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Buprenorphine-naloxone in the treatment of Codeine Dependence: A Scoping Review of Clinical Case Presentations.

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Abstract

Misuse of prescribed and over the counter (OTC) codeine containing medicines is an increasing public health concern in recent times. Studies have called for low threshold treatment services for individuals experiencing codeine dependence using buprenorphine naloxone therapy. We present a scoping review of clinical case presentation literature on the use of buprenorphine-naloxone in the treatment of codeine dependence. Seven records (four single case studies and three case series) on codeine dependence treated with buprenorphine-naloxone were included. Five themes emerged following a review of the cases for the treatment of codeine dependence with buprenorphine-naloxone. They are: (1) Patient Profiles; (2) History of Codeine Misuse; (3) Medical Problems; (4) Use of Other Substances; and (5) Buprenorphine-naloxone in the treatment of Codeine Dependence. The review highlights the complexities of patients with regards to pain, psychiatric illness, poly substance use and iatrogenic dependence, with findings encouraging in terms of patient stabilisation and recovery.

Key Words

Codeine, dependence, buprenorphine; buprenorphine-naloxone

Introduction

Misuse of prescribed and over the counter (OTC) codeine containing medicines is an increasing public health concern in recent times. Misuse definitions vary, but are broadly defined as '*the use of a medicine, with or without a doctor's prescription, clearly outside of accepted medical practice or guidelines, for recreational purposes or in the framework of self-medication, in greater dosages or for longer periods than were prescribed, in which the risks and problems associated with use outweigh the benefits'* (Casati, Sedefov, and Pfeiffer-Gerschel 2012:229-230). Codeine or 3-methylmorphine is a methylated morphine derivative present in the poppy seed, and is a short acting, weak to mid-range opiate (Tremlett, Anderson, and Wolf 2010) used for the symptomatic relief of mild to moderate pain or cough (Derry, Karlin, and Moore 2013). OTC formulations contain varying strengths of codeine in different countries (Van Hout and Norman 2015). Misuse of codeine combination analgesic products (ibuprofen or acetaminophen) is increasing where available OTC (McAvoy, Dobbin, and Tobin 2011). Stronger regulatory responses to tackle misuse have been debated (Tobin, Dobbin, and McAvoy 2013).

Typical side effects on use include altered perceptions and emotional responses to pain, euphoria and sedation, and the development of tolerance within relatively short timeframes on repeated use (Sproule, Busto, Somer, Romach, and Sellers 1999; Frei, Nielsen, Dobbin, and Tobin 2010; Kelly and Madadi 2012; Babalonis, Lofwall, Nuzzo, Siegel, and Walsh, 2013). Increased use of codeine stimulates neuro-adaptation and dependence (Nielsen, Cameron, and Pahoki 2010; McAvoy et al. 2011), with withdrawal symptomatology including preoccupation with seeking and taking codeine, craving and lack of control over use (Romach, Sprouole, Sellers, Somer, and Busto 1999). The variability of genetic metabolic response contributes to risk of misuse (Sproule et al. 1999; Ingelman-Sundberg,

Sim, Gomez, and Rodriguez-Antona 2007; Frei et al. 2010; Nielsen et al. 2010). Increases in mortality are reported (Pilgrim, Dobbin, and Drummer 2013; Handley and Flanagan 2014), with particular adverse health consequences such as hypokalaemia, gastrointestinal haemorrhage, acute haemorrhagic necrotizing pancreatitis and inflammatory bowel conditions centring on the misuse of combination analgesics containing codeine (Lambert and Close 2005; Dutch 2008; Evans, Chalmers-Watson, and Gearry 2010; Ernest, Chia, and Corallo 2010; Frei et al. 2010; Ng et al. 2011; Van Hout, Bergin, Foley, Rich, Rapca, Harris, et al. 2014). Psychiatric co-morbidity such as anxiety, depression and dysphoria is also reported (Romach et al. 1999; Dobbin and Tobin 2008; Frei et al. 2010; Nielsen et al. 2010; McAvoy et al. 2011; Manchia, Alda, and Calkin, 2013).

Treatment uptake for OTC codeine dependence is increasing in Australia, South Africa and the UK (Myers, Siegfried, and Parry 2003; McDonough 2011; Stannard 2013; Nielsen, Roxburgh, Bruno, Lintzeris, Jefferson, and Degenhardt 2015a). Recent qualitative studies have explored patient experiences of misuse and dependence in Ireland, the UK, South Africa and Australia (Nielsen et al. 2010; Nielson, Cameron, and Lee 2011; Nielsen, Cameron, and Pahoki 2013; Cooper 2011, 2013; Van Hout 2015; Van Hout, Horan, Santlal, Rich, and Bergin 2015a; Van Hout, Rich, Dada, and Bergin 2015b). Recent studies have called for enhanced targeted design of appropriate treatment services for individuals experiencing codeine dependence (Nielsen, Bruno, Murnion, Dunlop, Degenhardt, et al. 2015b; Marr and Hill 2015) as these individuals are different to other opioid dependent patients (Nielsen et al. 2011; Nielsen, Murnion, Dunlop, Degenhardt, Demirkol, et al. 2015c), by virtue of their lack of recognition of problematic use, perceptions around drug addiction and lack of self-identification, and experiences of stigma relating to mainstream drug addiction services

(Nielsen et al. 2010; Reed, Bond, Witton, Cornish, Hickman, and Strang 2011; Van Hout et al. 2015a;b Kean 2015).

Despite these differences, there is a limited evidence base to underpin best practice guidelines for the treatment of this form of opioid dependence (Cooper 2013; Conroy and Hill 2014; Hard 2014), with approaches generally centring on substitution treatment (National Institute for Health and Clinical Excellence 2007). One such form of pharmacological treatment of opioid dependence is buprenorphine –naloxone, commonly used in low threshold treatment of heroin dependence, and which is an effective opioid agonist treatment for prescription and OTC opioid analgesic dependence (Sigmon, Dunn, Badger, Heil, and Higgins 2009; Weiss, Potter, Fiellin, Byrne, Connery, et al. 2011). It is reported to benefit patients with codeine dependence (Department of Health -England and the Developed Administrations 2007; Stannard 2013; Royal College of General Practitioners 2014a-d; Nielsen et al. 2015; Van Hout et al. 2015a;b). There is an increasing evidence base of case studies implicating use of this therapeutic agent in successful treatment outcomes (Hard 2014; Conroy and Hill 2014; Kean 2015; Marr and Hill 2015; Van Hout, Delargy, Ryan, Flanagan, and Gallagher 2015c).Decisions to treat using buprenorphine naloxone centre on its safety profile (ceiling effect on respiratory depression and lower abuse potential), in comparison to other common opioid agonist treatments (ie methadone), reduced symptoms of withdrawal on cessation of use, lack of association with QT prolongation, and most importantly for these patients is the ability to continue with employment and enhanced social functioning, attributed to clarity of thought and the dislike of the sedating effect of methadone (Conroy and Hill 2014; New Zealand Ministry of Health 2014; Fiellin et al. 2014; Hard 2014). Additionally, with buprenorphine- naloxone patient transfer into opioid agonist treatment is easier, with stabilisation achieved relatively easily, and with cessation relatively easily within short

timeframes. In contrast, safe titration of methadone dose takes longer, and with high dose methadone posing an overdose risk. With this in mind, we therefore present a scoping review of available case presentation literature on the use of buprenorphine-naloxone in the treatment of codeine dependence.

Methods

Scoping review methods are emerging as an increasingly popular and accepted approach across many different disciplines in recent times (Anderson, Allen, Peckham, and Goodwin 2008; Arksey and O'Malley 2005; Daudt, van Mossel, and Scott 2013; Levac, Colquhoun, and O'Brien 2010; Pham, Rajić, Greig, Sargeant, Papadopoulos, et al. 2014). A scoping review is generally used to determine the significance of a full systematic review, summarise and disseminate findings of the research, and identify gaps in the current literature (Arksey and O'Malley 2005; Levac, Colquhoun, and O'Brien 2010).

For the purpose of this study, Daudt et al.'s (2013:8) scoping review definition was employed. They define a scoping review as a form of research synthesis with objectives to *"map the literature on a particular topic or research area and provide an opportunity to identify key concepts; gaps in the research; and types and sources of evidence to inform practice, policymaking, and research".* The decision to undertake a scoping review was due to this type of review being advantageous when the topic has not previously been reviewed at length (Hidalgo Landa, Szabo, Le Brun, Owen, and Fletcher 2011). Furthermore, scoping reviews are utilised as standalone projects that provide widespread descriptive summaries of the literature, comprising of a broad range of study designs and methodologies (Arksey and O'Malley 2005; Brien, Lorenzetti, Lewis, Kennedy, and Ghali 2010). Scoping reviews use

meticulous and transparent methods to recognise and analyse literature relevant to a specific topic (Arksey and O'Malley 2005; Rumrill, Fitzgerald, and Merchant 2010).

The present study adhered to a six stage method as developed by Arskey and O'Malley (2005) with advanced recommendations by Levac et al. (2010). These stages included: (1) identifying the central research question, (2) searching for relevant studies, (3) selection of studies, (4) charting the data, (5) and collating, summarizing and reporting the results. The scoping study began with the formation of the research team including those with expertise in the areas of pharmacy, addiction, harm reduction; and scoping and systematic reviews (Levac et al. 2010). The research team identified the underpinning research question: "*what do we know about cases of treatment of codeine dependence using buprenorphine-naloxone*?" The review aimed to collect extant clinical case presentation literature on codeine dependence treatment using buprenorphine-naloxone.

A comprehensive list of search terms was devised by the team which combined the terms 'Codeine' with 'Buprenorphine- naloxone'; 'Suboxone ®'; and 'clinical case presentation'. To ensure all literature relevant to the present study were included; a comprehensive search was carried out using the following databases: Science Direct, EBSCO Host, PsychINFO, and PubMED. The initial search identified 5,535 articles, and following exclusion of animal studies, duplicates, and lack of relevance specifically to the treatment of codeine with buprenorphine-naloxone, six case studies/series papers were identified to directly relate to the case presentations describing treatment of codeine dependence with buprenorphine-naloxone. We additionally scrutinised the bibliographies of studies identified in the literature search. This process discovered one further reference (n=1) with no subsequent records identified (Arskey and O'Malley 2005). A total of seven case presentation records (four single case

studies and three case series) on codeine dependence treated with buprenorphine-naloxone were included in the review. See Figure 1.

Insert Figure 1 about here

Results

Case studies were conducted in Scotland (Conroy and Hill 2014; Marr and Hill 2015), Wales (Hard 2014), United Kingdom (Kean 2015), Australia (Nielsen et al. 2015d,e) and Ireland (Van Hout et al. 2015). Details relating to the single case studies (Conroy and Hill 2014; Marr and Hill 2015; Hard 2014; Kean 2015) and the case series (Nielsen et al. 2015d,e; Van Hout et al. 2015c) are presented in Table 1. Five themes emerged following a review of the cases for the treatment of codeine dependence with buprenorphine-naloxone, as follows (1) Patient Profiles; (2) History of Codeine Misuse; (3) Medical Problems; (4) Use of Other Substances; and (5) Buprenorphine-naloxone in the treatment of Codeine Dependence.

Insert Table 1 about here

Patient Profiles

Of the four single case studies, three patients were female with their ages ranging from early to mid-twenties (Conroy and Hill 2014; Hard 2014; Marr and Hill 2015), with one male in his mid-thirties (Kean 2015). The three case series consisted of 53 female and 23 male participants with an age range of 38 to 57 years (Nielsen et al. 2015d,e; Van Hout et al. 2015c).

History of Codeine Misuse

Reasons for initiation to codeine use were: post-surgery pain (Conroy and Hill 2014); myalgic encephalopathy (Hard 2014); back pain (Kean 2015); dental pain (Marr and Hill 2015; Van Hout et al. 2015c); pain relief not specified (n=47); previous opioid dependence (n=8) (Nielsen et al. 2015d,e); pain relief for a broken wrist; migraines (Van Hout et al. 2015c), and reason not stated (n=14) (Nielsen et al. 2015d). Length of codeine use varied starting at two years (Marr and Hill, 2014), then 3 years (Van Hout et al. 2015c), 4 years (Kean 2015; Nielsen et al. 2015d), 7 years (Nielsen et al. 2015e), 10 years (Conroy and Hill 2014; Hard 2014; Van Hout et al. 2015c) and one case noted length of use as "several years" and another as "a long history" (Van Hout et al. 2015c).

Types of codeine medicines used both alone and/or combined were: codeine (Kean 2015); co-codamol, a combination analgesic containing codeine with paracetamol, (Marr and Hill 2014; Kean 2015; Van Hout et al. 2015c); dihydrocodeine (Conroy and Hill 2014; Van Hout et al. 2015c); codeine-ibuprofen (Van Hout et al. 2015c); and codeine-paracetamol (Hard 2014). Two studies (Nielsen et al. 2015d,e) did not specify the type of codeine medication used. Great variation in daily doses of codeine was evident beginning at 30mg (Hard 2014)180mg (Conroy and Hill 2014); 240mg (Kean 2015); 360mg (Conroy and Hill 2014); 1205mg (Kean 2015); and the highest dose was 2940mg daily (Hard 2014). One study (Nielsen et al. 2015c) did not state dosage and another (Nielsen et al. 2015e) stated a mean daily dosage of 564mg. All studies reported misuse of prescribed codeine medications however two reported the use of diverted codeine medicines (Conroy and Hill 2014; Kean 2015), one via street dealers (Conroy and Hill 2014) the other did not report where the diverted medicines were obtained (Kean 2015).

Medical Problems

Medical complications arising from excessive and long term use of codeine containing products included: Addisons Disease; haematemesis; pancreatitis; and gastro-intestinal (GI) haemorrhage (Van Hout et al. 2015c); collapse (Conroy and Hill 2014); constipation (Marr and Hill 2014); withdrawal symptoms related to codeine dependence (Conroy and Hill 2014; Hard 2014; Kean 2015). One study reported a series of mental health disorders: anxiety disorder (n=14); bipolar disorder (n=7); eating disorders (n=2); depression (n=31); psychiatric comorbidity (n=42); post-traumatic stress disorder (PTSD) (n=5); and schizophrenia (n=3) (Nielsen et al. 2015d).

Use of Other Substances

Other substances used concurrently with codeine by some of the patients were: nicotine (n=24); stimulants (n=3); cannabis (n=5); problematic alcohol (n=14); and benzodiazepines (n=17) (Nielsen et al. 2015d). Van Hout et al. (2015) reported the use of hypnotics; tramadol; and cough medicines with codeine containing medications. Heroin use was reported as a replacement for di-hydrocodeine by one patient when a prescription for di-hydrocodeine was unavailable to her (Conroy and Hill 2014) and 7 other patients reported a previous history of heroin use (Nielsen et al. 2015d). Three studies did not state any substances being used concurrently with codeine (Hard 2014; Kean 2015; Marr and Hill, 2014).

Buprenorphine-naloxone in the treatment of Codeine Dependence

Treatments other than and prior to treatment using buprenorphine-naloxone were methadone maintenance treatment (Conroy and Hill 2014; Nielsen et al. 2015d) and previous episodes of treatment for addiction (Nielsen et al. 2015d), however this was not reported in all studies. Length of treatment using buprenorphine-naloxone varied and was reported as: one month

(Nielsen et al. 2015e); three months (Van Hout et al. 2015c) several months (Conroy and Hill 2014), six months (Hard 2014; Kean 2015); and 11 months (Van Hout et al. 2015c) in duration, but was not reported in some cases (Marr and Hill, 2014; Nielsen et al. 2015d). Doses ranged between 4mg and 24mg daily with tapering of doses reported: 24mg to 16mg (Conroy and Hill 2014); 16mg to 10mg (Hard 2014); 8mg to 0mg (Kean, 2014) and 16mg tapering 2mg each month, stable on 8mg at time of study (Marr and Hill, 2014). Van Hout et al. (2015) reported dosages of between 4mg and 14mg per day. Median doses of 12mg to 16mg was reported by Nielsen et al. (2015b). One study did not report dosage levels (Nielsen et al. 2015d). One patient was reported as abstinent at the time of the case study (Kean 2015) and some patients were stabilised at the time of writing the paper (Conroy and Hill 2014; Hard 2014; Marr and Hill, 2014; Van Hout et al. 2015c) however this factor was not reported on all cases (Nielsen et al. 2015d,e).

Psychosocial treatments reported were: treatment for anxiety, peer mentoring, 12 step fellowship (Hard 2014); Social Behaviour and network Therapy (Kean 2015); CBT (Hard 2014; Kean 2015); and counselling (Van Hout et al. 2015c). One study reported psychosocial treatment was part of the process but no detail was given on which type of treatment (Conroy and Hill 2014).

Discussion

We present here a review of available case literature on the use of buprenorphine-naloxone in the treatment of codeine dependence. The seven case presentation (single and series) papers highlight the growing number of presentations where codeine is the primary drug of misuse and dependence. The wide range of people who become dependent on OTC codeine combination analgesics range from those with a history of complex and multiple addictions, personality and psychological difficulties to those where initial consumption of codeine occurred to treat legitimate pathology (Van Hout et al. 2015). The issue of iatrogenic opioid

analgesic dependence confounds treatment pathways and recovery outcomes (Stannard 2013; Marr and Hill 2015).Therefore, distinguishing between iatrogenic opioid dependence and that of misuse and problematic use leading to dependence is essential in facilitating enhanced treatment, particularly for pain patients (Marr and Hill 2015). The need for prescriber and pharmacist assessment of risk for codeine dependence through initial and ongoing routine screening is argued for (Bergin, Norman, Foley, Harris, Rapca, et al. 2015; Hard 2014; Van Hout et al. 2015; 2014). Of note was the high dose consumption of these codeine containing products, where recommended adult daily oral doses of codeine range between 30-60mg every four hours and to a maximum of 240mg (Derry et al. 2013).

Codeine dependent user demographics are different when compared to other strong prescription opioid dependent users, and pointing to the widening of patient access to buprenorphine naloxone as a low threshold treatment option (Nielsen et al. 2011; 2015c). Buprenorphine-naloxone treatment is more common for codeine dependent users than methadone, as it favours those who socially function well and wish to remain at work, thereby, reducing the potential for stigma and restrictive aspects often associated with methadone (Nielsen et al. 2014; Van Hout et al. 2015). The potential of effective opioid assisted treatment using buprenorphine naloxone with psychosocial interventions/counselling to treat this form of opioid dependence is gaining support from both clinicians (Conroy and Hill 2014; Hard 2014; Kean 2015) and codeine dependent users themselves (Van Hout et al. 2015a,b). The codeine dependent cases reviewed here highlights a more favourable response to treatment consisting of the use of buprenorphine-naloxone within a biopsychosocial approach, thereby creating for more positive recovery outcomes for individuals underpinned by enhanced social and occupational functioning.

In terms of dose titrations, codeine is of lower potency than many other opioids with codeine dependent individuals using lower doses of opioids when compared to oral morphine equivalents (Nielsen et al. 2015c). The Australian case series demonstrated that codeine dependent users were receiving higher sublingual buprenorphine doses than when calculated against the dose of codeine consumed and were similar to that of other service users being treated for heroin dependence or more potent opioids (Nielsen et al. 2015b). This suggests that clinicians using standard opioid conversion calculations (Fine, Portenoy, et al. 2009) are at risk of underestimating the buprenorphine-naloxone dose that codeine dependent users actually require resulting in poorer clinical outcomes, and also, suggesting that high doses of buprenorphine-naloxone (up to 32mg daily) appears safe and well tolerated by this group of codeine dependent users (Nielsen et al. 2015b). While individual dose titration is best practice (Gowing, Ali, Dunlop, Farrell, and Lintzeris 2014) a recommendation that codeine dependent individuals receive similar doses to that of other opioid dependents is suggested (Nielsen, Hillhouse, Mooney, Fahey, and Ling 2012), thereby improving treatment retention (Fareed, Vayalapalli, Casarella, and Drexler 2012).

Conclusion

A scoping review presented the clinical case presentation (single and series) literature in relation to the use of buprenorphine-naloxone in the treatment of codeine dependence. Findings illustrate the complexities of these distinct opiate dependent patients with regards to pain, psychiatric illness, poly substance use and iatrogenic dependence. Given this distinct form of opioid dependence, buprenorphine-naloxone as treatment modality is encouraging in terms of patient stabilisation and recovery, and warrants expansion of access within low threshold treatment service design. Further research is warranted to explore how the various treatment approaches (buprenorphine-naloxone and psychosocial interventions) influence long term outcomes for this unique cohort of codeine dependent individuals.

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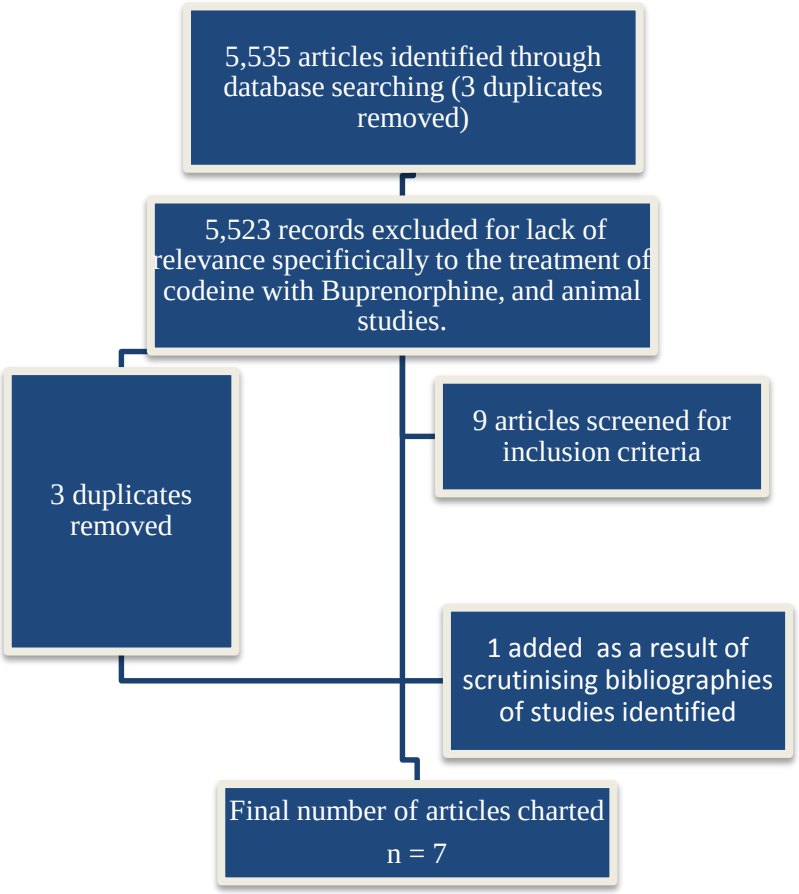
Figure

Figure 1. Flowchart



Table

Table 1 Clinical Case Presentations for Codeine Dependence treated with Buprenorphine-naloxone

Authors & Title	Year	Country	No. of Cases	Profile(s)	Codeine use	Medical Complications/Other Substance use	Other Treatment	Buprenorphine Treatment	Psychosocial treatment
Conroy and Hill. Failure to identify or effectively manage prescription opioid dependence acted as a gateway to heroin use—buprenorphine/naloxone treatment and recovery in a surgical patient.	2014	Scotland	1	Female, Early 20's. **Reason for codeine use:** Prescribed DHC for pain relief following laparoscopy in 2004. **Length of codeine use:** 10 years	DHC Began at 180mg daily. Over 4 years continued this and additional non-prescribed DHC bought from street dealers bringing daily dose to 360mg.	**Medical Complications:** A sudden collapse led to her GP being informed of her opioid use. Her prescription was not authorized and she experienced withdrawal symptoms. **Other Substances:** Went on to consume 3 bags of heroin daily, and then back to consuming just diverted DHC until 2009.	MMT for 21 months.	After relapse in 2013 with DHC daily, for several months buprenorphine was started. 24mg tapered to 16mg daily at time of writing paper.	Yes but no details given.
Hard Management of opioid painkiller dependence in primary care: ongoing recovery with buprenorphine/naloxone.	2014	Wales	1	Female, Mid 20's. **Reason for codeine use:** Myalgic encephalopathy (generalised aches and pains) in 2002. **Length of codeine use:** 10 years	Codeine-paracetamol 30mg/500mg q.i.d. This dose doubled over 4 years (16 tabs per day). After 10 years her dose had risen to 2940mg daily (85 tabs daily).	**Medical Complications:** Withdrawal symptoms 6-8 hours of not taking codeine-paracetamol. **Other Substances:**		Buprenorphine 16mg for 6months. Tapered to 10mg daily at time of writing paper.	A keyworker for anxiety; CBT; peer mentoring; and also 12 step fellowship.
Kean Illicit and over-the-counter codeine dependence after acute back pain-successful treatment and ongoing	2015	UK	1	Male, Mid 30's. **Reason for codeine use:** Low back pain initially in 2010. **Length of**	Prescribed 240mg of codeine daily, leading to 1250mg daily through use of	**Medical Complications:** Withdrawal symptoms when trying to reduce codeine use **Other Substances:**		Began on 8mg and tapered off completely in 6 months. Opioid abstinent in May 2015.	Social Behaviour and Network Therapy; CBT

recovery after buprenorphine/naloxone taper				**codeine use:** 4 years.	diverted codeine and OTC co-codamol.				
Marr and Hill Optimising service provision for prescribed opioid analgesic dependence.	2015	Scotland	1	Female, 24 years old. **Reason for codeine use:** Dental Pain initially. **Length of codeine use:** 2 years.	Prescribed Co-Codamol 30/500mg (daily dose not noted). OTC Co-Codamol /500mg then added. Prescribed tramadol 50mg (1-2 when required) given.	**Medical Complications:** Episode of severe constipation led to GP awareness of codeine abuse. **Other Substances:**		16/4mg tapering off by 2mg every 2 months	No
Nielsen et al. Comparing treatment-seeking codeine users and strong opioid users: Findings from a novel case series.	2015	Australia	53	Females (n=35). Males (n=18). Mean age = 38.6 **Reason for codeine use:** Pain (n=35) Previous opioid dependence (n=4) Other/not stated (n=14) **Length of codeine use:** Median=4.75yrs	Not stated	**Medical Complications:** Psychiatric comorbidity (n=42) Anxiety disorder (n=14) Depression (n=31) Schizophrenia (n=3) Bipolar disorder (n=7) PTSD (n=5) Eating disorder (n=2) **Other Substances (Current):** Nicotine (n=24) Cannabis (n=5) Stimulants (n=3) Problematic alcohol (n=14) Benzo's (n=17) IDU (n=0) **Other Substances (History):** Heroin (n=7)	Previous Alcohol/Drug Treatment (n=27). Methadone (n=3)	Bup maintenance (n=24). Bup Reduction (n=21).	Not stated
Nielsen et al. Treating codeine dependence with buprenorphine: Dose	2014	Australia	19	Female (n=16) mean age 41.2. Male (n=3) **Reason for codeine use:**	Mean dose codeine (specific type not stated) = 564mg	**Medical Complications:** **Other Substances:**	Not stated	Median dose = 12mg (day 7). 16mg (day 28). All (n=19) in BMT for	Not stated

requirements and induction outcomes from a retrospective case series in New South Wales, Australia.				Initially for pain = 63%. Previous heroin use (n=4). **Length of codeine use:** mean = 7.7 years		Nicotine = 42% Problematic alcohol = 32% Problematic Benzo = 42%		1month	
Van Hout et al. Dependence on over the counter (otc) codeine containing analgesics: Treatment and recovery with buprenorphine naloxone.	2015	Ireland	4	Female (n=2) Male (n=2) Ages 44-57yrs **Reasons for codeine use:** Pain due to broken wrist; dental pain; migraines; and back pain. **Length of codeine use:** 3 years, 10 years, "several years" and one stated "a long history".	Codeine containing tablets: OTC Codeine-Ibuprofen; Co-codamol; and DHC. Between 12-72 tabs per day	**Medical Complications:** Haematemesis; Pancreatitis; Addisons Disease; GI haemorrhage **Other Substances:** Alcohol; hypnotics; and cough medicines		Between 4mg and 14mg per day	Counselling