A Scoping Review of Codeine Use, Misuse and Dependence

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Glossary of Significant Terms and Abbreviations

Abuse: ‘A pattern of maladaptive substance use that is associated with recurrent and significant adverse consequences.’ (DSM-IV, 2000)

Codeine: The name codeine is derived from the Greek word kodeia (κώδεια) for ‘poppy head’ and is found naturally in the poppy plant ‘Papaver somniferum var. album’. Codeine is a phenanthrene derivative extracted from opium or produced synthetically by the methylation of morphine. Codeine or 3-methylmorphine is the most commonly consumed opiate worldwide and is used for its analgesic, antitussive and anti-diarrheal properties.

Consumption: Act of supplying a narcotic drug to any person or enterprise for retail distribution, medical use or scientific research.

Dependence: Substance dependence occurs following prolonged and sustained exposure to a drug and is defined as: ‘A compulsive pattern of substance use characterized by a loss of control over substance use and continued use despite the significant substance-related problems.’ (DSM-IV, 2000)

Drug: Substances included in Schedules I or II of the Single Convention on Narcotic Drugs, 1961 (United Nations), whether natural or synthetic.

Manufacture: All processes, other than production (see the definition below), by which drugs may be obtained and includes refining as well as the transformation of drugs into other drugs. Preparation - any mixture, solid or liquid, subject to international control owing to the fact that it contains a drug under international control. Preparations listed in Schedule III of the 1961 Convention are exempted from some control measures (when compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations).

Misuse: ‘The problematic consumption of a drug where risks and adverse consequences outweigh the benefits, and which includes use of codeine with or without prescription, outside of acceptable medical practice or guidelines, for
recreational reasons, when self-medicating, with higher doses and for longer than advisable’. (Casati, Sedefov, & Pfeiffer-Gerschel, 2012)

| Production: | Refers to the separation of opium, coca leaves, cannabis and cannabis resin from the plants from which they are obtained. |
| Stocks: | Amounts of drugs held in a country or territory for domestic consumption, manufacture of other drugs or export |

| APA | American Psychiatric Association |
| CDSCO | Central Drug Standards Control Organisation (India) |
| DSM | Diagnostic Statistical Manual |
| EC | European Community |
| EMA | European Medicines Agency |
| EMCDDA | European Monitoring Centre for Drugs and Drug Abuse |
| FDA | The Federal Drugs Agency USA |
| NHS | National Health Service UK |
| ICD-10 | International Classification of Diseases |
| INCB: | International Narcotics Control Board |
| LGBT | Lesbian, Gay, Bisexual and Transgender |
| NICE | National Institute for Health and Clinical Excellence |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| UNODC | United Nations Office on Drugs and Crime |
| UK | United Kingdom |
| US | United States of America |
| WHO | World Health Organisation |
Executive Summary

Background
Little is known about the extent of misuse of opioid analgesic medications in both the European Community (EC) and global context (Casati et al., 2012; UNODC 2011). Prescribed opioid analgesics are dispensed legally to patients for treatment of symptoms such as pain, cough and diarrhoea, and are also widely available and accessible to the public in over the counter preparations. Increased purchases of over-the-counter analgesics without medical consultation have resulted in increased use of potentially habit-forming substances (Peterson, 2005).

Misuse of prescribed and over the counter opioid analgesic medication1, is driven by a host of factors which include pharmaceutical marketing tactics, inappropriate and increased prescribing, access to licit and illicit drug sourcing, government drug policies, public misconceptions around safety, social influences, self-medication of emotional and physical pain and recreational popularity (Alexander, Mohajir, & Meltzer, 2005; Daniulaityte, Carlson, & Kenne, 2006; Maxwell, 2011; Ling, Mooney, & Hillhouse, 2011; Nosyk, Marshall, Fischer, Montaner, Wood, & Kerr, 2012; UNODC, 2011; UNODC, 2013). The patients and pharmacy customers misusing these medications are frequently not identified and their reasons for non-compliant medicinal use, overuse and intentional misuse for euphoric and other effects are not well understood, despite development of tolerance, misuse, excessive use, poly use of other medications and illicit drugs, and resultant adverse health consequences (Benyamin et al., 2008; Manchikanti & Singh; 2008, Nielsen, Cameron, & Pahoki, 2010). However, behavioural indicators of misuse of over the counter opioid analgesics include requesting certain drugs, hoarding of medications, use of multiple doctors and pharmacies, forging prescriptions, selling prescription opioids, stealing prescription opioids from other patients, injecting formulations, sourcing on the street, concurrent abuse of other licit and illicit drugs, multiple unsanctioned dose escalations, and repeated lost or stolen prescriptions (UNODC, 2011).

One such opioid analgesic medication which is of public health concern is the common weak opioid, codeine or 3-methylmorphine which is widely and frequently consumed worldwide for its analgesic, antitussive and anti-diarrhoeal properties. It is a listed narcotic drug under international control and is regulated by the medicine regulatory authority in individual countries. Pure codeine is listed under Schedule II, of the Single Convention on Narcotic Drugs, 1961. However, most codeine preparations are classified under Schedule III and are pharmacy controlled with a medical prescription required. Under Schedule III there is no requirement to keep controlled registers.

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1 Drugs available from pharmaceutical sources, i.e. manufactured by the pharmaceutical industry or made up by a pharmacist. Caffeine, antihistamines, codeine (an opiate) and alcohol are the most common psychoactive constituents of over-the-counter drugs.
Globally, the demand for codeine remains high and has risen by approximately 27% over the last decade. Recent reported figures estimate that global purchasing reached an all-time high at 269 tonnes in 2011 compared to 164 tonnes in 1992 (INCB 2012). Codeine products can be purchased on prescription from a medical or dental health professional and over the counter in pharmacies (Moore, Collins, Carroll, McQuay, & Edwards, 1998). In some countries codeine preparations are available without prescription in combination preparations (paracetamol, ibuprofen or aspirin) from licensed pharmacies and in retail outlets. Over the counter sales of products containing codeine generally must be supervised by the pharmacist. However, the regulation and control of codeine dispensing varies between countries with some restricting the visual display and advertisement of over the counter codeine preparations to the consumer. The amount of over the counter sales of codeine containing medications is not easy to determine due to trade exemptions and because disclosure of information might prejudice the commercial interests of any person or public authority, but there is little doubt that it forms a substantial proportion of pharmacy sales.

Contemporary research has underscored the need for ‘increased pharmacovigilance’ around codeine prescribing and over the counter dispensing. Deregulation of codeine has contributed to increased patient or customer consumerism, self-medication, as well as pharmacist empowerment around codeine supply over the counter (Albsoul-Younes, Wazaify, Yousef, & Tahaineh, 2010; Francis, Barnett, & Denha, 2005). As a result, efforts to quantify levels of misuse in the public and the impact of associated adverse health consequences remain problematic. Its opioid analgesic effect and potential risk of development of tolerance within a short timeframe of regular or excessive use contributes to potential misuse and dependence (Sproule, Busto, Somer, Romach, & Sellers, 1999). Of note is that individuals vary in their metabolism of codeine, estimation of safe dosages, reasons for use (misuse) of codeine and dependence potential.

Inappropriate use, misuse and abuse of codeine take a variety of forms. It can include individuals: using codeine and exceeding recommended doses and treatment duration; becoming dependent on codeine for medical reasons; using codeine to stave off opioid withdrawals; using codeine for its euphoric effects; or extracting from codeine based pharmaceuticals to manufacture homemade opiates such as desomorphine.

Codeine consumption and the appropriate use of codeine is a matter of public health concern, but little is known about codeine use, misuse and dependence as situated within medical, pharmacy and addiction treatment practice. Thus the need for this scoping review which examines the evidence in relation to the use, misuse and dependence of over the counter and prescribed codeine products. The evidence in relation to codeine regulation, prevalence rates, associated risk factors, consequences of use and misuse, prevention strategies and treatment options are explored. Recommendations for practice and policy and areas for further research are offered.
Aim and Objectives:
The aim of this scoping review is to report what is known about the regulation, production, distribution, prevalence, consequences and prevention in relation to the use, misuse and dependence of codeine in the partner countries (Ireland, UK, South Africa), across the EU and internationally and to identify gaps in the evidence base.

Specific objectives are:
- To map the existing literature examining codeine use, misuse and dependence.
- To identify gaps in the evidence base and make recommendations for future research.
- To make recommendations for practice and policy to promote improved understanding and awareness of codeine misuse and dependence.
- To provide an overview of the healthcare system, prescribing of codeine and addiction treatment in the three partner countries and presented as supplementary appendix to this report.

Methods
The scoping review was guided by Arksey & O'Malley’s (2005) six stage framework and was conducted by a team of researchers from academic and pharmacy practice backgrounds that were recruited to the CODEMISUSED project. A broad search was conducted in order to achieve a comprehensive scope of the field (Daudt, van Mossel, & Scott. 2013). Databases searched included PubMed, EBSCO Host, Science Direct, EMBASE, PsycINFO, Cochrane library and Medline from 1994 to 2014. Follow up search strategies included hand searching of pharmaceutical, health, medical and drug related websites, and contacting key organisations such as the World Health Organisation (WHO), International Narcotics Control Board (INCB), European Medicines Agency (EMA), European Monitoring Centre for Drugs and Drug Abuse (EMCDDA), authorised medicine boards in each of the European membered states, The Federal Drugs Agency (FDA) USA, the Canadian Pharmacy Authority, and the National Health Service (NHS) in the UK.

A spreadsheet was created to chart relevant data (data collection categories included author, setting, study aim and design/intervention, sample size, and results/outcomes), to enable the identification of commonalities, themes, and gaps in the literature. No restrictions were placed on inclusion so long as the article reported the results of research (collecting empirical data) or other systematic enquiry into the use or misuse of codeine. Inclusion criteria were established prior to the search and are reported in Chapter 2. Two reviewers independently screened titles and abstracts to determine inclusion status. A second screen of the full-text of each article, again by two independent reviewers, ensured that the studies were relevant to the focus of the review and, through a charting exercise (as per Levac, Colquhoun, & O’Brien, 2010),

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2 This objective is addressed in: 3Foley et al. (2014) Codeine consumption through prescribing in the Republic of Ireland, the Republic of South Africa and the United Kingdom, Supplement to the CODEMISUSED Scoping Review, CODEMISUSED Project, Funded by the European Commission 7th Framework Programme
identified the specific areas of the review to which they could contribute and extracted article data manually into a database. Disagreements were resolved through discussion.

A stakeholder consultation stage from addiction, nursing, psychiatry, psychology, health, pharmacy, drug control and pharmacovigilant backgrounds (Arksey & O’Malley, 2005; Daudt et al., 2013; Levac et al. 2010) with CODEMISUSED partners and the CODEMISUSED Expert Panel was undertaken and contributed to extraction of multifaceted perspectives from the extant literature on codeine throughout the review process.

**Results**
The findings are presented under seven headings: (1) Production, manufacture consumption and regulation of codeine; (2) Prevalence of codeine use, misuse and dependence and associated risk factors; (3) Use and efficacy of codeine within healthcare; (4) Consequences of codeine use, misuse and dependence; (5) Prevention of codeine misuse, abuse and dependence; (6) Interventions/treatment and codeine dependence and (7) Conclusions and implications for practice, policy and research.

1. **Production, manufacture, consumption and regulation of codeine**
   Globally, the demand for codeine remains high and has risen by approximately 27% over the last decade (INCB, 2012). Recent INCB figures demonstrate that global consumption reached an all-time high in 2011 at 269 tonnes. Both exports and manufacture of codeine have also seen a rising trend. In 2011, figures show that the UK was the highest codeine manufacturer globally representing 22%, followed by France (21%), US (17%) and Australia (8%).

Over the counter sales of codeine containing medications is not easy to determine. Sales of over the counter medicines information is protected because it is commercially sensitive and qualifies exemptions where information is a trade secret and where disclosure would likely prejudice the commercial interests of any person or public authority holding it. Over the counter sales of products containing codeine generally must be supervised by a pharmacist (European Medicines Agency, 2013). See table 3.1 on page 62 for details of the scheduling of codeine across the EU, Australia, Canada, United States of America, Asia and South Africa.

2. **Prevalence of codeine use, misuse and dependence and associated risk factors**
   EU prevalence data on the topic of codeine use, misuse and dependence is at present confined to French and Norwegian studies, but presumably widespread across other European countries (Casati et al. 2012; Fredheim, Skurtveit, Moroz, Breivik, & Borchgrevink, 2009). Trend in sales of opioid analgesic drugs like codeine in nine European countries recorded highest consumption of codeine in the UK in the period 2001-2003 (De Conno, Ripamonti, & Brunelle, 2005). The prevalence of the non-medical use of
prescription opioids in the USA (2008-2009) found that a substantial number of individuals reported using combination products containing codeine with paracetamol (Wang, Becker, & Fiellin, 2013).

The literature highlights a number of issues in relation to the prevalence of codeine use, misuse and dependence. These include paediatric use of codeine, codeine prescribed for pain, misuse of over the counter forms of codeine (i.e. Codeine Cough Syrups); codeine use in pregnancy, codeine products used to manufacture home-made drug solutions such as desomorphine and recreational use of codeine. Psychotic disorders, especially paranoid psychosis are a frequent psychiatric diagnosis associated with codeine cough mixture abuse, and along with symptoms of anxiety and depression, are associated with long term use (Dobbin & Tobin, 2008; Romach, Sproule, Sellers, Somer, & Busto, 1999). Codeine may also be an iatrogenic cause of psychiatric disturbances (Manchia, Alda, & Clakin, 2013). A withdrawal based medication overuse headache is associated with sustained long-term codeine use (Bendtsen et al. 2012; Katsarava & Jensen, 2007). Other health consequences relate to misuse of combination products containing ibuprofen and paracetamol, and include gastrointestinal haemorrhage, nephro-toxicity and hypokalaemia (Chetty et al., 2003; Ernest Chia, & Corallo, 2010; Frei, Nielsen, Dobbin, & Tobin, 2010).

There is a gap in the evidence base in relation to the extent of misuse and dependent use of over the counter analgesics containing codeine. For example, studies relating to codeine are often combined with general prescription opioid studies and therefore are not specific to codeine alone. We recommend more education of codeine users about variations in metabolism, and risks of long term use, risks associated with polypharmacy intake to challenge the widely held but misinformed perception that codeine based products are low risk in terms of their potential for dependence. Greater concentration of policy and practice focus on prevention, referral and support strategies for those who are at risk of or are currently problematic opioid users is required.

(3) Use and efficacy of codeine within healthcare practice
Codeine is widely used in healthcare. The main therapeutic indications for codeine are the relief of mild to moderate pain and cough suppression. It is also used to a lesser degree as an anti-diarrhoeal agent. Like all drugs, codeine, is not free of problems (Tremlett, Anderson, & Wolf, 2010). It is however generally viewed as a safe and effective analgesic, despite calls to withdraw it from the market (MacDonald & MacLeod, 2010; Tremlett et al., 2010).

The effectiveness and role of codeine in treatment of minor and moderate pain is debatable. The World Health Organisation has placed codeine on ‘step 2’ of its pain ladder, and it is commonly used in the management of mild to moderate pain in adults (often dental or post-partum) and under strict monitoring in children (Campbell, 2006; Cartabuke, Kelly & Madadi, 2012; European Medicines Agency (EMA), 2013; Tobias, Taghon, & Rice, 2013). Some authorities have suggested omitting ‘step 2’ due to the potential
dependent properties and side effects of codeine (and tramadol), and guidelines generally do not recommend codeine for management of pain, due to limited evidence of its effectiveness, variations in metabolism and availability of more predictable opioids.

A meta-analysis of six studies by Derry, Karlin, & Moore (2013), demonstrated combined ibuprofen (400mg) and codeine (25.6 to 60mg) has good analgesic efficiency, but underscored the lack of data relating to low dose codeine(<10mg), with limited data available on medium dose (10-20mg), and most relating to high dose (>20mg, 25.6 to 60mg). In general, codeine is thought to be effective in the treatment of non-cancer pain over a short period of time (less than 6 months). Long-term treatment with codeine cannot be supported as the evidence for its effectiveness is variable and the risk of misuse and abuse is significantly increased (Trescot et al., 2008).

Codeine is available in over the counter combination preparations with caffeine, paracetamol or ibuprofen. However, one of the main reasons for selling over the counter products as combined preparations is to decrease their addictive and abuse potential. However, misuse of combination products particularly ibuprofen is associated with gastrointestinal haemorrhage, nephro-toxicity, hypokalaemia and acute haemorrhagic necrotising pancreatitis. (Barreto, Tiong, & Williams, 2011; Chetty et al., 2003; Dobbin & Tobin, 2008; Dutch, 2008; Dyer, Martin, Mitchell, Sauven, & Gazzard, 2004; Ernest et al., 2010; Evans & Garry, 2010; Ford & Good, 2007; Frei et al., 2010; Hastier et al., 2000; Hou et al., 2011; Lambert & Close, 2005; McAvoy, Dobbin, & Tobin, 2011; Ng et al., 2011; Tormey, 2013).

Codeine appears more clinically useful when combined with paracetamol (Derry, Moore, & McQuay, 2010; Derry et al.; 2013; Iedema, 2011). Franceschi et al. (2013), suggest that codeine-paracetamol combined preparations should be the treatment of choice for mild to moderate pain (for example headache, post-operative, osteoarticular and post traumatic) rather than non-steroidal anti-inflammatory drugs. Baratta, Gandhi, & Viscusi (2013), reported limited evidence for single dose oral ibuprofen plus codeine being more effective for postoperative pain than either drug in isolation. A meta-analysis of opioids for osteoarthritis of the knee or hip reported that modest benefits of codeine were outweighed by adverse consequences (Nuesch, Rutjes, Husni, Welch, & Juni. 2009). Equally given the low dose codeine used in non-prescription medicines, it may be the case that non opioid analgesics perform better (Murnion, 2010). Moreover, ibuprofen (400mg) was shown to be statistically superior to dihydrocodeine (30mg, or 60mg) for relief of pain (Moore, 2011).

(4) Consequences of codeine use, misuse and dependence
The potential for overuse and misuse of codeine containing medications is not only detrimental to a person’s health but has economic and social implications (Feinberg, 2006). The adverse consequences of codeine use and misuse are considered under four categories (1) impairment, (2) injury, (3) adverse health effects and (4) dependence.
(5) **Prevention of codeine misuse and dependence**

The misuse, abuse and dependence on codeine products are a public health challenge throughout the world. Notwithstanding prescription misuse, codeine is present in a range of over the counter medicines that are dispensed to the public without prescription (Cooper, 2013a; Robinson, Robinson, McCarthy, & Cameron, 2010). Increased pharmacovigilance, for example prescription drug monitoring and screening in relation to codeine use within primary care and community pharmacies, is warranted (Jones, Mogali, & Comer, 2012; Kahan, Srivastava, Wilson, Gourlay, & Midmer, 2006). Recent innovative approaches for raising public awareness, identifying misuse, managing misuse and treating dependence are considered. Strategies to empower pharmacy staff as custodians of medicine are warranted alongside brief interventions to raise public awareness and support individuals experiencing tolerance and withdrawal.

(6) **Interventions and treatment for codeine misuse**

The majority of codeine dependent individuals do not view themselves as needing help and do not identify themselves as ‘drug addicts’. Hidden populations of codeine misusers include those with ‘iatrogenic’ dependence following medical use of codeine for pain, anxiety or insomnia, recreational drug users and problematic opiate dependents (Nielsen et al., 2010). The literature in relation to interventions for the treatment and management of codeine misuse is limited, lacks specificity to codeine protocols and requires further development despite potential for extrapolation from extant policy and practice protocols for the misuse of prescribed opioids and treatment of opiate dependence. Despite the use of criteria to establish codeine dependency, recent research has commented on the lack of evidence to guide development of specific treatment and referral pathways for codeine dependence. Further research is needed to guide the development of specific referral and treatment modalities for over the counter codeine misuse and dependence.

(7) **Conclusions and implications for practice, policy and research**

There is a societal need for improved understanding in relation to the risks and consequences of codeine use, misuse and dependence. A global emergence of ‘respectable addiction’ has occurred alongside a heightened awareness by the general public and health professionals with regard to this addiction issue (Cooper, 2013a, 2011; EMCDDA, 2011). Increasing public self-medication with over the counter available medications containing codeine, whilst beneficial to society, also warrants the continued surveillance of certain populations and products (Hughes, 2003).

Recommendations for practice and policy are addressed under the following headings: (1) raising awareness; (2) detecting and managing risk; (3) dispensing practices and (4) monitoring and surveillance of codeine.

**Raising Awareness**

A significant number of people who consume medications cannot identify the active ingredients in their chosen medications (Roumie & Griffin, 2004). A
minority of customers appear willing to accept risks associated with increased access to over-the-counter medications containing codeine and other active ingredients (Alexander et al. 2005). This is despite high public awareness of the abuse potential of over-the-counter medicine (Wazaiy, Shields, Hughes, & McElnay, 2005; 2005a) and pharmacists’ concerns in relation to safety and codeine misuse and dependence. Pharmacists are trusted by the public as a source of information about over-the-counter medications (Wawruch et al. 2013). Dobbin & Tobin (2008), have described particular characteristics of individuals misusing codeine-containing pharmaceuticals, whereby they may not identify as an addict, the medication prescribed infers safety and sanctioning by the prescriber, and with the products purchased having different legal consequences in comparison to illicit drug users. It is important to recognise variance in groups of codeine misusers and target patient and customer awareness initiatives appropriately.

Recommendations for raising public and professionals’ awareness of prescribed and over-the-counter codeine use, misuse and dependence:

Professional education and public awareness campaigns should seek to:

- Promote recognition and early detection by healthcare professionals of signs of dependence and withdrawals in relation to codeine-based products.

- Promote drug monitoring systems, drug workers and clinicians should be aware of potential presentations for emerging and harmful forms of home-produced drug abuse, particularly in the case of injecting drug use.

- Develop and disseminate key health-related messages about the risks of exceeding therapeutic dosages of codeine-based products.

- Promote improved awareness by professionals in relation to co-prescribing and effects on health.

- Heighten public awareness about the risks surrounding the use of codeine-based products whilst driving.

- Increase awareness and access to psychological treatments, for example, cognitive-behavioural therapy, biofeedback, and relaxation techniques for the treatment of chronic headache. (Eng & Lachenmeyer, 1996).

In addition we recommend the further development of:

- Brief interventions at point of sale to raise customer awareness of potential risk of tolerance and dependence over time.

- Parenting classes to highlight the potential side effects of codeine such as respiratory depression when prescribed for children. The evidence suggests that codeine should not be used for children with
neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures and be contraindicated in breastfeeding women. Moreover, calculations of dose should be based on ideal body weight and not actual body weight.

Detecting and Managing Risk
Evidence on the extent of use, non-compliant use and misuse of pharmaceuticals containing codeine is limited. We recommend more education for codeine misusers about the risks associated with poly use of medication and intake of alcohol and illicit drugs to challenge misinformed perceptions that codeine based products are low risk in terms of their potential for dependence.

Recommendations for detecting and managing risk are as follows:

- Develop community pharmacy practice strategies that promote safety strengthen warnings, or remove potential products of abuse from point of sale or sight.
- Develop and improve referral mechanisms to primary care teams for people suspected to be misusing codeine or to be dependent.
- Identify of patients who are in need of psychological services to assist in pain management.
- Develop strategies to detect deception especially in pain related cases thereby minimising risk for failing to improve or overdose.
- Increase availability of disposable containers for unused prescriptions.
- Incorporate routine enquiries about maternal medication use, including codeine-containing cough preparations, when evaluating new-born infants with evidence of cerebral infarction into assessment protocols.
- Assess opioid addiction with the misuse of ibuprofen-codeine combinations when assessing patients presenting with severe hypokalaemia, pancreatitis and medication overuse headache.
- Develop strategies to manage access and reduce treatment barriers in relation to codeine misuse and dependence. For example, the reluctance of problem opiate users to access treatment is an immediate concern.
- Develop clearer guidelines for interpretation of DSM V criteria for abuse and dependence in chronic pain patients, especially in cases of ‘maladaptive or aberrant behaviour’.
• In cases where substance misuse psychiatric disorders are suspected, a high index of suspicion for cough mixtures misuse/abuse is warranted.

• Develop appropriate harm reduction tactics (needle exchange, bleach distribution, hygiene, provision of filters, foil packs to encourage route reversals, and safer injection facilities), screening, treatment (opiate substitution therapy, antiretroviral therapy), therapy and prevention programmes which target injecting drug users who inject home drug solutions made from codeine.

**Dispensing Practices**

Safety is central to pharmacists’ decision making with regard to medication dispensing (Hanna & Hughes, 2010). Pharmacy practice strategies that promote safety in relation to codeine dispensing practices are detailed in chapter 3, table 1.

**Recommendations for dispensing practices:**

We recommend that dispensing practices

• Continue to expand the clinical and public health role of the community pharmacist with ongoing inter-disciplinary training for counter assistants, pharmacists and other health professionals.

• Adopt a ‘universal precautions’ systematic approach for each codeine sale, rather than a selective approach based on customer appearance.

• Introduce short term restricted dispensing practices of codeine based products.

• Provide clearer product labelling of the active ingredients in over the counter and prescribed products.

• Remove potential products of abuse from sight in community pharmacies.

• Refuse sales of codeine to users who are problematic misusers or dependent.

• Develop in house pharmacy based brief interventions at point of sale along with supported detoxification in pharmacies.

• Provide needle and syringe exchange services targeting opiate injecting.
Monitoring and Surveillance of Codeine

The monitoring and surveillance of codeine dispensing activity and estimations of levels of customer misuse (both intentional and non-intentional) remains problematic. In addition to therapeutic dependence and such forms of non-compliant use, the diversion, tampering, home manufacture and injecting of over the counter and prescribed pharmaceuticals (containing codeine and other opioids) is a pharmacy, drug surveillance and public health issue (Azbel, Dvoryak, & Altice, 2013).

Recommendations for monitoring and surveillance:

- Develop prescription drug monitoring and national online prescription systems.
- Develop and evaluate real time integrated monitoring of the dispensing of prescribed and over the counter use of codeine based products in community pharmacies.
- Ensure routine enquiries by health professionals of patients with regard to prescribed and over the counter codeine medication use.
- Monitor the use of prescription opioids in vulnerable groups (patients with chronic non-malignant pain, patients with cancer pain and illicit drug users) to identify if opioids are substituting for or complicating mental health and addiction treatment outcomes, thereby minimising risk of overdose.
- Share information in relation to codeine sales and consumers by pharmacists with other pharmacists.
- Develop and evaluate ‘early warning systems’ in relation to codeine use, misuse and dependence (i.e. recording of adverse events).
- Consider further development and roll-out to other countries of initiatives which are similar to the South African Codeine Care Project, using The TrustaTAG™
- Monitor and manage conflicts between commercial and customer interests; and between pharmacy, non-pharmacy and internet pharmacy outlets.

Recommendations for Future Research

A number of key areas are identified for further research in relation to prescribed and over the counter codeine use, misuse and dependence. Research recommendations are listed under six headings: (1) patterns of use, misuse and dependence; (2) prevalence; (3) treatment/interventions; (4) risk; (5) epidemiology and (6) policy.
Patterns of Use, Misuse and Dependence

Research, evaluation studies and reviews are needed to:

- Quantify the extent of prescribed and over the counter codeine use, misuse and dependence, whether intentional or non-intentional. This work should enable the creation of user profiles in relation to patterns and estimations of codeine use, misuse and dependence.

- Explore the views and experiences of users and misusers of various codeine and other products to better understand product interactions and illegal drug and poly pharmaceutical use patterns.

- Systematically review studies of poly medication use, for example, benzodiazepines, codeine, comorbidity and drug injecting transitions.

- Investigate motives for codeine misuse which range from self-treating of pain (physical and emotional), sleep and anxiety problems, pleasure and ease of access and personality types, for example, addictive personality.

- Explore the experiences of general practitioners of misuse of prescribed drugs, particularly codeine. These studies should investigate: the challenges encountered by primary care staff, incidence of problematic use, the drugs used in treatment, other treatments considered and referral patterns.

- Systematically review studies and conduct further studies to establish the risk of driving accidents with opioid and codeine use, including the effect of these drugs on driving ability on people with different genetic polymorphisms and on aging drivers. The effects of higher doses of codeine require particular investigation.

- Explore the views and experiences of the injecting user of home produced drugs made from codeine. These studies should pay particular attention to perceptions of harm, user practices, trajectories of use and experiences of services. Drug testing of field samples is warranted to establish content.

Prevalence

- Estimate the prevalence of use, misuse and dependence within the broad and ‘hidden’ spectrum of therapeutic and non-therapeutic patterns of codeine use and misuse. The literature is still unclear as to why the misuse of codeine occurs despite various levels of legislative control and preventative strategies in various countries.
• Estimate the prevalence of codeine misuse and dependence among methadone patients and opiate drug users.

• Estimate the prevalence of internet availability and purchase of medications without a legitimate prescription, including identification of customer characteristics.

• Estimate the prevalence and incidence of persistent and problematic use of codeine in patients with non-cancer chronic pain or non-pain patients.

• Estimate the prevalence and effects of parental social medication of children using codeine products.

• Estimate the prevalence of use of home-made drug solutions made from codeine containing pharmaceuticals.

Treatment/Interventions

• Establish the evidence base for the continued use of codeine compared to non-steroidal anti-inflammatory drugs in the management of mild to moderate pain. Overall the evidence presented to support codeine use as opposed to non-steroidal anti-inflammatory drugs is inconclusive and requires further study.

• Establish the effectiveness (benefits and harms) of codeine compared to alternative medications.

• Explore doctors’ and other prescribers’ preferences for prescribing codeine rather than alternative medications and their views on a standard starting dose and subsequent dose titration.

• Establish the effectiveness (benefits and harms) of long-term treatment with short-acting weak opioids.

• Establish the frequency with which prescribers co-prescribe codeine with benzodiazepine or Z drugs.

• Evaluate health professional training in the recognition and management of codeine aberrant behaviours such as forged or lost scripts, requesting certain medications, describing unresolved pain, visiting multiple pharmacies merits further study across a variety of regulatory systems.

• Establish the efficacy and effectiveness of non-pharmacological responses to pain management.

• Synthesise evidence from related fields to guide the development of specific treatment and referral pathways for individuals with codeine
dependence. Although general treatment for opiate dependency is primarily detoxification and psychosocial therapy, there is limited evidence available to guide specific policy development and implementation, management initiatives and the development and provision of specific referral and treatment pathways for over the counter codeine misuse and dependence.

- Synthesise evidence from related fields to guide the development of specific treatment protocols for codeine-users who have issues with pain management, have developed problematic opioid use or are co-dependent on benzodiazepines or Z-drugs.

- Explore the self-perception of codeine dependent individuals many of whom do not view themselves as needing help for their codeine dependence and their experience of interventions (counselling, community detoxification, switching onto other medication) in the management of codeine misuse.

- Identify treatment seeking barriers and experiences of people with codeine dependence.

- Evaluate therapeutic interventions, for example, brief interventions, and their efficacy in treating people who present with codeine related misuse and addiction problems.

- Establish the effectiveness of dihydrocodeine in maintenance, cross over and detoxification treatment of opiate dependency, to ensure a favourable risk/benefit ratio.

**Risk**

- Identify predictors of risk of codeine misuse and dependence and protective factors. Results could inform practices to minimise risk of dependence, guidelines for early detection and management of dependence and the pharmaceutical development of safer products.

- Identify genetic risk factors for opioid dependence, opioid induced hyperalgesia as potential targets for medication therapy and pharmaceutical development of abuse deterrent opioid formulations.

- Explore the characteristics and habits of opioid shoppers in clinical practices and the relationship between prescriber characteristics and risk.

- Synthesise studies of clinical profiles of people who are dependent on prescribed and over the counter codeine to identify subtypes of users at risk of adverse consequences and associated motives and trajectories of use.

- Establish levels of risk and impairment as a result of codeine use and misuse.
Epidemiology

- Develop pharmaco-epidemiological methods to investigate misuse, non-medical use, abuse and dependence on codeine based drugs for self-medication. This would facilitate real time monitoring of prescribing and dispensing activity with data linked to national medicines abuse systems.

- Investigate self-medication and patterns of codeine use among the following key groups: youth, older people, problematic drug users, pain patients, individuals prescribed antianxiety medication, methadone maintenance treatment patients and individuals accessing internet forums.

- Estimate street pricing of diverted prescription codeine and home-made drug solutions produced using codeine based pharmaceuticals.

Policy

- Guide the development of accessible and specific regulatory, pharmaceutical, treatment and community detoxification protocols for codeine misuse and dependence.
Chapter 1

Introduction

This chapter will present background contextual information in relation to codeine use, misuse and dependence. It will described what codeine is, its uses in ‘normal’ medical practice and adverse effects and highlight lack of consensus surrounding terminology such as ‘misuse’, ‘abuse’ and ‘dependence’.

Chapter 2 describes the methods used for the review and findings from the review are presented and discussed through chapters 3 to 9.

- Chapter 3 - Production, manufacture consumption and regulation of codeine internationally.
- Chapter 4 - Prevalence rates of codeine use, overuse, misuse and dependence and associated risk factors.
- Chapter 5 – Use and efficacy of within healthcare practice.
- Chapter 6 - Consequences of codeine use, misuse and abuse.
- Chapter 7 - Prevention of codeine misuse, abuse and dependence.
- Chapter 8- Interventions/Treatments and codeine dependence.
- Chapter 9 - Recommendations and implications for policy, practice and research.

Aim of Scoping Review:
To report what is known about the regulation, production, distribution, prevalence, consequences and prevention in relation to the use, misuse and dependence of codeine in the partner countries (Ireland, UK, South Africa), across the EU and internationally and to identify gaps in the evidence base.

Specific objectives are:
- To map the existing literature examining codeine use, misuse and dependence.
- To identify gaps in the evidence base and make recommendations for future research.
- To provide an overview of the healthcare system, prescribing of codeine and addiction treatment in the three partner countries.
- To make recommendations for practice and policy to promote improved understanding and awareness of codeine misuse and dependence.
1.1 Codeine

Codeine or 3-methylmorphine is the most commonly consumed opiate worldwide, widely used for its analgesic, antitussive and anti-diarrhoecal properties (Derry et al., 2013; Tremlett et al., 2010). The name codeine is derived from the Greek word *kodeia* (κώδεια) for ‘poppy head’ and it is found naturally in the poppy plant ‘*Papaver somniferum var. album*’. Codeine (Fig 1) is a phenanthrene derivative extracted from opium or produced synthetically by the methylation of morphine.

![Chemical Structure of Codeine Base](image)

**Fig 1.1: Chemical Structure of Codeine Base**

1.1.1 Available Formulations

Codeine exists as a base and a number of salts, but is used mainly as codeine phosphate, which occurs in a number of hydrated forms. It is usually a white or near white crystalline solid that is freely soluble in water. It is formulated in a number of ways for use in various conditions and by different routes of administration (Martindale, 2014). Uses and formulations vary in different countries, as do the laws that control its supply. ‘*Over-the-counter*’ supply varies from total prohibition to minimal regulation on supplies from community pharmacies. Typically preparations containing codeine of 30mg and above classify as a ‘*prescription only medicine*’ (Derry et al., 2013). The maximum recommended dosage is 240mg daily, and increasing the dose above 60mg four times a day does not increase efficacy (Campbell, 2006).

The main pharmaceutical form is the tablet (60%) but codeine is also available as a capsule, effervescent tablet, syrup, suppository and solution (EMA, 2013). Codeine products may also be marketed for subcutaneous or intramuscular injection. Intravenous use is not advised as it may cause hypotension and grand mal convulsions. Table 1.1 details the preparations and uses listed in the British National Formulary No.66 September 2013. Over the counter codeine based products contain typically between 8 and 15mg of codeine per tablet, and may be marketed as a single ingredient drug or more commonly in combination with Non-Steroidal Anti-Inflammatory Drugs such as ibuprofen (e.g. Nurofen Plus®), aspirin, paracetamol, caffeine and buclizine in order to enhance the synergistic effect of drug compounds (Tremlett et al., 2010). Examples of codeine containing over the counter medicines in the UK are shown in Table 1.2.
<table>
<thead>
<tr>
<th>Preparation</th>
<th>Indication</th>
<th>Route of Administration</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine Phosphate Tablets 15mg, 30mg, 60mg</td>
<td>Mild to Moderate Pain</td>
<td>Oral</td>
<td>ADULT over 18 years, 30–60 mg every 4 hours when necessary, to a max. of 240 mg daily CHILD 12–18 years 30–60 mg every 6 hours when necessary; max. 240 mg daily; max. 3 days</td>
</tr>
<tr>
<td>Codeine Phosphate Injection 60mg/ml 1ml Ampoule</td>
<td>Mild to Moderate Pain</td>
<td>Intramuscular Injection</td>
<td>ADULT over 18 years, 30–60 mg every 4 hours when necessary</td>
</tr>
<tr>
<td>Codeine Phosphate Syrup 25mg/5ml</td>
<td>Mild to Moderate Pain</td>
<td>Oral</td>
<td>ADULT over 18 years, 30–60 mg every 4 hours when necessary, to a max. of 240 mg daily CHILD 12–18 years 30–60 mg every 6 hours when necessary; max. 240 mg daily; max. 3 days</td>
</tr>
<tr>
<td>Codeine Phosphate with Paracetamol Tablets/Capsules/Dispersible Tablets (Co-codamol ) 8/500mg, 15/500mg, 30/500mg</td>
<td>Mild to Moderate Pain</td>
<td>Oral</td>
<td>ADULT over 18 years, 1–2 tablets in water every 4–6 hours when necessary; max. 8 tablets daily</td>
</tr>
<tr>
<td>Codeine Linctus BP 15mg/5ml</td>
<td>Cough Suppressant</td>
<td>Oral</td>
<td>ADULT over 18 years 5–10 ml 3–4 times daily</td>
</tr>
</tbody>
</table>
Table 1.2: Examples of Codeine Containing Medicines available Over-the-Counter in the UK

<table>
<thead>
<tr>
<th>Product</th>
<th>Ingredients</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-codamol Tablets</td>
<td>Paracetamol 500mg Codeine Phosphate 8mg</td>
<td>Co-codamol® is indicated in children older than 12 years of age for the treatment of acute moderate pain, which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).</td>
</tr>
<tr>
<td>Solpadeine Plus® Tablets</td>
<td>Paracetamol 500 mg Codeine Phosphate Hemihydrate 8mg Caffeine 30.0 mg.</td>
<td>Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain, which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen alone. Solpadeine Plus®. Tablets are recommended for the relief of migraine, headache, backache, rheumatic pain, period pains and dental pain.</td>
</tr>
<tr>
<td>Solpadeine Max® Tablets</td>
<td>Paracetamol 500 mg Codeine phosphate hemihydrate 12.8 mg.</td>
<td>Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain, which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen alone. Solpadeine Max ®Tablets are recommended for the relief of migraine, headache, dental pain, period pain, backache, arthritic &amp; rheumatic pain, strains &amp; sprains and sciatica.</td>
</tr>
<tr>
<td>Migraleve®</td>
<td>Pink Tablets: paracetamol 500mg Codeine Phosphate 8mg buclizine 6.25mg Yellow Tablets: paracetamol 500mg codeine phosphate 8mg</td>
<td>For the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone such as migraine attacks including the symptoms of migraine headache, nausea and vomiting.</td>
</tr>
</tbody>
</table>
| **Nurofen Plus®** | Ibuprofen 200mg  
|                 | codeine phosphate 12.8mg | Nurofen Plus® (which contains codeine) is indicated in patients older than 12 years of age for the short term treatment of acute, moderate pain (such as rheumatic and muscular pain, backache, migraine, headache, neuralgia, period pain and dental pain) which is not considered to be relieved by other analgesics such as paracetamol, ibuprofen or aspirin alone |
| **Co-codaprin Effervescent Tablets** | aspirin 400mg  
|                 | codeine phosphate 8mg | 1) For the relief of headaches, toothache, migraine, neuralgia, sore throat and period pains.  
|                 |                  | 2) For the symptomatic relief of influenza, feverishness, rheumatic pains, sciatica, lumbago, fibrositis, muscular aches and pains. |
| **Codeine Linctus BP** | codeine phosphate 15mg/5ml | Indicated in adults for relief of the symptoms of dry or irritating coughs |
1.1.2 Pharmacodynamics and Pharmacokinetics
Codeine is a short acting weak to mid-range opiate that has a low affinity and low intrinsic activity at the opioid receptors (Iedema, 2011). It is effectively a pro-drug meaning that the body must metabolize it to active metabolites before it becomes effective as a painkiller. The major metabolite is codeine-6-glucoronide, but most of the analgesic action is due to the production of morphine in the liver by the enzyme Cytochrome P450 2D6. The metabolism is by O- and N-demethylation.

Codeine has high oral / parenteral potency ratio with peak plasma concentrations occurring at 60 minutes, and with a plasma half-life of 3 to 3.5 hours in adults (Arora & Herbert, 2001; Band, Band, Deschamps, Besner, & Coldman, 1994). Through the oral route of administration, codeine is effectively absorbed by the GI tract with approximately 50% of the dose undergoing first pass metabolism (Tremlett et al., 2010), and with minimal loss of drug potency (in direct contrast with morphine which loses up to 90% potency). Speed of absorption via intramuscular route is similar to rectal administration (McEwan et al., 2000). Codeine and its metabolites are excreted almost entirely by the kidney (Campbell, 2006; Martindale, 2014). Of note is that the pharmacokinetics of codeine are poorly described in children, despite use over many years (Anderson, 2013). Intravenous use is contraindicated due to lack of first-pass metabolism by the liver inhibiting the drug outcome.

The analgesic effect of opioids is primarily mediated by mu-receptors in the central nervous system and to a lesser extent in the periphery. They act by inhibiting the transmission of nociceptive impulses caused as a result of damage to the tissues. Morphine also reduces the affective component of pain by a supraspinal action, possibly in the limbic system. This effect known as ‘opioid analgesia’ alters the perception and emotional response to pain. Opioids have poor efficacy in the management of pain with a neuropathic component (Rang, Ritter, Flower, & Henderson, eds., 1999; Williams, Patel, & Howard, 2002). Conversion to morphine by endogenous enzymes (human cytochrome P450 2D6) results in the analgesic effect (Kelly & Madadi, 2012), known as the ‘opioid analgesia’ which alters perception and emotional responses to pain (euphoric or dreamy feelings), and stimulatory effects by blocking neurotransmitters (Williams et al., 2002). In therapy, there is a codeine:morphine potency ratio of about 1:10 which means that 60mg of codeine has a morphine equivalence of 6mg (Anderson, 2013). However, it does have the advantage of relatively mild side effects (Martindale, 2014).

Genetic variations in activity of human cytochrome P450 2D6 vary rates (approximately 2-20%) of conversion to morphine (Cartabuke et al., 2013; Cascarbi, 2003; Iedema, 2011; Kelly & Madadi, 2012; Zhou, 2009) with 5% of the population not having the enzyme to convert codeine to morphine, with codeine preparations neither effective for pain relief, nor likely to cause dependence (Chew, White, Somogyi, Bochner, & Irvine, 2001). More than 60 alleles in the CYP2D6 gene have been identified leading to significant enzyme polymorphism. Phenotypes are classified as poor, intermediate, extensive or
ultra-rapid metabolizers. 7-10% Caucasians are slow metabolizers, but this varies with ethnicity and geographic origin (Table 1.3). While some ultra-extensive metabolizers can convert about 15% of a codeine dose into morphine, the majority of the population will convert between 1% and 10%.

<table>
<thead>
<tr>
<th>Population</th>
<th>Ultra-rapid Metabolisers%</th>
<th>Slow Metabolisers</th>
</tr>
</thead>
<tbody>
<tr>
<td>African/Ethiopian</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>3.4% to 6.5%</td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>5-30%</td>
<td>0-20%</td>
</tr>
<tr>
<td>Asian</td>
<td>1.2% to 2%</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>3.6% to 6.5%</td>
<td>7-10%</td>
</tr>
<tr>
<td>Greek</td>
<td>6.00%</td>
<td></td>
</tr>
<tr>
<td>Hungarian</td>
<td>1.90%</td>
<td></td>
</tr>
<tr>
<td>Northern European</td>
<td>1%-2%</td>
<td></td>
</tr>
<tr>
<td>Western European</td>
<td>8-10%</td>
<td>1-4%</td>
</tr>
<tr>
<td>Southern European</td>
<td>7-10%</td>
<td></td>
</tr>
<tr>
<td>Arabian</td>
<td>up to 20%</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.3: CYP2D6 phenotypes by ethnicity (Iedema, 2011; Madadi & Koren, 2008; Actavis, 2014).

The toxicity of codeine relates to its opioid effect (EMA, 2013). Codeine has minimal analgesic activity in slow CYP2D6 metabolizers due to their inability to produce sufficient morphine to incur the analgesic effect. However, adverse effects such as sedation, nausea or pruritus still occur, especially if the dose is raised or combination products are used (Anderson, 2013). Fast CYP2D6 metabolizers or ‘extensive metabolizers’ are at risk of opioid toxicity syndrome, and particularly respiratory depression (Derry et al., 2013; Ingelman-Sundberg, Sim, Gomez, & Rodriguez-Antona, 2007; Madadi et al. 2008; Somogyi, Barratt, & Coller, 2007; Willmann, Edginton, Coboeken, Ahr, & Lippert, 2009). This risk is also exacerbated if poly pharmacy is evident in co-consumption of other drugs such as benzodiazepines and phenobarbitone (Derry et al., 2013; Ingelman-Sundberg et al., 2007; Madadi, 2008; Somogyi, Barratt, & Coller, 2007; Willmann et al., 2009).

In addition to CYP2D6, other genetic factors affecting morphine metabolism, transit via blood brain barriers and opioid receptor kinetics can affect individual responses to codeine (Iedema, 2011). As patient responses vary, the dosage must be monitored on an individual basis, with the usual dose by mouth for adults is 30-60mg every four hours, to a maximum of 240mg per day (Derry et al., 2013). Medications such as phenytoin, rifampicin and dexamethasone can enhance the effect through enzymic induction of CYP450, with antidepressant drugs such as fluoxetine, paroxetine, sertraline and citalopram potentially compromising the analgesic effect through enzymic inhibition of CYP450 (Derry et al., 2013; Iedema, 2011).
1.2 Use of Codeine within Normal Medical Practice

1.2.1 Use in Adults
Codeine was used originally for the treatment of cancer pain, and extrapolated for the management of mild to moderate pain in adults and children (Campbell, 2006; Iedema, 2011; Kelly & Madadi, 2012; Cartabuke et al., 2013; EMA, 2013; Hall, Morant, Carroll, Gabriel, & McQuay, 2013; Anderson, 2013).

It is listed as step 2 in the WHO Analgesic Ladder after paracetamol and non-opioid analgesics for the treatment of cancer pain, although the step is sometimes omitted if deemed clinically appropriate (NICE, 2013; Cartabuke et al., 2013). It is also used as part of a stepwise approach for the management of mild to moderate non-cancer pain in combination with paracetamol and/or Non-Steroidal Anti-inflammatory Drugs after there is inadequate pain control with the agents alone (NICE, 2010). Recent discourse has suggested to skip ‘step 2’ due to problems with codeine (and tramadol) (Anderson, 2013; MacDonald & MacLeod, 2010), with guidelines generally not recommending codeine for management of pain, due to limited evidence of effectiveness, variations in metabolism and availability of more predictable opioids. It continues to be used for postoperative pain management (Stoneham & Walters, 1995), as it causes less sedation and potential respiratory depression than morphine, despite morphine incurring a safer, more potent and longer lasting effect (Goldsack, Scuplak, & Smith, 1996).

The advised dose of codeine is 30-60mg every four hours up to a maximum of 240mg daily (British National Formulary, 2013). Increasing the dose above 60mg does not increase its efficacy, as there is a ceiling effect at a daily dose of 240mg (Campbell, 2006). Lower doses (15mg) are recommended in the elderly, who are more susceptible to the side effects of weak opioids, in people with hypothyroidism and adrenocorticoid insufficiency and in moderate to severe renal impairment, where metabolites can accumulate (NICE, 2010). Also of note is that cough suppression does not correlate with analgesic and respiratory depressant activity of opioids, with the mechanism at receptor level remaining unclear. Codeine suppresses cough at sub-analgesic doses and is widely contained in cough medicines.

1.2.2 Use in Children
Codeine was prescribed for paediatric use, due to the lower incidence of opioid-related side-effects in situations where airway management and neurological assessment are critical (Semple, Russel, Doyle, & Aldridge, 1999). Codeine given its ease of administration as an oral syrup, capsule, suppository or tablet for post-operative, has been used in mild to moderate pain management in children (Tremlett et al., 2010). A recently published serial cross-sectional analysis of emergency department visits for patients between the ages of three and 17, drawn from a nationally representative Canadian sample found a small decline in codeine prescriptions issued (from 3.7% to 2.9% of all prescriptions issued) over a 10 years period, from 2001-2010 (Kaiser et al., 2014). This study found that the odds of codeine
prescription was higher for children aged 8 to 12 years and this did not decline significantly over the study period. The odds of codeine prescribing was lower for non-Hispanic black children, or those from low income families covered by a social healthcare programme (Medicade); possibly reflecting general opioid prescriber avoidance for these groups. Prescribing of codeine for cough or upper respiratory infection did not decline following the publication in 2006 of national guidelines recommending against its use; this is in line with other studies which show that practice guidelines have limited impact on prescriber behaviour for a variety of reasons, including lack of awareness and familiarity with established prescribing practice.

According to Tremlett et al. (2010), ‘the pharmacokinetics of codeine is poorly described in children despite use over decades’. Commentaries have expressed concerns for morbidity and mortality in paediatric use, especially considering the variability of the effects in patients and relating to ethnicity, body composition and physiology (Cartabuke et al., 2013; Madadi & Koren, 2008). It was originally considered a suitable analgesic for children after adenotonsillectomy.

Countries employ different regulations around the minimum age for codeine use, with the UK Medicine and Healthcare Products Regulatory Agency (2010) advising that codeine cough preparations should not be used by people under 18 years of age. In July 2013 a number of Medicines Regulatory Agencies issued restrictions prohibiting its use for this indication in children less than 18 years. This followed reports of deaths in children having a procedure for sleep apnoea, who died of respiratory depression. The children who died were ultra-rapid metabolizers of codeine and developed morphine toxicity.

In 2013, the European Medicines Agency (EMA) commissioned a report on the paediatric use of codeine amid concerns regarding toxicity and lack of consistent risk minimisation measures. They reported on the lack of data on the influence of childhood development on the efficacy and side-effects of codeine, highlighted the risks associated with some children who are ultra-rapid or extensive codeine to morphine metabolizers (EMA, 2013) and pointed to the need to exercise caution when interpreting the effect of age, genetic polymorphism and increasing enzymatic activity in young people. In their view, codeine is: contraindicated in paediatric patients up to 18 years that undergo tonsillectomy and/or adenoidectomy for Obstructive Sleep Apnoea Syndrome due to increased risk of loss of consciousness and respiratory arrest; contraindicated in patients known to be CYP2D6 ultra-rapid metabolizers; and is not recommended for use in children with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or after extensive surgical procedures.

The EMA (2013) recommends that codeine should be used only in children over 12 years for acute moderate pain, where paracetamol and ibuprofen have been ineffective. The maximum dose should not exceed 240mg with a minimum of 6 hours between doses for a maximum duration of 3 days. Parents should be given warning signs of codeine toxicity and advised to stop
treatment and seek immediate medical attention if they occur. Warning signs include: reduced levels of consciousness; lack of appetite; somnolence; constipation; respiratory depression; ‘pin-point’ pupils; nausea and vomiting.

Also of concern is the over the counter use of codeine containing preparations by parents, so called parental ‘social medication’, to incur positive child behaviour, control behaviour, and reduce the inconvenience of neonate and child sickness (for example teething) (Allotey, Reidpath, & Elisha, 2004). There is also the potential for unintentional paediatric overdoses, usually as unsupervised ingestions (Schillie, Shehab, Thomas, & Budnitz, 2009).

1.2.3 Use in Pregnancy and Lactation

Codeine has been prescribed and used over the counter during pregnancy as it is considered a safer option to other opiates. It is also is prescribed for obstetric purposes (Glover, Amonkar, Rybeck, & Tracey, 2003). However, its metabolites do cross the placental barrier and have been linked with neonatal abstinence syndrome and cerebral infarction. This problem is difficult to accurately describe as many women do not consider over-the-counter medicines to be dangerous and exact medication histories are problematic to obtain (Reynolds, Riel-Romero, & Bada, 2007). Codeine was originally viewed as having minimal risk to mothers and breast feeding infants (Seaton, Reeves, & McLean, 2007) however recent commentaries have presented serious concerns for morbidity and mortality in paediatric use (Cartabuke et al., 2013, Chang et al. 2012). Madadi & Koren (2008) have commented on the lack of empirical evidence available to support its use in children and breast feeding mothers, and emphasised variability in the efficacy of codeine in these patients.

Neonatal abstinence syndrome and cerebral infarction following maternal codeine use during pregnancy have been observed (Au et al., 2007; Reynolds et al., 2007; Van Leeuwen, Guthrie, & Stange, 1965). Breastfeeding is cautioned and requires close monitoring if codeine is prescribed for breastfeeding mothers, given the potential risks associated with CYP2D6 ultrafast metabolism (Kennedy, 2011). Codeine use while breastfeeding is associated with events in breast-fed infants, including apnea, bradycardia, drowsiness, and cyanosis (Darnall, Stacey, & Chou, 2012). Women with a rarer CYP2D6 genotype rapidly metabolize codeine into morphine, resulting in high breast milk and plasma levels in neonates, and can potentially cause infant death due to opioid toxicity (Madadi et al., 2007; 2011). Genetic screening is not standard practice, so contributing to a lack of clinician awareness of the potential for neonate opioid toxicity (Madadi et al., 2011).

As part of the warnings issued by the Medicines Regulatory Agencies in 2013 concerning the use of codeine in children, it was stated that ‘codeine should not be used by breastfeeding mothers because it can pass to the baby through breast milk and potentially cause harm’ (MHRA, 2013). In North America, it is standard practice to use codeine combined with paracetamol in obstetrics for the treatment of pain immediately post-partum, following caesarean section, the use of episiotomy or after 3rd or 4th degree tears of
perineal tissue. However, considering the recent recognition of the problems with codeine use in breastfeeding there have been calls to limit its use in favour of Non-Steroidal Anti-Inflammatory Drugs, which are shown to have a better risk-benefit ratio (Nauta, Landsmeer, & Koren, 2009).

1.2.4 Use in Older People
Misuse of pharmaceuticals among the older population is largely overlooked, under reported and hidden (McGrath, Crome, & Crome, 2005). Codeine specific literature is scant. The use of opioid analgesics increases with age (Roumie & Griffin, 2004). Pharmacogenetic variability in older people and reduced renal function leading to an accumulation of active metabolites (Derry et al., 2013), may result in increased susceptibility to opioids (Derry et al., 2013). Research shows that the prevalence of opioid misuse is highest in women, particularly if widowed, less educated, with lower income, in poor health and with reduced social supports (Francis et al., 2005). Older people are more likely to have pain issues, and are at greater risk of codeine related adverse events (Cherubino, Sarzi-Puttini, Zuccaro, & Labianca, 2012). Increases in the problematic use of over the counter codeine containing products have been observed amongst older people (Moore, 2008). Contraindications of codeine use include concurrent use of other medications, with associated heightened risk of sedation, confusion and collapse (Buckeridge et al., 2010; Iedema, 2011). Other adverse consequences include the risk of falls, fractures, injuries and impaired driving and road crashes (Amato et al., 2013; Bachs, Skurtveit, & Morland, 2003; Bachs, Engeland, Morland, & Skurtveit, 2009; Buckeridge et al., 2010; Francis et al., 2005; Leung, 2011; Mailis-Gagnon et al., 2012; Vestergaard, Rejnmark, & Mosekilde, 2006).

1.2.5 Use in the treatment of opiate dependence
Codeine, dihydrocodeine and oxycodone can be prescribed for use in substitution treatment and detoxification (Kurdyak et al., 2012). Oral short acting dihydrocodeine (half-life: 4 h) has been viewed as a viable alternative to methadone as substitution treatment for opiate dependence (Banberry, Wolff, & Raistrick, 2000; Krausz et al., 1995; Krausz, Verthein, Degkwitz, Haasen, & Raschke, 1998; Robertson et al., 2006). Some preference is shown for the prescribing of dihydrocodeine by general practitioners particularly within specialist drug services because it is considered: safe; offering a lower risk of addiction; having potential for retaining patients in treatment; efficacy for patients with less severe dependence (despite lack of data on positive clinical outcomes); avoids the need for frequent dosing; lessens the risk of patients oscillating between sedation and withdrawals, lessens the potential of poly drug use diversion and fatalities (Backmund, Meyer, Eichenlaub, & Schütz, 2001; Banbery et al., 2000; Robertson, Witcomb, Roberts, & Egan, 1990; MacLeod. Whittaker, & Robertson, 1998; Seymour, Black, Jay, & Oliver, 2001; Sheard et al., 2007; Stark & Gregory, 2005; Zamparutti, Schifano, Corkery, Oyefeso, & Ghodse, 2010).
1.3 Diversionary Use of Codeine outside of Normal Medical Practice

1.3.1 Non Medicinal and Recreational use of Codeine

Research shows that awareness of codeine’s abuse potential within problematic drug using networks is higher than in the general population, and that it has the potential to alleviate withdrawals from stronger opiates such as heroin (Agyapong et al., 2013; Cooper, 2013b). Recreational codeine use is characterised by consumption of high doses of codeine in ‘binge’ episodes with nasal, rectal, oral, inhalation and subcutaneous use most common (Ernest et al., 2010).

Reported forms of recreational use for intoxication include consumption of codeine cough syrups along with anti-nausea preparations such as promethazine and codeine crushed within caffeine laced drinks (i.e. Red Bull) popular in the US (Ernest et al. 2010), and in Thailand, the home production of ‘Kratom Cocktails’ (Chitrtrakarn, Penjamras, & Keawpradub, 2012). In the US, codeine has been labelled ‘Hillbilly Heroin’ with free base smoked on aluminium foil (similar to heroin ‘chasing the dragon’). Poly drug taking represents an additional confounding health consequences and drug outcomes for the recreational misuse of codeine (Reed et al., 2011).

According to Bardhi, Sifaneck, Johnson, Dunlap (2007) increased use and abuse of prescription pharmaceuticals (including vicodin, percocet, codeine, xanax, valium, adderall and so forth) have been documented, particularly among young, white, middle class, college educated women, who also report recreational poly drug use (marijuana, cocaine, ecstasy and alcohol). These authors reported on three forms of controlled pill use, recreational, quasi medical and legal medical, with awareness of side effects and shifting patterns described. Poly substance use using pills to enhance the effects of other drugs and reduce negative outcomes of illicit drugs was reported. No respondents in this study reported the temptation to use heroin. Few reported that their pill use interfered with employment and family life, and none reported contact with the police, or seeking treatment.

Amongst illicit drug users, extra medical use of pharmaceuticals including codeine occurs in varying degrees. Wilkins, Sweetsur, & Griffiths (2011), reported that amongst frequent users of ecstasy, there were low levels of morphine, methadone and ‘home bake’ morphine, but sizable levels of reported methylphenidate, benzodiazepines and codeine use. These prescription drugs are most commonly sourced from doctors/pharmacies, drug dealers, family members, and with opioids most commonly used for pain and withdrawal in street drug user regimes (Davis & Johnson, 2008).

1.3.2 Tampering with codeine containing pharmaceuticals

Drug or formulation tampering is defined as ‘physical or chemical alteration of a specific drug formulation for purposes of enhancing drug effect, increasing speed of onset of effects, eliminating undesirable actives and excipients, and chemically modifying actives’ (Cone, 2006). Tampering with pharmaceutical drug formulations by physical or chemical alteration is conducted to enhance
the psychoactive drug effect, heighten onset of drug effects, eliminate undesirable active substances and excipients, and chemically modify certain active substances (Budman, Grimes Serrano, & Butler, 2009; Cone, 2006 Vosburg et al., 2012; Webster, 2009). The extent of this form of drug misuse and dependence is unknown and is partly due to a lack of data and monitoring systems by health and drug professionals (UNODC, 2013).

With regard to the diversionary use of codeine, instructions on how to crush, separate excipients from undesirable actives, overcome time release formulations, purify and chemically alter formulations and intended route of administration, alongside recommended optimal routes of administration and dosage are readily available on the Internet (Cone, 2006; Raffa & Pergolizzi, 2010; Srimurugan, Su, Shum, Murugan, & Chen, 2012). Online user forums provide information for users on how to extract codeine from combination products by splitting tablets with a sharp blade, discarding the side containing ibuprofen and consuming the tablet side marked N+, and how to conduct ‘cold water extraction’ (CWE) processes using multi filtration of the product in order to yield the codeine base.

A review of the tampering of pharmaceutical formulations is beyond the scope of this study. Readers are referred to Cone’s (2006) excellent review on tampering with pharmaceuticals.

1.3.3 Home produced drugs made from codeine

In 2011, the European Monitoring Centre for Drugs and Drug Abuse (EMCDDA) reported on the rising illicit market of opioids other than heroin, for example pain relievers (morphine, fentanyl, codeine, oxycodone, hydrocodone) and substitution drugs used in the treatment of heroin dependence (methadone, buprenorphine). In South Asia namely Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka, the diversion, extra medical and injecting use of pharmaceutical opioids (buprenorphine, codeine, nalbuphine, dextropropoxyphene) is related to inadequate prescribing for pain, and a recent decline in natural opiate availability (Larance et al., 2011).

Of interest is the misuse of over the counter available medicinal preparations from pharmacies, despite efforts to regulate the sale of certain medicines, most notably codeine, pseudoephedrine, pentazocine, promethazine hydrochloride and dextromethorphan. These compounds are used to manufacture home-made amphetamine and opiate type drug solutions. Initial reporting of ‘home-made’ drug solutions’ often commences via the media, with scientific research somewhat slow to follow.

This new phenomenon of home production of drug solutions, often for injecting drug users centres on the use of cheap and readily available materials, low costs of production, and cheaper drugs with similar effects as heroin (Balakireva et al., 2006). The popularity of certain ‘home-made’ drugs depends on the ease of sourcing of ingredients, preparation and synthesis, its
market status relative to other available drugs, and the relative cost-benefit ratio of its use (Heimer, 2013).

In New Zealand, the small scale production of injectable heroin substitutes is known as ‘Home Bake’, and commonly made from morphine and codeine based pharmaceuticals (Bedford, Nolan, Onrust, & Siegers, 1987; Grund, Latypov, & Harris, 2013; Robinson, Kemp, Lee, & Cranston, 2000). The conversion process from morphine sulphate to diacetylmorphine or heroin is a relatively simple process that produces a product with few impurities and requires a spoon, heat source, baking soda, citric acid, water and acetic anhydride (AA) (Kemp & Aitken, 2004). AA or ‘double’ whilst strictly regulated (UNODC 2011), is readily available via illicit sources (Grund et al., 2013). In contrast, converting codeine based pharmaceuticals to diacetylmorphine is relatively complex, and involves additional reagents (Grund et al., 2013). This home produced opiate is then sold as powder for acetylation with AA, or in liquid form, and is reportedly relatively pure (Bedford et al., 1987).

The Soviet tradition of homemade substances is viewed as contributory to the production of new, accessible and affordable drug solutions (Azbel et al., 2013). Recent reports indicate that injecting drug users in Russia, Ukraine and other countries no longer source poppies or raw opium for home produced injectables and have diverted their attention to available medications containing codeine in pharmacies (Grund et al., 2013). A home-made product called ‘Braun’ is made from pharmaceuticals containing a mixture of morphine and codeine such as Alnagon ®, Korynal ®, Kodynal, Ippecarin ® (Zábranský, 2007).

Desomorphine (5a-17-methyl-4, 5-epoxymorphinan-3-ol) is generated from codeine (3-methylmorphine) via 2 intermediate steps (α-chlorocodide and desocodeine). Over the counter codeine medications (‘Codelac ®’ and ‘Terpincod ®’) are used for reduction of codeine using iodine, lighter fluid, hydrochloric acid, gasoline, industrial cleaning oil and red phosphorus in a similar short process to that of methamphetamine from pseudoephedrine (Gahr et al., 2012, a,b,c; Savchuk, Barsegyan, Barsegyan, & Kolesov, 2008; Skowronek, Celiński, & Chowaniec, 2012; UNODC, 2012). The home production of desomorphine known as ‘Russian Magic’ or better known as ‘Krokodil’ (крокодил or crocodile), emerged in Russia in 2003 (Savchuk et al., 2008)³. The rise in Russian ‘Krokodil’ addicts fuelled a shift toward regulation of codeine containing tablets in June 1st 2011. Print screen and online media reporting, whilst sensationalist and for the most part reporting on isolated cases have reported suspected clinical presentations and fatalities in the UK, Germany, Poland, Czech Republic, France, Belgium, Sweden, Norway and other European countries with Russian populations (Gahr et al., 2012b; Skowronek et al., 2012) and in late 2013 in the US.

³ The extensive review conducted by Grund, Latypov and Harris (2013) reports in its use in Russia, Ukraine, Georgia and Kazakhstan and comments on ‘Krokodil’ as a relatively new phenomenon, with estimates of between 20,000 and 100,000 injectors of the drug in 2011, and most commonly used opiate amongst OST patients in Georgia.
The presence of contaminants and residues of iodine, phosphorus, heavy metals and other chemicals such as iodocodeine, caffeine, paracetamol, diphenhydramine (an opioid potentiator); and co-injecting use of other drugs such as fentanyl (UNODC, 2012), tianeptine (an antidepressant) or tropicamide (eyedrops) further compound abuse trajectories.

1.4 Common side effects of codeine

1.4.1 Opioid Side Effects

Common side-effects are often a result of the action of codeine and its metabolites at the opioid receptors. Codeine is a weak agonist at mu-, kappa- and delta-opioid receptors. Its analgesic effect is primarily mediated through its metabolite morphine, which is a much stronger mu-agonist (Rang et al., 1999). It is assumed that the actions of codeine are largely due to morphine. However, there is evidence that some effects are related to codeine or its other metabolites (Bachs et al., 2003).

Drowsiness and nausea are common side effects with oral doses of 30-60mg and with regular dosing constipation is seen with 8-16mg (Campbell, 2006). At high dose it has a depressive effect on respiration and alertness, but to a lesser extent than morphine (Amato et al., 2013). Codeine is linked to an increase in motor accidents where opioids are implicated causing sedation, cognitive impairment and mental clouding (Bachs et al., 2003). Codeine toxicity syndrome with risk of coma or death occurs at very high oral doses, when part of poly drug or pharmaceutical use, and when injected intravenously (Dobbin & Tobin 2008; Heard, Sloss, Weber, & Dart, 2006; McAvoy et al., 2011; Paulozzi & Ryan, 2006; Zamparutti et al., 2010).

The effect of codeine on the central nervous system depends on dose, route of administration, previous exposure and genetic factors of the patient. Dose dependent effects include visual disturbances, mood changes, dependence, itching, nausea, vomiting, constipation, drowsiness, pupil constriction, bradycardia, tachycardia, palpitation, oedema, reduced breathing rate, sweating, flushing, clammy skin, postural hypotension, sexual difficulties, tremors, irritation, depression, ureteric spasm, miosis, dry mouth, urinary retention, sleep disturbances, headache, constipation, hallucinations, vertigo, euphoria, dysphoria, confusion, drowsiness, difficulty with micturition, urinary retention, rash, urticaria, pruritus and seizures (Iedema, 2011; McDonough 2011; Olesen et al., 2006; Williams, 2005). Tolerance and dependence can occur, especially with prolonged high dosage (Sanofi, 2014). Long term use for pain relief and/or high dosage over time results in adverse effects such as constipation and sedation, with dose related respiratory depression (Derry et al., 2013). There is a risk of respiratory depression, coma and death resulting from codeine toxicity at very high doses, after oral over-dosage, when injected, and used in combination with alcohol or other drugs (Bellville & Seed, 1968; Dobbin & Tobin, 2008).

Codeine is often used to manage headache, especially in the form of over-the-counter preparations. In common with other analgesics, misuse in the
form of repetitive daily use has been known to contribute to increased headaches known as ‘Medication Overuse Headache’ (Bendtsen et al., 2012). Other research comments on the use of analgesic drugs such as codeine to treat headache and to assist patients in coping with life (Ferrari et al., 2006). The extent of self-medicating behaviour for headache is unknown due to inconsistent patient contact with medical professionals, and inaccurate or the under reporting of this form of drug use (Leong & Lachenmeyer, 1996). Out-patient drug withdrawal therapy is required to treat patients with medication overuse headache followed by structured acute therapy and initiation of migraine prophylactic treatment (Diener & Katasarva, 2001; Linton-Dahlöf, P., Linde, M., & Dahlöf, 2000).

The effects on the gastrointestinal tract are complex and mediated by a number of mechanisms. Studies have shown that there is little difference between poor and extensive metabolisers of codeine on gastrointestinal transit and nausea, suggesting that total or at least some effects are due to itself or metabolites other than morphine (Bachs, Skurtveit, & Mørland, 2003).

Nausea and vomiting are common side effects at higher doses and the site of action is the *chemoreceptor trigger zone*, a region of the medulla where chemical stimuli induce the effect. There is also increased tone and reduced motility in many parts of the gastrointestinal system through stimulation of mu-opioid receptors and to a lesser extent delta- and kappa-. This can add to the feelings of nausea but also contribute to constipation, an effect that is occasionally used in the treatment of diarrhoea. It can also slow the absorption of other drugs.

### 1.4.2 Tolerance and Dependence

Codeine produces less euphoria than morphine and the risk of dependence is low with normal use. Euphoria appears to be mediated through mu-receptors and is balanced by the dysphoria associated with kappa-receptor activation. The euphoria produced by morphine depends considerably on the circumstances of the patient. In acute pain, a powerful sense of contentment and well-being is invoked, which helps mitigate the agitation and anxiety that is often a feature of the condition. However, in patients who have become accustomed to chronic pain, analgesia occurs without the euphoric effect and some patients even report restlessness under these conditions (Rang et al., 1999).

Tolerance to the effect of morphine, including analgesia develops rapidly via a number of mechanisms including metabolic degradation, reduced affinity for the opioid receptor and down regulation of opioid receptors. This means that the amount of opioid required for effective analgesia increases with time and physical and psychological dependence develop. It also means that dependents or people who have built tolerance can take large doses without problems such as respiratory depression occurring. An abstinence syndrome characterizes physical dependence, where patients show symptoms resembling severe influenza, with yawning, pupillary dilation, fever, sweating, piloerection, nausea, diarrhoea and insomnia. The symptoms are maximal for
about two days and mostly disappear after 8-10 days. Re-administration of the opioid rapidly alleviates the abstinence syndrome. Psychological dependence is associated with craving, lasting for months or years. It rarely occurs in patients being given opioids as analgesics (Rang et al., 1999).

Dependence has been reported in prescribed analgesics containing codeine (McBride & Meredith-Smith, 1995), with low risk of dependence in over the counter codeine preparation if taken as directed (Cooper, 2013b). Conflicting views exist with regard to codeine’s potential for addiction, particularly when considering combination products and the potential effects of other active ingredients such as ibuprofen, paracetamol and caffeine (Frei et al., 2010).

Although effects are milder than heroin, abuse potential remains of concern, with tolerance and neuro-adaptation occurring with regular use over a short period of time (Mattoo, Basu, Sharma, Balaji, & Malhotra, 1997; Nielsen et al., 2008; 2010; Oriols, Gaillard, Lapeyre-Mestre, & Roussin, 2009). Withdrawal effects in the case of physical dependency on codeine include classic opiate dependence symptomatologies, albeit less severe than with morphine, such as cravings, preoccupation with seeking and taking codeine, lack of control of consumption patterns despite negative side effects, insomnia, restlessness, runny nose, stomach pains, diarrhoea and chills (Cooper, 2013b). Psychological criteria of codeine dependence are less evoked than physiological dependence symptoms (tolerance and withdrawals) in non-cancer pain patients (Vallejo, Barkin, & Wang, 2011). Prolonged use of codeine is strongly associated with depression and dysphoric mood states (Romach et al., 1999).

1.4.3 Non-Opioid Side Effects
Codeine has effects on the body that are not mediated by opioid receptors. There is a dose-related release of histamine from mast cells, which can cause urticaria and itching, particularly at injection sites in the face and neck areas. It can also lead to anaphylaxis in rare cases and contribute to hypotension. Large doses have been known to have an action on the medulla causing bradycardia and further hypotension. Effects on smooth muscle other than that of the gastrointestinal tract are slight, though spasm of the ureters, bladder and uterus sometimes occur (Martindale, 2014; Rang et al., 1999).

Codeine can interact with other medication taken by patients. Alcohol and other central nervous system depressants can lead to increased sedation, respiratory depression and other central nervous system effects. Respiratory depression can occur with phenobarbital, which although not contraindicated, warrants caution and monitoring. Drugs that affect CYP2D6 can potentially affect the outcome of codeine. Enzymic inducers such as rifampicin, phenytoin and carbamazepine can increase the metabolism to its active metabolites, increasing adverse effects. Conversely, inhibitors of the enzyme such as fluoxetine, paroxetine, sertraline and citalopram slow down the metabolism, compromising analgesic activity (Baxter & Preston (eds.), 2014).
Serious chronic health consequences, particularly in the case of excessive or long term use of combination products containing ibuprofen and paracetamol include gastric ulcers, gastrointestinal bleeding, hepatotoxicity, hypokalaemia, inflammatory bowel conditions, and profound hypokalaemia associated with a severe myopathy, and often in users with no history of substance use disorders and co-morbidity (Barreto et al., 2011; Chetty et al., 2003; Dobbin & Tobin, 2008; Dutch, 2008; Dyer et al., 2004; Ernest et al., 2010; Evans, Chalmers-Watson, & Gearry, 2010; Frei et al., 2010; Ford & Good, 2007; Hastier et al., 2000; Hou et al. 2011; Lambert & Close, 2005; McAvoy et al., 2011; Ng et al., 2011; Tormey, Sabah, & Moore, 2013). Contraction of the gall bladder and constriction of the biliary sphincter increases the pressure in the biliary tract. This can lead to increased pain in patients with gallstones, rather than bring relief (Rang et al., 1999). Convulsions and acidosis have been associated with codeine and antihistamine (diphenhydramine) in antitussive medicine (Murao, Manabe, Yamashita, & Sekikawa, 2008). Other potential complications associated with long term use include symptoms of anxiety and depression (Dobbin & Tobin, 2008; Romach et al., 1999). Codeine may also be an iatrogenic cause of psychiatric disturbances (Manchia et al., 2013). Excessive doses of over the counter analgesics containing codeine in patients accessing emergency admissions have been recorded (Heard et al., 2006).

1.5 The problem of codeine misuse
The global misuse of pharmaceutical opioid analgesics is of increasing public health and drug monitoring concern (Forman, Woody, McLellan, & Lynch, 2006; Compton & Volkow, 2006; Fry, Smith, Bruno, O'Keefe, & Miller, 2007; UNODC, 2011). Misuse of prescribed and over the counter opioid analgesic medication4, (including codeine) is driven by a host of factors which include pharmaceutical marketing tactics, inappropriate and increased prescribing, access to licit and illicit drug sourcing, governmental responses, public misconceptions around safety, social influences, self-medication of emotional and physical pain and recreational popularity (UNODC 2011, 2013). Emerging patient demand for access to efficient analgesic drugs without consultation with medical professionals has contributed to the displacement of prescription only drugs to over the counter status, with resultant problems relating to the self-selection of opioid analgesic drugs by consumers (Peterson, 2005).

In their review of ‘Misuse of Medicines in the European Union’, Casati et al. (2012), underscore that whilst awareness of the misuse of opioid analgesics such as codeine is on the increase, data on the extent of the problem in the EU is scant, with similar global observations made by the UNODC in 2011. Given that these pharmaceuticals are legally dispensed to patients for treatment of medical conditions such as pain, and are more widely available and accessible to the public, epidemiological efforts to capture hidden patterns of non-medical use are difficult (UNODC 2011). Experts suggest that cohorts of pharmaceutical opioid misusers remain hidden, and reasons for non-compliant medicinal use, overuse and intentional misuse for euphoric and

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4 Drugs available from pharmaceutical sources,i.e. manufactured by the pharmaceutical industry or made up by a pharmacist. Caffeine, antihistamines, codeine (an opiate) and alcohol are the most common psychoactive constituents of over-the-counter drugs.
other effects are not well understood, despite potential for dependence, poly
use of other drugs, and adverse health consequences (Manchikanti & Singh,
2008; Nielsen et al., 2010).

Deregulation of medicines like codeine has created increased patient
convenience, self-management, response to advertising and pharmacist
empowerment in health decision making (Albsoul-Younes et al., 2010; Francis
et al., 2005). However emergence of misuse and abuse of non-prescription
medicine has increased along with associated harms (Bond & Hannaford,
2003; Eccles, 2006; Hughes, McElney, Hughes, & McKenna, 1999; Hughes,
McElney, & Fleming, 2001). Patient demand for access to efficient analgesic
drugs such as codeine without medical consultation, has contributed to high
numbers of products being available ‘over-the-counter’.

1.6 Misuse, Abuse and Dependence

1.6.1 Terminology
There is a lack of consensus in the literature as to definitions of the terms
misuse and abuse. This is further compounded by pharmaceuticals supplied
on prescription or over the counter and how these may differ to other
substances obtained illicitly (Barrett, Meisner, & Stewart, 2008). The variation
in the legal control of over the counter and prescription medicines such as
codeine creates difficulty in creating a consistent terminology resulting in
many terms used, for example, ‘nonmedical use, problem use, harmful use
and inappropriate use’. A lack of consensus of what constitutes associated
harm further compounds this problem (Casati et al., 2012).

Motives for use, whether medical, non-medical, recreational, problematic,
abuse or dependence exists within a dynamic continuum of use. The
variability of definitions across studies makes interpretation of results and
comparisons difficult. The interpretation of clinical findings and
characterisation of the issue are complicated by use of multiple criteria for
misuse and by lack of differentiation between them (Barrett et al., 2008). Such
variability of definitions across studies makes interpretation of results across
studies and comparisons difficult.

Here follows the range of terminology used in the literature:

Inappropriate medication use is defined on the basis of user characteristics
(e.g. any non-prescribed use), reason for use (e.g. recreation) or the presence
of clinically significant symptoms (e.g. diagnostic criteria for abuse and
dependence) (Barrett et al., 2008).

Variation in determining misuse and dependence exists (Hughes, Pillitteri,
Callas, Callahan, & Kenny, 2004), with Cooper (2013a) comment on the
generic use of the term ‘misuse’ to describe all forms of problematic over the
counter use, with little delineation between misuse, abuse and dependence
(Akram, 2000; Ajuoga, Sansgiry, Ngo, & Yeh, 2008; MacFadyen, Eadie, &
McGowan, 2001; Matheson, Bond, & Pitcairn, 2002; Myers, Siegfried, & Parry, 2003; Pates, McBride, Li, & Ramadan, 2002)

Wazaify et al. (2005), describe the misuse of an over the counter product as use for legitimate medical reasons but in higher doses or longer than advised, with abuse representing the non-medical use of over the counter preparations such as codeine for the euphoric effect. Fleming, McElnay, & Hughes, (2004) observe that misuse can apply to all medicines, with abuse relating to specific drugs such as codeine.

This review adopts Casati et al.’s, (2012) broad definition of ‘misuse’ which is:

‘The problematic consumption of codeine where risks and adverse consequences outweigh the benefits, and which includes use of codeine with or without prescription, outside of acceptable medical practice or guidelines, for recreational reasons, when self-medicating, with higher doses and for longer than advisable’

Albsoul-Younes et al. (2010) define abuse as:

‘The use of drugs for nonmedical purposes, i.e., to experience their mind-altering effects, while “misuse” is applied to the use of a drug for legitimate medical purposes, but in an incorrect manner, i.e., its use for longer duration than prescribed or in a higher dose than recommended on the packet’.

For the term ‘abuse’ the DSM-IV definition and criteria is used:

‘A pattern of maladaptive substance use that is associated with recurrent and significant adverse consequences’.

A diagnosis of substance abuse requires meeting at least one of the following four criteria due to recurrent substance use:

- Failure to fulfil obligations at home/school/work
- Use in situations that are physically hazardous
- Legal problems
- Social or interpersonal problems

It should be noted that few empirical studies of ‘pharmaceutical medication’ assess according to these criteria, often because the user does not perceive their use as abuse (Barrett et al., 2008).

Of interest is the inter-changeability of the term ‘patient’ for those attending hospital services (Mattoo et al., 1997; Myers et al., 2003), ‘client’ in pharmacy based interventions (Fleming et al., 2004), and ‘customer’ in studies of over the counter supply (Albsoul-Younes et al., 2010; McBride, Pates, Ramadan, McGowan, 2003).
There is distinct variation in the literature in terms of “pharmacodependence” (Orriols et al., 2009). The term ‘addiction’ is sometimes used (Hughes, 2003; Reay, 2009) or ‘dependence’ is the term of choice for codeine specific studies (Tinsley & Watkins, 1998; Orriols et al., 2009).

DSM V (American Psychiatric Association, 2000) combines previous DSM IV categories of substance abuse and substance dependence into a single disorder - substance use disorder, which is measured on a continuum from mild to severe.

Substance use disorders are patterns of symptoms resulting from use of a substance which the individual continues to take, despite experiencing problems as a result. These disorders span a wide variety of problems arising from substance use, and cover 11 different criteria:

1. Taking the substance in larger amounts or for longer than the you meant to
2. Wanting to cut down or stop using the substance but not managing to
3. Spending a lot of time getting, using, or recovering from use of the substance
4. Cravings and urges to use the substance
5. Not managing to do what you should at work, home or school, because of substance use
6. Continuing to use, even when it causes problems in relationships
7. Giving up important social, occupational or recreational activities because of substance use
8. Using substances again and again, even when it puts the you in danger
9. Continuing to use, even when the you know you have a physical or psychological problem that could have been caused or made worse by the substance
10. Needing more of the substance to get the effect you want (tolerance)
11. Development of withdrawal symptoms, which can be relieved by taking more of the substance.

Two or three symptoms indicate a mild substance use disorder, four or five symptoms indicate a moderate substance use disorder, and six or more symptoms indicate a severe substance use disorder.

Substance use disorders are one of two groups of substance-related disorders identified in DSM 5. The other group is substance-induced disorders, which are symptoms caused directly from the use of a substance that an individual continues to take, in spite of experiencing problems as a result; for example, intoxication, withdrawal and substance induced mental disorders.

When diagnostic criteria for dependence are met, along with tolerance and/or withdrawal, a physical dependence is diagnosed (Barrett et al., 2008). Of note, in the case of pharmaceutical dependence, this can occur following long term prescribed use and in the absence of intentional misuse (for example for
pain), and in illicit drug users as substitute medication (for example heroin) (Barrett et al., 2008).

Transitioning between misuse and abuse, in the form of involuntary addiction is less explored in the literature (Reay, 2009). Non-prescribed medication use includes a range of consumptive behaviours, motives, risk behaviours and user characteristics (Barrett et al., 2008). Non-prescribed use with therapeutic intentions is problematic due to lack of medical supervision, and often lack of medical diagnosis, but not as risky as forms of recreational use (Barrett et al., 2008).

Terminology is further complicated by the recognition that trajectories and symptoms differ, with use often for longer than intended, withdrawal on cessation, and with recreational users presenting unique consumptive patterns and symptoms of use. Indeed, “Not all drug users are necessarily addicted to drugs or are chaotic users, and many manage their drug use as part of their normal daily routine. Such misuse is termed recreational use” (Scottish Specialist in Pharmaceutical Public Health, 2004, p.24).

Poly substance users who misuse pharmaceuticals seek formulations which enhance the effect of other substances, for example the co-administration of opiates and stimulants, minimise undesirable effects, for example comedown symptomatology such as insomnia, and for prolonging drug episodes (Barrett et al., 2008).

1.6.2 Characteristics of codeine misusers

Whilst the potential for misuse and dependence on codeine is established in the literature, research on prevalence and incidence of persistent and problematic use of this weak opioid in patients with non-cancer chronic pain or non-pain patients is scant (Roussin, Bouyssi, Pouche, Pourcel, & Lapeyre-Mestre, 2013; Skurtveit, Faru, Borchgrevink, Handal, & Fredheim, 2011). Individuals who misuse prescription or over the counter pharmaceuticals may not identify themselves as addicts, because of an inferred degree of safety and sanctioning by prescribers and pharmacies. Moreover, there are different legal consequences of misuse in comparison to illicit drug use. It is important to recognise variance in groups of non-compliant codeine users and misusers so that initiatives to prevent misuse can be targeted appropriately.

Cooper (2011) identifies three distinctive groups of over the counter codeine medicine user based on quantity of consumption. They are (1) users that never exceed the maximum dose; (2) users who sometimes consume slightly higher than the recommended dose; and (3) those who consume significantly higher doses than recommended. No displacement between these three types was observed.

In terms of codeine dependence, two distinct cohorts of dependent user are identified. The first cohort commence codeine use for pain management (either prescribed or via pharmacy sale). They use it initially in an appropriate manner and intentionally or unintentionally increase their dosage or length of time administered in order to ease discomfort. This may be due to a lack of
awareness or poor pharmacy/health professional advice (Ford & Good, 2007; Hughes et al., 1999). The second cohort are opiate dependent and use codeine to manage withdrawals when unable to secure either heroin or prescribed methadone (Heard et al., 2006; National Council on Patient Information & Education, 2002; Reed et al., 2011; Roumie & Griffin 2004).

The prevalence of this public health issue remains unclear, with rates of dependence on pharmaceutical drugs such as codeine used for pain management lower than expected (Dobbin & Tobin, 2008; Fishbain, Cole, Lewis, Rosomoff & Rosomoff, 2008). Quantitative studies have found that individuals dependent on codeine are young and rate their health poorer than non-dependent users, report chronic pain, and represent greater numbers of females, when compared with other groups of opioid dependent individuals (Nielsen et al., 2011; Sproule, Busto, Somer, Romach, & Sellers, 1999). Nielsen et al. (2011), in their web survey of individuals self-reporting over the counter codeine use in Australia, reported that codeine dependent individuals differed from non-dependent users as follows; consumption of well above the recommended dose of over the counter codeine, for longer periods of time, younger, lower levels of employment and education, and with family history of substance dependence. This study also observed differences with other populations of opioid dependents.

More recently, three distinct types of codeine dependent users were identified using DSM-IV criteria for substance dependence. This ‘hidden’ population of codeine users includes those with ‘iatrogenic’ dependence following medical use of codeine for pain, anxiety or insomnia over time (Nielsen et al., 2010). Pseudo-addiction is defined as the under-treatment of pain (Bell & Salmon, 2009). An identified ‘blurring between therapeutic and problematic use’ serves to compound the individual’s problematic codeine use, particularly when opioid withdrawal symptoms are experienced, and individuals consume codeine to self-medicate (Nielsen et al., 2010).

The three subtypes of codeine dependent user are:

(1) **Therapeutic dependence**
This type of user is characterised by not exceeding therapeutic doses but still demonstrates features of codeine dependence and often having a picture of worsening pain. Some are consistent with descriptions of medication overuse headache.

(2) **Non-medical/recreational users:**
This type of user is characterised by use that is specifically for the euphoric effects of codeine. This group usually seeks and shares knowledge to reduce harms.

(3) **High dose dependence:**
This type of user is characterised by the use of high doses (multiple packets per day) and experiencing serious adverse effects from their use. Their use almost always stems from therapeutic use with users often having limited insight into their dependence for an extended period of time.
In some cases, use began for therapeutic use and escalated rapidly once euphoric effects of codeine were experienced. Of note, pharmaceutical dependence on codeine can occur following long term prescribed use and in the absence of intentional misuse (for example for pain), and in illicit drug users as substitute medication (for example heroin) (Barrett et al., 2008). Estimations of this public health issue remain cloudy, with rates of dependence on pharmaceutical drugs used for pain management lower than expected (Dobbin & Tobin 2008; Fishbain et al., 2008). A qualitative study conducted in the UK (Cooper, 2013b) described over the counter medicine dependents as aware of their addiction, but not identifying with the stereotypical drug user. They also reported self-blame in losing control over the medicine taken initially for medical use. Codeine contained in combination products was the main medicine used, and with subsequent use characterised by internet and multiple pharmacy sourcing, and centring on the opiate effect (‘the buzz’).Withdrawals were described, along with work and health problem inversely related to dosage, and concerns centred on standard forms of treatment available for opiate addicts.

1.6.3 Factors leading to misuse of codeine
A range of pharmacological, physiological, social and economic harms are associated with over the counter medicine misuse (Cooper, 2013). Misuse is related to the increasing dose of codeine, which increases abuse potential and likelihood of adverse effects, even when combined with safer analgesics such as paracetamol. The relationship between the misuse of over the counter medicines such as codeine containing products such as Nurofen Plus (ibuprofen and codeine) and illicit drug use, and the diversion of codeine to street drug markets has been reported in several studies (Levine, 2007; Matheson et al., 2002; Reay, 2009; Sproule et al., 1999). Motives for use range from self-treatment for physical or emotional pain consistent with intended uses, to recreational and problematic drug use (Boyd, McCabe, Cranford, & Young, 2006; Boyd & McCabe, 2008; Compton & Volkow, 2006a, b; Daniulaityte et al., 2006; Lankenau et al., 2007; McCabe, Cranford, Morales, & Young, 2006; McCabe & Teter, 2007; Teter et al., 2006, 2005; Volkow & Swanson, 2003) with greater prevalence of recreational motives among men (McCabe, Boyd, & Teter, 2009).

Repeated administration of codeine in the absence of pain causes tolerance and dependence (Derry et al., 2013). A Canadian study reported that codeine dependents are more likely to report chronic pain, and likely to use codeine for its pleasurable effect, to relax or reduce stress. Over half the sample reported using over the counter products with average doses of 179mg per day, and 80% of the sample reported using codeine 5 or more days per week (Sproule et al., 1999). In Frei’s study (Frei et al., 2010), individuals reported consuming between 435 and 602mg of codeine phosphate and 6800 to 9400mg of ibuprofen, and most had no previous history of substance use disorder.

Continued use can occur in response to withdrawals in the case of physical dependency on codeine and which include classic opiate dependence.
symptomatologies albeit less severe than with morphine such as cravings, preoccupation with seeking and taking codeine, lack of control of consumption patterns despite negative side effects, insomnia, restlessness, runny nose, stomach pains, diarrhoea and chills (Cooper, 2013b). Dependence has been reported in prescribed analgesics containing codeine (McBride & Meredith-Smith, 1995), with risk of dependence low in over the counter codeine preparation if taken as directed (Cooper, 2013b). Individuals with codeine dependence often commence codeine use in an effort to manage pain (Frei et al., 2010; Tennant & Rawson, 1982; with others describing ‘chemical coping’ in the case of codeine use for stress (Nielsen et al., 2010). That said, according to Pates et al. (2002), a “discrete group of possibly dependent users who may fail to seek help” due to a lack of identification of their use as potentially problematic may, nevertheless be aware of their increased use

1.6.5 Behavioural indicators of codeine misuse
Behavioural indicators of misuse and diversion of pharmaceuticals containing codeine include requesting certain drugs, hoarding of medications, use of multiple doctors and pharmacies, forging prescriptions, selling prescription opioids, stealing prescription opioids from other patients, injecting formulations, sourcing on the street, concurrent abuse of other licit and illicit drugs, multiple unsanctioned dose escalations, and repeated lost or stolen prescriptions (Chou et al., 2009; UNODC, 2011). As a result, health professionals may become unintentionally involved in diversion (Sheridan & Butler, 2008).

1.7 Conclusion
Codeine is an opiate widely used in the management of pain, cough and diarrhoea. It is prescribed by healthcare professionals on prescription and can also be bought over-the-counter in pharmacies. Its opiate analgesic effect means that there is potential for misuse, abuse and dependence and is becoming a global concern. The purpose of this scoping review is to map what is known about codeine with regard to regulation, production, distribution, prevalence, prevention and consequences of use. The next chapter outlines the methods used for this review.
Chapter 2

Methods

2.1 Introduction
This chapter outlines the methods used for this scoping review of codeine use, misuse and dependence. A key objective of the review was to map key concepts underpinning this area of study as situated within medical, pharmacy and treatment practices. This work was undertaken by a team of researchers from both academic and pharmacy practice backgrounds that were recruited to the CODEMISUSED project.

2.2 Approach
Scoping study methods are increasingly common and used for broad searching of literature on a specific topic (Arksey & O’Malley, 2005; Daudt et al., 2013; Levac et al., 2010). The scoping review was guided by Arksey & O’Malley’s framework using six stages (Arksey & O’Malley, 2005). Figure 2.1 (flow diagram) on the following page represents the broad framework used.

2.3 Methods
A broad search was conducted in order to achieve a comprehensive scope of the field (Daudt et al., 2013). Databases searched included PubMed, EBSCO Host, Science Direct, EMBASE, PsycINFO, Cochrane library and Medline from 1994 to 2014. Search terms used were in English and included: codeine; dihydrocodeine; opiate medication; opioid misuse/abuse/diversion/addiction; opioid dependence; over the counter codeine/medicine; analgesics; prescription opioids; self-medication; pain; pharmacy; medical; treatment’. Follow up search strategies included hand searching, searching of pharmaceutical, health, medical, drug related websites, and contacting key organisations such as the World Health Organisation (WHO), International Narcotics board (INCB) European Medicines Agency (EMA), European Monitoring Centre for Drugs and Drug Abuse (EMCDDA), authorised medicine boards in each of the European membered states, The Federal Drugs Agency (FDA) USA, the Canadian pharmacy authority, and the National Health Service (NHS) in the UK.

A spreadsheet was created to chart relevant data (data collection categories included author, setting, study aim and design/intervention, sample size, and results/outcomes), to enable the identification of commonalities, themes, and gaps in the literature. No restrictions were placed on inclusion so long as the article reported the results of research (collecting qualitative or quantitative data) or other systematic enquiry into the use or misuse of codeine. Two reviewers independently screened titles and abstracts to determine inclusion status. A second screen of the full-text of each article, again by two independent reviewers, ensured that the studies were relevant to the focus of the review and, through a charting exercise (as per Levac et al. 2010),
identified the specific areas of the review to which they could contribute and extracted article data manually into a database. Disagreements were resolved through discussion.

A hand search of reference lists from published peer reviewed studies was also undertaken. Articles beyond the search years (1995-2013) were reviewed to establish their relevance to the review.

Inclusion and exclusion criteria were set to determine the relevance of the literature with regard to the aim and objectives of the review.

**Inclusion criteria**
- Research studies of prevalence or incidence of prescribed and over the counter codeine use, misuse, abuse, diversion, treatment and dependence in adult populations.
- Research studies that describes the tampering of codeine containing medicines.

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**Figure 2.1** - Framework utilised in the scoping review (adapted from Arskey & O’Malley, 2005)
• Reports of interventions for the treatment of codeine dependence.
• Reports of pharmacy based interventions for codeine use and misuse.
• Research studies of at risk groups and other illicit drug users that use, misuse or is dependent on codeine.
• Research studies which examine the effectiveness of codeine in pain management
• Research studies examining pharmacovigilance, pharmacodynamics and pharmacokinetics with particular reference to codeine.
• Literature in relation to the sale, consumption and manufacture of codeine.
• Policy documents on the scheduling of codeine medicines products.
• Policy documents and guidelines with a particular reference to codeine.

Exclusion criteria
• Anecdotal and opinion based literature about prescribed and over the counter codeine use, misuse, abuse, diversion, treatment and dependence in adult populations.
• Literature not available in English.
• Articles where full text was not available.
• Empirical studies examining codeine in animal populations.

Two researchers screened literature titles and abstracts to determine their inclusion status. Full text articles were reviewed and screened by two independent researchers to ensure they met the inclusion criteria. Full text articles were placed in a shared file by author, year and title of study to avoid duplication. References were managed by the citation manager Endnote®. This software facilitated the recording and organisation of all relevant literature. This allowed the cross checking of data records, removal of duplicates and extraction of information from the papers included in the review.

Initial screening identified a total of 3,105 articles, of which 475 met the inclusion criteria. They were manually uploaded onto the shared folder and the Endnote database. Eight broad categories were identified to assist in the organisation of the literature and data extraction - see Table 2.1.

Table 2.1- Broad categories used to organise literature included in the review

<table>
<thead>
<tr>
<th>Categories relating to codeine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production, manufacture, consumption and regulation of codeine</td>
</tr>
<tr>
<td>Characteristics and profiles of codeine users</td>
</tr>
<tr>
<td>Therapeutic use of codeine within healthcare</td>
</tr>
<tr>
<td>Prevalence of codeine use, overuse, misuse and dependence</td>
</tr>
<tr>
<td>Prevention of codeine overuse, misuse and dependence.</td>
</tr>
<tr>
<td>Consequences of codeine use/misuse(health and society)</td>
</tr>
<tr>
<td>Over the counter and internet sale of codeine medication</td>
</tr>
<tr>
<td>Interventions and treatment for codeine misuse</td>
</tr>
</tbody>
</table>
The following information was extracted for each paper included in the review and tabulated: author; year; country of origin; study aims; methodology; sample size and setting; outcome measures; results and author's conclusions and specificity to codeine. Data was extracted for each paper by a single researcher and checked by a second researcher to ensure that data extraction was accurate and comprehensive. A qualitative synthesis of the literature was carried out within categories and sub-categories.

A stakeholder consultation stage from addiction, nursing, psychiatry, psychology, health, pharmacy, drug control and pharmacovigilent backgrounds (Arksey & O’ Malley, 2005; Daudt et al., 2013; Levac et al., 2010) with CODEMISUSED partners and the CODEMISUSED Expert Panel was undertaken and contributed to extraction of multifaceted perspectives from the extant literature on codeine throughout the review process.

2.4 Results of the search

*Figure 2.2* presents the flow diagram for the literature included in and excluded from the review.
2.5 Conclusion
This chapter outlined the methods used for the scoping review. Arksey & O'Malley’s framework using six stages was used to guide this process. The findings were synthesized under seven broad categories as outlined in table 2.1. The stages of this scoping review were similar to that of a systematic review, in that our search and review efforts aimed to achieve systematic selection, retrieval and synthesis of extant knowledge within a broad thematic remit (Mays, Roberts, & Popay, 2001). The process of navigating and redefining the findings was iterative, and we engaged with each stage in a reflexive manner, by fine tuning and repeating steps so as to ensure comprehensive synthesis of literature.
Chapter 3
Production, Manufacture, Consumption and Regulation of Codeine

3.1 Introduction
This chapter reports on the global production, manufacture, consumption and regulation of codeine. The reported figures are taken directly from the statistics produced by the International Narcotics Control Board (INCB) (INCB, 2012; INCB, 2013). Figures quoted are in metric tonnes.

3.1.1 Definition of terms
The following are definitions of terms as outlined by the INCB:

- **Consumption**: - act of supplying a narcotic drug to any person or enterprise for retail distribution, medical use or scientific research.
- **Utilisation** – refers to the use of codeine for the manufacture of other drugs.
- **Drug** - substances included in Schedules I or II of the 1961 Convention, whether natural or synthetic.
- **Manufacture**- all processes, other than production (see definition below) by which drugs may be obtained and includes refining as well as the transformation of drugs into other drugs.
- **Preparation** - any mixture, solid or liquid, subject to international control owing to the fact that it contains a drug under international control. Preparations listed in Schedule III of the 1961 Convention are exempted from some control measures (when compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations).
- **Production** - refers to the separation of opium, coca leaves, cannabis and cannabis resin from the plants from which they are obtained.
- **Stocks** - refers to the amounts of drugs held in a country or territory for domestic consumption, manufacture of other drugs or export.

3.2 Global stocks and requirements
In 2010, the global stock of codeine was 173 tonnes, with approximately 59% being held by five countries (United States, United Kingdom, Australia, France and India). Similarly for 2011, global stocks of codeine were 176 tonnes with 56% (approximately) of this global stock being held by four countries United States (36 tonnes); United Kingdom (25 tonnes); France (19 tonnes) and India (18 tonnes) - see figures 3.1 & 3.2. Fourteen other countries held quantities of codeine greater than 1 ton and included Australia, Japan, Canada, Hungary, Romania, Norway, Switzerland, Spain, Germany, South Africa, Italy, Russia, China and Turkey (INCB, 2012).
Table 3.1 presents the estimated world requirements of codeine and dihydrocodeine in grams for 2013 for Europe and other countries with high global stock requirements (INCB, 2013).

*Figure 3.1 – Major stockists (countries) of codeine 2010-2011*

Table 3.1 – Codeine and dihydrocodeine estimated requirements in grams 2013

<table>
<thead>
<tr>
<th>Country</th>
<th>Codeine (grams)</th>
<th>Dihydrocodeine (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albania</td>
<td>35 000</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>9 800 000</td>
<td>285 000</td>
</tr>
<tr>
<td>Austria</td>
<td>500 000</td>
<td>650 000</td>
</tr>
<tr>
<td>Belgium</td>
<td>4 700 000</td>
<td>482 000</td>
</tr>
<tr>
<td>Belarus</td>
<td>3 000 000</td>
<td></td>
</tr>
<tr>
<td>Bosnia and Herzegovina</td>
<td>78 000</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>3 600 001</td>
<td>1 000</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>4 000 000</td>
<td>40 000</td>
</tr>
<tr>
<td>Canada</td>
<td>29 231 000</td>
<td>200</td>
</tr>
<tr>
<td>China</td>
<td>10 400 000</td>
<td>450 000</td>
</tr>
<tr>
<td>China -Hong Kong</td>
<td>4 501 000</td>
<td>6 001</td>
</tr>
<tr>
<td>Croatia</td>
<td>205 000</td>
<td></td>
</tr>
<tr>
<td>Cyprus</td>
<td>35 000</td>
<td>1 000</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1 080 000</td>
<td>10</td>
</tr>
<tr>
<td>Denmark*</td>
<td>1 000 000</td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>450 000</td>
<td>3 000</td>
</tr>
<tr>
<td>Country</td>
<td>Acc. to 2011</td>
<td>1992</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------</td>
<td>------</td>
</tr>
<tr>
<td>Estonia</td>
<td>300</td>
<td>500</td>
</tr>
<tr>
<td>Finland</td>
<td>1 230 000</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>30 100 000</td>
<td>1 000</td>
</tr>
<tr>
<td>Germany</td>
<td>6 010 001</td>
<td>96 500</td>
</tr>
<tr>
<td>Greece*</td>
<td>700 000</td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>12 220 000</td>
<td>1 510 000</td>
</tr>
<tr>
<td>Iceland</td>
<td>130 000</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>65 000 000</td>
<td>1 100 000</td>
</tr>
<tr>
<td>Ireland</td>
<td>5 500 500</td>
<td>601 000</td>
</tr>
<tr>
<td>Italy</td>
<td>14 000 000</td>
<td>1 000 000</td>
</tr>
<tr>
<td>Japan</td>
<td>15 230 000</td>
<td>12 515 000</td>
</tr>
<tr>
<td>Latvia</td>
<td>301</td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Luxembourg</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Malta</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Montenegro</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>New Zealand</td>
<td>1 681 300</td>
<td>360 000</td>
</tr>
<tr>
<td>Norway</td>
<td>3 908 600</td>
<td>1</td>
</tr>
<tr>
<td>Poland</td>
<td>1 550 000</td>
<td>60 000</td>
</tr>
<tr>
<td>Portugal</td>
<td>450 000</td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>250 000</td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td>1 214 890</td>
<td>237 831</td>
</tr>
<tr>
<td>Serbia</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Slovenia</td>
<td>40 240</td>
<td>21 001</td>
</tr>
<tr>
<td>Slovakia</td>
<td>3 386 215</td>
<td>500</td>
</tr>
<tr>
<td>Spain</td>
<td>8 200 000</td>
<td>50 000</td>
</tr>
<tr>
<td>South Africa</td>
<td>10 860 000</td>
<td>395 000</td>
</tr>
<tr>
<td>Sweden</td>
<td>714 000</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>2 200 000</td>
<td>25 001</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>76 887 000</td>
<td>2 630 000</td>
</tr>
<tr>
<td>United States of America</td>
<td>83 201 856</td>
<td>90 000</td>
</tr>
<tr>
<td>Ukraine</td>
<td>4 693 342</td>
<td></td>
</tr>
</tbody>
</table>

**3.3 Global consumption**

Globally, the demand for codeine remains high and has risen by approximately 27% over the last decade. Recent reported figures estimate that consumption reached an all-time high at 269 tonnes in 2011 and compares to 164 tonnes in 1992 (INCB, 2012). Approximately 225 tonnes and 240 tonnes of codeine were consumed in 2008 and 2007 respectively. Codeine remains the second most widely administered opiate in medical practice and its total defined daily dose (assumed average maintenance dose per day for a drug used for its main indication in adults) is recorded at 2.7 billion (S-DDD) (INCB 2012). (Figure 3.2 – below details the emerging trend of codeine consumption over the years 2007-2011).
3.4 Global manufacture, exports and imports

It is estimated that approximately 90-95% of codeine manufactured globally is obtained from morphine through a semi-synthetic process. Codeine is mainly used for the manufacture of preparations under schedule III of the 1961 convention and to a lesser extent for the manufacture of dihydrocodeine and hydrocodone. Preparations listed under Schedule III accounts for 99% of the consumption of codeine (INCB, 2012). Codeine manufacture reached a peak of 381 tonnes in 2011 compared to 349 tonnes in 2007 (INCB, 2012).

In 2011, figures highlight that the UK was the highest codeine manufacturer (85 tonnes representing 22% of global manufacture); followed by France (78.3 tonnes - 21%); United States (64.6 tonnes - 17%) and Australia (31.9 tonnes - 8%). Figure 3.3 shows the global manufacture by tonnage for the four main countries in 2011.

World exports of codeine have continued to rise reaching 168.4 tonnes in 2011, highest level ever recorded. This figure is up from 160 tonnes in 2010 and almost double from the previous decade. France was the principal exporter of codeine at 28% (46.8 tonnes). Australia was the next leading exporter (16% - 26.3 tonnes), followed by the UK (13% - 21.1 tonnes) and Iran (10% - 16.8 tonnes).

The main countries importing codeine in 2011 were India (48.9 tonnes), Canada (20.2 tonnes), Switzerland (13 tonnes) and Germany (9 tonnes) – see figures 3.4 and 3.5.
Figure 3.3 – Global manufacture of codeine in 2011 (tonnes)
3.5 Codeine utilisation

Sixty eight percent (68%) of codeine used for the manufacture of schedule III drug preparations in 2011 was listed in six countries (India, UK, France, Iran, US, and Canada). It should be noted that utilization of codeine does not indicate consumption of these preparations. The major manufactures were India (50.3 tonnes) and the UK (50 tonnes). Each country has seen a rise in utilisation since 2010 with a 3.6% increase in manufacture in India, 2.9% (Iran), 1.7% (US) 1.6% (France) 1.4% (UK), and 0.2% (Canada). Figure 3.6 highlights codeine utilisation in 2010 for manufacture of preparations listed in Schedule III of the 1961 convention.

Utilisation of codeine for other preparations such as dihydrocodeine and hydrocodone has declined since 2007 (81.8 tonnes). In 2010, utilisation decreased to 52.6 tonnes but increased to 62.3 tonnes in 2011. The main reason was for the manufacture of hydrocodone in the US in 2011 (30.1 tonnes), 2010 (25.4 tonnes)), while the remaining was used for the manufacture of dihydrocodeine in Japan, the UK and Italy (INCB, 2012).
3.5.1 Utilisation, exports, imports and stocks of codeine in Ireland, South Africa and UK

This section presents data in relation to codeine utilisation for the manufacture of schedule III preparations and other drugs, exports, imports and stocks for each of the three participating countries (Ireland, South Africa and UK) for the past five years. The information presented is in response to a communication with the INCB (Stefano Berterame, Chief, Narcotics Control & Estimates Section, personal communication to Professor Charles Parry).

Over this five year period there was a decrease of just over 1 tonne (metric) in the utilisation of codeine in the manufacture of schedule III preparations in Ireland, while utilisation increased by over 1 metric tonne in South Africa and 18 metric tonnes in the UK - see figure 3.7.
Figure 3.7 - Quantity utilized for manufacture of preparation 2008-2012

Utilisation of codeine for preparation of other drugs was only recorded in the UK. While there have been some fluctuations in use recorded over the 5 year period, it remains at just over 12 metric tonnes - see Figure 3.8.

Figure 3.8 – Quantity utilized for the manufacture of other drug (UK 2008-2012)

UK imports for codeine showed significant fluctuations between 2008-2012, peaking at just under 14.5 metric tonnes in 2010. South Africa has seen limited importation at just 0.248kg in 2008 and zero in 2012. In Ireland imports have slightly decreased from 5.5 metric tonnes in 2008 to 3.9 metric tonnes in 2012. Figure 3.9 highlights codeine imports for each country in Kgs
Figure 3.9- Imports of Codeine 2008-2012

![Codeine Imports 2008-2012](image)

Codeine exports were highest in the UK ranging from over 26 metric tonnes in 2008 to 33.6 metric tonnes in 2012. Ireland’s exports of codeine peaked in 2008 at 67kg and have seen a sharp decrease since. Exports of codeine are rising in South Africa, but are significantly less than the UK at just 2.2kg in 2012. Figure 3.10 presents the exports of codeine from 2008-2012.

Figure 3.10 – Exports of codeine 2008-2012

![Exports of Codeine 2008-2012](image)

The total codeine stock held between all three countries in 2012 was 25.5 metric tonnes, with the UK holding the majority share. In 2012, Ireland held 571Kg of codeine stock with South Africa and the UK each holding 4.9 and 20 metric tonnes respectively. Figure 3.11 details the codeine stock in each of the countries from 2008-2012.

![Codeine Stock 2008-2012](image)
3.6 Over-The-Counter consumption of codeine preparations

Over the counter sales of codeine containing medications is not easy to determine due to commercial sensitivity, trade exemptions or where such disclosure of information might prejudice the commercial interests of any person or public authority. The major pharmaceutical manufacturing companies were contacted\(^5\) (Adlock Ingram, Johnson & Johnson, Sanofi, Glaxosmithkline, Pharagen, Teva) and requested to provide approximate figures for their sales of over the counter codeine products. All declined and quoted ‘commercial sensitivity’. IMS healthcare were also contacted but a subscription to this service was required.

UK market figures indicate that the over the counter drug market is worth over 553.3 million sterling, with adult analgesia accounting for approximately 350 million of all over the counter sales (PAGB, 2012). Walker, Evans and Meacham (2009) examined physical dependence and addiction to prescription and over the counter medication in Wales (UK) and obtained data from IMS health (Institute for Healthcare Informatics) on the consumption of 3 particular drugs: Nurofen plus® (ibuprofen 200mg + codeine 12.8mg), Solphadine plus® and Ultamo® (paracetamol 500mg, 8mg codeine) across 628 of the 714 pharmacies in Wales (Walker et al., 2009). Mean sales figures for Nurofen® during 2005-2008 was shown to be 6 packs per 1000 of the population, however some areas in Wales reported sales as high as 18 packs per 1000. Solpadeine Plus® and Soluble Ultramol had a mean number of packs at 24 per 1000 of the population based on the combined figures of 2005-2008. In one district of Wales - Blaenau Gwent in 2008, sales of these products was 400 packs per 1000 population.

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\(^5\) Contact was made by members of the CODEMISUSED team during November and December 2013
An attempt to quantify the sales of codeine by number of tablets or capsules per carton was carried out in England (Reed et al., 2011). The Propriety Association of Great Britain, the UK trade association for manufacturers of branded over-the-counter medicines and food supplements provided sales figures. These figures do not reveal how the medicines were used when sold but they do provide a useful indicator of the overall extent of use in the UK during this period. Table 3.2 was reproduced with permission from the Propriety Association of Great Britain. It should be noted that these data are prior to the introduction of restrictions on over the counter codeine in the UK. It is now permissible to sell only a maximum supply of 32 tablets in any single transaction.

Table 3.2 – The sales of over the counter codeine preparations

<table>
<thead>
<tr>
<th>Sales of codeine products by number of tablets or capsules per carton (Propriety Association of Great Britain 2009) (Reproduced with permission)⁶</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pack size (no. of tablets)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>392,748</td>
<td>303,360</td>
<td>297,718</td>
</tr>
<tr>
<td>12</td>
<td>2,621,434</td>
<td>1,844,933</td>
<td>1,229,799</td>
</tr>
<tr>
<td>16</td>
<td>263,767</td>
<td>1,298,902</td>
<td>1,577,164</td>
</tr>
<tr>
<td>20</td>
<td>1,809,488</td>
<td>1,610,965</td>
<td>1,486,898</td>
</tr>
<tr>
<td>24</td>
<td>3,126,146</td>
<td>1,690,097</td>
<td>1,346,093</td>
</tr>
<tr>
<td>30</td>
<td>2,536,960</td>
<td>2,580,571</td>
<td>2,680,489</td>
</tr>
<tr>
<td>32</td>
<td>5,390,315</td>
<td>10,604,674</td>
<td>11,152,623</td>
</tr>
<tr>
<td>48</td>
<td>734</td>
<td>327</td>
<td>240</td>
</tr>
<tr>
<td>60</td>
<td>2,128,283</td>
<td>125,117</td>
<td>5,980</td>
</tr>
<tr>
<td>100</td>
<td>1,328,271</td>
<td>1,385,378</td>
<td>1,467,327</td>
</tr>
<tr>
<td>Total</td>
<td>19,598,146</td>
<td>21,444,324</td>
<td>21,244,331</td>
</tr>
</tbody>
</table>

3.7 Regulation of Codeine

Codeine is a listed narcotic drug held under international control and regulated by the regulatory authority of medicines in individual countries. Pure Codeine is listed under Schedule II, of the 1961 convention on Narcotic drugs. However, most codeine products are classified under Schedule III due to being compounded with one or more other ingredients and not containing more than 100 milligrams of the drug per dosage unit with a concentration of not more than 2.5 per cent in undivided preparations (INCB, 2011).

Codeine preparations classified under Schedule III are pharmacy only. Under this schedule a prescription is required and must include full details of the form and strength of the preparation and the total quantity written in both 

⁶ Sales of codeine products by number of tablets or capsules per carton (Propriety Association of Great Britain 2009) (Reproduced with permission) Pack size (no. of tablets) (Reed et al. 2011)
words and figures. It is the ‘prescribers’ responsibility to minimise the risk of dependence and quantities of drugs should match the likely needs of the patient until their next clinical review.

Under Schedule III there is no requirement to keep controlled registers. In some countries codeine preparations are available without prescription in combination preparations (paracetamol, ibuprofen or aspirin) from licensed pharmacies in doses up to 12.8 mg of codeine phosphate. Concentrations of up to 28mg are permissible in some countries under pharmacy supervision. Over the counter (OTC) sales of products containing codeine generally must be supervised by the pharmacist. Some countries restrict the visual display and advertisement of over the counter codeine preparations to the consumer.

New regulations restricting the prescribing of codeine preparations to children are now in place. Codeine is now contraindicated in children (less than 18 years) undergoing surgical removal of tonsils or adenoids, in ultra-rapid cytochrome CYP2D6 metabolizers and breastfeeding women. The use of codeine is not recommended in children whose respiratory function may be compromised by respiratory conditions, trauma or extensive surgical procedures and should only be used where benefits outweigh the risks (EMA, 2013).

Table 3.3 details the scheduling of codeine across the EU, Australia, Canada, United States of America, Asia and South Africa. This information is taken from a number of sources. Information obtained through direct communications with the medicines agencies in the listed countries is indicated by a reference. The country, regulatory agency and regulation of over the counter and prescription codeine are detailed. Dihydrocodeine is listed where data were available.
### Table 3.3 – Regulation of codeine, over the counter (over the counter) and prescribed (including dihydrocodeine)

<table>
<thead>
<tr>
<th>Country</th>
<th>Regulatory agency</th>
<th>Over the counter preparations (over the counter) codeine/dihydrocodeine preparations sold in pharmacies</th>
<th>Prescription only medicine (POM) codeine/dihydrocodeine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Australia</strong></td>
<td>Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).</td>
<td>Preparations fewer than 12.5mg of codeine less than 5 days can only be sold under pharmacist’s supervision. Cannot be advertised directly to the consumer. Labelled with a recommended total daily dose of up to 100mg codeine (128 mg codeine phosphate).</td>
<td>POM when containing more than 5 days treatment and greater than 12mg of codeine (15.4mg codeine phosphate) per dosage unit. Labelled with a recommended total daily dose of up to 100mg codeine (128 mg codeine phosphate). Preparations containing pure codeine (e.g., codeine phosphate tablets or codeine phosphate linctus are considered controlled drug (CD) (Controlled Drug (Possession without authority is illegal)).</td>
</tr>
<tr>
<td><strong>Austria</strong></td>
<td>Austrian federal office for safety in Healthcare.</td>
<td>Generally not sold as an over the counter product but some provincial and municipal relegation which allows cities and provinces to regulate the selling of least regulated schedule of drugs as defined by the substance narcotic law. Pharmacy is self-regulating and can control sale and item quantities.</td>
<td>Dispensing of products containing codeine and similar drugs, dihydrocodeine, requires a prescription order from a doctor or the discretion of the pharmacist. Plain codeine hydrochloride tablets are controlled drugs as well as other non-injectable forms of codeine and must be dispensed in this way.</td>
</tr>
<tr>
<td><strong>Belgium</strong></td>
<td>Federal agency for medicine and health products.</td>
<td>Not sold as an over the counter medicine.</td>
<td>As of the 17 June 2013, all medicines containing codeine or codeine derivatives can only be issued on a medical prescription.</td>
</tr>
<tr>
<td><strong>Bulgaria</strong></td>
<td>Bulgarian drugs agency</td>
<td>Sold as an over the counter in combined preparations. Main products include Aceffeine® tablets (250mg paracetamol/250mg Acetylsalicylic acid/10 mg codeine phosphate/50mg caffeine Solpadeine® caps/soluble 8mg codeine phosphate/500mg paracetamol/30mg caffeine Paracofda® tablet – 200mg paracetamol/300mg metamizole sodium/20mg codeine phosphate/caffeine 30mg Caffetine forte® - 250mg paracetamol/210 mg propyphenazone /10 mg codeine phosphate and 50mg Caffeine. Products can be displayed in the pharmacy and sold without pharmacist’s supervision. There is no restriction on the number of tablets sold but must include warning of addiction.</td>
<td>Prescription only medicine in higher doses usually 30mg of codeine phosphate. Other product Sedalgin – neo ® 300mg paracetamol/150mg metamizole sodium/10mg codeine phosphate/15mg phenobarbital/50mg caffeine. No pure codeine products available in Bulgaria.</td>
</tr>
<tr>
<td><strong>Canada</strong></td>
<td>National Drug Scheduling Advisory Committee.</td>
<td>Over the counter codeine combination products available up to 8mg or its equivalent of codeine phosphate per tablet or per unit in other solid form or not more than 20 mg or its equivalent of codeine phosphate per 30 mL in a liquid preparation. Products may not be displayed and must be kept out of view of the consumer. No pharmacist shall sell or provide a preparation if the pharmacist has reasonable grounds to believe that the preparation is to be used</td>
<td>Stronger doses of greater than 8mg of codeine phosphate must be prescribed by a medical practitioner. Non-compounded Codeine is a schedule one drug in Canada and can only be prescribed by a medical professional.</td>
</tr>
<tr>
<td>Country</td>
<td>Organisation</td>
<td>Codeine availability</td>
<td>Codeine restrictions</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------------------</td>
<td>----------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>China - Hong Kong</td>
<td>Pharmaceutical service – Department of Health (HK)</td>
<td>Over the counter</td>
<td>Regulated under Schedule 1 of Hong Kong's Chapter 134 <em>Dangerous Drugs Ordinance</em>. It can be used legally only by health professionals. Must only be dispensed as a prescription item. Anyone who supplies the substance without a prescription or traffics the drug can be fined and or jailed.</td>
</tr>
<tr>
<td>Croatia</td>
<td>Agency for medicinal products and medical devices of Croatia</td>
<td>Not sold as an over the counter medicine.</td>
<td>Codeine containing medicines are available on prescription only. 3 main medicines available, Caffetin®, Codeine phosphatis and Plivadon®.</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>State Institute for drug control</td>
<td>Not sold as an over the counter medicine.</td>
<td>All codeine containing products are medical prescription drugs only.</td>
</tr>
<tr>
<td>Denmark</td>
<td>Danish health and medical authority</td>
<td>Sold as an over the counter medicine as combination products up to 9.6mg of codeine.</td>
<td>Prescription only medicine in preparations greater than 9.6mg.</td>
</tr>
<tr>
<td>Estonia</td>
<td>State agency of medicines</td>
<td>Sold as combination drug up to 8mg of codeine. 2 main products Co-Codamol® (codeine phosphate paracetamol 8/500) and Solpadeine® (codeine phosphate, paracetamol codeine 8/500/30).</td>
<td>Prescription only above a concentration of 8mg of codeine phosphate. 30/500 codeine phosphate/paracetamol combination, 30/400 codeine/ibuprofen combination. 1 dihydrocodeine product licenced containing 60mg of active drug.</td>
</tr>
<tr>
<td>Finland</td>
<td>Finnish medicines agency</td>
<td>Over the counter codeine preparations are not sold in Finland</td>
<td>10 codeine preparations licenced for use. Combination products with paracetamol (Pamol®, Paraceon® (500/30mg) and ibuprofen® (30mg/400) is only available on a medical prescription.</td>
</tr>
<tr>
<td>France</td>
<td>French national agency of medicine and health products safety</td>
<td>Over the counter codeine preparations sold as combinations under supervision at community pharmacies up to 20mg per dose. Thirteen analgesic formulations of drugs containing codeine can be requested without limit of duration of use. These drugs are placed behind the dispensing counter in the pharmacies, and patients must request them from a member of the pharmacy staff.</td>
<td>Combinations containing codeine over 20mg must be prescribed by a medical practitioner.</td>
</tr>
<tr>
<td>Germany</td>
<td>German central authority for health protection with regards to medicines products and medical devices</td>
<td>Generally not sold as an over the counter product but some provincial and municipal relegation which allows cities and provinces to regulate the selling of least regulated schedule of drugs as defined by the substance narcotic law. Pharmacy is self-regulating and can control sale and item quantities.</td>
<td>Dispensing of products containing codeine and similar drugs dihydrocodeine requires a prescription order from a doctor or the discretion of the pharmacist. Plain codeine hydrochloride tablets are controlled drugs as well as other non-injectable forms of codeine and must be dispensed in this way.</td>
</tr>
<tr>
<td>Greece</td>
<td>National organisation</td>
<td>Not sold as an OCT medicine.</td>
<td>Codeine is classed as an illegal drug in Greece and is a controlled drug. There is also strict regulation on importation. It is sold only with a prescription.</td>
</tr>
<tr>
<td>Country</td>
<td>Regulatory Authority</td>
<td>Codeine-containing Medications</td>
<td>Notes</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hungary</td>
<td>National Institute for quality and organisational development in healthcare and medicines.</td>
<td>Only 1 over the counter product sold called Erigon szirup (cough syrup).</td>
<td>All other codeine containing medications must be prescribed by a medical practitioner and dispensed by a pharmacist.</td>
</tr>
<tr>
<td>Iceland</td>
<td>Icelandic medicines agency.</td>
<td>Not sold as an over the counter product.</td>
<td>Preparations of paracetamol and codeine require a medical prescription in Iceland. Main products known as Parkódin® – codeine 10mg/paracetamol 500mg.</td>
</tr>
<tr>
<td>India</td>
<td>Central drug standards control organisation (CDSCO).</td>
<td>Not sold as an over the counter product.</td>
<td>Medicines containing codeine are only dispensed on prescription of Registered medical practitioner. There is a requirement to keep all documents, batch no., patient no and their address which required for auditing by drug inspector.</td>
</tr>
<tr>
<td>Ireland</td>
<td>Irish medicine board. Guided under the misuse of drugs act 1977.</td>
<td>Over the counter sales permissible in regulated pharmacies under supervision of the pharmacists without prescription. Usually in 8mg/500 and 12.8mg/500 combination drugs containing analgesics such as paracetamol and aspirin. Cannot be visually displayed or advertised to the consumer. Patient must be advised on its use at point of sale Must contain warning of addiction on pack.</td>
<td>Higher strength codeine formulations 15/300, 30/500 of codeine phosphate/paracetamol combinations are prescription only medicines. Codeine is also available combined with Ibuprofen; a common formulation is 12.8 mg Codeine alongside 200 mg Ibuprofen. Preparations containing pure codeine (e.g., codeine phosphate tablets is considered controlled drug (CD) (Controlled Drug (Possession without authority is illegal).</td>
</tr>
<tr>
<td>Italy</td>
<td>Italian Medicines Agency.</td>
<td>Not available over the counter.</td>
<td>Available on prescription for pain relief and cough.</td>
</tr>
<tr>
<td>Latvia</td>
<td>State Agency of Medicines of the Republic of Latvia.</td>
<td>Non-prescription medicinal products available over the counter Co-Codamol® 500 mg/8 mg tablets. Solpadeine® 500 mg/8 mg/30 mg tablets (effervescent and table). Sirupus Pini compositus syrup (Calcium lactate 64 mg, Codeine phosphate - 3 mg, Celandine liquid extract - 10 mg) Sirupus Tussipini (in 100 g syrup): Calcium lactate - 1 g, Codeine phosphate - 0.05 g, Celandine liquid extract, 0.16 g, Fennel tincture - 1 g, Pine liquid extract - 6.60 g.</td>
<td>Medical prescription required for all drugs over 8mg of codeine phosphate. No pure codeine products.</td>
</tr>
<tr>
<td>Malta</td>
<td>Medicines Authority of Malta.</td>
<td>Over the counter sales permissible in low doses less than 10mg of codeine per single dose. Must be sold in a pharmacy and under pharmacy supervision.</td>
<td>Higher dose require a medical prescription. If more than 100mg of codeine they are considered as controlled drugs with special prescription.</td>
</tr>
<tr>
<td>New Zealand</td>
<td>New Zealand Medicines and</td>
<td>Over the counter in doses less than 15 milligrams of codeine per solid dosage unit or per dose of liquid with a maximum daily dose</td>
<td>Prescription Only above 15mg of codeine phosphate and must be prescribed by a medical professional.</td>
</tr>
<tr>
<td>Country</td>
<td>Authority/Agency</td>
<td>Regulations and Restrictions</td>
<td>Notes</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Norway</td>
<td>Norwegian Medicine agency.</td>
<td>Over-the-counter sales of codeine are not permissible in Norway. Available on prescription only from a medical prescriber. Mainly supplied as combination formulations. Five common drugs include Codalgin®, Codaxol®, Paralgin®, Paramax® and Pinox®.</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>Main Pharmaceutical Inspectorate</td>
<td>Certain products are available over-the-counter in combination with other drugs. Maximum dose found in listed products is up to 20mg. Regulation states that codeine when compounded with one or more other ingredients and containing not more than 50 milligrams of the drug per dosage unit and with a concentration of not more than 1.5 per cent in undivided preparations are permissible. The pharmacist can refuse sales if it is considered that the health of the patient is endangered.</td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Medicines evaluation board.</td>
<td>Only one over-the-counter available <code>(Natterman Melrosum extra sterk stroop (RVS 03732)</code>: This cough suppressant product is in the category Pharmacy and Drugstore only (PDO) and must be under the supervision of the pharmacist. This product has low concentrate codeine (2.5mg). Products containing codeine/dihydrocodeine in the Netherlands are only available on prescription from doctor of specialist.</td>
<td></td>
</tr>
<tr>
<td>Russia</td>
<td>Russian medicines board.</td>
<td>Not available over-the-counter. All sales require a prescription.</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Spanish medicines agency.</td>
<td>Not available as an over-the-counter, but may be sold with discretion of the pharmacist. Medical prescription required.</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>South African medicines agency.</td>
<td>Over the counter preparations in combination with one or more therapeutically active substances, and containing 10 milligrams or less of codeine (calculated as base) per dosage unit. Pack sizes sold can contain up to 100 doses. Sold under supervision of the pharmacist. Sales of codeine containing products must be recorded in the pharmacy. POM medicine in doses over 10mg of codeine per dosage unit and are only available on medical prescription.</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Regulatory Agency</td>
<td>Sales Regulations</td>
<td>Additional Information</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sweden</td>
<td>Medical products agency</td>
<td>Over the counter sales of codeine are not permissible.</td>
<td>POM medicine only. 16 approved drug for use mainly in combination formulations with paracetamol and consisting of a dosage of 30mg/500. One combination product containing a lower dose of 15mg/500. Kodein Recip 25 mg tablet, is the only pure codeine containing drug which is classed as narcotic according to list III and is a controlled drug.</td>
</tr>
<tr>
<td>United Kingdom,</td>
<td>Medicine and healthcare products regulatory authority</td>
<td>Over the counter sales permissible in regulated pharmacies under supervision of the pharmacists without prescription. Usually in 8/500 and 12.8/500 combination drugs containing analgesics such as paracetamol and aspirin. Only 1 pack x 32 tablets allowed per customer transaction unless sanctioned by the pharmacist. Can be visually displayed and advertised to the consumer at the point of sale. Must contain warning of addiction on pack.</td>
<td>Higher strength codeine formulations 15/300, 30/500 of codeine phosphate/paracetamol combinations are prescription only medicines (POM). Codeine is also available combined with Ibuprofen; a common formulation is 12.8 mg Codeine alongside 200 mg Ibuprofen. Preparations containing pure codeine (e.g., codeine phosphate tablets) is considered a controlled drug (CD). (Possession without authority is illegal). No longer permitted for use under the age of 18 years (codeine containing linctus for cough).</td>
</tr>
<tr>
<td>United States of America</td>
<td>Federal drug Agency.</td>
<td>Federal regulations state that certain preparations containing not more than 200 milligrams of codeine per 100 millilitres or per 100 grams that also include a sufficient proportion of nonnarcotic active medicinal ingredients providing medicinal qualities beyond those possessed by codeine alone, are exempt from prescription requirements. Local regulation of over the counter codeine occurs in various states, with further detail found at <a href="http://www.nabp.net/boards-of-pharmacy/">http://www.nabp.net/boards-of-pharmacy/</a></td>
<td>Majority of codeine containing drugs are only available on medical prescription. Quantities over 90mg per single dose unit are list under the controlled drug schedule.</td>
</tr>
</tbody>
</table>

*Websites of each of the regulatory agencies for Human Medicines were accessed to retrieve information about the regulation and sale of codeine. Each regulatory agency was contacted individually by a member of the research team.*
Chapter 4
Prevalence Rates of Codeine Use, Misuse and Dependence and Associated Risk Factors

4.1 Introduction
This chapter explores prevalence in relation to codeine use, misuse and dependence and associated risk factors. The literature highlights a number of issues in relation to the prevalence of codeine use, misuse and dependence. These include paediatric use of codeine, codeine prescribed for pain, misuse of over the counter forms of codeine (i.e. Codeine Cough Syrups); codeine use in pregnancy, codeine products used to manufacture home-made drug solutions such as desomorphine and recreational use of codeine. This non-medical use of prescription opioids is associated with severe psychological distress and misuse of other medications, with tailoring of specific interventions for targeted high risk groups needed (Wang et al., 2013).

There is a gap in the evidence base in relation to the extent of inappropriate use of codeine, misuse and dependent use of over the counter analgesics containing codeine. For example, studies relating to codeine are often combined with general prescription opioid studies and therefore are not specific to codeine alone. We recommend greater education of codeine users about variations in metabolism, and risks of long term use, risks associated with polypharmacy intake to challenge the widely held but misinformed perception that codeine based products are low risk in terms of their potential for dependence. Greater concentration of policy and practice focus on prevention, referral and support strategies for those who are at risk of or are currently problematic opioid users is required.

4.2 Prevalence of codeine use
EU prevalence data on codeine use, misuse and dependence is at present confined to French and Norwegian studies, and it is not known whether prevalence rates are similar in other European countries (Casati et al., 2012; Fredheim et al., 2009). Sales trends of opioid analgesic drugs like codeine in nine European countries recorded the highest consumption of codeine in the UK in the period 2001-2003 (De Conno et al., 2005). The prevalence of the non-medical use of prescription opioids in the USA (2008-2009) found that a substantial number of individuals reported using combination products containing codeine with paracetamol (Wang et al., 2013).

Codeine is the most common opioid consumed in several European countries, particularly in Norway (Fredheim et al., 2009). The prevalence rates of codeine use in Norway in the year 2006 for men and women was estimated to be 7.3% and 9.3% respectively, with 12% of women and 9% of men being
moderate to high consumers (120 defined daily doses in 2006). It was estimated that 50% of the moderate to high consumers were also dispensed benzodiazepines or carisoprodol. Codeine use was mainly sporadic but a large sub-group was dispensed repeated prescriptions of the drug in combination with potential other drugs of abuse (Bachs, Bramness, Engeland, & Skurtveit, 2008). Prescribed combined codeine analgesics were most common in Norway, with an average of 30 defined daily doses per year consumed. Greater proportions of women reported weekly use that was sporadic, which increased for both men and women with age, with greatest use reported in older women (Eggen & Andrew, 1994).

A Norwegian prescription database (2004-2006) highlighted that one in 10 adults were dispensed codeine in 2005. A majority (58%) received codeine only once which was most likely for acute pain. However, a small minority (0.5%) of individuals on a minimum of one codeine prescription exceeded the maximum recommended dose of 730 defined daily doses of codeine per year, indicating problematic opioid use (Fredheim et al., 2009). This study highlights the need for more clinical trials to establish whether patients benefit from long-term treatment with short-acting weak opioids. Additionally, research on the treatment of codeine-using patients who appear to have developed problematic opioid use is required. Instead of making codeine less available, the analysis of this prescription database suggests that greater focus on prevention and helping those who are at risk of or are problematic opioid users is needed (Fredheim et al., 2009). A study in Iceland reported substantial increases in codeine sales and also in the number of treatment cases for over the counter codeine abuse (Almarsdóttir & Grimsson, 2000).

In France, a cross-sectional study sampling 53 pharmacy customers found that among those reporting codeine use in the past month, 15.1% misused it and/or used it for a non-medical reason, and 7.5% reported dependence as per the DSM-IV criteria (Orriols et al., 2009; Roussin et al., 2013) A French study reported that misuse and dependence on codeine analgesics was significantly higher than for paracetamol, with 19.5% reporting daily use of codeine for more than six months. Armand et al. (2004) in France recorded a continuous decrease in neocodion (codeine antitussive preparation with psychoactive effects) consumption between 1992 and 2002 (community pharmacy and the French drug dependence-monitoring program OPPIDUM data), but observed that 86% of those misusing neocodion were poly drug users, and that the product was less sought after for opiate maintenance than for its psychoactive effect.

Quantitative studies have found that codeine dependents are young and rate their health poorer than nondependent users, report chronic pain, and represent greater numbers of females, when compared with other groups of opioid dependent individuals (Nielsen et al., 2011; Sproule et al., 1999). In Australia, Nielsen et al. (2010) survey of 909 codeine users reported that 17.3% were likely to be codeine dependent. Codeine users were more likely to report consumption of well above the recommended dose of over the counter codeine, for longer periods of time, and were younger, with lower levels of employment and education, and more likely to have a family history
of substance dependence than members of the general population. This study also observed differences with other populations of opioid dependents.

To establish the prevalence of addiction to over the counter pharmaceuticals containing codeine, studies have sampled a range of groups and perspectives which include those of pharmacists, pharmacy customers, the public and dependent individuals (Cooper, 2013b). The literature highlights the prevalence of use and abuse of codeine to specific groups of people. Studies have reported a wide profile of individuals misusing codeine medicines ranging from the parental medication of children with codeine products (Allotey et al., 2004), the misuse of codeine cough mixtures among youth and drug users (Agnich, Stogner, Miller, & Marcum, 2013; Arndt et al., 2011; Banerij & Anderson, 2001; Chitrakarn et al., 2012; Elwood, 2001; Ford, 2009; Hart et al., 2013; Kitabayashi et al., 2000; Lam & Shek, 2006; Lao et al., 2010; Miyatake et al., 2002; Peters et al., 2003: 2007a,b,c; Shek & Lam, 2006;2008; Tang et al., 2012; Wilson et al., 2010), prescribed and over the counter codeine use among university students (Acocella 2005, Steinman 2006), adult male customers and treatment patients (Albsoul-Younes et al., 2010; Sweileh et al., 2004; Tetrault et al., 2007; Yang & Yuan, 2008), middle aged women accessing pharmacies (Akram, 2000), psychiatric patients (Agyapong et al., 2013) older people (Agaba, Agaba, & Wigwe, 2004; Roumie & Griffin, 2004) and ketamine injectors who frequently misuse codeine (Lankenu et al., 2007).

Tetrault et al. (2007) found that more men reported non-medical use of prescription opioids in the past year compared to women with men commonly using Percocet, Codeine, Oxycontin, Demerol, Morphine and Methadone. Sweileh et al. (2004) reported that males aged 20-40 years were more likely to misuse over the counter products including codeine. However, among the student population, females were more likely to misuse over the counter medicines containing codeine than males, with misuse higher in older, white and Native American students (Steinman 2006). With regard to pharmacist’s perspectives, Sweileh et al. (2004) reported males aged 20 -40 years was more likely to misuse over the counter products including codeine. Pates et al. (2002) observed that pharmacists were aware of all types of potential over the counter misusers. In terms of the student population, Steinman (2006) reported that females were more likely to misuse over the counter medicines containing codeine than males, with misuse higher in older white and Native American students.

Of note is that older people are the largest consumer group of prescribed and over the counter opioid analgesics (Francis et al., 2005). Sole misuse of prescribed opioid analgesics is prevalent among educated, high earning women who are over 35 years of age and do not report any other drug use or misuse (UNODC, 2011). Greater trends of non-medicinal use of opioid analgesics in students are reported (Fischer et al., 2013; Lord, Agaba, & Wigwe, 2011) with significant gaps in knowledge in adolescents using over the counter analgesics (Wilson et al., 2010). Tormoehlen, Mowry, Bodle, & Rusniak (2011) reported on an increase in adolescent risk to abuse of
prescription and over the counter opioid analgesics relating to availability and reduced perception of risk (Levine, 2007).

Fry et al., (2007) investigation of the prevalence and relationship between benzodiazepines, pharmaceutical opioid use and crime in Australia found that 27% of participants used codeine in the previous 6 months. Prescription drugs were reportedly relatively easy to obtain on the street with a low level of reported organised criminal activity related to the procurement of prescription pharmaceuticals. The study concludes that there may be a relationship between the use of prescription drugs, dependence and some criminal activity. A comprehensive national prescription drug misuse prevention monitoring system is proposed.

4.2.1 Codeine related deaths
A number of studies have explored the prevalence of drug poisoning deaths in relation to codeine use. Risk of fatal overdoses due to medicinal opioids (buprenorphine, codeine, dextropropoxyphene, fentanyl, methadone, oxycodone, tramadol) are present with poisonings by weak opioids (codeine and tramadol) associated with large, suicidal and accidental overdoses, particularly among females (Gerostamoulos, Burke, & Drummer, 1996; Hakkinen, Launiainen, Vuori, & Ojanpera, 2012; Wazaify et al., 2005). Co-administration of dihydrocodeine with heroin, methadone and benzodiazepines may increase risk of overdose (Wazaify et al., 2005; Zamparutti et al., 2010).

Morgan et al. (2006) found in the UK that there was an increase of codeine deaths from 26 in 1999 to 54 in 2004. The incidence and role of codeine in drug-related deaths was also examined in Victoria, Australia over a 5-year period. A total of 107 cases involving codeine, representing 9% of all drug-related deaths in this period in Victoria were examined. Six fatalities in which codeine was considered the major poison was identified with paracetamol the most common other drug found (Gerostamoulos et al., 1996). Paracetamol is usually combined with codeine and propoxyphene in many preparations for the treatment of pain and common colds. It is suggested that free codeine concentrations >0.4 mg/L and total codeine concentrations >2.0 mg/L may be sufficient to cause death in the absence of any other contributing factors (Gerostamoulos et al., 1996).

An analysis of the prevalence of opioid-related deaths in Finland from 2000 to 2008 found that of the 14–44 year-olds (n=12,891), 10,182 were men (Hakkinen et al., 2012). Several opioids were detected in 1363 cases (1103 men). For codeine use poisoning the manner of death was 43% accidental, 40% suicide and 16% unclear. There were no single drug codeine poisonings. Benzodiazepines were found more frequently than other opioids in codeine poisonings. Poisonings by the weak opioids, for example, codeine and tramadol, were found to be associated with large and often suicidal overdoses resulting in high drug blood concentrations (Hakkinen et al., 2012).
Zamparutti et al. (2010) analysed the prevalence of dihydrocodeine in fatalities that occurred in the UK among individuals with a history of opiate misuse. Data covering the period 1997–2007 was voluntarily supplied by coroners and analysed. 646 cases were identified as dihydrocodeine-related deaths. Dihydrocodeine, either alone or in combination with other drugs, was identified in 584 fatalities. In 44% of cases it was directly implicated in the cause of death. Typical dihydrocodeine cases identified were white males in their early thirties. Accidental deaths (96%) were likely to involve dihydrocodeine in combination with other psychoactive agents, for example, heroin, morphine, benzodiazepines and methadone. These findings highlight the importance of alerting opiate/opioid misusers about the risks associated with poly drug intake and for prescribers to consider alternative pharmacological interventions to dihydrocodeine (e.g. methadone, buprenorphine) when managing and treating opiate/opioid addiction.

4.2.2 Misuse of Codeine Cough Syrups

Whilst codeine is abused in pill or syrup form (Compton & Volkow, 2006b), the abuse of codeine cough syrup is well documented in the US (Blakley & Schilling, 2008), India (Mattoo et al., 1997; Wairagkar et al. 1994), Hong Kong (Lam et al., 1996; Shek & Lam, 2008), and Japan (Ishigooka, Yoshida, & Murasaki, 1991; Kitabayashi et al., 2000; Miyatake et al., 2002; Seno et al. 1996). Over the counter and prescribed forms of codeine cough syrup exists and contains varied percentages of codeine, dextromethorphan and promethazine hydrochloride, an antihistamine with sedative properties. In the US, and particularly in Southern States, codeine cough syrup is mixed with alcohol or soft drinks (i.e. Sprite) and called ‘Purple Drank’, ‘Syrup,’ ‘Barre’, ‘Purple Tonic’, ‘Sizzurp’; ‘Texas tea’, ‘Tsikuni’ and ‘Lean or Southern Lean’ (nicknamed for the slumped posture in intoxicated users) (Elwood, 2001; Peters et al., 2010, 2007a, 2003).

Poly drug users in the US report using codeine syrup due to its lack of legal sanction, is perceived to be safe, is free or inexpensive with Medicaid or private insurance and can be widely procured from doctors and hospital emergency rooms (Elwood et al. 2001). The purple-ish hue of ‘Purple Drank’ comes from the dyes in the cough syrup. Males, other drug users and those who prefer rap/hip hop music have significantly higher likelihood of using ‘Purple Drank’ (Hart et al., 2013). Southern rap music is inspired by intoxication on codeine and promethazine, with ‘chopped and screwed’ beats, typically significantly slower, skipped and relaxed, and characteristic of the codeine cough syrup induced cardiovascular depressant effect (Elwood, 1999).

When consumed in large quantities fatigue, loss of coordination, sedation, dissociation and altered levels of consciousness are reported (Elwood et al. 2001, Peters et al. 2003). Amongst younger cohorts, codeine cough syrup users’ beliefs centre on perception low risk and lack of adverse consequences or potential for dependence (Darboe 1996; Hou et al., 2011; Lam & Shek, 2006; Shek & Lam, 2008; Peters et al., 2007a, c: 2003).
Gaps in knowledge have been reported in adolescent use of over the counter analgesics containing codeine (Wilson et al., 2010). But prevalence rates are high among Native Americans, Hispanics, males, LGBT and urban students (Agnich et al., 2013). However, Tormoehlen et al. (2011) identified an increase in adolescent risk to abuse of prescription and over the counter opioid analgesics, which suggests a possible decrease in codeine use compared to other opioids.

Codeine cough syrup use is evident among males in urban black ethnic groups and lesbian, gay, bisexual, transgender (LGBT) minorities, and is associated with poly substance use, high levels of sexual activity and use of new psychoactives (Agnich et al., 2013; Elwood, 2001; Peters et al., 2007a,b,c, 2003; Peters et al., 2007a,b,c;). A survey assessing the prevalence of misuse of codeine cough syrup of 2,349 students was conducted in the USA (Agnich et al., 2013). The sample comprised White (69%), African American (24%), Hispanic (3%), Native American (3%) and Asian (1%) people with an average age of 20. Findings from this study highlighted that significant gaps in treatment may exist for both Hispanic and Native American students. They suggest also that urban male youth of all racial backgrounds are potential misusers of codeine cough syrup and that misuse may be most common within the LGBT community.

A retrospective study of cough mixture abuse (2009-2011) examined the medical records of patients with a diagnosis of cough mixture dependence who attended the substance abuse clinics at the Prince of Wales and North District Hospitals in Hong Kong (Tang et al. 2012). A total of 63 patients with the diagnosis of cough mixture abuse were identified. 89% were male with an average age of 34 and 83% reported being unemployed. The average age of onset of cough mixture abuse was 20 ± 5 years. The most common substances in the urine samples at first presentation were promethazine (75%), pseudoephedrine (67%), codeine (60%), ephedrine (57%), zopiclone (17%), and hydrocodone (16%). The study suggests that psychotic disorders are the most frequent psychiatric diagnosis associated with cough mixture abuse. Paranoid psychosis manifesting as persecutory delusions and derogatory hallucinations are common among users who abuse cough mixtures containing promethazine, ephedrine, pseudoephedrine, codeine and hydrocodone. Psychiatric symptoms develop at any time between two and 13 years after onset of abuse (Tang et al., 2012).

Similar forms of cough syrup misuse include the home production of ‘Kratom Cocktails’ in Thailand, and consisting of boiled kratom leaves, Coca-Cola, a codeine cough syrup, and sometimes the addition of alpraxolam. This mixture is popular amongst youth and served with ice, yoghurt or coffee. Active ingredients of ‘Kratom Cocktails’ reportedly include mitragynine, caffeine, codeine, chlorpheniramine (antihistamine) and phenylephrine (decongestant) (Chittrakarn et al., 2012). Kratom leaves contain over 25 alkaloids including mitragynine, paynantheine, mitraphylline, and 7-hydroxymitragynine, with mitragynine the major psychoactive constituent (Chittrakarn et al., 2012). ‘Kratom Cocktails’ are illegal in Thailand but not in Europe or the US, where the herbal mixture of kratom leaves and tramadol (a synthetic opioid
analgesic) dubbed ‘Krypton’ is popular (Arndt et al., 2011). Kratom is typically sold on the internet, and in smart or headshops in the form of whole or crushed green leaves, or green powder and capsules.

4.2.3 Codeine use in pregnancy

Codeine is prescribed for obstetric purposes (Glover et al., 2003). Codeine was originally viewed as having minimal risk to mothers and breast feeding infants (Bar-Oz et al., 2003; Seaton et al., 2007) however recent commentaries have raised serious concerns about the risk of morbidity and mortality in paediatric use (Cartabuke et al., 2013; Chang, Cheng, & Chang, 2012). Madadi & Koren (2008) have commented on the lack of empirical evidence available to support its use in children and breast feeding mothers, and emphasised variability in the efficacy of codeine in these patients. The use of codeine by breastfeeding mothers has been found to cause adverse central nervous system events in breastfed infants (Madadi et al., 2008a, b). Arguably, physicians need to recognize codeine use during breastfeeding as a cause of central nervous system depression in infants, and breastfeeding mothers should be made aware of the possibility of adverse events before being offered codeine (Madadi et al. 2008 a, b).

There is a lack of data with regard to use of codeine during pregnancy. This problem is difficult to accurately describe as many women do not consider over-the-counter medicines to be dangerous and exact medication histories are problematic to obtain (Reynolds et al., 2007). However, it is known that the use of ibuprofen is quite common and consumed at unexpectedly high rates although is contraindicated in pregnancy (Glover et al., 2003). For example, a longitudinal study (26 months) of medication usage and discontinuation to identify medications that are consumed by a rural obstetric population (n=578) during pregnancy was conducted in the USA (Glover et al., 2003). 2,086 interviews were conducted in relation to the use of prescription, over-the-counter and herbal medicines. 96% of the participants reported taking prescription medications; 93% self-medicated with over-the-counter medications and 45% used herbal medications. Over time, consumption of over-the-counter medications exceeded prescription medication use. 15% of the pregnant women took ibuprofen at some point during the pregnancy (5.7% in the third trimester). 8% of the women were noncompliant with 20% of these poorly compliant with prenatal vitamin and mineral formulations.

4.2.4 Pain

Individuals with codeine dependency often commence codeine use in an effort to manage pain (Frei et al., 2010; Tennant & Rawson, 1982). Patients with co-existing pain and addiction may have decreased pain tolerance, increased anxiety, depression and insomnia. A high rate of cross dependence (18%) on codeine has been reported and suggests that chronic pain requires better medical care, in particular chronic cephalalgia, with subsequent prevention of drug-related chronic headache (Roussin et al., 2013). Pan, Ho, Lu, Lin, & Wang (2013) investigated the prevalence of opioid consumption in Taiwan and found that prescriptions and expenditure increased steadily from 2002-2007 similar to nearby Asian countries, but remained much lower than in
developed countries. Notably, 67% of patients took codeine for cancer pain in 2002 compared to 73% in 2007.

Other research points with regards to the self-medicating use of codeine to manage emotional pain, anxiety or stress (Nielsen et al., 2010). Sproule et al. (1999) found that codeine dependents are more likely to report chronic pain and will use codeine for its pleasurable effects, to relax or reduce stress, otherwise referred to as ‘chemical coping’ (Nielsen et al., 2010). Sproule et al. (1999) identified that over half of their sample using over the counter products had average doses of dependence of 179mg per day, with 80% using codeine 5 or more days per week. Frei et al. (2010) suggested that users were consuming mean daily doses of between 435 and 602mg of codeine phosphate and 6800 to 9400mg of ibuprofen, with the majority having no previous history of substance use disorder.

Repeated administration of codeine in the absence of pain causes tolerance and dependence (Derry et al., 2013). However, research on prevalence and incidence of persistent and problematic use of this weak opioid in patients with non-cancer chronic pain or non-pain patients is limited (Roussin et al., 2013; Skurtveit et al., 2011). Misuse in the form of repetitive daily use has been known to contribute to increased headache called “Medication Overuse Headache”. This withdrawal headache is also one of the most frequent reasons for persistent daily use leading to misuse and dependence on codeine analgesics. Roussin et al. (2013) reported that half of daily codeine users reported headaches, with headache also reported as a reason for use in codeine dependents.

For those with pain management issues, often stimulating initial misuse of codeine, the re-emergence of pain creates a barrier to successful treatment completion (Tennant & Rawson, 1982), and highlights the need for coexisting pain management supports (Dobbin & Tobin, 2008; Fishbain et al., 2008). The misuse of opioid analgesic medication can complicate chronic pain management (Ives et al. 2006). Chronic use of prescription opioids for non-cancer pain is higher in patients with mental health or substance use disorders (Edlund et al., 2010). Indeed, long term opioid use is particularly prevalent in women with chronic pain (Darnall et al.; 2012). Studies describe poor long term outcomes for codeine dependents at 12 month follow up (Otto et al., 2009; Zahradnik et al., 2009).

4.2.5 Recreational Use

Recreational codeine use is characterised by consumption of high doses of codeine in ‘binge’ episodes (Ernest et al., 2010). Reported forms of misuse for recreational purposes include consumption along with anti-nausea preparations promethazine, codeine linctus, products with higher proportions of codeine, and crushed within caffeine laced drinks (i.e. Red Bull). Codeine can also be smoked as free base, Poly drug taking represents an additional risk in terms of potential drug outcomes and adverse health consequence on recreational misuse of codeine (Reed et al., 2011). Online user forums
provide information on how to split tablets and extract codeine using the cold water extraction methods for removal of additives.

Whilst codeine is abused in pill or syrup form (Compton & Volkow, 2006b), the abuse of codeine cough syrup is well documented in the US (Blakley & Schilling, 2008); India (Mattoo et al., 1997; Wairagkar et al., 1994), Hong Kong (Lam et al., 1996; Shek & Lam, 2008), and Japan (Ishigooka et al., 1991; Kitabayashi et al., 2000; Miyatake et al., 2002, Seno et al., 1996). These syrups contain codeine, dextromethorphan and promethazine hydrochloride.


4.2.5 Illicit drug use

The relationship between the misuse of over the counter medicines containing codeine such as Nurofen Plus® (ibuprofen and codeine), illicit drug use and the diversion of codeine to street drug markets is reported (Levine 2007, Matheson et al., 2002; Reay, 2009; Sproule et al., 1999). Research shows that awareness of codeine’s abuse potential within problematic drug using networks is relatively high with use potentially to alleviate withdrawals from stronger opiates such as heroin (Agyapong et al., 2013; Cooper, 2013b). Amongst illicit drug users, extra medical use of pharmaceuticals occurs in varying degrees (Wilkins et al., 2011). Wilkins et al. (2011) reported that amongst frequent users of ecstasy, low levels of morphine, methadone and ‘home bake’ morphine, and sizable levels of methylphenidate, benzodiazepines and codeine use are reported. Furthermore, Wilkins et al. (2011) found that many injecting drug users tend to get prescriptions for codeine (41%) and benzodiazepines (41%) as a means for using extra medical pharmaceuticals and occurs in varying degrees.

In terms of using over the counter and black market sourced codeine, increasing trends relating to home manufacture of injecting drug solutions has been observed in Eastern Europe, Russia, South Asia, Australia and New Zealand (Harris, 2013). Popularity of these home drug solutions made from codeine appears dependent on the availability of natural opiates such as heroin, levels of policing and user awareness of harms (Booth, 2013; Grund et al., 2013). The Soviet tradition of homemade opiate type substances such as ‘Braun’ and ‘Krokodil’ is viewed as contributory to the production of new, accessible and affordable drug solutions (Azbel et al., 2013). In New Zealand, ‘Home Bake’ is made from morphine and codeine based over the counter and illicitly sourced pharmaceuticals (Grund et al., 2013).

According to Gahr et al. (2012b) no scientific qualitative chemical analysis of the solution known as ‘Krokodil’ exists. Savchuk et al. (2008) in their work (part i) observed the synthesis of desomorphine using different recipes and conditions, and identified four synthetic analogues of desomorphine, of
codeine and other compounds in ‘desomorphine’ samples, and ranging from trace to 75%. They commented on the different procedures and conditions involved in the synthesis of desomorphine in various regions of Russia. Grund et al. (2013) emphasize the need for field testing of samples and continued efforts for empirical research on ‘Krokodil’ s synthetic pathways, the effect of presence of certain medicines, chemicals and reagents on chemical reactions and manufacturing processes.

4.3 Conclusion

Codeine is one of the most prevalent opioids consumed worldwide. The prevalence of the non-medical use of prescription opioids suggests that significant numbers use codeine with paracetamol. Issues in relation to codeine use, misuse and dependence include codeine related deaths; oral misuse of codeine cough syrups; codeine use in pregnancy, codeine prescribed for pain, recreational use of codeine and codeine used in problematic injecting drug use. Psychotic disorders, especially paranoid psychosis, are a frequent psychiatric diagnosis associated with codeine cough mixture abuse with dysphoric mood states associated with sustaining long-term codeine use.

Relatively little is known about the use of over the counter analgesics containing codeine. Codeine misusers would benefit from education about the risks associated with poly drug intake to challenge widely held but misinformed perceptions that codeine based products are low risk in terms of their potential for dependence.

Clinical trials to establish the benefits or otherwise from long-term treatment with short-acting weak opioids are warranted. Research is also needed into treatments for codeine-users who have developed problematic opioid use and to evaluate as prevention strategies to help those who are at risk of or are currently problematic opioid users. Harm reduction and clinical treatment warrants further development in response to the injecting use of codeine containing home-made drug solutions.
Chapter 5
Use and Efficacy of Codeine within Healthcare Practice

5.1 Introduction
This chapter explores the evidence with regard to the use of codeine within healthcare practice and its effectiveness when compared to other medications. The frequency with which codeine is prescribed and the reasons why people misuse are briefly examined.

The World Health Organisation has placed codeine as a ‘step 2’ (weak opioid) on its pain ladder (Cartabuke et al., 2013). It was originally used for treatment of cancer pain, and extrapolated for the management of mild to moderate pain in adults and children (Campbell, 2006; Cartabuke et al., 2013; EMA, 2013; Hall et al., 2013; Kelly & Madadi, 2012; Lebeda, 2011). It is frequently used in the management of mild to moderate pain in adults (often dental or postpartum) and under strict monitoring in children (Campbell, 2006; Cartabuke et al., 2013; EMA, 2013; Kelly & Madadi, 2012). Some commentaries have speculated on its therapeutic uses and limited role in palliative care (Therapeutic Guidelines, 2007). Recent discourse has suggested to skip ‘step 2’ due to problems with codeine (and tramadol), with guidelines generally not recommending codeine for management of pain, due to limited evidence of effectiveness, variations in metabolism and availability of more predictable opioids.

The main therapeutic indications for codeine are the relief of mild to moderate pain and cough suppression (British National Formulary, 2013). While codeine is widely used in healthcare, its effectiveness and role in the treatment of minor and moderate pain is debatable. In general, codeine is thought to be effective in the treatment of non-cancer pain over short periods of time (less than 6 months). Long-term treatment with codeine is not supported as the evidence of effectiveness is variable and the risk of misuse and abuse increases significantly over time (Trescot et al., 2008).

Codeine is available over the counter in combination preparations with paracetamol or ibuprofen. It has been shown that combination effects of different analgesics have additive effects (Moore, Derry, Derry, Straube, & McQuay, 2012). However, there is limited evidence suggesting that combination preparations are better than same doses of either medication taken together (Derry et al., 2013). A reason for selling over the counter products as a combined preparation is to decrease their addictive and abuse potential.

7 Background information on the therapeutic use of codeine is described in chapter one.
The effectiveness of codeine or combined codeine based products for post-operative treatment, chronic pain, opiate dependency treatment and detoxification medication, children and breastfeeding are now explored.

5.2 Post-operative treatment
A meta-analysis of six studies concluded that a combined formulation of codeine (25.6 mg to 60mg) and ibuprofen (400mg) as a single dose treatment for post-operative treatment has good analgesic efficacy (Derry et al., 2013). This finding was for use of high doses of codeine only with limited available data on low and medium doses. However, there are some concerns in prescribing combined preparations because of the potential for the misuse of over the counter preparations containing codeine (Derry et al., 2013).

Franceschi et al. (2013) suggest that codeine-paracetamol combined preparations should be the treatment of choice for mild to moderate pain rather than using non-steroidal anti-inflammatory drugs. They argue that the effectiveness of codeine and paracetamol combinations is not inferior to non-steroidal anti-inflammatory drugs and that the risks from non-steroidal anti-inflammatory drugs side effects and their ability to induce potentially life-threatening conditions is greater than codeine and paracetamol based combinations. This recommendation is especially directed for use in older people and those with chronic pain requiring long-term treatment (Franceschi et al., 2013).

A systematic review by Nauta et al. (2009) found non-steroidal anti-inflammatory drugs to be equipotent to paracetamol-codeine preparations. However, there is a better risk/benefit ratio when using non-steroidal anti-inflammatory drugs compared to paracetamol-codeine combination as fewer adverse effects were reported.

No difference has been found in the efficacy of the relief of post-operative pain in dental patients and headaches between the use of aspirin and paracetamol-codeine combinations (Abt, 2012). A single dose of dihydrocodeine used for the treatment of post-operative pain was found to be less effective in providing adequate pain relief (Moore et al., 2011). Moreover, ibuprofen (400mg) was shown to be statistically superior to dihydrocodeine (30mg, or 60mg) for relief of pain (Moore et al., 2011). It continues to be used for postoperative pain management (Stoneham & Walters, 1995), as it causes less sedation and potential respiratory depression than morphine, although morphine is safer, more potent and has a longer lasting effect (Goldsack et al., 1996).

Despite clinical arguments against the use of codeine, it still holds an important place in mild to moderate pain treatment (Tremlett et al., 2010). Overall the evidence in support of codeine use as opposed to non-steroidal anti-inflammatory drugs is inconclusive.
5.3 Chronic pain

Codeine is commonly used to manage dental pain (Gatoulis, Voelker, & Fisher, 2012) and post-partum pain (Nauta et al., 2009). Codeine and paracetamol combination was assessed against hydrocodone and ibuprofen for effectiveness in the treatment of chronic pain (Palangio et al., 2000). Hydrocodone is six to eight times more effective than codeine. The dose of two tablets of the combined preparation of codeine (30mg) and paracetamol (300mg) was as effective as a dose of one tablet of hydrocodone (7.5mg) and ibuprofen (200mg), but less effective than a dose of two tablets of hydrocodone and ibuprofen. The authors concluded that hydrocodone (7.5mg) and ibuprofen (200mg) combination is a therapeutic alternative to codeine (30mg) and paracetamol (300mg) (Palangio et al., 2000).

The misuse of opioid analgesic medication can complicate chronic pain management (Ives et al., 2006). Chronic use of prescription opioids for non-cancer pain is higher in patients with mental health or substance use disorders (Edlund et al., 2010) with long term opioid use being particularly prevalent in women with a chronic pain condition (Darnall et al., 2012).

5.4 Opiate replacement treatment

The use of codeine and dihydrocodeine as an opiate replacement treatment has not been widely studied. Oral short acting dihydrocodeine (half-life: 4 h) has been viewed as a viable alternative to methadone as substitution treatment for opiate dependence (Banberry et al., 2000; Krausz et al., 1998; 1995; Robertson et al., 2006). Dihydrocodeine and codeine are particularly useful within the primary care and prison settings, for substitution treatment and for use in cross over detoxification from methadone (Backmund et al. 2001; Banbery et al., 2000; MacLeod et al. 1998; Robertson et al., 1990; Seymour et al., 2001; Sheard et al., 2007; Stark & Gregory, 2005; Zamparutti et al., 2010). Strang et al. (2005) have reported on dihydrocodeine prescribing in UK based primary care services for the treatment of opiate dependence, and as a drug of choice for opiate withdrawals for those in police custody (Pearson, Robertson & Gibb, 2000). Preference is shown for the prescribing of dihydrocodeine for patients with less severe opiate dependence by general practitioners due its reduced toxicity with shorter half-life and more rapid onset of action, reduced abuse potential and potential for injecting use, perceived safety, potential retention of patients, its flexibility and portability thereby impacting less negatively on the patient’s lifestyle, and its capacity to reach wider groups of opiate dependent drug users (Krausz et al., 1998; MacLeod et al., 1998; Robertson et al., 1990, 2006; Swadi, Wells, & Power,. 1990). Some studies have measured the efficacy of dihydrocodeine as an alternative maintenance and detoxification treatment. Banberry et al. (2000) report that on consecutive use a “steady-state” condition for dihydrocodeine is achieved and weaning can be achieved successfully with minimal complications within a few days. Dihydrocodeine maintenance treatment is typically low threshold, less bureaucratic, increases patient choice and retention, and is prescribed by general practitioners in the form of capsules and juice (Krausz et al., 1998).
The use of both codeine and dihydrocodeine in maintenance or detoxification of opiate addicts is unlicensed in the UK (British National Formulary, 2013). The National Institute for Health and Care Excellence has produced a guideline for UK health professionals, which states that dihydrocodeine could be used in opioid detoxification treatment. However, it is not a first-line treatment and should not be used routinely for that purpose (NICE, 2007).

Krausz et al. (1998) examined the use of codeine in detoxification and maintenance of opiate addicts in Germany. The results in maintenance treatment were promising and comparable to methadone (Krausz et al., 1998). However, codeine was inferior to methadone for drug users completing a detoxification program (Backmund et al., 2001).

Unfavourable results for the use of dihydrocodeine treatment of opiate detoxification compared to buprenorphine has been reported (Wright et al., 2007). Robertson et al. (2006) found no difference in outcomes between dihydrocodeine and methadone when used for maintenance treatment. Despite this weak evidence, the unlicensed use of dihydrocodeine is recommended by the UK Department of Health in the ‘Drug Misuse and Dependence guideline’ as an alternative, but not routine treatment for maintenance of opiate dependence. (Department of Health, 2007).

This recommendation was shown to be ignored by forensic physicians who were found to routinely prescribe dihydrocodeine as a treatment of choice for withdrawal symptoms (Stark & Gregory, 2005). The efficacy of dihydrocodeine in maintenance and detoxification treatment of opiate dependency, to ensure a favourable risk/benefit ratio has yet to be established.

There are however concerns of concomitant dihydrocodeine use amongst problematic drug users and potential for street diversion (Robertson et al., 1990; Seymour et al., 2001). Lower rates of compliance with dihydrocodeine and its misuse have also been reported, compared to rates recorded in methadone maintenance studies (Elías, 1990; Friessem & Tashner; 1991, Swadi et al., 1990). Dihydrocodeine can be prescribed as a painkiller to individuals with opiate dependence even post detoxification (Larson et al., 2007). Nordmann et al. (2013) have described regional trends in France of doctor shopping for dihydrocodeine for pain related reasons. Concomitant consumption of dihydrocodeine with heroin, methadone and benzodiazepines is a major problem in patients with opioid dependence (Backmund et al., 2005) and may increase risk of overdose (Wazaify et al., 2005; Zamparutti et al., 2011).

5.5 Children and Breastfeeding
Codeine was originally viewed as having minimal risk to mothers and breast feeding infants (Seaton et al., 2007). However, recent commentaries have presented serious concerns in relation to morbidity and mortality in paediatric use (Cartabuke et al., 2013; Chang et al., 2012). There is a lack of evidence to support codeine use in children and breastfeeding mothers, and variability in the efficacy of codeine in this group of users (Madadi & Koren, 2008).
Commencing in 2012 the EMA conducted a review led by the Pharmacovigilance Risk Assessment Committee (PRAC) under Article 31. The (PRAC) was requested to give its opinion on whether the marketing authorisations for codeine-containing medicinal products indicated in the management of pain in children, should be maintained, varied, suspended or withdrawn.

The report highlighted: the risks associated with some children who are ultra-rapid or extensive codeine to morphine metabolisers (EMA, 2013); and the need to exercise caution when interpreting the effect of age, genetic polymorphism and increasing enzymatic activity with age. The report concluded that codeine should only be administered at the lowest effective dose for the shortest period possible, and limited to 3 days with maximum of 240mg per day. In their view, codeine is contraindicated in paediatric patients under 18 years that undergo tonsillectomy and/or adenoidectomy for Obstructive Sleep Apnoea Syndrome due to increased risk of loss of consciousness and respiratory arrest and also contraindicated in patients known to be CYP2D6 ultra-rapid metabolisers (EMA, 2013).

It is recommended that codeine should not be used in children with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. The report also recommends codeine be contraindicated in breastfeeding women (EMA, 2013). Furthermore, Cartabuke et al. (2013) highlight that parents need to be educated to recognize the potential side effects of codeine such as respiratory depression when prescribed for children and calculations of dose should be based on ideal body weight and not actual body weight.

5.6 Frequency of codeine prescribing versus other analgesics
This review could only find limited empirical evidence in relation to adherence of doctors to pain management guidelines in non-cancer patients. This represents a knowledge gap in determining how doctors decide which patients receive opioid treatments; the frequency doctors prescribe codeine rather than other analgesics and what is regarded as a standard starting dose.

It was noted, however, that doctors follow advice from the World Health Organisation Analgesic Ladder, when making decisions in relation to treatments for pain. Also, it was suggested that countries generate their own guidelines, for example, ‘Opioids for Persistent Pain: Good Practice’ released by The British Pain Society (The British Pain Society, 2010). This document was drafted to support prescribing doctors and to assist them to use interventions that are evidence based. This guide specifies when opioid treatments are appropriate and when to prescribe them.
5.7 Motives for misuse of codeine
Motives for misuse of opioid pharmaceuticals including codeine range from self-treatment for pain consistent with the drug’s main indication to recreational use (Boyd & McCabe, 2008; Boyd, McCabe, Cranford, & Young, 2006; Compton & Volkow, 2006 a, b; Daniulaityte et al., 2006; Lankenau et al., 2007; McCabe et al., 2006, 2007; McCabe & Teter, 2007; Teter, McCabe, LaGrange, Cranford, & Boyd, 2006; Volkow & Swanson, 2003) with greater prevalence of recreational motives among men (McCabe et al. 2009).

The number of studies that specifically examine what motivates people to overuse and misuse codeine is limited. Two studies specific to motives of codeine misuse are identified. Daniulaityte et al. (2006) conducted in-depth interviews with 24 people who had a history of opioid abuse. Their use of codeine was connected with self-medicating for physical pain associated with daily tasks and to psychological well-being. Some started taking codeine for genuine reasons and over time developed their addiction; while others took codeine to feed their already established addiction to heroin, especially when heroin was not readily available (Daniulaityte, 2006).

Similar findings are reported by McCabe et al. (2009) who identified motives for codeine misuse ranging from self-treatment of pain (physical and emotional), sleep and anxiety problems and pursuit of pleasure. Ease of access and personality types (for example, addictive personality) may also play a role. Use of codeine for its pleasurable effects, to relax or reduce stress was also reported (Nielsen et al., 2010).

A qualitative study investigating over the counter medicine abuse which included codeine in the UK (Cooper, 2013b) revealed that individuals considered themselves ‘addicted’, and different to illicit drug dependents by virtue of social and economic activity. Self-blame for perceived loss of control was described, with medicine use (codeine, decongestant and antihistamine) commencing for genuine reasons. Subsequent use occurred for opiate effects, and with little difficulty sourcing from pharmacies and online. Withdrawal symptoms for all dose ranges were reported, and work/health problems occurred within higher dose ranges. Standard drug treatment was viewed as inappropriate.

Research highlights that awareness of codeine’s abuse potential within problematic drug using networks is relatively high with use potentially to alleviate withdrawals from stronger opiates such as heroin (Agyapong et al., 2013; Cooper, 2013b). These issues need further study given the high levels of misuse and abuse of prescription medications (Boyd et al., 2006).

5.8 Conclusion
This chapter explored the evidence with regard to the use of codeine within healthcare practice and its effectiveness when compared to other medications. The frequency with which codeine is prescribed and the reasons why people are misusing are briefly examined. The evidence is inconclusive.
and there is a need to explore these issues further given the high levels of misuse and abuse of prescription opioid medications.
Chapter 6
Consequences of Codeine Use, Misuse and Dependence

6.1 Introduction
Like all drugs, codeine is not free of problems. Consequences such as dependence and side effects in the use of opiates are thought to influence the way in which they are prescribed, with clinicians opting to err on the side of caution and prescribe lower doses than required to produce analgesic effects (Benyamin et al., 2008). Codeine is considered to be an unpredictable drug with increased risk of toxicity in combination products (Iedema, 2011).

The potential for overuse and misuse of codeine containing medications is not only detrimental for a person’s health but has broader consequences in terms of its cost and implications for the wider society (Feinberg, 2006). In this review a total 26 papers were found examining the consequences of codeine use, misuse and abuse. These studies are grouped under four main categories: (1) impairment (2) injury (3) adverse health effects and (4) dependence.

6.2 Impairment
Three studies looked specifically at impairment as a consequence of codeine use. The literature suggests that codeine metabolises partly to morphine by the liver enzyme CYP2D6 and that the analgesic effects of codeine are due to the morphine metabolite. However, codeine effects other than analgesia have not been extensively investigated and it is suggested that sedation, for example, might be independent of morphine formation.

Bachs et al. (2003) examined the effects of codeine alone, without concomitant presence of morphine, on a clinical test for drunkenness performed in relation to suspected drugged driving. 43 cases of suspected drugged drivers from a national database were examined that tested positive for codeine in blood samples but negative for morphine and other drugs. Codeine appeared to have a dose-dependent effect on the central nervous system that may have led to impairment as judged by the clinical test for drunkenness measurement, independent of measurable blood morphine concentrations. These findings support the view that some codeine effects do not seem to be mediated by morphine.

A recent double-blind, randomized, placebo-controlled study examined impairment in driving with 16 healthy young adults to evaluate the dose–effect relationship of three therapeutic doses of codeine/paracetamol (Amato et al., 2013). Driving performance, responses to psychomotor vigilance tests, and
scales reflecting alertness were evaluated the morning after drug intake. Findings did not reveal any significant impairment in performance of driving or vigilance nor demonstrate a dose effect relationship with the usual therapeutic doses of codeine/paracetamol in a single intake. However, some correlations suggested a blood concentration effect, which is important to take into account because the metabolism of codeine is genetically polymorphic. The study suggests that while epidemiological studies point to an elevated risk of driving accidents with opioid and codeine use, further research is needed to quantify the effects of these drugs on driving ability, such as those on different genetic polymorphisms or on aging drivers. The effects that higher doses of codeine may have require further investigation (Amato et al., 2013).

Hou et al. (2011) conducted an experimental study comparing brain images of codeine cough syrup addicts and matched healthy individuals. Brain scans and the volume and weight of the bilateral corpus striatum and the ratio of the corpus striatum to the whole brain were measured in the 22 codeine cough syrup addict participants and compared to 27 healthy individuals. The study showed changes to the bilateral corpus striatum and decreased weight and volume and ratio to the whole brain in the codeine cough syrup addict participants. The result of the scans suggested alterations in the dopaminergic system responsible for cognitive and motor action. The study concludes that chronic codeine cough syrup abuse may cause serious damage to the brain and neuroimaging findings further illustrate the mechanism of codeine cough syrup dependence.

While these studies have small sample sizes they are nevertheless specific to codeine use. Further evidence is required to determine the exact levels of impairment as a result of codeine use.

6.3 Injury
Medications that have central nervous system side effects, for example, sedation and compromised coordination are known to intensify the risk of injury particularly in older adults. Buckeridge et al. (2010) examined hospital and medical service records from 2001-2003 in Quebec, the second largest province in Canada. Population-based health databases were used to measure pre-existing risk factors for injuries in 2001/02 and drug use and injuries during follow-up in 2003. The records examined included prescription medications, quantity, duration, diagnosis, procedure and location (e.g., emergency, department, intensive care unit). In total 403,339 adults over 65 were followed up over a one year period to estimate the risk of injury associated with opioid use.

The results demonstrated that 3.7% of the total population sustained an injury, with fractures and lacerations being the most common. 15.3% of this population were prescribed an opiate of which 10.8% was codeine. Following adjustment for patient characteristics and other risk factors there was an increased risk of injury associated with opioid use (p<0.05) and a 127% increase in risk per one adult dose within the group prescribed codeine combinations (Hazard ratio 2.27, 95% CI 2.21-2.34). The study concludes that
older adults commonly use opioids along with other medications that have sedating side effects. Higher doses of low-potency opioids, particularly codeine combinations, were prevalent and result in twice the risk of injury. Early detection and intervention in the increasing use of opioids for pain management may reduce the risk of injury (Buckeridge et al., 2010).

In Denmark, a study that examined the effects of morphine and opiates on fracture risk suggested that codeine was amongst opiate medication associated with an increase in overall fracture risk (OR, 1.16, 95% CI 1.12-1.20) (Vestergaard et al., 2006). This study examined all subjects on a nationwide register in the year 2000 (n=124,655) who were taking opiate medication and were matched to three cases of the general population. While the study may not have measured medication compliance, issues of misuse or other pre-existing conditions, it concludes that an increased fracture risk is seen in users of morphine and opiates and this may be related to the risk of falls due to central nervous system effects, for example, dizziness.

6.4 Adverse health effects
The harmful effects of codeine abuse are well recognised by the medical community (Davis, Baum, & Graham, 1991; Gerostamoulos et al., 1996; Hou et al., 2011; Romach et al., 1999). Adverse health effects as a result of codeine use are reported by a significant number of studies. In general reported health outcomes of excessive, long term or dependent use of codeine and combination codeine products include perforated gastric ulcers, gastrointestinal bleeding, hepatotoxicity, hypokalaemia, inflammatory bowel conditions, and profound hypokalaemia associated with a severe myopathy, and often in users with no history of substance use disorders and co-morbidity (Chetty et al., 2003; Dutch, 2008; Dyer et al. 2004; Ernest et al. 2010; Frei et al. 2010; Lambert & Close 2005; Lewis et al. 2005; Nielsen et al. 2010; Robinson et al., 2010). Serious chronic health consequences relating to gastrointestinal haemorrhage, nephro-toxicity, hypokalaemia and opioid dependence are associated with the misuse of ibuprofen-codeine combination products (Chetty et al., 2003; Ernest et al., 2010; Frei et al., 2010; Ng et al.’ 2011). Many of these health effects are a result of additives in combination products.

Madadi et al (2007) reported the death of a new-born male after his mother was prescribed Co-Codamol (30/500mg) post-partum. While it appears the mother was consuming normal therapeutic doses of codeine, the findings of the case report revealed that both the mother and infant were fast metabolisers of morphine, the metabolite of codeine producing a higher than normal levels of metabolite resulting in the infant’s death. Reynolds et al. (2007) assessed the effects of maternal drugs and medications on neonates. They reported two separate case studies involving neonatal death which found that codeine containing cough medicine had been given to the mothers during pregnancy and was subsequently identified as the cause of neonatal abstinence syndrome. The study recommends that doctors need to ask about maternal medication use, including codeine-containing cough preparations, when evaluating new-born infants with evidence of cerebral infarction.
A quantitative mechanistic modelling study conducted in Germany on the risk to the breast-fed neonates from codeine treatment to the mother demonstrates that mother’s codeine and morphine clearance rates and neonate’s morphine clearance rates are the most critical determinants of morphine accumulation in infants. They conclude that unmonitored use of codeine for post-labour pain in breast-feeding mothers should not be considered a safe practice (Willmann, 2009).

The use of codeine for dental pain management is not uncommon. A reported case of a 19 year old male who received erythromycin and co-codamol®(30/300mg) following dental pain for one week experienced a rare psychotic episode which subsequently resolved with discontinuation of the drugs and a 5 day course of antipsychotic therapy. Arguably, a pharmacokinetic interaction occurred between both medications and resulted in the psychotic disturbance. While psychiatric disturbances are often experienced by those who abuse opiate medication, the result of this adverse event is considered rare and it was impossible to ascertain if this incident was as a result of a medication interaction only. However, clinicians should be aware that these commonly prescribed drugs may have an iatrogenic cause for psychiatric disturbances and that these adverse events are more likely to occur during their concomitant use (Manchia et al., 2013).

Furthermore, Lam, Lee, Shum, & Chen (1996) from a retrospective chart review of psychiatric admissions of 27 patients admitted with psychiatric disorders over a 54 month period, either suffering from acute organic brain syndrome, psychosis or affective episodes found all were misusing codeine cough syrup. They suggest that in cases where substance misuse psychiatric disorders are suspected, a high index of suspicion for cough mixtures misuse/abuse is warranted (Lam et al., 1996). Paranoid psychosis manifesting as persecutory delusions and derogatory hallucinations can occur in patients abusing cough mixtures containing promethazine, ephedrine, pseudoephedrine, codeine, and hydrocodone (Tang et al., 2012).

Over and prolonged use of non-steroidal anti-inflammatory drugs combined with codeine to give additional analgesic effects can result in adverse health effects, such as gastrointestinal problems and renal tubular acidosis. Ng et al. (2011) examined four cases of life-threatening hypokalaemia associated with ibuprofen and identified that all 4 patients had taken excessive amounts of ibuprofen over a prolonged period with 2 of the patients having taken ibuprofen combined with codeine. The four patients had developed hypokalaemia due to ibuprofen-induced renal tubular acidosis. Ibuprofen cessation and support therapy allowed complete recovery within days for all. The study concluded that opioid addiction with the misuse of ibuprofen-codeine combinations is common and needs to be considered in patients presenting with severe hypokalaemia (Ng, 2011).

A number of other case studies found similar outcomes in relation to hypokalaemia and codeine use. For example, Ernest and colleagues reported severe hypokalaemia in a patient who consumed 72 Nurofen Plus® in 3 days,
24 cans of Red Bull® energy drink, 2.5 litres of a homeopathic preparation in addition to taking prescribed medications (galoperidol, diazepam, alprazolam and salbutamol). While, the cause of the patient's hypokalaemia was clouded by the unusually high doses of multiple substances ingested, the authors consider that the patient's hypokalaemia was most probably attributable to the significant ingestion of Nurofen Plus®. The codeine content and the ready availability of Nurofen Plus® as an over-the-counter medication make it a potential drug for misuse (Ernest et al., 2010). Other cases of Ibuprofen/codeine induced hypokalaemia are also reported in the UK (Lambert & Close, 2005).

Barreto et al. (2011) found from a retrospective analysis of patients presenting with acute pancreatitis in Australia, that five of the 11 confirmed cases were associated with drug ingestion and were most likely due to codeine medication use (Barreto et al., 2011). Similarly, Hastier et al. (2000), reported four cases of acute pancreatitis in France which had resulted after all patients had taken therapeutic doses of codeine 1-3 hours before the onset of symptoms (Hastier et al., 2000). The death of a female in the UK in 2013 as a result of toxic levels of codeine coupled with methadone and morphine is also reported (Tormey et al., 2013). Additionally, the misuse of Nurofen Plus® in two patients in Australia resulted in perforated gastric ulcers (Dutch, 2008).

Chronic headache is also reported among those who use/misuse codeine. Eng and Lachenmeyer (1996) describe a patient with chronic headache resulting from a history of 25 years of self-medication of paracetamol/codeine. Their study highlights the need to identify patients who are in need of psychological services to assist in pain management and highlight the value of psychological treatments, for example, cognitive-behavioural therapy, biofeedback, and relaxation techniques for the treatment of chronic headache (Eng & Lachenmeyer, 1996). Furthermore, a study of 12 female patients with chronic daily headaches revealed cellular changes caused by prolonged misuse, and withdrawal from the prescribed analgesics (codeine) resulted in a decrease of mediators involved in headache pain for a majority over a 4 week period which was significantly more improved one month further (Hering et al., 1993).

Co administration of dihydrocodeine with heroin, methadone and benzodiazepines can also potentially increase risk of fatal poisoning (Wazaify et al., 2005; Zamparutti et al., 2010) and are associated with large, suicidal and accidental overdoses, particularly among females (Gerostamoulos et al., 1996; Häkkinen et al., 2012; Wazaify et al., 2005).

Home produced drug solutions based on codeine and other over the counter compounds are associated with a myriad of dangers relating to contamination and high risk injecting practices (Booth, 2013; Grund et al., 2013). The risk of blood borne virus transmission (BBV) such as HIV and HCV is high, when considerate of needle sharing and use of open containers of homemade drug solutions. Perhaps most concerning, as outlined by Grund et al. (2013), is the excessive harms reported by ‘Krokodil’ users whereby the skin of the user becomes scale like, discoloured (green, black) and ulcerated. High and
multiple injecting without a filter (particularly in the case of ‘Krokodil’) causes great harm to the user in the form of severe and life-threatening phlegmon, gangrene or internal damage to parenchymatous organs or muscles (Gahr. et al. 2012a, b; Grund et al., 2013).

6.5 Dependence
A limited number of studies examine dependence on codeine, with much of the evidence focusing on opioids as a group of medications only. Therefore, it is a challenge to determine the extent of codeine dependence among drug dependent users. Conflicting views exist with regard to codeine’s potential for addiction, particularly when considering combination products and the potential effects of other active ingredients such as ibuprofen, paracetamol and caffeine (Frei et al., 2010; Wills 2005). Although effects are milder than heroin, tolerance occurs with regular use over a short period of time (Mattoo et al., 1997; Nielsen et al., 2008, 2010; Orriols et al., 2009). Withdrawals include classic opiate dependence symptomatologies albeit less severe than with morphine such as cravings, preoccupation with seeking and taking codeine, lack of control of consumption patterns despite negative side effects, insomnia, restlessness, runny nose, stomach pains, diarrhoea and chills (Cooper, 2013b).

Estimations of the levels of codeine dependence in the public remain cloudy, with rates of dependence on pharmaceutical drugs used for pain management lower than expected (Dobbin & Tobin, 2008; Fishbain et al., 2008). As outlined in Chapter 1, dependence in the case of codeine has been identified by Nielsen et al. (2010:5) as three distinct types of codeine user, namely (direct cite);

1. Therapeutic dependence; characterised by not exceeding therapeutic doses but still demonstrating features of codeine dependence and often having a picture of worsening pain. Some cases were consistent with descriptions in the literature of medication overuse headache.

2. Non-medical/recreational users; characterised by use specifically for the euphoric effects of codeine. This group were generally seeking and sharing knowledge to reduce harms.

3. High dose dependence; characterised by the use of high doses (multiple packets per day) and experiencing serious adverse effects from their use. Use almost always stemmed from therapeutic use with participants often having limited insight into dependence for an extended period of time. In some cases use began for therapeutic use and escalated rapidly once euphoric effects of codeine were experienced.

Dependent codeine users can also be categorised as either: those who commence codeine use for pain management (either prescribed or via pharmacy sale), initially use appropriately and who intentionally or unintentionally due to lack of awareness or pharmacy/health professional advise increase their dosage or length of time administered in order to ease discomfort (Good & Ford, 2007; Hughes et al., 1999); or those who are opiate dependent, may be in methadone maintenance treatment, and using codeine to manage withdrawals when unable to secure either heroin or prescribed
methadone (National Council on Patient Information and Education, 2002; Heard et al., 2006; Reed et al., 2011; Roumie & Griffin, 2004).

A prospective cohort study following patients recorded on a national database from 2005 to December 2008 was conducted in Norway to determine the extent in which new users of weak opiates develop persistent or problematic use (Skurtveit et al., 2011). 245,006 patients were new users of weak opioids of which 216,902 were prescribed codeine. Although not exclusive to codeine medication, on examination, 191 subjects met the criteria for probable problematic opioid use. 0.3% and 0.08% developed prescription patterns indicating persistent opioid use and problematic opioid use respectively. The study concluded that only a very small minority of patients starting with weak opioids develop a prescription pattern indicating persistent use or probable problematic use of opioids. Therefore, it is argued that the fear of developing problematic opioid use should not hamper the use of weak opioids for moderate or severe acute pain (Skurtveit et al., 2011).

Fleming et al. (2007) examined substance dependence in 801 patients from 235 family practices in the USA (Fleming, Balousek, Klessig, Mundt, & Brown, 2007). The aim of the research was to present a comprehensive picture of substance use disorders in a sample of patients receiving opioid therapy from primary care physicians. Additionally, the study tried to determine the relationship of positive urine screens and aberrant drug behaviours to opioid use disorders. Of the 801 patients, 68 (8.6%) were prescribed 30/500mg co-codamol. While the study was not specific to codeine only, the frequency of opioid use disorder was four times higher in patients prescribed an opioid when compared to the general population and linked aberrant behaviour to opioid use disorders.

A study examining dependence on legal psychotropic drugs among 130 alcohol dependent users found that 29% had developed a high dose dependence on codeine (Johansson, Berglund, Hanson, Pohlen, & Persson, 2003). When this group were compared to a control group of 120, 13% were dependent on codeine compared to 1% of the normal population. More than half of the alcohol and codeine dependent users were also dependent on benzodiazepines.

Busto et al. (1998) in a mixed method study in Canada found high dependence on codeine in a group of opioid dependent patients (n=58) admitted for treatment (Busto, Sproule, Knight, Romach, & Sellers, 1998). The most commonly used opioids were codeine at 52% with doses at between 343 and 554mg per day.

Daniaulaityte et al. (2006) conducted in-depth interviews with 24 people who had a history of opioid abuse. Their use of codeine was connected with self-medicating for physical pain associated with daily tasks and to psychological well-being. Some started taking codeine for genuine reasons and over time developed their addiction; others took codeine to feed their already established addiction to heroin, especially when heroin was not readily available.
In conclusion, a limited number of studies examine dependence on codeine, with much of the evidence focusing on opioids as a group of medications only. The relationship between the misuse of over the counter available medicines such as codeine containing products such as Nurofen Plus (ibuprofen and codeine) and illicit drug use, and the diversion of codeine to street drug markets warrants further investigation (Levine, 2007; Matheson et al., 2002; Reay, 2009; Sproule et al., 1999). It is important to recognise variance in groups of codeine misusers and target research, policy and practice initiatives appropriately.

6.6 Conclusion
Codeine is considered to be an unpredictable drug with increased risk of toxicity in combination products (Iedema, 2011). The potential for overuse and misuse of codeine containing medications is not only detrimental for a person’s health but has broader consequences in terms of its cost and implications for the wider society (Feinberg, 2006). This review examined the consequences of codeine use, misuse and abuse and four main categories were identified: (1) impairment, (2) injury, (3) adverse health effects and (4) dependence. Recommendations for practice and areas for further research are offered.
Chapter 7
Prevention of Codeine Misuse, Abuse and Dependence

7.1 Introduction
The misuse, abuse and dependence on codeine products are an emerging public health challenge in many countries throughout the world. Deregulation has contributed to compounding the issue, with codeine present in a range of over the counter medicines (Cooper, 2013a; Robinson et al., 2010). Much of the evidence on codeine misuse and dependence originates from the United States (US) where codeine based products are now not available over the counter. However, there are a growing number of studies now emerging in other parts of the world on over the counter codeine use and misuse, for example, in the United Kingdom (UK) and Australia. The literature in relation to the medical prescribing of codeine and pharmacy related activities are presented with regard to the prevention of codeine misuse, abuse and dependence. Some innovative approaches for managing such issues are offered.

7.2 Medical Practice and Pharmacovigilance
Increased pharmacovigilance in primary care is advised (Kahan et al., 2006; Jones et al., 2012). There is increased emphasis on responsible prescribing in the literature on the misuse of prescribed opioid analgesics (including codeine) to include risk assessments, prescribing agreements and treatment contracting without compromising legitimate access to opioids for analgesia (Ling et al., 2011; Maxwell, 2011).

Education in administration of paediatric medication containing codeine is needed (Cartabuke et al., 2013). Those caring for paediatric patients taking codeine should be advised to seek medical assistance if symptoms of toxicity occur (EMA, 2013; Ng et al., 2011; Schillie et al., 2009).

Health professionals involved in prescribing need to monitor use in vulnerable groups (patients with chronic non-malignant pain, patients with cancer pain and illicit drug users). The objective of such monitoring is to identify if opioids such as codeine are substituting for or complicating pain, mental health and addiction treatment outcomes, thereby minimising risk of overdose (Edlund et al., 2010; Manchikanti & Singh, 2008; Roxburgh, Bruno, Lrance, & Burns, 2011). Indeed, dependence by health professionals themselves to both prescribed and over the counter opioids such as codeine are also issues of concern (Des Roches et al., 2010).
7.2.1 Co-prescribing and effects on health
Frequent co-prescribing, for example benzodiazepines and opioids, can have negative consequences for health, potential overdose lethality and treatment outcomes and requires patient monitoring and responsible prescribing practices (Maxwell, 2011). Practitioners need to be aware of excessive consumption of combination products, with health consequences relating to additives in causing severe hypokalaemia complicated by myopathy (Chetty et al., 2003; Ernest et al., 2010; Frei et al., 2010; Ng et al., 2011), and also the iatrogenesis of psychiatric disturbances relating to codeine use (Manchia et al., 2013).

7.2.2 Pain
Pseudo-addiction is defined as the under-treatment of pain (Bell & Salmon, 2009). Concerns are evident for the under treatment of patients in pain, due to fears of addiction, and complications in estimating prevalence and characteristics of dependents according to DSM-IV criteria particularly among chronic pain patients (Brands, Blake, Sproule, Gourley, & Bust, 2004). Medical practitioners can be reluctant to treat such patients due to concerns relating to over prescribing (Olsen & Daumit, 2002). The National Institute on Drug Abuse (NIDA) in the US has observed the under prescribing of codeine due to general practitioners’ overestimation of patient potential for addiction (otherwise known as ‘opiophobia’), which can result in the sub management of pain (Bell & Salmon 2009; Brennan, Carr, & Cousins, 2007; Rupp & Delaney, 2004). However, in other studies, pain management specialists observe a low incidence of misuse and dependence, with risks outweighing the potential for improved functioning and quality of life (Cowan, Allan, & Griffiths, 2002). Despite this, the emergence of patient dependence on opioids such as codeine is viewed as compromising therapeutic relations due to the belief that “pain exists whenever the patient says it does” which hampers detection of deception and increases the risk of inadequate pain control and overdose (Modesto-Lowe, Johnson, & Petry, 2007).

Bailey, Hurley, & Gold (2010), describes the crossroads of pain and opioid dependence as characterised by: travelling long distances to the pain clinic; inability or unwillingness to obtain records; requests for medications with abuse potential; use of street vernacular; focus on opioids; activity in street dealing; obtaining medication from friends and relatives; doctor shopping; unwillingness to consider non opioid adjuncts; interventional treatment modalities and physical therapy; aversions or allergies to non-opioid medication; unwillingness to produce urine for screening; physical signs of illicit drug use; appearance not correlating with physical dysfunction and hepatitis B or C. Future preventative strategies need to be aware of such user characteristics.

7.2.3 Prescription drug monitoring
Studies recommend the development of prescription drug monitoring and national online prescription systems (Francis et al., 2005; Maxwell, 2011; Roxburgh et al., 2011). Pharmaceutical opioid seeking behaviours are often
characterised by visiting multiple prescribers, feigning prescription loss, requesting early refills of prescriptions, seeking strong opioids, avoiding combination products and paying in cash (Brands et al., 2004; Cepeda et al., 2013, 2012a, b; Fountain et al., 1998; Kamien, 2004). Prescribers aged 70-79 years, male and prescribing stronger opioids have increased likelihood of having opioid shoppers as patients (Cepeda et al., 2012b). Nordmann et al. (2013) have described regional trends in France of doctor shopping for dihydrocodeine and oxycodone.

In terms of codeine cough syrup, students suggest that doctors and pharmacists are the greatest facilitators of acquisition (Peters et al. 2007). Many doctors do not question patients around over the counter use of analgesics, resulting in undetected problems, and the increased availability of over the counter analgesics such as codeine in certain countries may contribute to patient delays in consulting their doctors for potentially serious conditions (Francis et al., 2005). Furthermore, a survey conducted by ‘Over-Count’ estimated that the majority of codeine misusers are female and that their first purchase of codeine products was to treat minor ailments; most often sourcing the products via the Internet with low rates of support from doctors (Reay, 2009).

General practitioners report that they often receive ‘verbal threats’ from patients with prescribed drug problems and that tactics adopted by them to manage such threats include the documentation of incidents, suggestion of alternative drugs and cessation of prescribing such drugs (commonly benzodiazepines and opioids) (Sheridan, Jones, & Aspden, 2012). Primary care treatment strategies should promote the availability of disposal containers for unused prescriptions and referral to addiction services (Lessenger & Feinberg 2008).

7.2.4 Screening

Standard screeners, for example, the Screener and Opioid Assessment Tool for Patients with Pain (SOAPP), the Opioid Risk Tool (ORT) (Bailey et al. 2010), the Prescription Misuse Index (Knisely, Wunsch, Cropsey, & Campbell, 2008) and the current opioid misuse measure are used for pain patients on long term opioid therapy to screen for patient aberrant behaviours (Butler et al., 2007). Management of aberrant opioid behaviours requires patient education, monitoring, testing, adjunct support, treatment of comorbid conditions with a primary focus on treatment of dependence (Bailey et al., 2010).

Breastfeeding is cautioned and requires close screening and monitoring if prescribing codeine to breastfeeding mothers, given the potential risks associated with CYP2D6 ultrafast metabolism (Kennedy, 2011). Codeine use while breastfeeding is associated with events in breast-fed infants, including apnoea, bradycardia, drowsiness and cyanosis (Darnall et al., 2012). Women with the cytochrome P450 2D6 (CYP2D6) genotype rapidly metabolise codeine into morphine, resulting in high breast milk and plasma levels in neonates, and can potentially cause infant death due to opioid toxicity.
However, genetic screening is not standard practice, thus contributing to a lack of clinician awareness of potential for neonate opioid toxicity (Madadi et al., 2011). Screening and education in the administration of paediatric medication is needed (Cartabuke et al., 2013). Health professionals caring for paediatric patients taking codeine should be advised to seek medical assistance if symptoms of toxicity occur (EMA, 2013; Ng et al., 2011; Schillie et al., 2009).

7.2.5 Clinical presentations of injecting use of home produced drug solutions

The diversion, tampering, home manufacture and injecting use of over the counter and prescribed pharmaceuticals (containing codeine and other opioids) remains a public health and drug monitoring concern (Azbel et al., 2013). Tampering with pharmaceutical formulations and home production of opiates using pharmaceuticals containing codeine impacts on primary care and treatment provisions. Simple procedures to alter medication formulations are preferred by substance users (Cone, 2006), with users generally deterred by homemade drugs which are difficult to produce (Katz et al., 2006) or inject (Partanen, Wunsch, Cropsey, & Campbell, 2009). Pharmaceutical drug formulation technologies are continuously developing in order to create disincentives to reduce the incidence of product tampering and abuse (Coleman et al. 2005; Coleman, Schuster, & DuPont, 2010; Cone 2006; Hamed & Moe, 2010; Katz et al., 2011).

Drug monitoring systems, drug workers and clinicians should be aware of potential presentations for emerging and harmful forms of home produced drug abuse, particularly in the case of injecting drug use (Gahr et al., 2012a, b). The adverse health consequences associated with these tampered substances demands provision of coordinated services comprising medical support, counselling, HIV counselling and testing, wound and infection management, outreach support and rehabilitation (Elovich & Drucker, 2008; Gahr et al., 2012a, 2012b; Harris et al., 2002; Skowronek et al., 2012).

Research in countries experiencing diffusion of homemade codeine containing drug use and injecting have reported on the negative impact of policing effective drug treatment (Azbel et al., 2013; Grund et al., 2013; Mimiaga et al., 2010; Sarang, Rhodes, Sheon, & Page, 2010), with evidence suggesting inequitable treatment of injecting drug users by health professionals with subsequent reluctance of users to access treatment (Booth, 2013; Grau et al., 2002; Harris et al., 2002; Wolfe, 2007; Wolfe et al., 2010).

A proactive approach to developing appropriate harm reduction tactics (needle exchange, bleach distribution, hygiene, provision of filters, foil packs to encourage route reversals, and safer injection facilities), screening, treatment and therapy (opiate substitution therapy, antiretroviral therapy) and prevention programmes is therefore essential (Alistar, Owens, & Brandeau, 2011; Bojko, Dvoriak, & Altice, 2013; Chintalova-Dallas, Case, Kitsenko, & Lazzarine, 2009; Hallinan, Osborn, Cohen, & Dobbin, 2011; Hedrich, Kerr, &
Development of strategies to manage access and treatment barriers in relation to the reluctance of injecting drug users to access treatment is of concern.

7.3 Pharmacy Practice and Preventative Strategies

The de-regulation of prescription only medicines to pharmacy status over the counter drugs has evolved to reduce government drug budgets, general practitioner’s workloads, and to extend the screening and patient education roles of community pharmacists (Cooper, 2011b; MacFadyen et al., 2001; Robinson et al., 2010).

Pharmacists are regarded as a trusted source of information in relation to over the counter medications (Wawruch et al. 2013). However, the literature suggests that a significant number of people who consume medications cannot identify the active ingredients in their chosen medications (Roumie & Griffin 2004). This is despite high reported public awareness of the abuse potential of over the counter medicine (Wazaify et al., 2005, 2005a) and pharmacists’ concerns in relation to safety and codeine misuse, abuse and dependence (Albsoul-Younes et al., 2010; Ball & Wilde, 1989; Hughes et al., 1999; MacFayden et al., 2001; Matheson et al., 2002; Paxton & Chapple, 1996; Reed et al., 2011; Roumie & Griffin, 2004; Wazaify et al., 2005).

A minority of customers appear willing to accept the risks associated with increased access to pharmaceuticals (Alexander et al. 2005). Perceptions of risk amongst over the counter users generally do not conform to current medical thinking or correlate with self-reports of analgesic usage, with users who view analgesics as necessary reporting analgesic use, at greater doses and frequencies (French & James, 2008). However, customers who are self-selecting and purchase products online have inadequate access to information and advice at point of sale (Bessell, Anderson, Silagy, Sansom, & Hiller, 2003).

Other concerns regarding patient awareness of overuse of over the counter codeine and lack of translation into appropriate codeine consumption by disregarding product packaging or simple lack of patient comprehension that dosage is excessive have been recorded in emergency departments. Clearer product labelling of active ingredients in over the counter codeine has been advised (Heard et al., 2006, Roumie et al., 2004). Recent research on codeine misuse and customer awareness in Australia by Nielsen et al. (2010) identified three distinct forms of codeine misuse, namely:

- individuals conscientiously disobeying product instructions so as to experience a drug induced euphoric effect from the codeine present.
- individuals becoming addicted to codeine based products, aware of their dependence but continuing to use them in response to cravings and to avoid withdrawals.
- individuals unknowingly misusing codeine based products within the recommended limits but frequently and regularly using them to treat drug-induced withdrawal symptoms such as headache.
Screening and patient education roles for community pharmacists have resulted as a consequence of the de-regulation of prescription only medicines to pharmacy status over the counter drugs (Basak, van Mil, & Sathyanarayana, 2009; Cooper 2013b, 2011; MacFadyen et al., 2001, Robinson et al., 2010). Furthermore, pharmacists’ decision-making in relation to product selection and the role of clinical evidence suggests that safety and patient demand for certain products influences their decision making processes. Hanna & Hughes (2010)’s research into pharmacists’ decision-making processes regarding product selection and the role of clinical evidence in reaching such decisions, found that safety and patient demand for certain products influenced the recognition of patient demands. Evidence of effectiveness of the selected product was rarely part of the decision-making process. Communication between medicines counter assistants and customers in community pharmacies in the UK is promoted as source of primary care advice, and viewed as a complex process relating to retail, medical and pharmaceutical sources of information despite being characterised by conflict (Banks, Shaw, & Weiss, 2007). Although the self-medication of non-prescription drugs is beneficial to patients, health professionals, pharmaceutical industries and governments (Orriols et al., 2009; Wawruch et al., 2013), monitoring of certain populations and products, data recording and patient monitoring is required to promote safer use of medicines (Hughes, 2003).

In France, Orriols et al. (2009) conducted a cross sectional pharmaco-epidemiological study using pharmacy customer data to explore non-medical use, misuse, abuse and dependence on self-medicated drug use. Statistically significant differences in non-medical use and misuse, abuse and dependence were present for codeine based products. Nielsen et al. (2013) investigated perspectives of over the counter codeine users who met DSM-IV criteria for dependence about dependence in the pharmacy setting. Participants reported that ease of access to codeine was related to better appearance and presentation, and also commented on standard pharmacist questioning, minimal interventions from staff and occasional refusals to supply. Codeine users in this study did not describe pharmacy staff offering advice and reported employing tactics including wearing business suits to promote product acquisition (Nielsen et al., 2013). This study also found that the ‘hassle’ of pharmacy shopping was an important driver for eventual treatment seeking.

7.3.1 Pharmacy Preventative Strategies
Research by Hamer, Spark, Wood, & Roberts (2013) describes challenges in pharmacy management of codeine dependent individuals. Community pharmacies can solve or partly solve drug related problems without involvement of general practitioners (Frøkjær et al. 2012). Pharmacists commonly observe opioid intoxication and aberrant opioid behaviours in their practice, but report difficulties in the communication of concerns to doctors (Kahan et al. 2011).
Communications between counter sales assistants and customers in community pharmacies are promoted as a medium for providing pharmaceutical advice despite consultations sometimes being characterised by conflict (Banks et al., 2007). Challenges in relation to the pharmacy management of codeine dependent users are described (Hamer et al., 2013). For certain populations who use over the counter products, for example, codeine, data recording and user monitoring are required so that safer use of such medicines is realised (Hughes, 2003). Safety is central to pharmacists’ decision making with regard to medication supply (Hanna & Hughes, 2010). Pharmacy practice strategies that promote safety include the removal of potential products of abuse from sight; brief interventions to raise user awareness of potential harms; refusing sales; doctor referral and in some instances the supply of small amounts of the requested drug (Alabsoul-Younes et al., 2010; Matheson et al., 2002; Pates et al.’ 2002). Broader strategies have been proposed that centre on the monitoring of web sales, raising visibility of warnings on product labels and restrictions in relation to advertising (McBride et al., 2003). Clearer product labelling of the active ingredients in over the counter codeine is a concern expressed by emergency room staff following patient presentations in relation to the overuse of over the counter codeine as a result of disregarding product packaging or lack of understanding of therapeutic dose ranges (Heard et al., 2006; Roumie & Griffin, 2004).

There is a need for further protective mechanisms in the pharmacy profession in order to track and monitor codeine misuse in so called ‘respectable addicts’, in order to provide support and treatment options for those affected, along with the option for pharmacy led treatment withdrawal (Cooper, 2011; 2013a;b). Research has underscored how the de-regulation of prescription only medications toward pharmacy status medications has moved toward self-care and the reduction of GP workloads, and reciprocally spotlighted the need for an ‘early warning system’ in pharmacies, along with inter agency educational, screening, life skills and harm reduction initiatives to reduce codeine misuse (Basak et al., 2009; Gruenewald et al. 2009; Hughes et al. 1999; MacFadyen et al., 2001; McBride et al., 2003; Wazaify et al., 2006).

The expansion of the clinical role of the community pharmacist should include a thorough assessment of the customers’ problem prior to counter prescribing (Francis et al., 2005). Fleming et al. (2004) developed a harm reduction tool to identify and treat over the counter drug misuse and abuse by community pharmacists. This harm reduction tool consists of three phases: (1) patient identification and recruitment, (2) treatment and referrals, and (3) data collection/outcomes measurement.

The potential use of real-time online prescribing information systems of prescribed records could be a possible medium for effective monitoring of codeine use, misuse and abuse (Chee & Schneberger, 2003; Dobbin & Tobin,

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8 See Chapter 3, table 1- Regulation of Codeine over the counter and Prescribed
While a minority of users appear willing to accept the risks associated with increased access to pharmaceuticals (Alexander et al., 2005), those who are self-selecting and purchasing products online have inadequate access to information and advice at point of sale (Bessell et al., 2003). Innovative developments based on national integrated prescriber and pharmacy monitoring of medicines using real time reporting (RTR) analysis have emerged in the US, Canada, South Africa and Australia (Le Roux, 2013; Shand et al., 2013; UNODC, 2011).

7.4 Conclusion
The misuse, abuse and dependence of codeine products is an emerging public health issue (Cooper, 2013a; Robinson et al., 2010). Of note is that pharmaceutical opioid misusers already have regular contact with health professionals, thereby highlighting the preventative and monitoring role of pharmacists and prescribing doctors using real-time online prescribing information systems of prescribed records (Dobbin & Tobin, 2008; Chee & Schneberger, 2003; UNODC, 2011; Wrobel, 2003). Continuing interdisciplinary training for counter assistants, pharmacists and health professionals is required (Basak et al., 2009; Bissell et al., 2000; Butler & Sheriden, 2010; Wazaify et al., 2005). The literature in relation to the medical prescribing of codeine and pharmacy related activities highlights the need for more preventative strategies in relation to codeine overuse, misuse and dependence. Some innovative approaches for managing such issues are at an early stage of development.
Chapter 8
Interventions/Treatment and Codeine Dependence

8.1 Introduction
This chapter describes interventions used in the initiation and treatment of codeine dependence. Increases in treatment uptakes relating to codeine dependency and concerns for appropriate design of treatment protocols have been recorded across a variety of countries (Bell, 2010; Cooper, 2011a, b; EMCDDA Annual Report, 2011; Roche, McCabe, & Smyth, 2011; Romelsjo et al., 2010; SAMHSA, 2009; Thekiso & Farran, 2010). Many codeine dependent individuals do not view themselves as needing help (Cooper 2013b, Nielsen et al., 2010) and the evidence base for treatment of codeine dependence is limited. With regard to treatment interventions, there is varying uptake by individuals dependent on codeine in drug services due to issues relating to treatment stigma and poor consideration of needs (Reed et al., 2011). The potential for ‘discrete’ groups of codeine dependents who fail to seek help due to lack of recognition of their dependence or identification of their codeine use as a problem is described (Pates et al., 2002). We describe here the stages of potential intervention on prevention of pharmaceutical tampering, initial identification, referral and uptake into treatment.

8.2 Extractability Rating System (ERS)
In a non-codeine specific intervention, Katz et al. (2006) describe the development of an Extractability Rating System for use by the pharmaceutical industry and regulators. The ERS was used to evaluate the extractability of five prescription opioids. The motivation for this project was to develop abuse-resistant formulations. Extractability is the extent to which extraction procedures are performed on a drug product that results in quantities of active ingredients relevant to substance abuse.

The development of the ERS followed five stages. Open-ended interviews were conducted with an initial group of experts that included professionals in the field of substance abuse as well as individuals who had abused opioid medications. Several experts in the field were participants in subsequent stages to further develop and refine the ERS. The main outcome of the study was the creation of a comprehensive inventory of extraction techniques used by substance abusers. The authors acknowledge limitations in the study and that the ERS requires further work to improve standardisation and reliability.

8.3 Harm-Minimisation Intervention Model
The harm-minimisation intervention model was developed and piloted by Fleming et al. (2004). This model is designed to be used by community pharmacists in conjunction with other healthcare professionals. It addresses
the abuse and misuse of opioid, antihistamine and laxative-containing product groups which are highlighted as problematic by pharmacists in practice. The model has three elements:

(1) To identify those at risk of abuse
Identification is via an information campaign and by keeping records of sales. Once the pharmacist has identified a customer suspected of abusing or misusing over the counter medicines, they are approached. This approach utilises communication techniques, for example, motivational interviewing and details of all approaches are recorded on a record sheet designed for the purpose.

(2) How and when to intervene and propose treatment
This involves two treatment algorithms showing possible treatment paths. The treatment path chosen depends on the product involved and if the product is being abused or misused.

(3) To measure the overall outcome of the intervention
Individualised confidential records are initiated. These include details of the client’s demographics, history of product use and treatment interventions (including details of medications dispensed). These records are updated each time the customer attends the pharmacy so enabling the pharmacist to monitor the customer's progress and outcomes.

Two pharmacists participated in a pilot study of the model. They were provided with training which incorporated the use of communication techniques. While identifying abusing/misusing customers was relatively simple due to the initiated record keeping, implementation of the intervention was more problematic as customers were generally uncomfortable in taking part in any discussion regarding misuse/abuse.

A total of 18 customers suspected of abusing/misusing products were identified and the two pharmacists discussed inappropriate over the counter use with 14 of them. Both pharmacists reported that it was easier to approach clients whom they suspected were misusing products, as opposed to those suspected of abusing products. While it was agreed that the training in communication skills had been helpful, a more intensive training programme on this aspect of the model was recommended (Fleming et al., 2004).

A limitation of this intervention appears to be the reluctance of customers to take part. Abuse/misuse of over the counter products is a sensitive subject and it is not surprising that customers were disinclined to have documented their history of product use. It is likely that customers who are highly motivated will benefit from this intervention (Fleming et al., 2004).

Although successful in a number of areas, the completion of the pilot has identified opportunities for further refinement of the model. Future work focusing on improving pharmacists' communication skills, particularly in the area of motivational interviewing was recommended (Fleming et al., 2004).
Wazaify et al. (2006) examined the use of the harm-minimisation intervention model in a follow up study conducted in six community pharmacies in Belfast, Northern Ireland. This study included testing the model and exploring the experiences of pharmacists conducting the intervention. As recommended by the pilot study (Fleming et al., 2004), the participating pharmacists received two full days of training before commencing the study. Training included motivational interviewing techniques which are known to support change in behaviours, particularly in alcohol and substance abuse/misuse management.

Pharmacists identified 196 cases of suspected abuse/misuse. They approached 70 of the identified clients during the six month study. Some clients agreed to stop using the product of abuse/misuse, use an alternative, or switch to maintenance prescription under general practitioner supervision. No client proceeded to completion of the follow-up phase (e.g. health-related quality of life).

The study concluded that some difficulties were encountered in implementing the harm minimisation model, but these may be alleviated by further training and more collaborative working by all concerned. The harm-minimisation model should be considered for wider implementation within community pharmacies.

8.4 Assessment and Management of Codeine Dependence
Research has previously called for the use of standardised criteria to determine client codeine dependence (Tinsley & Watkins 1998). There is also a lack of evidence to guide development of specific treatment and referral pathways for over the counter codeine dependence (Cooper, 2011; 2013a, b; Reed et al., 2011; Thekiso & Farren, 2010,).

Clinical profiles of codeine dependents vary but are over represented by females, those in middle to late age, poly substance users, alcohol users and those with underlying psychiatric conditions (Agyapong et al., 2013; Johansson et al., 2003; Otto et al., 2009; Thekiso & Farren, 2010; Robinson et al., 2010). Codeine misusers in Ireland were more likely to be older, male and with a longer drug dependence history (Cohen, Unoh, Barry, O'Connor, 2009). Research in South Africa shows that combination codeine product abuse may also present as a secondary problematic substance and was ranked second to benzodiazepine dependency, with primary over the counter/prescription medication abuse most common in females aged over 40 years, and secondary over the counter/prescription medication abuse most common in males over 40 years (Myers et al., 2003).

In another study, average daily intake of codeine in psychiatric patients diagnosed with harmful over the counter codeine dependence was 261mg per person, with greater trends in those who were older, male and with co morbid psychiatric, physical and poly substance illnesses (Thekiso & Farren, 2010). Codeine cough mixture treatment patients are primarily young (Wairagkar et al., 1994). Another study observed dependence trajectories for young codeine cough syrup treatment seeking patients, often initiated through friends and for
curiosity, with daily use progressing in less than 6 months to higher than therapeutic doses (Mattoo et al., 1997)

Research by McAvoy et al. (2011) reported on high average over the counter codeine analgesic tablet consumption amongst patients attending detoxification (49-65 tablets daily), long duration of misuse, and a history of prior alcohol or other drug misuse or mental health disorder. Brands et al. (2004) found that those patients dependent on prescribed opioids alone, reported an average consumption of 21 tablets of codeine daily, and were less likely to use illicit non opioid drugs or report injecting drug use. Those that used prescription opioids only or initially before using heroin reported ongoing pain problems and psychiatric treatment. In Ireland, regulatory controls on non-prescribed over the counter available codeine medication were observed to have the potential to reduce abuse among psychiatric patients (Agyapong et al., 2013).

Codeine dependence can be managed with residential treatment programmes, opiate substitution therapy or lofexidine (an alpha-2 agonist used to attenuate opiate withdrawal effects) in community detoxification (Kelly & Madadi, 2012; Mattick et al., 2008). Additionally, patients suspected of opioid misuse can be treated with time restricted structured opioid therapy in the form of weekly dispensing, urine testing and tapering of dose, if not seeking opioids from other sources (Kahan et al., 2006).

Codeine dependent individuals need to taper their use under medical supervision. The primary modes of treatment are similar to that of heroin dependence and focus on a variety of detoxification modalities ranging from no medical support, the prescribing of sedatives, (benzodiazepines and sedative anti-psychotic medication), the prescribing of Lofexidine (i.e. Britoflex®) and buprenorphine (i.e. Subutex®) (Frei et al. 2010). Rehabilitation involves inpatient and cognitive behavioural therapy. Other options include maintenance therapy in the form of opioid substitution treatment using naloxone or dihydrocodeine. Psychosocial support and regular aftercare is vital for positive treatment outcomes (Backmund et al., 2001; Otto et al., 2009). Websites such as ‘Over-Count’ and ‘Codeine Free Me’ offer useful support for individuals experiencing codeine dependence (Reay, 2009).

A limited number of papers relating to interventions to treat the misuse of analgesics were identified for review. However, a harm-minimisation model for the identification and treatment of over-the-counter over the counter drug use and misuse that could be used by community pharmacists in conjunction with other health care professionals is described (Fleming et al., 2004; Wazaify et al., 2006). The development of the Extractability Rating System for use by the pharmaceutical industry and regulators to assist drug developers who wish to develop opioid products that are abuse-resistant is also available (Katz et al. 2006). ‘Withdrawal Therapy’, an intervention for patients with chronic daily headache and frequent long-term use of headache symptomatic medication is also reported (Linton-Dahlöf, 2000).
A retrospective analysis of an intervention using drug withdrawal therapy of patients with chronic daily headache with frequent long-term use of headache symptomatic medication reported the following results (Linton-Dahlöf, 2000). One hundred and one adult patients (74 women and 27 men, aged between 16 and 72 years), were evaluated 1±3 months after total drug withdrawal therapy without substitution. The total withdrawal period was approximately eight weeks. Results indicated that 57 (56%) patients were significantly improved (defined as at least 50% reduction in number of headache days). Patients with misuse of codeine (n=14) were also able to accomplish outpatient withdrawal and report a similar pattern of abstinence symptoms in comparison with patients with misuse of non-psychotropic drugs. Patients who experienced no improvement after drug withdrawal therapy were offered treatment with amitriptyline and 36% experienced a significant (50%) reduction of headache days. The study concluded that out-patient drug withdrawal therapy is the treatment of choice in patients with chronic daily headache. It is estimated that about one quarter of chronic daily headache patients do not respond to drug withdrawal therapy only.

Reed et al. (2011) conclude their review on codeine based products by highlighting the need to consider the wide variety of clinical profiles and harms incurred for codeine users, misusers and dependents, and the need for timely evidence to guide the development of treatment policy for over the counter codeine misuse or dependence. Comprehensive training programmes and coordinated supports for pain and addiction specialists in the assessment and management of coexisting addiction and chronic non-malignant pain via didactic and experiential training requires further development (Bailey et al., 2010, Daniulaitye et al., 2006, Maxwell, 2011, Roxburgh et al., 2011).

8.5 Barriers to Treatment Completion

Myers et al. (2003) points to the need to develop primary health care protocols for detection, management and referral of patients misusing over the counter/prescription drugs and the need to debate the re-scheduling of codeine as a prescription-only substance.

Studies describe poor long term outcomes for codeine dependents at 12 month follow up (Otto et al. 2009, Zahradnik et al. 2009). However, for those with pain management issues, a re-emergence of pain creates a barrier to successful treatment completion (Tennant & Rawson, 1982), and highlights the need for coexisting pain management supports (Dobbin & Tobin, 2008, Fishbain et al., 2008). Patients with co-existing pain and addiction may have a ‘syndrome of pain facilitation’ characterised by decreased pain tolerance, increased anxiety, depression and insomnia (Compton et al. 2001). Even when detoxified, pharmaceutical opiate dependents may need help for pain (Larson et al., 2007) and may have abnormal pain perception (Pud et al., 2006), leading to drug cravings (Ren et al., 2009).

Concomitant consumption of benzodiazepines and opioids is a major barrier in treating patients with opioid dependence and is associated with daily alcohol or barbiturate use, early onset of opioid use, unemployment, family
history of dependence and history of imprisonment, with codeine dependents reporting significantly greater daily intake than heroin dependents (Backmund et al., 2006). A review of codeine based products has highlighted the need to consider the wide variety of clinical profiles and harms incurred for codeine users, misusers and dependents, and the need for timely evidence to guide the development of treatment policy for over the counter codeine misuse or dependence (Reed et al., 2011).

8.6 Conclusion
Many codeine dependent individuals do not view themselves as needing help for their codeine dependence. Indeed, the literature in relation to the use of interventions in the management of codeine misuse is limited, lacks specificity and requires further research and development. Despite the use of criteria to establish dependency, recent research has commented on the lack of evidence to guide development of specific treatment and referral pathways for over the counter codeine dependence. With this in mind, there is a need for further research to guide the development of treatment policy for over the counter codeine misuse and dependence.
Chapter 9
Conclusions and Implications for Practice, Policy and Research

9.1 Introduction
This chapter provides a discussion of the findings of this scoping review of codeine use, misuse and dependence. Key recommendations are addressed under the headings: (1) raising awareness; (2) detecting and managing risk; (3) dispensing practices and (4) monitoring and surveillance. Some key areas for further research are identified and presented under six headings: (1) patterns of use, misuse and dependence; (2) prevalence; (3) treatment/interventions; (4) risk; (5) epidemiology and (6) policy. Additionally, the limitations of the review are discussed, in order that the findings are interpreted in context.

9.2 Improved Understanding and Pharmacovigilance
A global emergence of ‘respectable addiction’ has occurred alongside a heightened awareness by the general public and health professionals with regard to this addiction issue (Cooper 2013a, 2011; EMCDDA 2011). There is a societal need for improved understanding in relation to the risks of codeine use, misuse and dependence. The potential risks relating to prescribed and over the counter codeine use, misuse and dependence, and the impact that pharmacy controls and interventions may have is an area that requires further development (Agyapong et al., 2013; Reed et al., 2011; Wazaify et al., 2005).

Prescribed misuse, diversion, deregulation and over the counter availability of codeine compounds the potential for user adverse consequences and medical and pharmacy practice interventions (Ferner & Beard, 2008; Pawaskar & Balkrishnan, 2007). Health professionals need to be more aware of public lay drug definitions around pharmaceutical opioid use, both prescribed and over the counter, in order to avoid misunderstandings within their practice (Björnsdóttir, Almarsdóttir, Traulsen, 2009).

This scoping review has revealed that while the appropriate directed use of codeine based products incurs little risk, excessive or long term use of such products contributes to dependence, associated side effects and adverse and life threatening situations. The unpredictable nature of codeine’s pharmacokinetics gives rise to concerns in relation to safety (MacDonald & McLeod, 2010; Tremlett et al., 2010). Continuous review and pharmacovigilance of codeine based products is an essential activity that needs to be adhered to by both medical and pharmaceutical healthcare professionals.

Prescribed opioid drug use is grounded in a mutual responsibility for transparent communication between service users and health professionals.
Coordinated responses are required to address drug compliance of service users (Robinson et al., 2011). Medical practitioners are advised to question those receiving opioid therapy about current, past and family histories with regard to misuse and addiction (Kahan et al., 2006), and their levels of over the counter and prescribed opioid use (Bradley et al. 1998, Lessenger & Feinberg, 2008).

Raising professional awareness with enhanced efforts to improve skills, confidence and commitment in relation to codeine misuse and dependence is required (Cooper 2013a; Lessenger & Feinberg, 2008; Bride et al., 2003; Reay 2009; Williams & Kokotailo 2006). Management of codeine related issues requires a concerted effort by all stakeholders (prescribers, pharmacists, wholesalers, treatment specialists and drug education specialists). Therefore, a number of specific recommendations in relation to codeine use, misuse and dependence are presented.

9.3 Key recommendations:
Recommendations are presented under the following four headings (1) raising awareness; (2) detecting and managing risk; (3) dispensing practices and (4) monitoring and surveillance of codeine.

9.3.1 Raising Awareness
A significant number of people who consume medications cannot identify the active ingredients in their chosen medications (Roumie & Griffin, 2004). A minority of customers appear willing to accept risks associated with increased access to over the counter medications containing codeine and other active ingredients (Alexander et al. 2005). This is despite high public awareness of the abuse potential of over the counter medicine (Wazaify et al., 2005, 2005a) and pharmacists’ concerns in relation to safety and codeine misuse and dependence. Pharmacists are a trusted by the public as a source of information about over the counter medications (Wawruch et al., 2013). Dobbin & Tobin (2008) have described particular characteristics of individuals misusing codeine containing pharmaceuticals, whereby they may not identify as an addict, the medication prescribed infers safety and sanctioning by the prescriber, and with the products purchased having different legal consequences in comparison to illicit drug users. It is important to recognise variance in groups of codeine misusers and target patient and customer awareness initiatives appropriately.

Recommendations for raising public and professionals’ awareness of prescribed and over the counter codeine use, misuse and dependence:

Professional education and public awareness campaigns should seek to:
- Promote recognition and early detection by healthcare professionals of signs of dependence and withdrawals in relation to codeine based products.
• Promote drug monitoring systems, drug workers and clinicians should be aware of potential presentations for emerging and harmful forms of home produced drug abuse, particularly in the case of injecting drug use.

• Develop and disseminate key health related messages about the risks of exceeding therapeutic dosages of codeine based products.

• Promote improved awareness by professionals in relation to co-prescribing and effects on health.

• Heighten public awareness about the risks surrounding the use of codeine based products whilst driving.

• Increase awareness and access to psychological treatments, for example, cognitive-behavioural therapy, biofeedback, and relaxation techniques for the treatment of chronic headache. (Eng & Lachenmeyer, 1996).

In addition we recommend the further development of:

• Brief interventions at point of sale to raise customer awareness of potential risk of tolerance and dependence over time.

• Parenting classes to highlight the potential side effects of codeine such as respiratory depression when prescribed for children. The evidence suggests that codeine should not be used for children with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures and be contraindicated in breastfeeding women. Moreover, calculations of dose should be based on ideal body weight and not actual body weight.

9.3.2 Detecting and Managing Risk
Evidence on the extent of use, non-compliant use and misuse of pharmaceuticals containing codeine is limited. We recommend more education for codeine misusers about the risks associated with poly use of medication and intake of alcohol and illicit drugs to challenge misinformed perceptions that codeine based products are low risk in terms of their potential for dependence.

Recommendations for detecting and managing risk are as follows:

• Develop community pharmacy practice strategies that promote safety and include the removal of potential products of abuse from point of sale or sight.

• Develop and improve referral mechanisms to primary care teams for people suspected to be misusing codeine or to be dependent.
- Identify patients who are in need of psychological services to assist in pain management.

- Develop strategies to detect deception especially in pain related cases thereby minimising risk for failing to improve or overdose.

- Increase availability of disposable containers for unused prescriptions.

- Incorporate routine enquiries about maternal medication use, including codeine-containing cough preparations, when evaluating new-born infants with evidence of cerebral infarction into assessment protocols.

- Assess opioid addiction with the misuse of ibuprofen-codeine combinations when assessing patients presenting with severe hypokalaemia, pancreatitis and medication overuse headache.

- Develop strategies to manage access and reduce treatment barriers in relation to codeine misuse and dependence. For example, the reluctance of problem opiate users to access treatment is an immediate concern.

- Develop clearer guidelines for interpretation of DSM V criteria for abuse and dependence in chronic pain patients, especially in cases of ‘maladaptive or aberrant behaviour’.

- In cases where substance misuse psychiatric disorders are suspected, a high index of suspicion for cough mixtures misuse/abuse is warranted.

- Develop appropriate harm reduction tactics (needle exchange, bleach distribution, hygiene, provision of filters, foil packs to encourage route reversals, and safer injection facilities), screening, treatment (opiate substitution therapy, antiretroviral therapy), therapy and prevention programmes which target injecting drug users who inject home drug solutions made from codeine.

9.3.3 Dispensing Practices
Safety is central to pharmacists’ decision making with regard to medication dispensing (Hanna & Hughes, 2010). Pharmacy practice strategies that promote safety in relation to codeine dispensing practices are detailed in chapter 3, table 1.

Recommendations for dispensing practices:

We recommend that dispensing practices
• Continue to expand the clinical and public health role of the community pharmacist with on-going inter-disciplinary training for counter assistants, pharmacists and other health professionals.

• Adopt a ‘universal precautions’ systematic approach for each codeine sale, rather than a selective approach based on customer appearance.

• Introduce short term restricted dispensing practices of codeine based products.

• Provide clearer product labelling of the active ingredients in over the counter and prescribed products.

• Remove potential products of abuse from sight in community pharmacies.

• Refuse sales of codeine to users who are problematic misusers or dependent.

• Develop in house pharmacy based brief interventions at point of sale along with supported detoxification in pharmacies.

• Provide needle and syringe exchange services targeting opiate injecting.

9.3.4 Monitoring and Surveillance of Codeine
The monitoring and surveillance of codeine dispensing activity and estimations of levels of customer misuse (both intentional and non-intentional) remains problematic. In addition to therapeutic dependence and such forms of non-compliant use, the diversion, tampering, home manufacture and injecting of over the counter and prescribed pharmaceuticals (containing codeine and other opioids) is a pharmacy, drug surveillance and public health issue (Azbel et al., 2013).

Recommendations for monitoring and surveillance:

• Develop prescription drug monitoring and national online prescription systems.

• Develop and evaluate real time integrated monitoring of the dispensing of prescribed and over the counter use of codeine based products in community pharmacies.

• Ensure routine enquiries by health professionals of patients with regard to prescribed and over the counter codeine medication use.

• Monitor the use of prescription opioids in vulnerable groups (patients with chronic non-malignant pain, patients with cancer pain and illicit drug users) to identify if opioids are substituting for or complicating
mental health and addiction treatment outcomes, thereby minimising risk of overdose.

- Share information in relation to codeine sales and consumers by pharmacists with other pharmacists.

- Develop and evaluate ‘early warning systems’ in relation to codeine use, misuse and dependence (for example the recording of adverse events).

- Consider further development and roll-out to other countries of initiatives which are similar to the South African Codeine Care Project, using The TrustaTAG™

- Monitor and manage conflicts between commercial and customer interests; and between pharmacy, non-pharmacy and internet pharmacy outlets.

9.4 Recommendations for Future Research

A number of key areas are identified for further research in relation to prescribed and over the counter codeine use, misuse and dependence. Research recommendations are listed under six headings: (1) patterns of use, misuse and dependence; (2) prevalence; (3) treatment/interventions; (4) risk; (5) epidemiology and (6) policy.

9.4.1 Patterns of Use, Misuse and Dependence

Research, evaluation studies and reviews are needed to:

- Quantify the extent of prescribed and over the counter codeine use, misuse and dependence, whether intentional or non-intentional. This work should enable the creation of user profiles in relation to patterns and estimations of codeine use, misuse and dependence.

- Explore the views and experiences of users and misusers of various codeine and other products to better understand product interactions and illegal drug and polypharmaceutical use patterns.

- Systematically review studies of poly medication use, for example, benzodiazepines, codeine, comorbidity and drug injecting transitions.

- Investigate motives for codeine misuse which range from self-treating of pain (physical and emotional), sleep and anxiety problems, pleasure and ease of access and personality types, for example, addictive personality.
• Explore the experiences of general practitioners of misuse of prescribed drugs, particularly codeine. These studies should investigate: the challenges encountered by primary care staff, incidences of problematic use, the drugs used in treatment, other treatments considered and referral patterns.

• Systematically review studies and conduct further studies to establish the risk of driving accidents with opioid and codeine use, including the effect of these drugs on driving ability on people with different genetic polymorphisms and on aging drivers. The effects of higher doses of codeine require particular investigation.

• Explore the views and experiences of the injecting user of home produced drugs made from codeine. These studies should pay particular attention to perceptions of harm, user practices, trajectories of use and experiences of services. Drug testing of field samples is warranted to establish content.

9.4.2 Prevalence
• Estimate the prevalence of use, misuse and dependence within the broad and ‘hidden’ spectrum of therapeutic and non-therapeutic patterns of codeine use and misuse. The literature is still unclear as to why the misuse of codeine occurs despite various levels of legislative control and preventative strategies in various countries.

• Estimate the prevalence of codeine misuse and dependence among methadone patients and opiate drug users.

• Estimate the prevalence of internet availability and purchase of medications without a legitimate prescription, including identification of customer characteristics.

• Estimate the prevalence and incidence of persistent and problematic use of codeine in patients with non-cancer chronic pain or non-pain patients.

• Estimate the prevalence and effects of parental social medication of children using codeine products.

• Estimate the prevalence of use of home-made drug solutions made from codeine containing pharmaceuticals.

9.4.3 Treatment/Interventions
• Establish the evidence base for the continued use of codeine compared to non-steroidal anti-inflammatory drugs in the management of mild to moderate pain. Overall the evidence presented to support codeine use as opposed to non-steroidal anti-inflammatory drugs is inconclusive and requires further study.
• Establish the effectiveness (benefits and harms) of codeine compared to alternative medications.

• Explore doctors’ and other prescribers' preferences for prescribing codeine rather than alternative medications and their views on a standard starting dose and subsequent dose titration.

• Establish the effectiveness (benefits and harms) of long-term treatment with short-acting weak opioids.

• Establish the frequency with which prescribers co-prescribe codeine with benzodiazepine or Z drugs.

• Evaluate health professional training in the recognition and management of codeine aberrant behaviours such as forged or lost scripts, requesting certain medications, describing unresolved pain, visiting multiple pharmacies merits further study across a variety of regulatory systems.

• Establish the efficacy and effectiveness of non-pharmacological responses to pain management.

• Synthesise evidence from related fields to guide the development of specific treatment and referral pathways for individuals with codeine dependence. Although general treatment for opiate dependency is primarily detoxification and psychosocial therapy, there is limited evidence available to guide specific policy development and implementation, management initiatives and the development and provision of specific referral and treatment pathways for over the counter codeine misuse and dependence.

• Synthesise evidence from related fields to guide the development of specific treatment protocols for codeine-users who have issues with pain management, have developed problematic opioid use or are co-dependent on benzodiazepines or Z-drugs.

• Explore the self-perception of codeine dependent individuals many of whom do not view themselves as needing help for their codeine dependence and their experience of interventions (counselling, community detoxification, switching onto other medication) in the management of codeine misuse.

• Identify treatment seeking barriers and experiences of people with codeine dependence.

• Evaluate therapeutic interventions, for example, brief interventions, and their efficacy in treating people who present with codeine related misuse and addiction problems.
• Establish the effectiveness of dihydrocodeine in maintenance, cross
over and detoxification treatment of opiate dependency, to ensure a
favourable risk/benefit ratio.

9.4.4 Risk
• Identify predictors of risk of codeine misuse and dependence and
protective factors. Results could inform practices to minimise risk of
dependence, guidelines for early detection and management of
dependence and the pharmaceutical development of safer products.

• Identify genetic risk factors for opioid dependence, opioid induced
hyperalgesia as potential targets for medication therapy and
pharmaceutical development of abuse deterrent opioid formulations.

• Explore the characteristics and habits of opioid shoppers in clinical
practices and the relationship between prescriber characteristics and
risk.

• Synthesise studies of clinical profiles of people who are dependent on
prescribed and over the counter codeine to identify subtypes of users
at risk of adverse consequences and associated motives and
trajectories of use.

• Establish levels of risk and impairment as a result of codeine use and
misuse.

9.4.5 Epidemiology
• Develop pharmaco-epidemiological methods to investigate misuse,
non-medical use, abuse and dependence on codeine based drugs for
self-medications. This would facilitate real time monitoring of prescribing
and dispensing activity with data linked to national medicines abuse
systems.

• Investigate self-medication and patterns of codeine use among the
following key groups: youth; older people, elderly, problematic drug
users, pain patients, individuals prescribed anti-anxiety medication,
methadone maintenance treatment patients and individuals accessing
internet forums.

• Estimate street pricing of diverted prescription codeine and home-
made drug solutions produced using codeine based pharmaceuticals.

9.4.6 Policy
• Guide the development of accessible and specific regulatory,
pharmaceutical, treatment and community detoxification protocols for
codeine misuse and dependence.
9.5 Limitations of the review
This scoping review was conducted as an exercise aiming to provide a starting point for future research in the area of codeine use, misuse and dependence by mapping the existing evidence base and capturing what challenges are presented. The management of codeine related issues requires a concerted effort by all stakeholders and this is a varying global challenge specific to individual countries. A number of specific recommendations in relation to codeine use, misuse and dependence are presented.

The review of the literature followed a systematic process but cannot claim to be exhaustive in its coverage. In particular, there may be ongoing, as yet unpublished pieces of research not described here. It must also be acknowledged that while our search was comprehensive and included an extensive body of literature, across varying populations, conditions and study designs, that some literature may have been missed. Furthermore, social media is constantly evolving leading to challenges in keeping the search updated. While many specific topic areas were identified, further analysis of these areas is now required. For example, peer reviewed publications in relation to prevalence and codeine, and the development and implementation of policy to guide treatment and practice for over the counter codeine use, misuse and dependence are needed.
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Ford, C., & Good, B. (2007). Dependence on over the counter drugs: Over the counter drugs can be highly addictive. *British Medical Journal*, 334(7600), 917-918.


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Structural and individual barriers and facilitators to HIV medication adherence among injection drug users in Kiev, Ukraine. *AIDS Care*, 22(11), 1305–1313.


review of published English and international evidence and available data to inform consideration of the extent of dependence and harm. London and Bristol, UK: The National Addiction Centre, Kings College London and School of Social and Community Medicine, University of Bristol, United Kingdom.


randomised controlled trial comparing dihydrocodeine and buprenorphine for opiate detoxification. *Trials, 8*(1), 1-5


Substance Abuse and Mental Health Services Administration, *Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings*, NSDUH Series H-48, HHS Publication No. (SMA)


Tremlett, M., Anderson, B. J., & Wolf, A. (2010). Pro-con debate: is codeine a drug that still has a useful role in pediatric practice? *Pediatric...


Appendix 1

Characteristics of the research studies included in the review
<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Research aim</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention / outcome measure</th>
<th>Findings</th>
<th>Author’s conclusions/recommendation</th>
<th>Theme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abt 2012, USA</td>
<td>Pain treatment with aspirin versus paracetamol with codeine</td>
<td>Randomized controlled study</td>
<td>302 patients in this dental pain study, 676 patients in the headache study</td>
<td>The 2 main outcome measures were the sum of pain intensity differences from baseline over 6 h and the sum of pain relief scores at 30 min, 1, 2, 3, 4, 5, and 6 h after taking medication.</td>
<td>For the dental study, aspirin and paracetamol with codeine showed a statistically significant benefit when compared to placebo at all-time points. In the tension-type headache study, both aspirin and paracetamol with codeine were significantly better than placebo at all-time points but were not significantly different from each other.</td>
<td>Aspirin provides a statistically significant benefit for relief of dental pain and tension-type headaches compared to placebo, and similar pain relief when compared to paracetamol and codeine.</td>
<td>Therapeutic use-effectiveness when compared to other drugs or placebo</td>
</tr>
<tr>
<td>Agnich et al. 2013, USA</td>
<td>To determine the prevalence and characteristics of purple drank users among a sample of college students in the United States.</td>
<td>Quantitative survey assessing misuse of codeine cough syrup</td>
<td>2,349 students The sample was 51.6% female, 68.9% White, 24.4% African American, 2.8% Hispanic, and 3.0% Native American, had a mean age of 20.06 (SD = 3.01),</td>
<td>Prevalence rates Purple drank use was: 1) Much higher among students from urban areas (12.2% urban versus 7.3% suburban, 4% rural) 2) Lowest use was reported among African Americans, (5%) along with Asian Americans. (5.1%) 3) Hispanics (15.65) and Native Americans (16.7%) were significantly higher. Students who had lower GPAs, identified as a member of the LGBT community, and used marijuana and alcohol were more likely to report purple drank use.</td>
<td>Significant gaps in treatment may exist for both Hispanic and Native American students practitioners should consider urban male youth of all racial backgrounds as potential misusers of codeine cough syrup, and note that misuse may be more common within the LGBT community.</td>
<td>Prevalence of cough mixture misuse - students</td>
<td></td>
</tr>
<tr>
<td>Allotey et al. 2004,</td>
<td>To identify the patterns of use of over the counter medications are used as a</td>
<td>Qualitative study using in-</td>
<td>40 parents with</td>
<td>There were 3 striking and readily apparent themes in the use of over the counter</td>
<td>over the counter medications are used as a</td>
<td>Prevalence of cough mixture misuse - students</td>
<td></td>
</tr>
</tbody>
</table>

150
Australia

over-the-counter medications among children

depth interviews. Snowball sampling was utilized

children <5 years of age

the counter medicines

medications among children. Codeine was given in 8 cases. One was the administration of over the counter medications as a form of “social medication,” to give parents control over children’s behaviour that they perceived as fractious and irritating.

A related theme was the use of over the counter medications to reduce the inconvenience to the parents of having a sick child, again giving parents greater control and better time-management abilities. Finally, paracetamol was considered by many parents to have almost miraculous properties in calming, sedating, and lifting the mood of children.

form of social medication for the control and maintenance of “good” behaviour among children. The use of over the counter medications for the treatment of minor ailments among children is widespread, despite the lack of evidence.

Almarsdotir & Grimsso่น 2000, Denmark

To investigate the impact of increased access of over-the-counter codeine on its use in Iceland

Inferences about the impact of the legislation are based on an interrupted time series that contrasts the monthly use of over-the-counter pain relievers containing codeine before and after the legislation took effect.

Monthly sales data of codeine medication sold over the counter

Behavioural changes in purchasing codeine over the counter

The total use of over-the-counter pain relievers containing codeine as well as those containing paracetamol and codeine has risen steadily throughout the period under study. The interrupted time series did not show a substantial effect from the legislative change on the use of all over-the-counter codeine pain relievers, paracetamol with codeine, and aspirin with codeine combinations.

The assumption that increased access leads to irrational use of over-the-counter medicines is not substantiated in the case of over-the-counter pain relievers containing codeine.

Amato et al. 2013, France

Effects of three therapeutic doses of codeine/paracetamol on driving performance, a Psychomotor Vigilance Test, and subjective

Balanced cross-over randomised, double-blind placebo controlled study.

16 subjects (50% female) with minimum 2 years driving experience

Gelatin capsules containing Codeine/Paracetamol 20mg/400mg, 40/800mg

No statistical difference on the driving tests or relating to dose. However, significant, though modest, correlations were observed between the driving parameters and both morphine and codeine blood concentrations. Statistical dose-related difference in the subjective Karolinska Sleepiness Scale (20mg/400mg vs. 40mg/800mg).

The study did not demonstrate a dose-effect relationship, but did suggest a blood concentration – effect relationship. This is important to take into account because metabolism of codeine is genetically polymorphic.

Consequences of Codeine use, misuse and Abuse – Impairment of
| Backmun d et al. 2001, Germany | Completion of detoxification program using methadone or codeine in interventions heroin users | Retrospective study of heroin users in detoxification programme | 1070 patients | Completed detoxification program | Rates of completion 50.4% (OR 1.8) of methadone substituted, 45.5% (OR 1.5) of codeine substituted patients and 35.9% (OR 1) of injecting illicit heroin users (control) | This was statistically significant P= 0.006
Thus, drug users treated with methadone have better outcome in detoxification treatment |
| Basu et al. 2010, India | To document changes in patients registered in a de-addiction centre in north India over three decades. | Retrospective study | Case notes of all patients registered in the centre from September 1978 till December 31, 2008 was reviewed. Comparisons were made among three decades. | Use of opioids; Dependence on opioids | The number of registered subjects increased eight-fold over the decades, and age of the subjects presenting for the treatment decreased. The percentages of subjects presenting for the treatment with opioid dependence were 36.8% 42.9% and 53.2% respectively for the three decades. The proportion of subjects using natural opioids decreased over the three decades with a concomitant increase in prescription opioids such as buprenorphine, codeine and dextropropoxyphene | Our results showed major shifts in the patterns of substance abuse in clinic-attending patients in north India over the three decades from 1978 till 2008. These have important implications for all the stakeholders concerned with combating the challenge of psychoactive substance abuse in our society. |
| Bachs et al., 2003 Norway | The effects of codeine alone and not due to its morphine metabolite on clinical test for drunkenness | Review of database at National Institute for Forensic Toxicology, Oslo, Norway | 43 cases of suspected drugged drivers with codeine in blood samples but no morphine | Codeine blood concentration was compared with the conclusion from the corresponding controls. 23 were judged as “not impaired”, and 20 as “impaired”. There was a statistically significant difference in concentration between the two groups. The odds ratios for being judged as impaired were 6 (95% CI 1–32, P=0.04) and 19 (95% CI 2–182, P=0.01) for a “medium high” concentration group and a “high” concentration group. | Codeine appears to have some dose-dependent effect on the central nervous system that may lead to impairment as judged from a Clinical Test for Drunkenness, independent of measurable blood morphine concentrations. | Consequences of Codeine use, misuse and Abuse – Impairment of performance |
### Bachs et al. 2008, Norway

To explore the use of codeine analgesics in individual patients in Norway, giving special attention to the 10% who consume the highest amounts.

| Norwegian Prescription Database on patients who were dispensed at least one codeine analgesic prescription during 2006. | 386,836 patients | Age and gender specific 1-year periodic Prevalence rates. | In the year 2006, a total of 386,836 individuals filled at least one prescription for codeine analgesics excluding cancer patients. The crude prevalence for the use of codeine analgesics was 7.3% and 9.3% of the male and female Norwegian population, respectively. 12% of women and 9% of men who filled codeine prescription received 120 defined daily doses (DDD) or more of codeine analgesics in 2006 (moderate to high consumers). 50% of those patients (21,759) were also dispensed large amounts of benzodiazepines or carisoprodol over the same period. | This supports the view that some codeine effects do not seem to be mediated by morphine. | Prevalence of codeine analgesic use in Norway |

### Barreto et al. 2011, Australia

To analyse drug-induced acute pancreatitis

| A retrospective analysis of patients presenting with acute pancreatitis | 328 patients admitted to hospital between January 2006 and April 2011 | To measure the incidence, presentation, course and outcome of drug-induced acute pancreatitis | 11 patients out of the 328 were found to have pancreatitis associated with drug ingestion. 5 of these were probably due to codeine. 2 of these patients had a history of pancreatitis following codeine ingestion that wasn’t recognized as a factor at the time. 1 of the codeine patients had a prior cholecystectomy. Codeine was the drug most commonly associated with the causation of acute pancreatitis. Routine prescription drugs, as an aetiological factor, accounted for 3.4% of cases of acute pancreatitis. This is likely to be an under-estimated due to the stringent criteria to determine causality | Adverse health effects |

### Brands et al. 2004, Canada

To characterize prescription opioid dependent patients in a methadone maintenance treatment (MMT) program

<p>| Detailed retrospective chart review of new admissions | 178 new admissions: Four groups were identified: 24% had used prescription opioids only; 24% used prescription opioids only; 24% used prescription opioids only; 24% used prescription opioids only. | Profiles of opioid users based on social class | DSM IV dependent codeine users were relatively common. Those dependant on prescription opioids such were codeine (45.5%) and oxycodone (46.6%) respectively. There were no significant differences found amongst the groups in measures of social stability. Those dependant on prescription opioids alone were less likely to use illicit non-opioid drugs or to be associated with injection drug use. Those that used prescription opioids only or initially were more likely to have ongoing pain is a common feature of those on prescription opioids in the methadone programme Better understanding of the complex relationships between pain, mental health and addiction in order to develop optimal prevention and treatment strategies for prescription opioid dependence. | Characteristics of prescription opioid dependent patients |</p>
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Title</th>
<th>Study Design</th>
<th>Participants</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buckeridge et al. 2010, Canada</td>
<td>Risk of Injury Associated with Opioid Use in Older Adults</td>
<td>A historical cohort study</td>
<td>403,339 adults over 65 years on a database held by a universal public health insurance programme</td>
<td>Over a 1-year follow-up period the database was analysed to estimate the risk of fall-related injuries associated with the use of opioids. During the study 15.3% were prescribed an opioid with codeine containing products being the most common (10.8%). After adjustment for patient characteristics, there was a statistically significantly greater risk of injury with opioid use. Within low-potency opioids, codeine combinations were associated with the greatest risk, a 127% increase in risk of injury per one adult dose increase. Higher doses of low-potency opioids, particularly codeine combinations, are prevalent and result in twice the risk of injury. Early detection and intervention in increasing use of opioids for pain management may be beneficial in reducing the risk of injury.</td>
</tr>
<tr>
<td>Busto et al. 1998, Canada</td>
<td>A mixed method study of the characteristics, patterns of drug use, treatment and outcome of patients severely dependent on opioids</td>
<td>Prospective structured interviews Additional information from charts</td>
<td>58 patients admitted consecutively to the medical unit of an addiction research foundation with a diagnosis of severe oral opioid dependence</td>
<td>Levels of dependence</td>
</tr>
<tr>
<td>Butler &amp; Sheridan 2010, Australia</td>
<td>To understand issues for primary care health practitioners in relation to prescription drug misuse (PDM), by exploring the attitudes and experiences of healthcare professionals with respect to PDM.</td>
<td>Cross-sectional. Qualitative interviews to explore attitudes to PDM</td>
<td>General practitioner s (17), community pharmacist s (16) and ‘key experts’ (18)</td>
<td>Attitudes to abuse Experience s of abuse</td>
</tr>
<tr>
<td>Cartabuk e et al. 2013, USA</td>
<td>Use of codeine by Paediatricians</td>
<td>Quantitative survey examining differences in paediatric codeine prescribing among medical and healthcare professionals. 298 participants - response rate 26.7%</td>
<td>Impact of years of experience on prescribing practice</td>
<td>43.3% prescribed codeine for pain management in children. There was no significant difference among providers based on years of experience. 98% of sample used actual body weight instead of ideal body weight. All respondents stated that they instructed parents to contact the physician if their child became lethargic or unresponsive, 10.9% did not specifically counsel parents to seek assistance if their child developed difficulty breathing. Calculations of dose should be based on ideal body weight. Parents should be educated to recognize the potential side effects of codeine such as respiratory depression.</td>
</tr>
<tr>
<td>Cooper 2011, UK</td>
<td>To describe and understand current issues relating to over the counter medicine addiction by investigating the experiences of Cooper 2011, UK</td>
<td>Qualitative, semi-structured interviews by telephone, in-person -audio recorded and one participant</td>
<td>Three purposively sampled groups. First group of 16 key stakeholder s from</td>
<td>Evaluate opinion over the counter use</td>
</tr>
</tbody>
</table>
individuals affected by over the counter medicine addiction in the United Kingdom (UK), pharmacists and medicines counter assistants (MCAs), and key UK stakeholders. Additional aims involved exploring the role of the internet, pharmacy involvement, and different types of medicine use.

requested email/text-based communication.

organisatio ns and employm en t related to over the counter medicine addiction. Second group of 10 pharmacist s and 7 MCAs. Third group of 25 individuals recruited via two UK on-line medicine addiction support groups (Over count and Codeine Free)

migraine, and period, joint or post-operative pain.

Recurrent patterns of drug-seeking behaviour were described, including purchasing and use rituals such as brand specificity, deception and secretiveness, anxiety when supplies diminished, and intentionally varying the pharmacies.

Individuals raised safety concerns about internet-supplied medicines. All individuals had attempted to stop but some were still taking an over the counter medicine. None sought pharmacy advice, and some explicitly rejected medical help or support from help forums due to concerns about their addiction being recorded, concerns about lack of GP understanding, or a desire to hide their addiction. Individuals were aware of risks associated with over the counter medicines.

Stakeholders held mixed views about pharmacists and their role, and viewed the internet availability of medicines as a currently small but significant future issue. Pharmacists could be grouped into those who were negative about pharmacy involvement in supporting over the counter medicine abuse or addiction.

Greater awareness of the addiction potential of over the counter medicines is needed for the public, pharmacists and medical prescribers, along with appropriate communication about, and reviews of, treatment and support options, for this distinct group.

Cooper 2013b, UK To describe the experiences and views of those self-reporting over the counter medicine abuse, and why medicines were taken, how they were obtained and associated treatment and support sought. Qualitative study using in-depth mainly telephone interviews. A purposive sample of 25 adults, aged 20–60s, 13 women. View on taking over the counter medicines Individuals considered themselves ‘addicted’, but socially and economically active and different from illicit substance misusers. They blamed themselves for losing control over their medicine use, which usually began for genuine medical reasons and not experimentation and was often linked to the cessation of, or ongoing, medical prescribing. Codeine, in compound analgesics, was the main medicine implicated with three distinct dose ranges emerging with decongestant and sedative antihistamine abuse also being reported. who sometimes took slightly higher than recommended doses; and type III included those who took significantly higher doses than recommended. All three types described withdrawal symptoms and using the product for different reasons than clinically indicated

Individuals considered themselves ‘addicted’, but socially and economically active and different from illicit substance misusers. They blamed themselves for losing control over their medicine use, which usually began for genuine medical reasons and not experimentation and was often linked to the cessation of, or ongoing, medical prescribing. Codeine, in compound analgesics, was the main medicine implicated with three distinct dose ranges emerging with decongestant and sedative antihistamine abuse also being reported.

Addiction/misuse/a buse of over the counter medicine s
Subsequent use was for the ‘buzz’ or similar effects of the opiate, which was obtained by having lists of pharmacies to visit and occasionally using internet suppliers. Perceived withdrawal symptoms were described for all three dose ranges, and work and health problems were reported with higher doses. Mixed views about different treatment and support options emerged with standard drug treatment services being considered inappropriate for over the counter medicines and concerns that this ‘hidden addiction’ was recorded in medical notes. Most supported the continued availability of over the counter medicines with appropriate addiction warnings.

| Cooper 2013a, UK | To explore the experiences and views of community pharmacy staff to over the counter medicine abuse | Qualitative study using semi-structured interviews with 10 pharmacists and 7 medicine counter assistants | Experience and views | To explore the experience and views of community pharmacy staff in relation to current practices and concerns, management and support relating to over the counter medicine abuse | A surveillance role was apparent for assistants, who placed emphasis on regulations, procedure and monitoring frequency of purchases to manage abuse, with referral on to pharmacists. Frequency of purchase was central to assistants’ definition of those suspected of over the counter medicine abuse, which pharmacists also utilised as well as a distinction between intentional abuse and unintentional medicine misuse. A lack of information about customers, easy access to, and poor communication between community pharmacies were emergent barriers to pharmacists providing more support. | Policy implications include the need for improved knowledge for community pharmacy staff about signposting to relevant services, increased awareness of who might be affected, and a review of how pharmacists can have more information about patients to inform over the counter medicine sales. | Views/experience on over the counter medicine use/abuse |

| Daniufait ye et al. 2006, USA | To develop appropriate treatment and prevention programs, the population of pharmaceutical | Exploratory study based on qualitative interviews | Participants discussed a number of different reasons, including self-medication of emotional and physical pain, legitimate medical prescriptions related to chronic pain management, social influences, recreation, and easy access to pharmaceutical opioids. | Interventions development | }
<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Participants</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis, &amp; Johnson, 2008, USA</td>
<td>To document patterns of (prescription opioid) PO use, misuse, and diversion among street drug users, and begins to indicate how drug culture practices interact with the legitimate therapeutic goals of PO prescriptions (e.g. pain management).</td>
<td>Brief interviews on the various motivations or aims for PO use. 586 participants recruited from outreach and locales frequented by heroin/methadone users.</td>
<td>Methadone was used (71.9%) and sold (64.7%) at a higher level than OxyContin, Vicodin, and Percocet. 33% used codeine and 18.5% sold it POs are an important component of street drug users’ drug-taking regimes, especially those who are Physically Ill Chemical Abusers</td>
</tr>
<tr>
<td>Derry et al. 2013, UK</td>
<td>Treatment of acute postoperative pain with a single dose oral ibuprofen plus codeine</td>
<td>Meta-analysis of 4 studies 1342 participants from six studies</td>
<td>Compared ibuprofen plus codeine with placebo and with the same dose of ibuprofen alone. In four studies (443 participants) using ibuprofen 400 mg plus codeine 25.6 to 60 mg (high dose codeine) 64% of participants had at least 50% maximum pain relief with the combination compared to 18% with placebo. The NNT was 2.2 (95% CI 1.8 to 2.6). In three studies (204 participants) ibuprofen plus codeine (any dose) was better than the same dose of ibuprofen (69% versus 55%) but the result was only borderline significant with a relative benefit of 1.3 (95% CI 1.01 to 1.6). In two studies (159 participants) ibuprofen plus codeine appeared to be better than the same dose of codeine alone (69% versus 33%)</td>
</tr>
<tr>
<td>Dutch 2008</td>
<td>Misuse of Nurofen Plus® leading to Case Reports</td>
<td>Two adult patients</td>
<td>Both patients were found to have confirmed perforated gastric ulcers</td>
</tr>
<tr>
<td>Country</td>
<td>Condition</td>
<td>A&amp;E Admission</td>
<td>History of Drug Use</td>
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<tr>
<td>Australia</td>
<td>perforated gastric ulcers</td>
<td>admitted to A&amp;E, one with epigastric and one with abdominal pain</td>
<td>high use of Nurofen Plus® for three weeks and the other had taken ‘a packet a day’ for the previous year</td>
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</table>

| Dyer et al. 2004, UK | Case report of hypokalaemia with ibuprofen and codeine | Case Report | Hypokalaemia following suspected Nurofen Plus® (Ibuprofen and Codeine) ingestion. Patient denied taking on some occasions | There were complicating factors with this case such as the patient's denial of Nurofen Plus® usage, psychiatric history and substance misuse. However, there is a possibility that the ibuprofen lead to the hypokalaemia | Ibuprofen use should be considered in patients presenting with hypokalaemia, especially considering it combination with a drug with abuse potential, codeine in an over the counter formulation |

| Eggen, & Andrew 1994, Norway | To investigate the use of controlled analgesics in a general population. | All prescriptions dispensed during one year were quantitatively analysed. | All prescriptions for controlled analgesics dispensed from the three pharmacies in the municipality of Troms, Norway. 5354 persons had 10 824 prescriptions. | About 8% of the population had obtained one or more prescriptions of controlled analgesics. The sporadic users were in the majority. About 8% of the population had obtained one or more prescriptions of controlled analgesics. Combined codeine preparations were by far the most frequently prescribed sub-groups. The users of buprenorphine and entazocine differed in several aspects from the codeine users. The | Monitoring of prescribing and use of controlled analgesics according to certain criteria may uncover possible misuse. Use of controlled analgesics is common, but sporadic use is dominant. Drug use increases with age, and women use more drugs than men. | Adverse health effects |

<p>| | | | | | | Prevalence of codeine analgesics in a general population. | | |</p>
<table>
<thead>
<tr>
<th>Source</th>
<th>Methodology</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elwood 2001, USA</td>
<td>To explore emerging drug trend of codeine syrup abuse and codeine overdose leading to fatalities</td>
<td>A literature search of scientific journals and news media, interviews with community authorities, and guided interviews with 25 adults who reported using codeine cough syrup in the 30 days preceding their interviews. The procurement and misuse of codeine cough syrup in Houston has increased over the past three years. It appears that lean/syrup use has grown in response to the poor quality of illegal drugs and the relative ease of its procurement without fear of arrest.</td>
</tr>
<tr>
<td>Eng &amp; Lachenmeyer 1996, USA</td>
<td>Codeine self-medication in a headache patient</td>
<td>Case report of a chronic headache patient. Guided qualitative interviews with 25 adults who reported using codeine cough syrup in the 30 days preceding their interviews. Views on trends in codeine cough syrup abuse. Study highlights the need to identify patients who are in need of psychological services to assist in pain management.</td>
</tr>
<tr>
<td>Ernest et al. 2010, Australia</td>
<td>To analyse profound hypokalaemia due to Nurofen Plus® and Red Bull misuse</td>
<td>Case Report 39-year-old Adult male presenting to A&amp;E with hypokalaemia. After detoxification program, the patient began cognitive-behavioral treatment. The cause of the patient’s hypokalaemia was clouded by the unusually high doses of multiple substances ingested. The authors consider that the patient’s hypokalaemia was most probably attributable to the significant ingestion of Nurofen Plus.</td>
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</table>

Adverse health effects

The procurement and misuse of prescription cough syrup is a sticky business that requires prevention, treatment, and social welfare precautions to ameliorate the problem.

Characteristics of codeine misusers

The value of psychological treatments and cognitive-behavioral, biofeedback, and relaxation techniques for headache treatment should be explored.
161 days. The patient was also taking prescribed haloperidol, diazepam, alprazolam and salbutamol for various conditions. He had also ingested 24 cans of Red Bull energy drink and 2.5 bottles (1875mL) of the homeopathic preparation, Nervatona Calm over three days. Another potential contributor to the hypokalaemia and myopathy may have been the caffeine from the Red Bull. The Nervatona Calm may have contributed to the myopathy.

**Evans et al. 2010, New Zealand**

**Combination non-steroidal anti-inflammatory drugs codeine preparations and gastrointestinal toxicity**

**Case Study**

| 35-year-old Adult male admitted to hospital and admitted taking 100 Nurofen Plus® per day for back pain for an unspecified duration |
| The patient was prescribed a reducing codeine dose as an opiate substitute. |
| Gastroscopy revealed a significant gastrointestinal pathology secondary to the gross overuse of combination non-steroidal anti-inflammatory drug/codeine products |

It is known that non-steroidal anti-inflammatory drugs can cause multiple adverse effects. The addition of codeine causes an addictive potential.

It is hoped that the reclassification to Pharmacist-only will reduce the abuse potential and subsequent clinical adverse effects as seen in this patient.

**Fitzcharles et al. 2011, Canada**

**To evaluate the reported use of opioids and the associations there of in patients**

| A chart review of all patients referred to a tertiary care pain centre |
| All patients referred to a tertiary care pain centre |
| Use of opioids Characteristics of opioid |
| Opioid use by 32% of 457 patients referred to a multidisciplinary fibromyalgia clinic, with over two thirds using strong opioids. 16% of this sample used codeine. |

Any physician prescribing opioids for a patient with fibromyalgia should practice responsible prescribing behaviours with

Characteristics of opioid users.
<table>
<thead>
<tr>
<th>Study</th>
<th>Overview</th>
<th>Methods</th>
<th>Findings</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleming, McElhinney, &amp; Hughes 2004, Netherlands</td>
<td>To develop and pilot a harm-minimisation model for the identification and treatment of over-the-counter (over the counter) drug abuse/misuse by community pharmacists.</td>
<td>Focus group study with 24 experts consisting of GPs, pharmacists, health promotion practitioners, sociologist and psychiatrics</td>
<td>Some success was noted in that clients agreed to stop using the product and/or to try safer alternatives. As expected, some sales had to be refused, as the client was unwilling to accept the pharmacist’s intervention.</td>
<td>Although successful in a number of areas, the completion of the pilot has identified opportunities for further refinement of the model. Future work will focus on improving pharmacist communication skills, particularly in the area of motivational interviewing.</td>
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</table>

Opioid use was more commonly associated with lower education, unemployment, disability payments, current unstable psychiatric disorder, a history of substance abuse, and previous suicide attempts. **Attention to function and psychological status, use of screening tools or treatment agreements where appropriate, and be alert to any indication of aberrant drug behaviour.**

The use of opioids in fibromyalgia requires further study in order to examine health outcome parameters.
<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Data Collection</th>
<th>Outcome Measure</th>
<th>Methods</th>
<th>Findings</th>
<th>Conclusions</th>
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</thead>
<tbody>
<tr>
<td>Fleming et al. 2007, USA</td>
<td>Looking at Substance Use Disorders in a Primary Care Sample Relationship of positive urine screens and aberrant drug behaviours to opioid use disorders</td>
<td>A quantitative study using a 15 point scale for chronic pain, 12 point aberrant scale, prescription medication survey, substance dependence severity scale and addiction severity index</td>
<td>801 participants from the primary care practices of 235 family physicians</td>
<td>Dependence on opioids</td>
<td>Codeine was prescribed (30/500 for 68 of the patients 5.6% of the group) The 6 most common pain diagnoses were degenerative arthritis, low back pain, migraine headaches, neuropathy, and fibromyalgia The point prevalence of current (DSM-IV criteria in the past 30 days) substance abuse and/or dependence was 9.7% (n = 78) and 3.8% (30) for an opioid use disorder</td>
<td>This study found that the frequency of opioid use disorders was 4 times higher in patients receiving opioid therapy compared with general population samples (3.8% vs 0.9%) The study also provides quantitative data linking aberrant drug behaviours to opioid use disorders</td>
</tr>
<tr>
<td>Forman et al. 2006, USA</td>
<td>To determine the availability of web sites offering to sell opioid medications without prescriptions and to develop basic knowledge about parameters affecting the types of web sites obtained in searches.</td>
<td>Forty-seven Internet searches were conducted</td>
<td>2 researchers</td>
<td>No of Hits for opioid search terms</td>
<td>In searches with terms such as “no prescription codeine” and “Vicodin,” over 50% of the links obtained were coded as “No Prescription Website (NPW).” The proportion of links yielding NPWs was greater when the phrase “no prescription” was added to the opioid term. More than 300 opioid NPWs were identified and entered into a database</td>
<td>The emergence of NPWs introduces a new vector for unregulated access to opioids. Research is needed to determine the effect of NPWs on prescription opioid use initiation, misuse, and dependence.</td>
</tr>
<tr>
<td>Frei et al. 2010, Australia</td>
<td>To investigate morbidity related to misuse of over-the-counter (over the counter) Codeine-ibuprofen analgesics.</td>
<td>Prospective case series collected from Victorian hospital-based addiction medicine specialists between May Twenty-seven patients with serious morbidity were included, mainly with Morbidity associated with codeine–ibuprofen misuse.</td>
<td>The patients were taking mean daily doses of 435–602mg of codeine phosphate and 6800–9400mg ibuprofen. Most patients had no previous history of substance use disorder. The main treatment was opioid substitution treatment with buprenorphine–naloxone or methadone.</td>
<td>Although codeine can be considered a relatively weak opioid analgesic, it is nevertheless addictive, and the significant morbidity and specific patient characteristics associated with overuse of codeine–ibuprofen analgesics; Addiction/misuse/alcoholism of over the counter medicine; Consequences of</td>
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<tr>
<td>Fredheim et al. 2009, Norway</td>
<td>To determine whether codeine is primarily used for acute pain or whether there is a prescription pattern indicating problematic opioid use.</td>
<td>3 years of prescription data 2004-2006 in Norway</td>
<td>All users of codeine compounds recorded in the Norway prescription data base (NorPD) during the years 2004, 2005 and 2006.</td>
<td>Patterns of codeine use for non-malignant pain</td>
<td>About one in 10 adult persons in Norway were dispensed codeine in 2005. A majority (58%) received codeine only once, most likely for acute pain, whereas a small minority (0.5%) had a prescription pattern indicating problematic opioid use.</td>
<td>Clinical trials are needed in order to establish whether patients benefit from such a long-term treatment with short-acting weak opioids. Research is also needed on the treatment of the small but important group of codeine-using patients who appear to have developed problematic opioid use. Instead of making codeine less available, the results of this study indicate that one should concentrate on preventing and helping those who are at risk of or have already developed problematic opioid use.</td>
</tr>
<tr>
<td>Fry et al. 2007, Australia</td>
<td>Understanding of the relationship between benzodiazepine and pharmaceutical opioid use and crime.</td>
<td>Multiple methods: Qualitative key informant interviews; quantitative survey; and data collection law enforcement and health sectors in three select Australian jurisdictions (Melbourne, Hobart, Darwin)</td>
<td>Stage 1: A total of 33 key informant Stage 2: a face-to-face survey of people who inject drugs n=303</td>
<td>Crime rate based on 27% of participants used codeine in the previous 6 months Prescription drugs are reportedly relatively easy to obtain on the street. Low level of reported organised criminal activity related to the procurement of prescription pharmaceuticals.</td>
<td>There may be some relationship between the use of prescription drugs, dependence and some criminal activity. Poly-drug use as a feature of illicit prescription pharmaceutical markets. There remains a need in Australia for a type of comprehensive national prescription drug misuse prevention monitoring system.</td>
<td>Prevalence of opioid misuse who participate in crime</td>
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<tr>
<td>Study</td>
<td>Title</td>
<td>Type</td>
<td>Methods</td>
<td>Findings</td>
<td>Conclusions</td>
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<tr>
<td>Furlan et al. 2006, Canada</td>
<td>Effectiveness and side effects of opioids in treatment of chronic non-cancer pain</td>
<td>Meta-analysis</td>
<td>6019 patients from 41 randomized trials</td>
<td>Outcomes measures included pain, function or side effects</td>
<td>Opioids were more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain or fibromyalgia. Strong, but not weak, opioids were significantly superior to naproxen and nortriptyline, and only for pain relief. Among the side effects of opioids, only constipation and nausea were clinically and statistically significant. Despite the relative shortness of the trials, more than one third of the participants abandoned treatment.</td>
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<tr>
<td>Gerostamoulos et al. 1996, Australia</td>
<td>To investigate the incidence and role of codeine in drug-related deaths in Victoria over a 5-year period.</td>
<td>Case studies - autopsy reports</td>
<td>There were a total of 107 cases involving codeine, representing 8.8% of all drug-related deaths in this period in Victoria. There were only six fatalities in which codeine was considered the major poison. These 6 case studies are</td>
<td>Findings of 6 case studies: The mean (±SD) blood concentration of total codeine was 4.0 ± 2.3 mg/L. Findings of 101 other fatalities: Cause of death was given as toxicity due to codeine and other drugs. These cases had a mean blood total codeine concentration of 1.8 ± 3.3 mg/L (range, 0.04-26 mg/L). Paracetamol was the most common of the “other” drugs found. Paracetamol is usually combined with codeine and propoxyphene in many preparations for the treatment of pain and common colds.</td>
<td>Weak and strong opioids outperformed placebo for pain and function in all types of chronic non-cancer pain. Other drugs produced better functional outcomes than opioids, whereas for pain relief they were outperformed only by strong opioids. Therapeutic use-effectiveness when compared to other drugs or placebo.</td>
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Free codeine concentrations >0.4 mg/L and total codeine concentrations >2.0 mg/L may be sufficient to cause death in the absence of any other contributing factors. Occurrences of death due to codeine.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Research Question</th>
<th>Design</th>
<th>Participants</th>
<th>Outcome Measures</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Glover et al. 2003, USA</td>
<td>To identify the medications that is consumed by a rural obstetric population during pregnancy.</td>
<td>Longitudinal study (26 months) of medication usage and discontinuation. 2086 qualitative interviews concerning the use of prescription, over-the-counter and herbal medicines.</td>
<td>578 (pregnant women)</td>
<td>Level of consumption</td>
<td>95.8% of the participants took prescription medications, 92.6% of the participants self-medicating with over-the-counter medications, and 45.2% of the participants used herbal medications. Over time, consumption of over-the-counter medications exceeded prescription medication use. Fifteen % of the pregnant women took ibuprofen at some point during the pregnancy (5.7% in the third trimester). Eight % of the women were noncompliant and 20% incompletely compliant with prenatal vitamin and mineral formulations.</td>
<td>Medication use was substantial in this population. Medications (eg, ibuprofen) that are contraindicated in pregnancy were used at unexpectedly high rates. Of the three medication classes, over the counter medications were used most frequently.</td>
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<tr>
<td>Hall et al. 2013, UK</td>
<td>Epidemiology and treatment of neuropathic pain</td>
<td>Observational descriptive study</td>
<td>5,920 patients with post-herpetic neuralgia (PHN), 5,340 with painful diabetic neuropathy (PDN), and 185 with phantom limb pain P (PLP)</td>
<td>Recording of neuropathic back and post-operative pain.</td>
<td>First line treatment of PDN &amp; PLP is with amitriptyline or gabapentin. PHN pain treated with amitryptaline or Co-Codamol® co-Paracetamol, co-dydramol (paracetamol-dihydrocodeine) and capsaicin were also prescribed in one or more condition.</td>
<td>The UK incidence of diagnosed PHN has increased with the incidence of back-pain and post-operative pain unclear. While use of licenced antiepileptics increased, prescribing of therapy with little evidence of efficacy in neuropathic pain is still common. Treatment was often not in-line with current guidance.</td>
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<tr>
<td>Hamer et al. 2013, Australia</td>
<td>To explore how the up scheduling of over the counter combination analgesics containing codeine (CACC)</td>
<td>A descriptive qualitative design was used, with data collected via face-to-face semi-structured 11 pharmacist s</td>
<td>Experience s in supply of over the counter codeine</td>
<td>Pharmacists were found to monitor the supply of over the counter CACC by recording sales and to intervene when they felt that the medication was being used too frequently. They perceived a number of challenges surrounding the provision of over the counter CACC including: supply from other pharmacies, establishing.</td>
<td>A number of challenges faced by community pharmacists to ensure the safe provision of over the counter CACC and to assist codeine dependent people were identified, highlighting the</td>
<td>Impact of access to over the counter meds</td>
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<tr>
<td>Authors</td>
<td>Title</td>
<td>Study Design</td>
<td>Participants</td>
<td>Findings</td>
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<td>Hart et al. 2013, USA</td>
<td>To examine the relationship between musical preferences and experimentation with purple drank.</td>
<td>Cross sectional survey in a large university in the southeastern United States of America</td>
<td>2,349 students</td>
<td>Those who prefer rap/hip-hop music and rock/alternative have the highest risk for reporting purple drank use. Males, other drug users, and those that prefer rap/hip-hop music have a significantly higher likelihood of using purple drank.</td>
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<tr>
<td>Hastier et al. 2000, France</td>
<td>Case Reports of Codeine-induced acute pancreatitis</td>
<td>Case Reports</td>
<td>4 confirmed cases of acute pancreatitis</td>
<td>All patients had taken therapeutic doses of codeine 1-3 hours before the onset of abdominal symptoms. All cases had a history of cholecystectomy. 3/4 had a history of pancreatitis after codeine ingestion.</td>
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<tr>
<td>Hering et al. 1993, UK</td>
<td>Cellular changes in patients with chronic daily headaches caused by ergotamine and analgesic misuse</td>
<td>Assays of blood and 3 visits to the clinic.</td>
<td>12 female patients</td>
<td>All patients stopped the offending medication and at the end of four weeks, 8 out of 12 patients had experienced relief from chronic daily headache. Withdrawal of analgesics produced a significant decrease in thrombin-stimulated inositol phosphate production at one month; this was further decreased a month later.</td>
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<td>Hou et al. 2011, China</td>
<td>The neurological effects of Codeine-Containing Cough Syrup addiction</td>
<td>Experimental study comparing Brain Scan images of codeine containing cough syrup - dependent subjects with 22 dependent subjects and 27 healthy volunteers</td>
<td>The volume (V) and weight (W) of bilateral corpus striatum as well as the ratio of corpus striatum to whole brain in codeine containing cough syrup-dependent subjects</td>
<td>The study showed changes to the appearance of the bilateral corpus striatum, with decreases in weight, volume and ratio to whole brain, in codeine containing cough syrup-dependent subjects. CCS abuse may induce significant neurological changes. The dopaminergic system alterations may play a role in the pathophysiology of codeine containing cough syrup dependence. More research is required.</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Objectives</td>
<td>Methods</td>
<td>Results</td>
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<tr>
<td>Hakkinen, Launiainen, Vuori, &amp; Ojanpera 2012, Finland</td>
<td>Quantitative analysis of all deaths in Finland in which a case was registered.</td>
<td>To evaluate the drug and alcohol findings as well as the cause and manner of death in opioid-related post-mortem cases in Finland from 2000 to 2008.</td>
<td>Of the 14–44-year-olds, 12,891 cases (10,182 men), several opioids were detected in 1363 cases (1103 men). In codeine use poisoning; 43% were accident and 40% were suicide and was higher than other cause of death but not statistically significant however no deaths were reported for codeine use alone.</td>
<td>Noticeable differences in the manner of death, showing evidence of very few suicides by methadone and buprenorphine as opposed to tramadol and codeine. Codeine poisonings could be well distinguished from other causes of death based on a high codeine concentration, and tramadol poisonings could be distinguished based on high tramadol and O-desmethyltramadol concentrations.</td>
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<td>Hughes et al. Northern Ireland (UK)</td>
<td>Cross-sectional study using Questionnaire with 509 community pharmacists</td>
<td>To investigate abuse of over the counter products in Northern Ireland</td>
<td>The perception of pharmacists was that the abuse of over the counter was on the increase. The suspected number of patient that were abuse ranged from 0-700 (median 10) with 55 persons being regular customers. The most common technique described to combat abuse was to keep the product out of site. The participants agreed that their role could be expanded with regards to misuse of over the counter products.</td>
<td>The frequency of abuse of over the counter is perceived to be common in over the counter.</td>
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<td>Ives et al. 2006, USA</td>
<td>Observational cohort study</td>
<td>To determine the one-year incidence and predictors of opioid misuse in a cohort of patients enrolled in a chronic pain disease management program within an academic general internal medicine practice.</td>
<td>Sixty-two (32%) patients committed opioid misuse. Detection of cocaine or amphetamines on UTS was the most common form of misuse (40.3% of misusers). Misusers were more likely than non-misusers to be younger, have past alcohol abuse, past cocaine abuse, or have a previous drug or DUI conviction. Race, income, education, depression score, disability score, pain score, and literacy were not associated with misuse.</td>
<td>Patients with a history of alcohol or cocaine abuse and alcohol or drug related convictions should be carefully evaluated and followed for signs of misuse if opioids are prescribed. Characteristic of opioid misusers - includes codeine.</td>
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<tr>
<td>Authors</td>
<td>Study Title</td>
<td>Methodology</td>
<td>Results</td>
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<tr>
<td>Johansson et al. 2003, Sweden</td>
<td>A quantitative study of the dependence on legal psychotropic drugs among alcoholics</td>
<td>Anonymous questionnaires given to alcoholics in open and institutionalized care. 130 alcoholics in open care, 23 alcoholics in institutionalized care and 120 healthy control subjects</td>
<td>Levels of dependence. Alcoholics were more often psychotropic drug dependent (17%) than were healthy controls (2%). Benzodiazepines were the most common psychotropic drug. 3% of the open care and 13% of the institutionalized alcoholics were dependent on codeine. This is compared to 1% of the healthy volunteers. 29% of the codeine-dependent alcoholics had developed high dose dependence. More than half of the codeine-dependent subjects were also dependent on benzodiazepines.</td>
<td>Alcoholics are more dependent on psychotropic drugs than their healthy controls. Benzodiazepines are the most common, but small percentage use codeine.</td>
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<td>Kahan et al. 2011, Canada</td>
<td>To explore pharmacists’ beliefs, practices, and experiences regarding opioid dispensing.</td>
<td>Cross-sectional emailed survey 652 pharmacists</td>
<td>86% of pharmacists reported they were concerned about several or many of their patients who were taking opioids. Participants’ most common concerns in the 3 months before the survey were patients coming in early for prescription refills (39%), suspected double-doctoring (12%), and requests for replacement doses for lost medication (16%). Pharmacists reported difficulty in reaching physicians directly by telephone (43%), and indicated that physicians frequently did not return their calls promptly (28%). Pharmacists commonly observe opioid intoxication and aberrant drug-related behaviour in their patients but have difficulty communicating their concerns to physicians. System-wide strategies are urgently needed to improve the safety of opioid prescribing and to enhance communication between physicians and pharmacists.</td>
<td>Pharmacists commonly observe opioid intoxication and aberrant drug-related behaviour in their patients but have difficulty communicating their concerns to physicians. System-wide strategies are urgently needed to improve the safety of opioid prescribing and to enhance communication between physicians and pharmacists.</td>
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<tr>
<td>Katz et al. 2006, USA</td>
<td>Describe the development of an Extractability Rating System for use by the pharmaceutical industry and regulators.</td>
<td>Five stages. (eg. Concept mapping, development of rating system). Stage one was qualitative interviews. Information was gathered from opioid abusers. Nine prescriptio n opioid abusers with a range of extraction experience and six experts participated in this</td>
<td>Extractability of prescription opioid products. The majority of users preferred oral intake (45.4%) to injection (36.4%) or smoking/inhalation (0%) in this small group. Extractions are performed mostly by individual opioid abusers (as opposed to “street chemists”). The qualitative phases were extremely informative and shaped our understanding of the prescription opioid abuse problem as it relates to the extractability of prescription opioids, as well as caused a shift in our thinking about how a tool could be the most clinically and socially</td>
<td>Despite several limitations, this effort serves as a call for standardized testing and reporting so that products can be accurately rated, and should help establish goals for drug developers who wish to develop “abuse-resistant” opioid products.</td>
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regarding the actual phenomenology of extractability. stage Among the opioid abusers, four were female and five male, age ranged from 26 to 48 years (mean 37), eight were white and one was African-American, and seven had completed at least the twelfth grade. meaningful.

<p>| Study (Krausz et al. 1998, Germany) | Use of codeine for maintenance treatment of opiate addicts | Three-year follow-up study with use of Standardised interviews, medical examinations and patients’ questionnaires. | 199 people | Measures of health, living conditions, employment, criminal activities and drug use were collected at baseline and follow-up. | Improvement in general health and mental problems. The living and working situation remained more or less unchanged and stabilized at a satisfactory level. The same applies to the consumption of drugs. | The patients’ progress shown in this study was comparable to that achieved by methadone maintenance in similar geographical regions. Codeine has a weaker pharmacological effect and our results suggest that codeine maintenance treatment deserves more attention and controlled trials to assess the benefits compared with methadone (or other opioids). |
| Study (Kurdyak et al. 2012, Canada) | To determine the extent to which other opioids are prescribed to patients receiving methadone | Retrospective cohort study | 18759, age group 15-64 years old | The primary outcome was the proportion of methadone | 18.4% received at least one prescription for non-methadone opioids for more than 7 days duration. Most frequently used opiate was codeine. Many patients receiving methadone | Co-preservation of other opioids with methadone is common despite current practice guidelines for drug monitoring during MMT. This problem could be mitigated | Prevalence of opioids prescribed to patients |</p>
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Details</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lambert and Close 2005, UK</td>
<td>Case report of hypokalaemia with ibuprofen and codeine</td>
<td>Maintenance therapy in Ontario receive overlapping prescriptions for other opioids, often for extended periods. This suggests that many such prescriptions may be duplicitious. The most frequently prescribed drugs were codeine and oxycodone.</td>
</tr>
<tr>
<td>Lam et al. 1996, Hong Kong</td>
<td>A review of psychiatric admissions due to cough medicine misuse</td>
<td>The ibuprofen had caused type 2 proximal renal tubular acidosis and life threatening hypokalaemia. The case is an important issue to raise as the ibuprofen was bought over-the-counter and abuse of such preparations can go unnoticed.</td>
</tr>
<tr>
<td>Lankena et al. 2007, USA</td>
<td>To check prevalence and patterns of prescription drug misuse among young ketamine injectors</td>
<td>Rates of use of prescription drugs. Higher rates of lifetime nonmedical prescription drug use compared to NSDUH data. New polydrug combinations, such as injecting OxyContin and ketamine, which were associated with drug overdoses. Codeine was among one of the frequently misused medication 62% (L.A) and 51% (New York). Simultaneous and/or sequential use of prescription drugs in various polydrug combinations. Future research studies should report misuse of multiple classes of prescription drugs. Nonmedical prescription drug use was not an ancillary practice an integral part of drug using behaviours.</td>
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<tr>
<td>USA</td>
<td>prescription drug misuse amongst young IDUs in Los Angeles and New York.</td>
<td>interviews and 25 years old who had engaged in misuse of a prescription drug</td>
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<td>Linton-Dahlöf, Linde, &amp; Dahlöf 2000, Sweden</td>
<td>To analyse the effect of drug withdrawal therapy in patients with chronic daily headache associated with long-term misuse of headache medication.</td>
<td>Retrospective analysis of the effect of drug withdrawal therapy in patients with chronic daily headache and frequent long-term use of headache symptomatic medication.</td>
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<tr>
<td>Lord et al. 2011, USA</td>
<td>To (1) assess the feasibility of implementing a survey study about prescription medication misuse with college students on Facebook and (2) identify the characteristics, motivations, beliefs, and attitudes associated with</td>
<td>Mixed method. A quantitative and qualitative survey of motives and attitudes associated with nonmedical prescription opioid medication use among college students was conducted on Facebook.</td>
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<tr>
<th>Study Title</th>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Findings</th>
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<tr>
<td>Experimental versus regular misuse of prescription opioid analgesic medications.</td>
<td>MacFadyen et al. 2001, Scotland</td>
<td>2001</td>
<td>Scotland</td>
<td>To explore community pharmacists’ experience of over-the-counter medicine misuse in Scotland</td>
<td>Postal questionnaire</td>
<td>87 pharmacists</td>
</tr>
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<td>Safety of codeine in breast feeding</td>
<td>Madadi et al. 2007, Canada</td>
<td>2007</td>
<td>Canada</td>
<td>Case Report</td>
<td>New-born male infant</td>
<td>Genotype analysis revealed that the mother was an ultra-fast metabolizer of codeine to morphine and both the infant and mother were fast metabolizers of morphine to its more potent metabolite, morphine-6-glucuronide. The subsequent high levels of these substances in the infant lead to death.</td>
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<tr>
<td>Repeated Erythromycin/Codeine-Induced Psychotic Mania</td>
<td>Manchia et al. 2013, Canada</td>
<td>2013</td>
<td>Canada</td>
<td>Case Report</td>
<td>19 year old male admitted for psychotic episode, one week after tooth extraction</td>
<td>The temporal relationship between his taking erythromycin, paracetamol with codeine, and the onset of psychiatric symptoms and the rapid offset of symptoms with discontinuation of these drugs points to the diagnosis of substance-induced mood disorder with psychosis. It is proposed that a pharmacokinetic interaction between erythromycin and codeine could explain the observed association with symptoms of psychotic mania. Complete resolution of psychosis within 5 days following antipsychotic therapy.</td>
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<tr>
<td>To study the socio-</td>
<td>Mattoo et al. 1997</td>
<td>1997</td>
<td>Observational; case series.</td>
<td>46 consecutive</td>
<td>Type of client group</td>
<td>The combination of an opioid and caffeine may be an iatrogenic cause of psychiatric disturbances and that these adverse events are more likely to occur during their concomitant use.</td>
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<td>Country</td>
<td>Study Details</td>
<td>Findings/Implications</td>
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<td>India</td>
<td>Demographic and clinical profile of patients seeking treatment for abuse of codeine-containing cough syrups.</td>
<td>Sympathomimetic agent in the codeine containing cough syrup may cause a special, distinct euphoric effect. This effect, along with the low price, easy availability and ‘pure’ preparation of codeine containing cough syrups, may be responsible for the rapidly rising popularity of the codeine containing cough syrups as drugs of abuse in India.</td>
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<td>India</td>
<td>Cross-sectional study of patients presenting to a regional, open-access detoxification clinic covering the Greater Auckland area between 1 January and 31 March 2010.</td>
<td>Over the counter codeine analgesics in both countries are not sufficient to limit non-medical use of these products. As a result, cases identified in these two countries escalated the number of self-administered tablets taken daily for misuse, resulting in codeine dependence and serious non-steroidal anti-inflammatory drugs toxicity secondary to this dependence.</td>
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<td>United Kingdom</td>
<td>To explore the views of experts within the fields of pharmacy and addiction on the value of current strategies and possible alternatives and to reach an agreement on best practice in the sale of medicines.</td>
<td>Findings suggest a need for improvements to existing strategies, including national policies with central co-ordination, a greater emphasis on training and improved communication between primary health-care professionals. The panel wisely reminds us that new policies and practices cannot prevent all over the counter supply.</td>
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<td>McBride et al. 2003, UK</td>
<td>Using a modified Delphi approach, three stage postal questionnaire was conducted that generated both qualitative and quantitative data.</td>
<td>A consensus was reached on the strategies considered the most important and effective. Key areas include improving access to current information, improved staff training, addressing the issues of non-pharmacy outlets and Internet pharmacy sites. Concerns were expressed regarding the possible conflict between commercial and customer interests.</td>
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of over-the-counter (over the counter) medicines which are liable to misuse.

<table>
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<tr>
<th>Study</th>
<th>Methodology</th>
<th>Participants</th>
<th>Characteristics by subtype</th>
<th>Misuse Characteristics</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>McCabe et al. 2009, USA</td>
<td>A self-administered randomised design Web survey</td>
<td>3639 undergraduates (53.6% women and 46.4% men), attending a large Midwestern U.S. university.</td>
<td>Nonmedical prescription drug misuse including codeine was 20% and 13%, respectively. Approximately 13% of those who reported any nonmedical prescription drug misuse were classified in the recreational subtype, while 39% were classified in the self-treatment subtype and 48% were classified in the mixed subtype based on motive, route of administration, and co-ingestion with alcohol. There were significant differences in the subtypes in terms of gender, race and prescription drug class. Approximately 50% of those in subtypes other than self-treatment screened positive for drug abuse. The odds of substance use and abuse were generally lower among self-treatment subtypes than other subtypes. Future clinical and research efforts should differentiate between subtypes of nonmedical prescription drug misuse because subtypes can be associated with different rates of drug use and drug related problems, especially for pain medication.</td>
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<td>Moore et al. 2011, UK</td>
<td>Meta-analysis</td>
<td>194 participants from three reports compared dihydrocodeine with placebo and one (120 participants) compared dihydrocodeine</td>
<td>For a single dose of dihydrocodeine 30 mg in moderate to severe postoperative pain the NNT for at least 50% pain relief was 8.1. Pooled data showed significantly more participants to have reported adverse effects with dihydrocodeine 30 mg than with placebo. When compared to ibuprofen 400 mg both dihydrocodeine 30 mg and 60 mg were significantly inferior. A single 30 mg dose of dihydrocodeine is not sufficient to provide adequate pain relief in postoperative pain. Statistical superiority of ibuprofen 400 mg over dihydrocodeine (30 mg or 60 mg) was shown. Therapeutic use-effectiveness when compared to other drugs or placebo.</td>
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<td>Authors</td>
<td>Study Objective</td>
<td>Data Source</td>
<td>Key Findings</td>
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<tr>
<td>Morgan et al. 2006, England &amp; Wales</td>
<td>To report trends in death due to drug misuse 1993-2004</td>
<td>National deaths database</td>
<td>Drug-poisoning deaths are extracted from the national deaths database. Between 1993 and 2004 there were 12,687 deaths related to drug misuse among males and 3,401 deaths among females. Mortality rates were highest in young adults. Codeine deaths were reported at 26 in 1999 to 54 in 2004. Drug-misuse-related poisoning is a significant cause of mortality in England and Wales. Meaningful interpretation of surveillance data needed to plan effective strategies to reduce the number of drug-misuse-related deaths depends on understanding the size of the drug using population and the risk of fatal poisoning among drug users.</td>
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<tr>
<td>Myers et al. 2003, South Africa</td>
<td>To provide community-level public health surveillance information on over-the-counter (over the counter) and prescription medicine misuse</td>
<td>A retrospective study of over the counter and prescription medicine misuse. 9063 patients (forms) from 23 specialist substance abuse treatment centres in Cape Town, South Africa, between 1998 and 2000. Use of over the counter medicines over the counter and prescription medicine misuse places a burden on health and social services in South Africa. Analgesic misuse is most often accounted for by the use of codeine-containing medicines, many of which are available over the counter. Patients using over the counter/prescription medicines as their primary drug of abuse are significantly more likely to be female, and aged over 40 years. In contrast, patients using over the counter/prescription medicine as an additional drug of abuse tend to be male and over 40 years of age. This study points to the need to develop primary health care protocols for detection, management and referral of patients misusing over the counter/prescription drugs and the need to debate the re-scheduling of codeine as a prescription-only substance. The study also points to the need for further community-based research on the nature and extent of over the counter/prescription drug misuse among the general population.</td>
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<td>Nielsen et al. 2011, Australia</td>
<td>To compare the characteristics of an Australian drug treatment sample presenting</td>
<td>Cross-sectional. A structured quantitative interview A convenience sample of 192 treatment</td>
<td>Most treatment entrants reported a history of injection drug use and use of both heroin and POA. Minority (13%) were using codeine as their primary POA. There are many similar characteristics between those with primary problems with heroin and POA. This finding contrasts with characteristics of misusers of opioid analgesic</td>
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with pharmaceutical opioid analgesics (POA) as their primary drug of concern and a sample presenting with heroin as their primary drug of concern.

- Collected data on demographic characteristics, substance use, self-perceived mental and physical health, crime and harms resulting from drug use.
- Entrants were recruited from alcohol and drug treatment services in four Australian jurisdictions.
- However, those with primary POA problems were less likely to report an overdose history and more likely to initiate opioid use for pain than those with primary heroin problems.
- While most of the POA group were similar to heroin users in demographics, health and injecting drug use, there was a small, distinct group of primary POA problem users that did not typically inject and who commonly initiated opioid use for pain and also experienced elevated physical and mental health disability. For the non-injecting group few had problems with heroin (8%) instead the problem drug was typically codeine (35%).

Nielsen et al. 2010, UK

- Understanding the nature of dependence to over the counter codeine.
- A web survey, qualitative, semi-structured interviews with primary healthcare practitioners and other key experts as well as qualitative interviews with codeine dependent people. Sampling for both groups was purposive.
- Web survey: Participants classified as codeine dependent were found to be more likely to report chronic pain, have higher ratings of psychological distress, have experienced alcohol and drug treatment and have used doses higher than the maximum dose. Participant interviews: three types of codeine users were identified I. Therapeutic dependence II. Non-medical/recreational users III. High dose dependence. Blurring between therapeutic and problematic use was also a feature where participants described being in a vicious cycle of medicating opioid withdrawal thinking they were medicating pain. Key Expert Interviews: Pharmacist’s descriptions were based more on appearance than other characteristics, consistent with descriptions of over the counter codeine users reporting appearance being related to codeine supply. Reporting appearance being related to codeine supply. Pharmacists also highlighted the challenges in responding to codeine dependence with information available with current systems.

Nielsen et al. 2013

- Perspectives of over-the-counter (over the counter)
- Qualitative research methodology
- 20 participants
- Experience of over the counter
- Key themes identified included experience of participants acquiring over the counter codeine and participants’ interactions with

Pharmacist can play an important role in raising general awareness regarding potential over the counter codeine dependence and harms. Requirement for greater interaction between the pharmacist and the public for over the counter codeine purchases

Pharmacist can play an important role in raising general awareness regarding potential over the counter codeine dependence and harms. Requirement for greater interaction between the pharmacist and the public for over the counter codeine purchases

Addiction/misuse/abuse of over the counter medicine and views/experience on over the counter medicine use/abuse
<table>
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<tr>
<th>Country</th>
<th>Study Title</th>
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<th>Findings</th>
<th>Recommendations</th>
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<tr>
<td>Australia</td>
<td>Australia codeine users and issues relating to codeine dependence in the community pharmacy setting.</td>
<td>using interviews with over the counter codeine users and met DSM IV criteria for codeine dependence.</td>
<td>Pharmacists. The over the counter codeine-dependent participants found it generally easy to access over the counter codeine, describing ‘standard’ questioning, minimal intervention from pharmacists and only occasional refusal to supply. A better appearance and presentation was generally linked to easy codeine supply.</td>
<td>Dependence. Targeted interventions are required to reduce over the counter codeine harm.</td>
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<td>Ng et al. 2011, Australia</td>
<td>To look at cases of life-threatening hypokalaemia associated with ibuprofen</td>
<td>Case Reports 4 patients admitted to hospital with life-threatening hypokalaemia All 4 patients had taken excessive amounts of ibuprofen over a prolonged period. 2 of the patients had taken the ibuprofen combined with codeine.</td>
<td>The four patients had developed hypokalaemia due to ibuprofen-induced Renal Tube Acidosis. Ibuprofen cessation and support therapy allowed complete recovery within a few days for all the patients.</td>
<td>Opioid addiction with the misuse of ibuprofen-codeine combinations is common. It should be considered in patients presenting with severe hypokalaemia.</td>
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<tr>
<td>Noysk et al. 2012, Canada</td>
<td>To identify changes in the availability of Prescription Opioids and other illicit drugs among drug users in a Canadian setting.</td>
<td>Data were derived from the baseline assessments of a series of ongoing open prospective cohort studies involving illicit drug users. 1871 participants 31% Female</td>
<td>Availability of codeine increased from 17% to 40% from 2006-2010. Codeine and other drugs were more immediately to people over 45. Immediate availability of POs increased significantly from 2006 to 2010. These increases persisted after adjustment for changes in the characteristics of individuals entering the cohorts under study.</td>
<td>Policy and programmatic responses should acknowledge that POs may be used as a primary drug of abuse, as a temporary solution to opioid withdrawal, or as genuine pain relief. The demand, and context of the use of prescribed opioids requires closer consideration.</td>
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<td>Nuesch et al. 2009, UK</td>
<td>Treatment of osteoarthritis of the knee or hip</td>
<td>Meta-analysis 2268 participants Effectiveness of opioid preparation against placebos</td>
<td>Overall, opioids were more effective than control interventions in terms of pain relief (SMD -0.36, 95% CI -0.47 to -0.26) and improvement of function (SMD -0.33, 95% CI -0.45 to -0.21). No substantial differences in effects according to type of opioid, analgesic.</td>
<td>The small to moderate beneficial effects of non-tramadol opioids are outweighed by large increases in the risk of adverse events. Nontramadol opioids should be used with caution.</td>
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<tr>
<td>Authors</td>
<td>Objective</td>
<td>Method</td>
<td>Findings</td>
<td>Implications</td>
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<td>Pan et al. 2013, Taiwan</td>
<td>To investigate opioid consumption patterns in Taiwan, compare the results with those from selected countries, identify differences between patients with and without cancer, and determine the associated expenditure.</td>
<td>Data on prescriptions for three so-called strong opioids (fentanyl, morphine, and pethidine [meperidine]) and one so-called weak opioid (codeine) were obtained.</td>
<td>From 2002 to 2007, opioid consumption in Taiwan increased by 55% from 362 to 560 defined daily dose per million inhabitants per day. Among the investigated opioids, prescriptions for transdermal fentanyl and oral morphine increased markedly from 2002 to 2007. 33% took codeine in 2002 and 27% in 2007 for non-cancer patients. 67% took codeine for cancer pain in 2002 and 73% in 2007.</td>
<td>Opioid prescriptions and expenditure increased steadily from 2002 to 2007 in Taiwan, as in nearby Asian countries, but remained much lower than in developed countries. Pethidine (meperidine) was predominantly prescribed to non-cancer patients, whereas morphine and fentanyl were mainly prescribed for cancer patients.</td>
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<tr>
<td>Reynolds et al. 2007, USA</td>
<td>To assess effects of maternal drugs and medications on neonates</td>
<td>2 case studies</td>
<td>Occurrence of a cerebral infarction</td>
<td>Codeine-containing cough preparations given to pregnant mothers have been identified as a cause of neonatal abstinence syndrome. However, many women do not consider prescription cough syrups when asked about drug use. Maternal medication or illicit drug use has been identified as a cause of perinatal arterial stroke.</td>
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<td>Palangio et al. 2000, USA</td>
<td>Treatment of chronic pain with a combination of hydrocodone and ibuprofen versus combination of codeine and paracetamol</td>
<td>Randomized, parallel-group, double-blind, repeated-dose, active comparator, 4-week, multicentre study</td>
<td>469 patients</td>
<td>Efficacy of drug. The overall mean daily pain relief score was significantly greater in the HI2 group (2.25 f 0.87) than in the HI group (1.96 * 0.87) (P = 0.003) or the CA group (1.85 f 0.96) (P &lt; 0.001).</td>
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<tr>
<td>Name</td>
<td>Study Title</td>
<td>Study Design</td>
<td>Study Population</td>
<td>Principal Findings</td>
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<tr>
<td>Piccoliori et al. 2013, Italy</td>
<td>Management of low back pain in general practice</td>
<td>Observational study using quality indicators</td>
<td>475 patients</td>
<td>In 93.3% of those receiving a medication, 88.3% had non-steroidal anti-inflammatory drugs, 6.3% Paracetamol, 10.4% Paracetamol combined with Codeine, and 9% muscle relaxants. 50% of GPs did not fully follow locally established guidelines.</td>
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<tr>
<td>Robinson et al. 2010, New Zealand</td>
<td>To review cases of codeine dependency from over-the-counter (over the counter) combination analgesics admitted to a hospital detoxification unit.</td>
<td>Case records of all admissions following an index case were reviewed over a 2-year period.</td>
<td>7 cases</td>
<td>There were 7 cases reporting chronic excess of Nurofen Plus®, of which 6 had prior or current histories of alcohol dependency. Complications which were likely contributed by excessive ibuprofen consumption included: gastric ulcer (4 patients), gastrointestinal bleeding (3), hepatotoxicity (1), and inflammatory bowel conditions (2). These patients described patterns of visiting multiple pharmacies, sometimes travelling considerable distances, to obtain the Nurofen Plus®. Many of the patients suffered significant opioid withdrawal symptoms despite treatment with ancillary medications.</td>
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<tr>
<td>Roussin et al. 2013, France</td>
<td>To investigate the prevalence of misuse, abuse, and dependence on non-prescription psychoactive drugs.</td>
<td>Cross-sectional. Quantitative survey to investigate misuse/abuse of non-prescription drugs</td>
<td>383 questionnaires handed out in pharmacies were available for analysis.</td>
<td>Misure and dependence on codeine analgesics concerned 6.8%. Headache was the most frequent reason for persistent daily use. High rate of dependence on codeine (18% of users).</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Data Collection</td>
<td>Findings</td>
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<td>Stark &amp; Gregory 2005, UK</td>
<td>The clinical management of substance misusers in police custody</td>
<td>Quantitative questionnaire examining current practice in managing substance misuse detainees and attitude to drug addiction and management in custody. 409 members of the Association of Forensic Physicians</td>
<td>Use of substance for methadone replacement. The mean dose of dihydrocodeine prescribed by doctors was 313mg in 24 hours. 44 doctors prescribe doses between 201 and 300mg. Max dose they were willing to prescribe was 960mg in 24hr period. 80% of doctors thinking substance misusers are unreliable and deceitful. 65% of doctors felt that substances misusers did not comply with treatment.</td>
<td>The majority of respondents did not follow guidelines on prescribing. Large variation in practice between doctors. Doctors display negative attitudes to those who are misusing substances.</td>
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<td>Skurtveit et al. 2011, Norway</td>
<td>To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use</td>
<td>Prospective cohort study following patients recorded on a national database from 2005 to December 2008. Probable problematic opioid use defined as receiving opioids at least once a year from 2005 to 2008: 245,006 patients who were new users of weak opioids in 2005 (216,902 codeine, 26,326 tramadol, 1778 dextropropoxyphene). Dependence on opioids. 686 patients were dispensed more than 365 defined daily doses of opioids in 2008 and are probably persistent users. There were 191 subjects who met the criteria for probable problematic opioid use.</td>
<td>In a cohort of new opioid users who started treatment with weak opioids, only 0.3% and 0.08% developed prescription patterns indicating persistent opioid use and problematic opioid use, respectively.</td>
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<td>Swadi et al. 1990, UK</td>
<td>To report the results of an investigation into the level of DF118 misuse (excluding other dihydrocodeine preparations) among opiate addicts</td>
<td>The clinic notes of all opiate addicts at a central London drug dependency treatment centre were inspected for 143 active clients on the register for opiate addiction, 99 men and 44 women, with mean ages of 30. No of misuser of DF118: Among the 143 clients positive urine tests were recorded for the following substances: DF 118, amphetamine 21, barbiturates 79, benzodiazepines one, cocaine one, codeine 38, heroin 122, methadone 71, morphine 101, phenothiazine’s 11, morphine 101, phenothiazines 11,</td>
<td>The potential for DF 118 misuse was confirmed by clients, who reported that it is widely misused and preferred to other dihydrocodeine preparations. Prevalence of misuse among opiate addicts.</td>
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<td>Tang et al. 2012, Hong Kong</td>
<td>To explore the following: 1) The content of the local cough mixture (Cough mixture is the third most commonly abused substance in patients attending the Prince of Wales Hospital Substance Abuse Clinic.) 2) Paranoïd psychosis manifesting as persecutory delusions and derogatory hallucination, as well as mood symptoms, which are common in these patients. 3) The natural history and outcome of such psychoses associated with cough mixture abuse</td>
<td>Retrospective study of cough mixture abuse in Hong Kong</td>
<td>The medical records of patients, with a diagnosis of cough mixture dependenc e according to the ICD-10 Mental and Behavioural Disorders criteria, who attended the substance abuse clinics of the PWH, Alice Ho Miu Ling Nethersole Hospital, and North District Hospital from October 2009 to December 2011, were reviewed.</td>
<td>Abuse rates</td>
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<td>Tobin et al. 2013, Australia</td>
<td>Analysis of the policy response by Australia’s National Drugs and Poisons Schedule Committee (NDPSC) and comparison with recommendations by expert advisory committees in New Zealand and the United Kingdom.</td>
<td>Analysis of public policy documents of relevant regulatory authorities was conducted.</td>
<td>Data were extracted regarding changes to over-the-counter (over the counter) codeine analgesic scheduling, indications, maximum unit dose, maximum daily dose, maximum pack size, warning labels, consumer medicine information and advertising.</td>
<td>Expert advisory committees in Australia, NZ and the UK defined the policy problem of over the counter codeine misuse and harm as small relative to total use and responded by restricting availability. Pharmacist supervision was required at the point-of-sale and pack sizes were reduced to short-term use.</td>
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| Tormey et al. 2013, UK | To determine the effects of methadone and codeine on acute haemorrhagic necrotising pancreatitis | Case Report written as a letter to editor | 37 year old female found dead at home | 80ml methadone from detoxification programme, Benzodiazepines from the street, Paracetamol and codeine | Toxic levels of codeine with potentially lethal levels of methadone and morphine were found in the blood. Benzodiazepine levels were insignificant. Paracetamol levels were difficult to interpret but were compatible with those seen taken for pain relief. | The data in this case may represent a co-incidence of poisoning with codeine and methadone in a case of acute pancreatitis or may represent an example of opiates as the cause of the pancreatitis. Whether opiates caused the pancreatitis or were the consequence of self-medication for pain is impossible to differentiate. | Adverse health effects |
| Tormoehlen et al. 2011, USA | This study was undertaken to determine the number and severity of prescription opioid-related cases in adolescents reported to the Indiana Poison Center (IPC) between the years 1994 and 2007. |
| Retrospective case series of opioid exposures | 1634 adolescent opioid-related cases with 187 cases developing medical complications. |
| Poisonings, medical complications and number of deaths | 1) Calls to the Indiana Poison centre (IPC) related to adolescent opioid exposures significantly increased. (OR 1.69) however a decrease was observed in codeine use) |
| The increased reported opioid cases and associated complications following JCAHO pain initiative correlates with increased drug availability. Drug prevention campaigns should simultaneously promote awareness of the dangers of these drugs to adolescents. |

| Vestergaard et al. 2006, Denmark | Fracture risk associated with opiates |
| Case control study | All subjects with any fracture sustained in 2000 on a nationwide register (n = 124,655) compared with matches in the general population (n = 373,962) |
| Use of morphine or opiates in subjects with fracture | Codeine (1.16, 95% CI 1.12–1.20) was associated with an increase in overall fracture risk No change in risk was seen for combinations of aspirin and codeine |
| An increased fracture risk is seen in users of morphine and opiates. The reason for this may be related to the risk of falls due to central nervous system effects such as dizziness. |

| Wang et al. 2013, USA | To (1) describe the prevalence of nonmedical use of prescription opioids in urban and rural counties, (2) determine the correlates of nonmedical use of prescription opioids among urban and rural residents, (3) describe the differences |
| 2008–2009 National Survey on Drug Use and Health in USA. | 75,964 respondents |
| Prevalence of non-medical use of prescription opioids Correlates of use | 3.5% of rural respondents versus 1.9% of urban respondents admitted to use of codeine with paracetamol. Urban and rural residents with severe psychological distress and nonmedical use of other prescription medications were more likely to report non-medical use of opioids. Urban residents whose first use of illicit drugs was between the age of 18 and 25 and who reported alcohol use were more likely to report nonmedical use. Black and Hispanic urban residents were less likely to use prescription opioids non-medically compared to white urban residents. Rural residents were more likely than urban |
| Prevention and treatment interventions may need to be tailored for specific communities. |
| The prevalence of nonmedical use of prescription opioids |
between urban and rural residents who use opioids nonmedical and (4) determine which opioids are used most frequently in urban and rural counties.

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<th>Study</th>
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<td>Wairagka et al. 1994, India</td>
<td>To ascertain the drug use pattern in both states (Assam &amp; Nagaland) and to assess the magnitude and patterns of this form of drug abuse. Consumption was dependent on the concentration of codeine in cough syrups and brands with a higher concentration and easy availability seemed to be popular. Abuse of cough syrups might be due to their addictive potential, easy availability over the counter, lesser expenditure involved milder forms of withdrawals and also due to the ease in consuming cough syrup without the need for privacy. Mild forms of physical and psychiatric disorders were reported. Easy over-the-counter availability, lesser expenditure, milder withdrawals and ease of consumption without secrecy were some of the reasons for the emergence of this new form of addiction in Assam and Nagaland.</td>
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<td>Wawruch et al. 2013, Slovak Republic</td>
<td>To evaluate the perception of the risk of over the counter medications by elderly patients. To identify patient associated characteristics which determine elderly persons who consider over the counter medications as safe. Majority (75.5 %) of the respondents considered over the counter medications as safe. over the counter medicines were used daily (OR 2.09). Prepared a wide range of products in pharmacies (OR 2.86). Considered over the counter medications as effective OR(10.33). Obtaining information on over the counter drugs from pharmacists (OR1.91), willingness to possibly purchase over the counter medicines outside of pharmacy (OR0.23). The survey identified various factors that influenced the perceptions of the safety of over the counter medications by the elderly and indicated that pharmacists represent the most trusted source of information about over the counter medications.</td>
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<td>Wazaify et al. 2006, Northern Ireland</td>
<td>To test an intervention model which sought to minimise over-the-counter (over the counter) drug misuse and abuse in community pharmacies</td>
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<td>Wazaify et al. 2005, UK</td>
<td>To investigate the general public’s opinion and perceptions of over the counter medicines, including the misuse/abuse of such preparations.</td>
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<td>Wilkins et al. 2011, New Zealand</td>
<td>To examine the rates of pharmaceutical drug use, and level of prescription use and injection of pharmaceutical drugs by frequent injecting drug users (IDU), frequent methamphetamine users and frequent ecstasy users in New Zealand for 2006–2009</td>
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<td>Williams et al. 2002, UK</td>
<td>Treatment of pain in paediatric patients after adenotonsillectomy</td>
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<td>Willmann et al. 2009, Germany</td>
<td>Risk to the Breast-Fed Neonate From Codeine Treatment to the Mother</td>
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<td>Wilsey et al. 2010, USA</td>
<td>To determine the prevalence of multiple providers</td>
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<td>Source</td>
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<td>Wright et al. 2007, UK</td>
<td>Use of Buprenorphine versus dihydrocodeine for opiate detoxification (Open label randomized controlled trial, 60 patients)</td>
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<td>Zamparutti et al. 2010, UK</td>
<td>To analyse involvement of dihydrocodeine in fatalities that occurred between 1997 and 2007 among individuals with a history of opiate/opioid (Data covering the period 1997–2007 voluntarily supplied by coroners were analysed, 646 cases identified as dihydrocodeine-related deaths in This opiate/ Opioid misusers’)</td>
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<td>misuse.</td>
<td>population</td>
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