.	Codeine dependence more likely to be treated with BPN than MTD. Codeine dependence more likely to receive withdrawal management rather than longer-term pharmacotherapy.		NR	(VL)
Nielsen 2015c (38)	Retrospective chart review	New South Wales, Australia	19	41 (SD 9)	16/19 Female	Subset of the Nielsen 2015b that were prescribed BPN as a maintenance treatment. Most report OTC codeine.	BPN maintenance treatment provided by drug treatment services. Five were treated as inpatients and 14 as outpatients.	Median dose of 12-16 mg BPN, 4 patients continued to use opioids. BPN doses higher than estimated based on codeine dose.	All patients retained at 28 days, longer-term outcomes not reported	(VL)

Study ID	Study Design	Study location	Sample size	Mean age (years)	Gender	Other population details	Treatment approach	Details of treatment outcomes including adverse events	Treatment duration and retention	Other notes / Evidence quality (GRADE)
Nilsen 2010 (39)	CBT based clinical trial with partial or complete codeine reduction	Trondheim and Aalesund, Norway	11	43	9 /11 Female	Not noted if codeine OTC or prescribed	Two specifically trained physicians treated the patients with six CBT sessions using verbal reattribution techniques and behavioural experiments, tapering codeine gradually within 8 weeks.	Codeine use significantly reduced from (mean 237 mg pre-treatment) to 45 mg post-treatment), 6 ceased codeine. All patients reported withdrawal symptoms, one used clonidine. 10 reported craving, 3 reported diarrhoea and 3 reported sleep disturbance.	8-week treatment duration. All patients completed 3 month follow up assessment.	Craving was especially bothersome for 2 patients with anxiety. One male patient took 14 weeks in total to reduce dose and complete CBT due to an alleged past history of seizures on reduction of opioids (VL)
Norman 2016 (40)	Mixed methods (Systematic review + qualitative interviews)	Ireland United Kingdom South Africa	Interviews with key experts, n=23	NR	NR	Not specific to OTC codeine dependence though this was a focus	BPN and MTD used in substitution therapy. Notes CBT efficacy in opioid dependence.	Outlined 'best practices' in treatment reported by stakeholders, suggested 'innovations' for treatment. Did not assess treatments.	NR	Avoidance of blame, reinforcement of positive coping styles, reinforcing positive social supports, need a robust relapse prevention plan. (VL)
Romach 2000 (41)	Open label pilot trial	Toronto, Canada	14	41 (SD 6.6)	5/14 Female	Codeine source (prescribed or OTC) not noted	Fluoxetine 20 mg/day as CYP2D6 inhibitor (began to taper opioids over 8 weeks of active treatment).	All patients decreased their opiate use (range, 30%-100% of baseline use). Depressive symptoms also declined.	8 of 14 completed treatment phase	Brief behavioural therapy' conducted during first 3 visits. (L)
Thekiso 2010 (13)	Retrospective chart review	Dublin, Ireland	20	49.2 (SD 23.4)	13/20 Female	6 diagnosed with 'harmful opioid use', 14 diagnosed with opioid dependence. OYC codeine.	Treated for substance withdrawal with standard pharmacological protocol-driven regimes, underwent up to 4 weeks' comprehensive inpatient treatment program. Withdrawal regime included tapering benzodiazepines and clonidine.	Ave length of stay 42 days. Required treatment for withdrawal for average of 16 days.	Relapse rate 35% within 6 months.	Comorbidities including depression and bipolar disorder also treated using antidepressant and mood stabilising medication with 'psycho-education' (VL)
Van Hout 2015 (14)	Qualitative interviews	Dublin, Ireland	21	39, range 26 - 62	12/21 Female	NR	14 patients (67%) treated with MTD, 3 patients (14%) treated with BPN. Supportive medical care and a slow approach to tapering of codeine products themselves or substitution. Duration not reported. 18/20 report OTC codeine primary drug.	BPN in particular was viewed very positively in removal of craving and withdrawal effects. Relapse with codeine tapering was universal due to lack of effect on cravings, & 'topping up' with OTC.	Stigma a barrier to treatment access and retention, particularly for pharmacy supervised MTD consumption.	Help-seeking efforts were overall positive and grounded in pharmacist and treatment service intervention. Some participants suggested that the pharmacist could support them in tapering down from over the counter codeine containing products (VL)

Key: BPN Buprenorphine (+/- naloxone), CBT Cognitive Behavioural Therapy, GP General Practitioner; MTD Methadone, NR Not Reported, OTC Over-the-counter, (VL) Very Low; (L) Low.

References in Tables 1-3

1. Cooper R. J. 'I can't be an addict. I am.' Over-the-counter medicine abuse: A qualitative study, *BMJ Open* 2013; 3: e002913.
2. Dada S., Burnhams N. H., Van Hout M. C., Parry C. D. H. Codeine misuse and dependence in South Africa - learning from substance abuse treatment admissions, *S Afr Med J* 2015; 105: 776-779.
3. Fredheim O., Skurtveit S., Moroz A., Breivik H 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.
4. Frei M. Y., Nielsen S., Dobbin M. D., Tobin C. L. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases, *Med J Aust* 2010;193: 294-296.
5. McAvoy B. R., Dobbin M. D., Tobin C. L. Over-the-counter codeine analgesic misuse and harm: characteristics of cases in Australia and New Zealand, *N Z Med J* 2011; 124: 29-33.
6. McDonough M. A. Misuse of codeine-containing combination analgesics, *Med J Aust* 2011; 194: 486.
7. 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.
8. 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.
9. Nielsen S., Roxburgh A., Bruno R., Lintzeris N 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.
10. Nielsen S., Murnion B., Dunlop A., Degenhardt L et al. Comparing treatment-seeking codeine users and strong opioid users: Findings from a novel case series, *Drug Alcohol Rev* 2015; 34: 304-311.
11. Qiu Y. W., Su H. H., Lv X. F., Jiang G. H. 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.
12. Sproule B. A., Busto U. E., Somer G., Romach M. K et al. Characteristics of dependent and nondependent regular users of codeine, *J Clin Psychopharmacol* 1999; 19: 367-372.
13. Thekiso T. B., Farren C. Over the counter' (OTC) opiate abuse treatment, *Ir J Psychol Med* 2010; 27: 189-191.
14. Van Hout M. C., Horan A., Santlal K., Rich E et al. 'Codeine is my companion': misuse and dependence on codeine containing medicines in Ireland, *Ir J Psychol Med* 2015; 1-14.
15. Ammit M. Over-the-Counter Codeine Dependency: A Case Analysis of an Inpatient Nursing Intervention, *Aust Nurs Midwifery J* 2016; 23: 28-31.
16. Dutch M. J. Nurofen Plus misuse: an emerging cause of perforated gastric ulcer, *Med J Aust* 2008; 188: 56-57.
17. Dyer B. T., Martin J. L., Mitchell J. L., Sauven N. C et al. Hypokalaemia in ibuprofen and codeine phosphate abuse, *Int J Clin Pract* 2004; 58: 1061-1062.
18. Faierman D., Jacobs S. Liver injury from elixir of terpin hydrate with codeine, *Mt Sinai J Med* 1973; 40: 56-59.
19. Karamatic R., Croese J., Roche E. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics, *Med J Aust* 2011; 195: 516.
20. 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.

21. Ng J. L., Morgan D. J. R., Loh N. K. M., Gan S. K et al. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis, *Med J Aust* 2011; 194: 313-316.
22. Page C. B., Wilson P. A., Foy A., Downes M. A et al. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis, *Med J Aust* 2011; 194: 614.
23. Roussin A., Bouyssi A., Pouche L., Pourcel 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.
24. Wylie A. S., Fraser A. A. Hazards of codeine plus paracetamol compounds, *Br J Gen Pract* 1994; 44: 376.
25. Bedi R. S. Dependence on a common cough linctus, *Indian J Chest Dis Allied Sci* 1991; 33: 227-228.
26. Eng E. L., Lachenmeyer J. Codeine self-medication in a headache patient, *Headache* 1996; 36: 452-455.
27. Evans C., Chalmers-Watson T. A., Gearry R. B. Combination NSAID-codeine preparations and gastrointestinal toxicity, *N Z Med J* 2010; 123: 92-93.
28. Gruber C. M., Nelson G. M. Codeine addiction, *Annals of Internal Medicine* 1948; 29: 151-153.
29. 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.
30. 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.
31. Lake I. A. E. Screening and behavioral management: Medication overuse headache - The complex case, *Headache* 2008; 48: 26-31.
32. Marr E., Hill D. Optimising service provision for prescribed opioid analgesic dependence, *Heroin Addict Relat Clin Probl* 2015; 17: 13-18.
33. Robinson G. M., 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.
34. Senjo M. Obsessive-compulsive disorder in people that abuse codeine, *Acta Psychiatr Scand* 1989; 79: 619-620.
35. Van Hout M. C., Delargy I., Ryan G., Flanagan S 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.
36. Vaughan J. V., Fleischl P., Nathan M., Taylor R. C. Chronic renal disease and analgesic abuse, *N Z Med J* 1967; 66: 794-797.
37. Fernandes L. C., Kilicarslan T., Kaplan H. L., Tyndale R. F et al. Treatment of codeine dependence with inhibitors of cytochrome P450 2D6, *J Clin Psychopharmacol* 2002; 22: 326-329.
38. Nielsen S., Bruno R., Murnion B., Dunlop A 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.
39. Nilsen H. K., Stiles T. C., Landro N. I., Fors E. A. et al. Patients with problematic opioid use can be weaned from codeine without pain escalation, *Acta Anaesthesiol Scand* 2010; 54: 571-579.
40. Norman I. J., Bergin M., Parry C. D., Van Hout M. C. Best practices and innovations for managing codeine misuse and dependence, *J Pharm Pharm Sci* 2016; 19: 367-381.
41. Romach M. K., Otton S. V., Somer G., Tyndale R. F et al. Cytochrome P450 2D6 and treatment of codeine dependence, *J Clin Psychopharmacol* 2000; 20: 43-45.