



## LJMU Research Online

**Bergin, M, Norman, I, Foley, M, Harris, R, Rapca, A, Rich, E and van Hout, MC**

**Practice implications and recommendations for managing codeine misuse and dependence**

<http://researchonline.ljmu.ac.uk/9687/>

### Article

**Citation** (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

**Bergin, M, Norman, I, Foley, M, Harris, R, Rapca, A, Rich, E and van Hout, MC (2015) Practice implications and recommendations for managing codeine misuse and dependence. Acta Pharmaceutica, 65 (4). pp. 351-364. ISSN 1330-0075**

LJMU has developed **LJMU Research Online** for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact [researchonline@ljmu.ac.uk](mailto:researchonline@ljmu.ac.uk)

<http://researchonline.ljmu.ac.uk/>

## Practice implications and recommendations for managing codeine misuse and dependence

MICHAEL BERGIN<sup>1</sup>  
IAN NORMAN<sup>2</sup>  
MICHELLE FOLEY<sup>3</sup>  
RICHARD HARRIS<sup>4</sup>  
ANNA RAPCA<sup>4</sup>  
EILEEN RICH<sup>5</sup>  
MARIE-CLAIRE VAN HOUT<sup>1</sup>

<sup>1</sup> School of Health Sciences  
Waterford Institute of Technology  
Waterford, Ireland

<sup>2</sup> Kings College London, Florence  
Nightingale Faculty of Nursing and  
Midwifery, London, United Kingdom

<sup>3</sup> School of Health Sciences, Waterford  
Institute of Technology, Waterford, Ireland

<sup>4</sup> H. I. Weldrick Ltd, Doncaster  
United Kingdom

<sup>5</sup> Alcohol, Tobacco and Other Drug  
Research Unit, South African Medical  
Research Council, Pretoria, South Africa

Codeine, a weak opiate, requires increased pharmacovigilance relating to availability, heterogeneous nature of misuse, dependence and associated harm. A scoping review of literature on codeine was conducted using Arksey & O'Malley's framework (1). Databases searched included PubMed, EBSCO Host, Science Direct, EMBASE, PsycINFO, Cochrane library and Medline from 1994 to 2014. Follow-up search strategies involved hand searching and searching of pharmaceutical, health, medical and drug related websites. Initial zscreening identified 3,105 articles with 475 meeting the inclusion criteria. Eight broad categories organised the literature, data charting and qualitative synthesis. This paper presents implications for practice and makes recommendations to address these issues. Themes identified relate to raising public and practitioner awareness, risk management, dispensing practices and monitoring and surveillance of codeine. Evidence to inform law enforcement, drug surveillance, public health initiatives, harm reduction approaches, pharmacy, clinical and treatment practices is warranted.

*Keywords:* codeine, over the counter, misuse, dependence, policy

Accepted October 14, 2015

Codeine or 3-methylmorphine is a weak opioid, widely used for its analgesic, antitussive and anti-diarrheal properties, and most commonly in the management of mild to moderate pain and is available in non-prescription products in low doses (2, 3). However, codeine does not compare favourably to commonly used non opioid analgesic alternatives such as NSAIDs or paracetamol and appears more clinically useful when combined with paracetamol (2). The global demand for codeine has, however, risen by approximately 27 % over the last two decades with recent figures estimating that codeine consumption reached an all-time high at 269 tonnes in 2011 (compared to 164 tonnes in 1992) (4). More-

---

\* Correspondence; e-mail: mcvanhout@wit.ie

over, policy across the European Union (EU) member states varies in relation to public access to over the counter (OTC) sales of codeine containing medicines. Currently, 15 of the 28 EU member states do not permit OTC codeine sales (5).

Codeine is a listed narcotic drug under international control and is regulated to varying degrees by the regulatory authority of medicines in individual countries (5). Pure codeine is listed under Schedule II of the 1961 Convention on Narcotic Drugs. However, most codeine preparations classified under Schedule III are pharmacy controlled with no requirement to keep controlled registers (5). Deregulation of OTC codeine containing medicines has led to increased choice, self-medication and pharmacist empowerment around codeine dispensing (6, 7). Both therapeutic and non-therapeutic misuse of these products centre on use outside acceptable medical guidelines, instructions on the dispensing labels or the intended purposes (7).

### *Codeine use and misuse*

EU prevalence data on codeine use, misuse and dependence is largely confined to French and Norwegian studies with prevalence rates in other European countries unclear (5, 7). A prevalence study 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 (8). The misuse of combination products containing non-opioid analgesics (ibuprofen, paracetamol, aspirin) and codeine is increasing in countries where OTC products are available (5), with increased levels of tampering with OTC cold and flu products to extract codeine for intoxication purposes reported (9). Furthermore, OTC sales of codeine containing medicines is difficult to determine due to trade exemptions and the fact that disclosures of such information might prejudice commercial interests (7).

The displacement of public OTC purchasing of analgesic drugs without medical consultation has led to an increase in self-medication with potentially habit forming medications (10). Conflicting views exist with regard to codeine's potential for addiction, particularly when considering combination products and the potential adverse effects of other active ingredients such as ibuprofen, paracetamol and caffeine on excessive or long term use (11–13). Although effects are milder than those of heroin, tolerance occurs with regular use over a short period of time (14, 15). Withdrawals include classic opiate dependence symptoms, which are generally less severe than with morphine (16).

Efforts to understand and quantify levels of public misuse of OTC codeine containing medicines and the impact of associated adverse health consequences remain problematic due to its heterogeneous nature and the broad nature of misuse. Issues relating to codeine misuse include widespread retail availability in OTC products and inability of pharmacies and regulatory agencies to monitor misuse (5, 7). Codeine's opioid analgesic effect and development of tolerance within a short time frame contribute to its potential habit forming use, misuse pathways and addiction (11). Consequences of codeine use and misuse can be grouped under four main categories: (i) impairment, (ii) injury such as greater risk of fractures, particularly in older people (iii) adverse health effects relating to combination analgesics such as perforated gastric ulcers, gastrointestinal bleeding, hepatotoxicity, hypokalaemia and inflammatory bowel conditions, and (iv) dependence (5, 12–14).

Motives for misuse of opioid pharmaceuticals such as codeine range from self-treatment for pain (physical and emotional) consistent with the drug's main indication to that of recreational use for intoxicating purposes (15–17), with greater prevalence of recreational use among men (18). Misuse and inappropriate use for management of sleep, stress and anxiety problems, its pleasurable effects, ease of access and some personality types (for example, addictive personality) are reported in the literature (5, 14, 17, 18). Codeine misuse and diversion also occur within problematic drug using networks (15, 16).

### *Codeine dependence*

Individuals dependent on codeine often commence use in an effort to manage pain (12, 19), while others describe use of codeine containing medicines for 'chemical coping' in the case of its use for stress (14, 16). Codeine dependents are more likely to report chronic pain and use codeine for its intoxicating effects (11, 14). Moreover, many individuals dependent on codeine do not view their use as problematic or see themselves as drug addicts needing help (11, 16, 19). 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 (5, 14, 19). Being able to acquire codeine containing products with no great difficulty for therapeutic purposes lessens the patient's ability to recognise that their use may be problematic, recognise withdrawals or that they are dependent (16, 20). Gaps in knowledge currently centre on identification of risk profiles of codeine misusers and dependents, understanding of therapeutic and non-therapeutic pathways and trajectories to misuse and dependence, as well as consumer displacement between prescriber, pharmacy supply and illicit sourcing *via* diversion or web retail (5, 7, 16)

Clinical profiles of patients dependent on codeine vary but are overrepresented by females, those in middle to late age, polysubstance users, alcohol users and those with underlying psychiatric conditions (5, 11, 13, 15, 16, 19). There is a need for the use of standardised criteria to determine client codeine dependence, with limited evidence available to guide the development of specific treatment and referral pathways for codeine dependence (6, 19–22). Furthermore, there is varying uptake of treatment interventions by individuals experiencing problematic use of codeine containing medicines due to issues relating to treatment stigma and poor consideration of needs (15, 16, 19, 20).

### *Managing codeine related issues*

There is a need for 'increased pharmaco-vigilance' around codeine prescribing and over the counter dispensing. For example, advising patients and customers about the benefits and risks of codeine containing medications, drug monitoring and screening in relation to codeine use within primary care and community pharmacies is required (5, 14, 19–22). Current pharmacy strategies include removal of codeine containing products displayed at the point of sale, refusal or restriction of quantity sold to customers suspected of misusing, information provision by counter staff, on-site recording of suspected misuse and pharmacist interventions through supplementary questioning and referral to other health care professionals (14, 23). Strategies to empower pharmacy staff as custodians of medicine is warranted alongside patient information and brief interventions to raise pub-

lic awareness and support individuals experiencing tolerance and withdrawal (5, 16, 21). For example, 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 (24). Regulatory tactics to date have largely focused on guidelines for restricted supply (22, 23) and have met with some resistance from the pharmaceutical industry (25, 26).

Codeine use, misuse and dependence are a public health concern and little is known about such issues within medical, pharmacy and addiction treatment practice. CODEMIS-USED is a Marie Curie FP7 EU funded project exploring codeine use, misuse and dependence and involves both academic and industry partners from three countries – Ireland, the UK and South Africa (3). The project aims to establish what is known in relation to codeine use, misuse and dependence and address information gaps with regard to practice, policy and research. As part of this project, a scoping review (4) of the literature was carried out to explore and provide an overview of the type, extent and quantity of research on codeine use, misuse and dependence. The objective of this paper, therefore, is to present the findings arising from this scoping review, with a particular focus on practice. A number of implications and recommendations for policy and practice are identified.

#### DATA SOURCES

The scoping review that informs this paper was guided by Arksey & O'Malley's framework (1). The following databases were searched: PubMed, EBSCO Host, Science Direct, EMBASE, PsycINFO, Cochrane library and Medline from 1994 to 2014. Search terms used were: '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 involved hand searching, searching of pharmaceutical, health, medical and drug related websites, and contacting the following organisations: 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 member states, Food and Drug Administration (FDA) USA, the Canadian pharmacy authority and the National Health Service (NHS) in the UK.

A spreadsheet was created to chart relevant data (author, setting, study aim, design/intervention, sample size, and results/outcomes) and to identify themes, sub-themes and gaps in the literature. Two reviewers independently screened titles and abstracts to determine inclusion status. A second screen of the full-text article by two other independent reviewers ensured that the studies were relevant to the aim and objectives of the review. A charting exercise identified the specific areas of the review, to which they could contribute, and data were extracted manually into a database. Disagreements of the relevance of data were resolved through discussion.

A hand search of reference lists from published peer reviewed studies was also undertaken. Articles beyond the search years were reviewed to establish relevance. Inclusion and exclusion criteria were set to determine the significance of the literature with regard to the aim and objectives of the review (Table I).

*Table I. Inclusion and exclusion criteria*

---

*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 describe the tampering of codeine containing medicines.
- 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 are 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 based products.
- Policy documents and guidelines with 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 the 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 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 (Table II).

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, authors' conclusions and specificity to codeine. Data were extracted for each paper by a single researcher and checked by a second researcher to ensure that it was accurate and comprehensive. A qualitative synthesis of the literature was carried out within categories and sub-categories (Fig. 1).

Review outcomes were further validated with a key stakeholder consultation exercise by virtue of the CODEMISUSED Expert Panel representing medicine control, pharmacy regulator, addiction and pharmacovigilant sectors.

Table II. Broad categories used to organise the literature

---

Categories relating to codeine
Production, manufacture, consumption and regulation of codeine.
Characteristics and profiles of codeine users.
Therapeutic use of codeine within healthcare.
Prevalence of codeine use, overuse, misuse and dependence.
Prevention of codeine overuse, misuse and dependence.
Consequences of codeine use/misuse(health and society).
Over the counter and internet sale of codeine medication.
Interventions and treatment for codeine misuse.

---

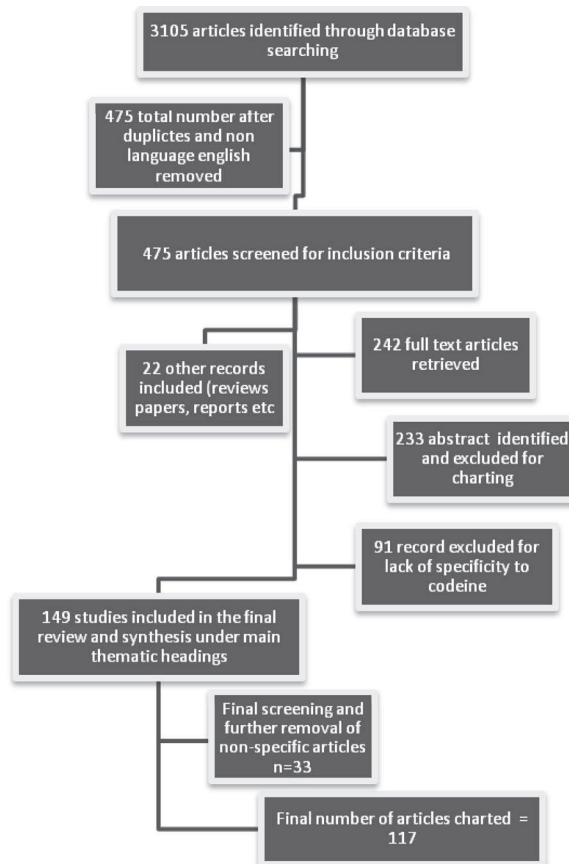


Fig. 1. Flow diagram for inclusion and exclusion of the literature.

## RESEARCH OUTCOMES

A number of implications and recommendations for practice were identified and are presented under the following four main headings: (i) raising awareness, (ii) detecting and managing risk, (iii) dispensing practices, and (iv) monitoring and surveillance (4). These four headings were informed by the broad categories used in the scoping review to organise the literature (see Tables II and III).

### *Raising awareness*

This theme illustrates the need to raise public and professional awareness of the safe use of medicines containing codeine, particularly in terms of compliant and appropriate use, recognising patient aberrance, the risks of dependence and associated health consequences of excessive and/or long term use. A significant number of patients who consume medications cannot identify active ingredients in their chosen medications (28). A minority of customers appear willing to accept risks associated with increased access to over the counter medications containing codeine and other active ingredients (29). This is despite high public awareness of the abuse potential of OTC medicines (25) and pharmacists' concerns about the safety and codeine misuse and dependence (5, 7, 19, 20). Pharmacists are trusted by the public as a source of information about over the counter medications (29, 30). Dobbin and Tobin (20) have described particular characteristics of individuals misusing codeine-containing pharmaceuticals, whereby they may not be identified as addicts, the medication prescribed infers safety and sanctioning by the prescriber, and the products purchased have different legal consequences in comparison with illicit drug users. It is important to recognise variance in groups of codeine misusers, for example, parental medication of children, recreational users, university students, pharmacy customers, elderly, women, psychiatric patients, injecting drug users, non-treatment seeking individuals and drug treatment patients and target patient and customer awareness initiatives appropriately (5, 7, 19, 20). To challenge misinformed perceptions that codeine based products are low risk, more education for users of codeine containing medicines, targeted at codeine misusers, is needed about the risks associated with poly use of medication and intake of alcohol and illicit drugs (5) (see Table III).

### *Detecting and managing risk*

This theme presents recommendations relating to harm reduction, public, patient and customer monitoring around inappropriate use of codeine containing medicines, misuse and aberrance, and pharmaceutical risk management. Evidence of the extent of use, non-compliant use and misuse of pharmaceuticals containing codeine is limited (5, 7, 14, 19, 20, 30). For example, in their review of the misuse of medicines across the European Union, Casati *et al.* (7) suggest that literature specifically targeting codeine misuse is limited beyond countries such as Norway and France but assume that misuse is widespread. The need to identify and carry out routine enquiries for all consumers, and particularly in relation to maternal medication use and suspected substance misuse, and psychiatric disorders and their use of codeine-containing preparations, is recommended. Furthermore, clearer guidelines for the interpretation of DSM V criteria for abuse and dependence in chronic pain patients are needed.



Table III. Practice implications and recommendations for managing codeine misuse and dependence

Raising awareness	Detecting and managing risk	Dispensing practices	Monitoring and surveillance of codeine
<p><i>Use and misuse:</i></p> <ul style="list-style-type: none"> <li>• Develop and disseminate key health related messages about the risks of exceeding therapeutic dosages of codeine based products.</li> <li>• Heighten public awareness about the risks surrounding the use of codeine based products whilst driving.</li> <li>• Further development of brief interventions at point of sale to raise customer awareness of potential risk of tolerance and dependence over time.</li> <li>• Further development of parenting classes to highlight the potential side effects of codeine such as respiratory depression when prescribed for children. 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 is contraindicated in breastfeeding women. Moreover, calculations of dose should be based on ideal body weight and not actual body weight.</li> </ul> <p><i>Dependence:</i></p> <p>Professional education and public awareness campaigns should seek to:</p> <ul style="list-style-type: none"> <li>• Promote recognition and early detection by healthcare professionals of signs of dependence and withdrawal in relation to codeine based products.</li> </ul>	<p><i>Use and misuse:</i></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Identify patients who are in need of psychological services to assist them in pain management.</li> <li>• 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'.</li> <li>• In cases where substance misuse psychiatric disorders are suspected, a high index of suspicion for cough mixtures misuse/abuse is warranted.</li> </ul> <p><i>Dependence:</i></p> <ul style="list-style-type: none"> <li>• Assess opioid addiction with the misuse of ibuprofen-codeine combinations when assessing patients with severe hypokalaemia, pancreatitis and medication overuse headache.</li> </ul> <p><i>Managing codeine related issues:</i></p> <ul style="list-style-type: none"> <li>• Develop community pharmacy practice strategies that promote safety and include removal of potential products of abuse from the point of sale or sight.</li> </ul>	<p><i>Use and misuse:</i></p> <ul style="list-style-type: none"> <li>• Adopt a 'universal precautions' systematic approach to each codeine sale, rather than a selective approach based on customer appearance.</li> <li>• Provide clearer product labelling of the active ingredients in over the counter and prescribed products.</li> <li>• Remove potential products of abuse from sight in community pharmacies.</li> </ul> <p><i>Dependence:</i></p> <ul style="list-style-type: none"> <li>• Refuse sales of codeine to users who are problematic misusers or dependent.</li> </ul> <p><i>Managing codeine related issues:</i></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Introduce short term restricted dispensing practices of codeine based products.</li> </ul>	<p><i>Use and misuse:</i></p> <ul style="list-style-type: none"> <li>• Develop prescription drug monitoring and national online prescription systems.</li> <li>• Develop and evaluate real time integrated monitoring of the dispensing of prescribed and over the counter use of codeine based products in community pharmacies.</li> <li>• Ensure routine enquiries by health professionals of patients with regard to prescribed and over the counter codeine medication use.</li> </ul> <p><i>Dependence</i></p> <ul style="list-style-type: none"> <li>• Identify treatment seeking barriers and experiences of people with codeine dependence.</li> </ul> <p><i>Managing codeine related issues:</i></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Share information in relation to codeine sales and consumers with other pharmacists.</li> </ul>

Raising awareness	Detecting and managing risk	Dispensing practices	Monitoring and surveillance of codeine
<ul style="list-style-type: none"> <li>Promote drug monitoring systems drug workers and clinicians should be aware of potential emerging harmful forms of home produced drug abuse, particularly in the case of injecting drug use.</li> </ul> <p><i>Managing codeine related issues:</i></p> <ul style="list-style-type: none"> <li>Promote improved awareness by professionals in relation to co-prescribing and effects on health.</li> <li>Increase awareness and access to psychological treatments, for example, cognitive-behavioural therapy, biofeedback and relaxation techniques for the treatment of chronic headache.</li> <li>Stronger awareness of and connections between the macro, meso and micro levels for policy development and analysis with regard to codeine use, misuse and dependence is required.</li> <li>Policy development to manage variability in OTC sales of codeine medicines across countries.</li> <li>Policy development to guide development and implementation of identified strategies across countries.</li> </ul>	<ul style="list-style-type: none"> <li>Develop and improve referral mechanisms to primary care teams for people suspected to be misusing codeine or to be dependent.</li> <li>Develop strategies to detect deception, especially in pain related cases, thereby minimising risk of failing to improve or overdose.</li> <li>Increase availability of disposable containers for unused prescriptions.</li> <li>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.</li> <li>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 that target injecting drug users who inject home drug solutions made from codeine.</li> </ul>	<ul style="list-style-type: none"> <li>Develop in house pharmacy based brief interventions at the point of sale along with supported detoxification in pharmacies.</li> <li>Provide needle and syringe exchange services targeting opiate injecting. Marketing and promotion of more effective non-opioid combinations of simple analgesics.</li> </ul>	<ul style="list-style-type: none"> <li>Develop and evaluate 'early warning systems' in relation to codeine use, misuse and dependence.</li> <li>Consider further development and roll-out to other countries of initiatives that are similar to the South African Codeine Care Project, using The TrustaTAG™.</li> <li>Monitor and manage conflicts between commercial and customer interests and between pharmacy, non-pharmacy and internet pharmacy outlets.</li> </ul>

The development of community pharmacy strategies that promote safety and include the removal of potential codeine containing products of abuse from the point of sale or sight is recommended. Furthermore, improved referral mechanisms to primary care teams for people suspected of misusing codeine or being dependent is needed as well as the development of appropriate harm reduction tactics for injecting drug users who purchase codeine for home manufacture of deso-morphine (needle exchange, bleach distribution, hygiene, provision of filters, foil packs to encourage route reversals, and safer injection facilities), along with screening, treatment and prevention programmes for all patients affected by codeine misuse and dependence.

### *Dispensing practices*

This theme illustrates details relating to pharmacy precaution, and protocols for sales and refusal to supply, training and support of staff, provision of needle and syringe programmes and manufacturer health warnings. Safety is central to pharmacists' decision making with regard to medication dispensing (31). Pharmacy practice strategies that promote safety in relation to codeine dispensing practices are warranted (22, 31). For example, continual expansion of the clinical and public health role of the community pharmacist with on-going inter-disciplinary training for counter assistants, pharmacists and other health professionals is recommended. The use of a 'universal precautions' approach for all codeine sales rather than the current selective type methods based upon customer appearance with further development of in house pharmacy based brief interventions at the point of sale, along with supported detoxification in pharmacies warrants consideration, albeit given the challenges of the busy retail environment. Additionally, clearer product labelling of the active ingredients in OTC and prescribed codeine products with the removal of potential products of abuse from sight in community pharmacies is recommended, and with greater visibility of warnings on labels and leaflets that clearly highlight 'risk of addiction' or advise short term use of such medicines. Restrictions on pack sizes, advertising codes, prevention of public advertising, restrictions on product visibility and customer self-selection, pharmacy record keeping and direct involvement of pharmacists in sales are recommended (22, 23). Also, marketing and the promotion of more effective non-opioid combinations of simple analgesics could alleviate concerns of potential misuse and dependence, and discourage potential pathways toward habit forming use in unsuspecting or ill-informed consumers.

### *Monitoring and surveillance of codeine*

This theme presents recommendations relating to the monitoring and surveillance of codeine dispensing activity and estimations of the levels of customer use and misuse (both intentional and non-intentional) that remain problematic (5, 7, 14, 19, 20, 22, 31). For example, the development of national online prescription systems with real time integrated monitoring of the dispensing of prescribed and OTC codeine based products in community pharmacies is recommended. Furthermore, routine enquiries by health professionals of users with regard to prescribed and OTC codeine medication use must be promoted. In addition to therapeutic dependence and such forms of non-compliant use, the diversion, tampering, home manufacture and injecting of OTC and prescribed pharmaceuticals (containing codeine and other opioids) is a pharmacy, drug surveillance and public health issue (5, 32).

There is a societal need for improved understanding of the risks of codeine use, misuse and dependence (5, 7, 14, 19–22). The potential risks relating to prescribed and OTC codeine use, misuse and dependence, and the impact that pharmacy controls and interventions may have is an area that requires further development (9, 20, 22, 29). A global emergence of ‘respectable addiction’ has occurred alongside a heightened awareness by the general public and health professionals with regard to this covert and hidden addiction issue, and with a need for data monitoring of trends (22, 32).

### *Relevance to existing literature and implications of results*

Prescribed misuse, diversion, de-regulation and OTC availability of codeine compounds open the potential for user adverse consequences and medical and pharmacy practice interventions (5, 7, 19–21). Health professionals need to be more aware of public lay drug definitions around pharmaceutical opioid use, both prescribed and OTC, in order to avoid misunderstandings within their practice (5, 30). Equally, medical and pharmacy practitioner awareness relating to customer access to codeine based products, rising public displacement toward self-medication, and frequent interplay with pain conditions, coupled with the potential for unintentional misuse, health harms and overdose is warranted in order to maintain public surveillance and monitor those experiencing misuse.

While 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 (3, 5). 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 (5). Recent developments include risk management and real-time monitoring of dispensing activity in order to prevent patient opioid aberrant behaviour in the form of ‘double doctoring’ and ‘pharmacy hopping’ or consultation of multiple prescribers and pharmacy retailers (5, 24).

Prescribed opioid drug use is grounded in a mutual responsibility for transparent communication between patients and health or pharmacy professionals (6, 29, 31). Coordinated responses in the form of patient or customer (in the case of OTC) education, screening for risk of abuse, patient agreements and screening are generally required to address drug compliance (15). Medical practitioners are advised to question those receiving opioid therapy about current, past and family histories with regard to misuse and addiction (5, 17), and their levels of over the counter and prescribed opioid use (7). Displacement patterns have been observed between initial prescribed and OTC forms of misuse (16).

The management of codeine related issues requires a concerted effort by all stakeholders given the link between the misuse of OTC codeine medicines and product availability (32, 33). Raising further lay and professional awareness with enhanced efforts to improve the knowledge, skills, confidence and commitment in relation to codeine use, misuse and dependence is required (19, 20, 32). Continued research, pharmacy practice innovation for risk management and drug surveillance, anti-tampering formulations, medical and pharmacy practitioner education, and design of specific pharmacy based screening and treatment (both pharmacological and non-pharmacological) protocols is warranted.

## CONCLUSIONS

This paper presents the findings arising from a scoping review of codeine use, misuse and dependence with a particular focus on implications and recommendations for practice. We found many relevant papers, highlighting a growing interest in issues relating to codeine use, misuse and dependence. While the correct medical use of codeine based products is comparatively safe, the unpredictable nature of codeine's pharmacokinetics gives rise to concerns in relation to safety (3, 5). Recent initiatives relating to risk management and real-time monitoring of dispensing activity in order to prevent patient opioid aberrant behaviour underpinned by public availability are welcome developments (5, 23). While many specific topic areas are identified, further research and analysis of these areas is required.

While the scoping review followed a systematic process, it cannot claim to be exhaustive in its coverage. In particular, there may be on-going, as yet unpublished pieces of research not described here. It must also be acknowledged that while our search was comprehensive and included a wide body of literature, across varying populations, conditions and study designs, some literature may have been missed. Furthermore, social media are constantly evolving, leading to challenges in keeping the search updated.

*Acknowledgements.* – The research leading to these results has received funding from the European Community's Seventh Framework Programme FP7/2007–2013 under grant agreement No. 611736.

## REFERENCES

1. H. Arksey and L. O'Malley, Scoping studies: towards a methodological framework, *Int. J. Soc. Res. Method.* 8 (2005) 19–32.
2. S. Derry, R. A. Moore and H. McQuay, Single dose oral codeine, as a single agent, for acute post-operative pain in adults, *Cochrane Database System Rev.* 4 (2010) CD008099; DOI: 10.1002/14651858.CD008099.pub2.
3. European Medicines Agency, *Assessment Report for Codeine-containing Medicinal Products Indicated in the Management of Pain in Children*. Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data. Procedure number: EMEA/H/A-31/1342, Assessment 24 June 2013 EMA/441891/2013, London; [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Referrals\\_document/Codeine\\_containing\\_medicinal\\_products/Recommendation\\_provided\\_by\\_Pharmacovigilance\\_Risk\\_Assessment\\_Committee/WC500147065.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Codeine_containing_medicinal_products/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500147065.pdf); last access August 2, 2015.
4. International Narcotics Control Board, *Narcotic Drugs, Estimated World Requirements for 2012, Statistics for 2010*, United Nations, New York, 2012; [https://www.incb.org/incb/en/narcotic-drugs/Technical\\_Reports/2011/narcotic-drugs-technical-report\\_2011.html](https://www.incb.org/incb/en/narcotic-drugs/Technical_Reports/2011/narcotic-drugs-technical-report_2011.html); last access August 2, 2015.
5. M. Van Hout, M. Bergin, M. Foley, E. Rich, A. I. Rapca, R. Harris and I. Norman, *A Scoping Review of Codeine Use, Misuse and Dependence*. Final Report CODEMISUSED Project European Commission 7th Framework Programme, Brussels 2014.
6. S. A. Francis, N. Barnett and M. Denham, Switching of prescription drugs to over-the-counter status: is it a good thing for the elderly? *Drugs Aging* 22 (2005) 361–370; DOI: 10.2165/00002512-200522050-00001.
7. A. Casati, R. Sedefov and T. Pfeiffer-Gerschel, Misuse of medicines in the European Union: A systematic review of the literature, *Eur. Addict. Res.* 18 (2012) 228–245; DOI: 10.1159/000337028.

8. K. H. Wang, W. Becker and D. A. Fiellin, Prevalence and correlates for nonmedical use of prescription opioids among urban and rural residents, *Drug Alc. Depend.* **127** (2013) 156–162; DOI: 10.1016/j.drugalcdep.2012.06.027.
9. M. C. Van Hout, Kitchen chemistry: A scoping review of the diversionary use of pharmaceuticals for non-medical use and home production of drug solutions, *Drug Test. Anal.* **6** (2014) 778–787; DOI: 10.1002/dta.1622.
10. G. M. Peterson, Selecting nonprescription analgesics, *Am. J. Ther.* **12** (2005) 67–79.
11. B. A. Sproule, U. E. Busto, G. Somer, M. K. Romach and E. M. Sellers, Characteristics of dependent and nondependent regular users of codeine, *J. Clin. Psychopharmacol.* **19** (1999) 367–372.
12. M. Y. Frei, S. Nielsen, M. D. Dobbin and C. L. Tobin, Serious morbidity associated with misuse of over-the-counter codeine–ibuprofen analgesics: a series of 27 cases, *Med. J. Aus.* **193** (2010) 294–296.
13. G. Robinson, S. Robinson, P. McCarthy and C. Cameron, Misuse of over-the-counter codeine-containing analgesics: dependence and other adverse effects, *N. Z. Med. J.* **123** (2010) 59–64.
14. S. Nielsen, J. Cameron and S. Pahoki, *Over the Counter Codeine Dependence*, Turning Point Drug and Alcohol Centre, Victorian Department of Health, Melbourne, 2010; [http://atdc.org.au/wp-content/uploads/2011/02/OTC\\_CODEINE\\_REPORT.pdf](http://atdc.org.au/wp-content/uploads/2011/02/OTC_CODEINE_REPORT.pdf); last access September 30, 2015.
15. S. Nielsen, R. Bruno, S. Carruthers, J. Fischer, N. Lintzeris and M. Stooive, *Investigation of Pharmaceutical Misuse Amongst Drug Treatment Clients*, Turning Point Drug and Alcohol Centre, Victorian Department of Health, Melbourne 2008; [https://www.burnet.edu.au/system/publication/file/3364/2008\\_Investigation\\_of\\_pharmaceutical\\_misuse\\_amongst\\_drug\\_treatment\\_clients.pdf](https://www.burnet.edu.au/system/publication/file/3364/2008_Investigation_of_pharmaceutical_misuse_amongst_drug_treatment_clients.pdf); last access September 30, 2015.
16. R. Cooper, ‘I can’t be an addict. I am.’ Over-the-counter medicine abuse: a qualitative study, *BMJ Open* **3** (2013) e002913; DOI: 10.1136/bmjopen-2013-002913.
17. S. E. McCabe, J. A. Cranford, C. J. Boyd and C. J. Teter, Motives, diversion and routes of administration associated with nonmedical use of prescription opioids, *Addict. Behav.* **32** (2007) 562–575; DOI: 10.1016%2Fj.addbeh.2006.05.022.
18. S. E. McCabe, C. J. Boyd and C. J. Teter, Subtypes of nonmedical prescription drug misuse, *Drug Alcohol Depend.* **102** (2009) 63–70; DOI: 10.1016/j.drugalcdep.2009.01.007.
19. G. Reay, *An Inquiry into Physical Dependence and Addiction to Prescription and Over-the-counter Medication*, The All-party parliamentary drugs misuse group, 2007–2008 Parliamentary session, London 2008; [http://www.stop-heroin.co.uk/pdf/Prescription\\_drugs\\_2008.pdf](http://www.stop-heroin.co.uk/pdf/Prescription_drugs_2008.pdf); last access September 30, 2015.
20. M. Dobbin and C. Tobin, *Over-the-counter Ibuprofen/Codeine Analgesics: Misuse and Harm*, Victorian Drugs Policy and Services Branch, Department of Human Services, Melbourne 2008.
21. K. Reed, A. Bond, J. Witton, R. Cornish, M. Hickman and J. Strang, *The Changing Use of Prescribed Benzodiazepines and Z-drugs and of Over-the-counter Codeine-containing Products in England: a Structured Review of Published English and International Evidence and Available Data to Inform Consideration of the Extent of Dependence and Harm*, The National Addiction Centre, Kings College London and School of Social and Community Medicine, University of Bristol, Bristol 2011; <http://www.appgita.com/wp-content/uploads/2011/05/Report-1-NAC-Benzos-and-z-drug-addiction.pdf>; last access September 27, 2015.
22. R. J. Cooper, *Respectable Addiction – a Qualitative Study of Over the Counter Medicine Abuse in the UK*, School of Health and Related Research (SchARR), University of Sheffield. Sheffield 2011; [http://www.pharmacyresearchuk.org/waterway/wp-content/uploads/2012/11/respectable\\_addiction\\_richard\\_cooper\\_2011.pdf](http://www.pharmacyresearchuk.org/waterway/wp-content/uploads/2012/11/respectable_addiction_richard_cooper_2011.pdf); last access October 1, 2015.
23. A. M. Hamer, J. M. Spark, P. J. Wood and E. Roberts, The upscheduling of combination analgesics containing codeine: The impact on the practice of pharmacists, *Res. Soc. Admin. Pharm.* **10** (2014) 669–678; DOI: 10.1016/j.sapharm.2013.08.004.

24. F. L. Shand, G. Campbell, W. Hall, N. Lintzeris, M. Cohen and L. Degenhardt, Real-time monitoring of Schedule 8 medicines in Australia: evaluation is essential, *Med. J. Aus.* **198** (2013) 80–81; DOI: 10.5694/mja12.10785.
25. B. McAvoy, M. Dobbin and C. Tobin, Over-the-counter codeine analgesic misuse and harm: characteristics of cases in Australia and New Zealand, *New Zeal. Med. J.* **124** (2011) 29–33.
26. C. Tobin, M. Dobbin and B. McAvoy, Regulatory responses to over-the-counter codeine analgesic misuse in Australia, New Zealand and the United Kingdom, *Aust. New Zeal. J. Pub. Health* **37** (2013) 483–488; DOI: 10.1111/1753-6405.12099.
27. H. M. L. Daudt, C. van Mossel and S. J. Scott, Enhancing the scoping study methodology: a large, inter-professional team’s experience with Arksey and O’Malley’s framework, *Med. Res. Method.* **13** (2013) 48; DOI: 10.1186/1471-2288-13-48.
28. C. L. Roumie and M. R. Griffin, Over-the-counter analgesics in older adults: a call for improved labelling and consumer education, *Drugs Aging* **21** (2004) 485–498.
29. G. C. Alexander, N. Mohajir and D. O. Meltzer, Consumers’ perceptions about risk of and access to nonprescription medications, *Am. Pharm. Assoc.* **45** (2005) 363–370; DOI: 10.1331/1544345054003868.
30. M. Wazaify, E. Shields, C. M. Hughes and J. C. McElnay, Societal perspectives on over-the-counter (over the counter) medicines, *Fam. Pract.* **22** (2005) 170–176; DOI: 10.1093/fampra/cmh723.
31. L. A. Hanna and C. M. Hughes, ‘First, do no harm’: factors that influence pharmacists making decisions about over-the-counter medication: a qualitative study in Northern Ireland, *Drug Saf.* **33** (2010) 245–255; DOI: 10.2165/11319050-000000000-00000.
32. R. J. Cooper, Over-the-counter medicine abuse: a review of the literature, *J. Subst. Use* **18** (2013) 82–107; DOI: 10.3109/14659891.2011.615002.
33. M. Foley, R. Harris, E. Rich, A. Rapca, M. Bergin, I. Norman and M. C. Van Hout, The availability of over-the-counter codeine medicines across the European Union, *Public Health* (2015) in press; DOI: 10.1016/j.puhe.2015.06.014.