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Best Practices and Innovations for Managing Codeine Misuse and Dependence

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ABSTRACT - Purpose. Promoting and ensuring safe use of codeine containing medicines remains a public health issue given the rise in reporting of misuse and dependence particularly in countries where available over-the-counter (OTC). The aim of this unique study was to identify best practices in management of opioid abuse and dependence, particularly codeine, and innovations to meet challenges surrounding safe and compliant use, patient awareness-raising, reducing health harms and enhancing successful treatment of dependence. **Methods.** A mixed methods approach using three data points was used that included : (1) analysis of data from existing scoping reviews to identify potential areas for innovation (2) interviews with key national stakeholders from public health, pharmaceutical, regulatory, primary care and addiction practice in three distinct regulatory regimes (Ireland, United Kingdom and South Africa); and (3) a circular email request for information on potential innovations to members of the European Medicine's Agency European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP). Data from these three sources were analysed to identify best practices and opportunities for innovation. **Results.** Best practices and potential innovations were identified under the nine headings: (1) manufacture; (2) product information and public education; (3) responsible prescribing; (4) monitoring and surveillance; (5) dispensing, screening and brief interventions in community pharmacies; (6) safety in the workplace and on the road; (7) internet supply of codeine and online support; (8) treatment of codeine dependence; and (9) learning resources and training for health professionals. **Conclusions.** Challenges ensuring availability of codeine containing medicines for legitimate therapeutic use, while minimising misuse, dependence and related health harms warrant consideration of new innovations. Most promising innovative potential lies across the products' retail lifecycle from manufacture to prescriber and community pharmacy practitioner.

This article is open to **POST-PUBLICATION REVIEW**. Registered readers (see "For Readers") may **comment** by clicking on ABSTRACT on the issue's contents page.

BACKGROUND

Codeine, or 3-methylmorphine, is the most commonly consumed opiate worldwide, widely used for its analgesic, anti-diarrhoeal and antitussive properties (1). Many countries restrict supply to prescription only, with over-the-counter (OTC) availability with differing regulatory policies on advertising, shelf visibility and direct pharmacist intervention at point of sale implemented in many countries including Australia, New Zealand, Canada, South Africa, France, Ireland and the United Kingdom (UK) (2-3). The rise in misuse of

OTC codeine-containing products is of increasing concern and has stimulated calls for upscheduling, increased pharmaco-vigilance and development of innovative proactive public health, primary care and community pharmacy initiatives (3, 6-7). Misuse, when referring to use of medicines, is defined as *'the problematic consumption outside of acceptable medical practice or medical guidelines, when self-medicating at higher doses and for longer than is*

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advisable, for intoxicating purposes and when risks and adverse consequences outweigh the benefits' (4).

Codeine has an identified abuse potential due to its opiate effect and development of tolerance within a short timeframe (8), and by reported patient dependence (9). Neuro-adaptation occurs with repeated use (therapeutic and non-therapeutic) within a short period of time (10, 11). Prolonged use is strongly associated with depression and dysphoric mood states, and how codeine can interact with other substances leading to respiratory depression and other central nervous system effects (3,5). Of particular public health concern is that long term or excessive use of codeine combination products containing additives (ibuprofen and paracetamol/acetaminophen) can lead to chronic headache, gastrointestinal haemorrhage, inflammatory bowel conditions, hypokalaemia, acute haemorrhagic necrotising pancreatitis, and neurological damage (3,5). The rise in patient uptake of addiction treatment services for this form of opioid analgesic dependence is equally concerning (12, 13).

Challenges for policy makers and practitioners centre on how to ensure availability of codeine containing medicines for legitimate therapeutic use, while minimising consumer risk of misuse, dependence and related health harms (6-7, 14-15). This is complicated by the complexity of inter-relationships between pharmacological, social, economic, legal and individual factors which shape consumption patterns; the heterogeneous nature of misuse; blurring between therapeutic use and misuse; focus of drug agencies on surveillance of opiate users and dependents; difficulties in estimating prevalence of misuse given the broad definition of misuse and the covert nature of medicinal misuse itself; and the presence of displacement between public sourcing of prescribed, OTC and internet sourced products (3, 6, 14).

In September 2013 a 3-year, European Union funded, multi-country research project between academic and community pharmacy sectors was initiated in Ireland, the UK, and South Africa. This project called CODEMISUSED, aimed to investigate codeine use, misuse and dependence in partner countries. A scoping review of the literature on codeine was conducted (5, 15) and this review was used to identify existing and specific

best practice strategies to address codeine misuse and dependence centring on: product manufacture; product information and public education; responsible prescribing; monitoring and surveillance; dispensing, screening and brief interventions in community pharmacies; safety in the workplace and on the road; internet supply of codeine and technological support; treatment of codeine dependence; and training for health professionals. In this paper we build on these reviews (5, 15) by presenting the key identified best practices and potential innovations to meet challenges in management of codeine use, misuse and dependence.

For the purpose of our analysis we defined innovations as '*a novel concept or a new way of doing things to reduce the risk of codeine misuse and dependence which has not yet become best practice.*' Distinguishing an innovation from best practice (which might once have been innovations, but are now widely implemented), involved professional judgement by the authors based upon evidence garnered in this study. Disagreements between the authors about whether an intervention or practice was an example of innovation or was best practice were resolved through discussion, with reference to the available evidence.

METHODS

A mixed methods approach using three data points that included: (1) further analysis of data collected from the scoping reviews to identify areas for innovation (5,15); (2) interviews with key national stakeholders from public health, pharmaceutical, regulatory, primary care and addiction practice in three distinct regulatory regimes (Ireland, UK and South Africa); and (3) a circular email request for information on potential innovations to members of the European Medicine's Agency European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP).

Scoping Reviews of the Global Literature on Codeine Use, Misuse and Dependence (5,15)

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*'; and *'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 US Federal Drug Administration (FDA), the Canadian pharmacy authority, and the UK National Health Service (NHS). See Table 1 for inclusion and exclusion criteria.

Two reviewers independently screened titles and abstracts to identify articles reporting an innovation to reduce the risk of misuse of codeine or other over the counter medication with misuse potential. Disagreements were resolved by discussion with a third researcher. Reference lists of retrieved papers were hand searched for any additional relevant papers. 117 articles remained following application of exclusion criteria and removal of duplicates. See Figure 1.

Interviews with National Stakeholders in Ireland, UK and South Africa

Conversational interviews were conducted with a purposive sample of key informants based in Ireland (n=5), the UK (n=6) and South Africa (n=9) who were identified as having either a strategic role nationally or internationally in the development of codeine misuse and dependence services and/or experience of developing and implementing innovations across the codeine misuse or OTC medication field. The sample was identified through community pharmacy organisations in each country. Snowball sampling was used whereby each interviewee was asked to nominate other potential individuals at the forefront of innovations relating to codeine misuse and dependence.

The interview guide was informed by a scoping of the literature with regards to challenges and heterogeneities of codeine misuse, current best practices, and identified areas for innovative approaches – see for example the report produced by the National Treatment Agency for Substance Misuse in the UK (16). Interviews were conducted either face-to-face or by telephone. Interview

Table 1: Study 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 medicine products.
- Policy documents and guidelines with particular reference to codeine.

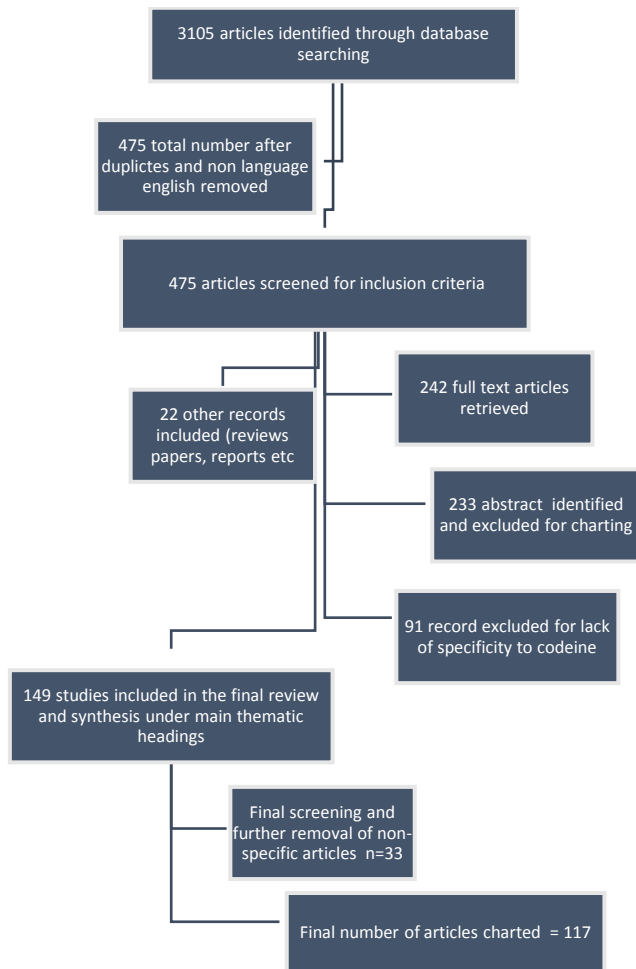
Exclusion criteria

- 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.

duration ranged between 20 and 90 minutes and were audio recorded.

Email Request for Information on Innovations to Members of the ENCEPP

A circular email was sent by the ENCEPP network of the European Medicines Agency, London, UK to all European centres (n=139) requesting them to contact the CODEMISUSED Principal Investigator (author four) with information relating to innovations they were aware of for managing codeine misuse and dependence. Three responses were received.

Figure 1: Flow diagram of articles accessed through the scoping review

Data Analysis

Data was analysed collectively and summarised under nine headings: (1) manufacture; (2) product information and public education; (3) responsible prescribing; (4) monitoring and surveillance; (5) dispensing, screening and brief interventions in community pharmacies; (6) safety in the workplace and on the road; (7) internet supply of codeine and online support; (8) treatment of codeine dependence; and (9) learning resources and training for health professionals.

RESULTS

We present here the results in two sections, namely 'Best Practices' and 'Innovations'.

Best Practices

Manufacture

Abuse deterrent formulations can prevent drug users extracting the active ingredient in order to consume greater amounts, or the home manufacture of deso-morphine for injecting purposes (17). Formulations can also be designed to deter reinforcing effects of opioids through the incorporation of antagonists or other ingredients that become active only when the analgesic is used improperly (18).

Product Information and Public Education

Measures such as increased visibility of warnings on labels and leaflets (i.e. 'Can cause addiction. For 3 days use only'), (19) are features of the retail environment of community pharmacies in many European countries designed to deter codeine misuse and dependence. However, key informants pointed out that in their experience the public ignore such information.

Responsible Prescribing

Multidisciplinary assessments of opioid dependence are advocated that incorporate physical, psychological, social, and environmental factors. Monitoring strategies include patient reports of side effects and therapeutic effects, urine testing, pill counts, consulting prescription databases, interviews with family and caregivers and patient observations. Prescribers and other health providers are advised to assess and monitor risk by asking opioid patients about current, past and family history of addiction (20) and current/past levels of OTC use (21). Doctor questioning about over-sedation, feeling intoxicated, requesting early refills, self-increasing dosage have also been identified as useful screening questions to predict patients at risk (22). Savage (23) also includes amongst opioid aberrant behaviours: so called patient 'drug allergies' which limit treatment options; frequent late or missed appointments; patient history of no therapeutic response to any pharmacological treatment except opioids; requests for medications at the end of a consultation; negative description of prior interactions with prescribers; and presence of pain out of proportion to identified nociceptive process. Opioid agreements have also been used to establish a contract between prescribers and patients and have been used as grounds for discontinuation of opioid

prescribing.

Monitoring and Surveillance

Well-designed real-time reporting systems aim to track and monitor levels of dispensing of opioid containing medicines, reduce inappropriate prescribing, prescription shopping and unsanctioned use, prevent 'pharmacy-hopping' in the event of refusal of sale and reduce adverse events such as overdose. However, these systems typically do not include codeine and require extensive evaluation and process monitoring, with potential unintended consequences including: overly cautious prescribing of higher schedule opioids and a shift toward mid-range scheduled opioids to avoid scrutiny; displacement of consumer behaviour to include alcohol, other prescription drugs and illicit drugs; increases in pharmacy and warehouse theft; and inconsistent responses by doctors to real-time reporting information (24-26).

Dispensing, Screening and Brief Interventions in Community Pharmacies

Regulatory responses to misuse of OTC codeine have to date included changes in pack sizes, maximum unit doses, maximum daily dose, warning labels, consumer medicine information, pharmacist intervention at point of sale, restriction of self-selection and advertising (27). Suspected misuse in pharmacies centres on customer repeated requests for certain codeine containing products by name; refusal to consider single ingredient products (i.e. paracetamol, aspirin or ibuprofen); requesting specific pack sizes; and agitation when pharmacists intervene. Pharmacy tactics currently include removal of codeine containing products displayed at point of sale, refusal of sale or restriction of the quantity sold in the event of suspect requests, on-site recording of incidences of suspected misuse, medicines information provision by medicines counter assistants and pharmacists, direct pharmacist intervention by additional customer questioning, and customer referral to primary care professionals.

Safety in the Workplace and on the Road

Various workplace intervention programmes exist to train workers to recognise, intervene and refer co-workers with a substance abuse problem. Specific work place drug testing methods (urine and

hair) are implemented in certain settings, with some countries implementing drug driving legislation (28). However, testing is hampered by cross-sensitivity between illicit and prescription opioid drugs.

Treatment of Codeine Dependence

Buprenorphine and methadone are presently used in substitution treatment. Cognitive behaviour therapy as adjunct has demonstrated efficacy as both a monotherapy and as part of combination treatment strategies to address opioid dependence (29). These include helping the client to monitor internal and external cues for craving and manage the urge to take the substance through techniques such as self-soothing, distraction techniques, physical exercise or staying with the craving without succumbing. Avoidance of blame, reinforcement of positive coping styles, reinforcing positive social supports and a robust relapse prevention plan are central to treatment approaches.

Learning Resources and Training for Health Professionals

Strategies to improve pharmacist counselling skills and enhance customer engagement in health care advice, screening and brief intervention processes have also been implemented in some settings. Education and training programmes advise health professionals to include detail on the patient characteristic of non-medical use of pharmaceutical opioids and dependence, risks and benefits of prescribed and OTC opioids, clinical care issues relating to identification of opioid aberrant behaviours, pain management, how to refuse opioid seeking behaviours, monitoring approaches and appropriate referral mechanisms for treatment (30). Comprehensive training programmes and coordinated inter-agency supports for doctors in the assessment, identification of potential misusing patients, and management of coexisting addiction and chronic non-malignant pain exist and include training in conflict resolution and techniques for declining patient demands (31).

Innovations

Forty five opportunities for innovation were identified in nine areas. Table 2.

Table 2: Listing of Innovations by Area

| | # | Intervention |
|--|----|---|
| Manufacture | 1 | Development of barriers to tampering and deterrent of misuse of combination codeine tablets by using binders in oral formulations, coating, bead or crush resistant compounds, time release matrixes, gel capsules |
| | 2 | Increase safety of combination codeine-paracetamol products through including an antidote to prevent paracetamol overdose |
| | 3 | Tamperproof preparations should be required and backed by legislation and drug companies provided with incentives to invest in these products |
| | 4 | Bar code individual tablets in a blister pack to allow the providence of tablets to be traced in cased where problems arise |
| | 5 | Manufacture smaller packs of codeine which would give only 3-days' supply |
| | 6 | Colour coding of all dependence producing tablets |
| | 7 | Review the safety of all available opioids (including codeine) to identify a single opioid that has the maximum safety, to be used in all combination preparations sold over the counter |
| Product Information & Public Education | 8 | Parenting classes highlighting the potential side effects of codeine, relating to metabolism and harms such as respiratory depression and sedation |
| | 9 | Increase media coverage of the problem of codeine misuse and dependence |
| | 10 | Development of a logo to identify all dependence producing medications/preparations |
| | 11 | Increase the visibility of health warnings on the outside of packs of tablets containing codeine |
| | 12 | Increasing the visibility of the names of generic drugs included in combination medications, and related harms in excessive or long term use |
| | 13 | Public health campaigns that highlight that anyone can become addicted to codeine products when used long term or excessively |
| Responsible Prescribing | 14 | Development of a protocol to guide health professionals how to approach screen and advise members of the public to raise their awareness of the risks of codeine misuse and dependence |
| | 15 | Cochrane review to evaluate the effectiveness of codeine for acute pain |
| | 16 | Promote an extensive opioid prescribing resource on all facets of prescribing both weak and strong opioids (including recommendation to assess psycho-social issues that might be precipitating or supporting the dependence) |
| | 17 | Abuse risk of codeine to be clearly indicated at time of prescription in the prescribing manuals and on prescribing decision computer software |
| | 18 | Handwritten prescription and the regular three monthly review of prescriptions to avoid repeat prescriptions which can occur almost by default |
| | 19 | All patients prescribed codeine products to be registered at a nominated community pharmacy |
| | 20 | Prescriptions for codeine preparations should be for a maximum of one week |
| | 21 | Prescribing of codeine to be confined to prescribers who are trained in addiction |
| | 22 | Discharge patients from pain clinics and hospital with non-opioid containing medications |
| | 23 | Development and testing of a gold standard patient risk assessment tool or procedure for codeine misuse and dependence |

Table 2 Cont'd

Table 2 Cont'd

| | | |
|---|----|--|
| Monitoring & Surveillance | 24 | National integrated prescriber and pharmacy monitoring of medicines using real time reporting analysis |
| | 25 | Monitoring prescribed and OTC codeine sales and purchases through shared patient records |
| | 26 | Purchases of OTC and prescribed medications recorded on the patients' own data card |
| | 27 | Systematic monitoring to establish the prevalence of codeine dependence |
| | 28 | Periodic audits of codeine prescription and dispensing practices |
| | 29 | Adopt the methodologies implemented by the Codeine Care Initiative, South Africa -- which uses a 2D barcode printed on the packs of all codeine containing medicines to advise the customer and dispenser of amount of codeine purchased per month |
| | 30 | Develop secure central database to monitor the purchases of codeine nationally |
| Dispensing, Screening & Brief Interventions in Community Pharmacies | 31 | Pseudo-customer visits to audit pharmacist intervention at point of sale and performance feedback |
| | 32 | Health information posters in community pharmacies |
| | 33 | Require customers to sign on receipt of codeine preparation to indicate they are aware of its dependence potential |
| | 34 | Develop and validate brief self-screening measure to identify pharmacy customers who misuse codeine |
| | 35 | Develop and test a brief intervention modelled on the Very Brief Advice on Smoking Intervention developed by the National Centre for Smoking Cessation and Training (NCSCT) |
| | 36 | Incorporate codeine related enquiry within pharmacists' medication use reviews, and with enhanced communication between prescribers and pharmacists |
| | 37 | Strengthen the contribution of community pharmacists to treatment of codeine misuse and dependence through direct referral to primary and secondary care services; and delivery of community detoxification programmes in conjunction with the prescriber |
| Safety in the Workplace & on the Road | 38 | Integrating an employee assistance programme with drug testing to include opioids |
| | 39 | Compulsory urine testing for codeine in certain workplaces |
| Internet Supply of Codeine & Online Support | 40 | Use mobile phones as a medium for delivery of targeted patient health information and support interventions |
| | 41 | Regular audit of top ranked Google websites to check accuracy of health information on codeine use and misuse |
| | 42 | Health warnings as a pop-up feature of Internet shopping sites |
| Treatment of Codeine Dependence | 43 | Supplement the work of pain clinics by patient self-help courses, courses on pain management and self-help websites Investment in m-Health: Further development and testing of mobile phone messaging to support adherence to treatment (part of innovation 40 above) |
| | 44 | Establish specialist codeine treatment clinics |
| | 45 | Motivational interviewing (MI) training for all health professionals |
| Learning Resources & Training for Health Professionals | | |

Manufacture

Some key informants believed that combination products (e.g. codeine with paracetamol) should not be manufactured because of risk of liver damage with prolonged use and that it would be safer to sell the drugs as separate items. Others were concerned that single codeine products would result in misuse and risk of tampering. It was further suggested that if these combination products continue to be manufactured, that all such preparations should contain an antidote (e.g. methionine sold with paracetamol). The technology is now also available to bar code tablets within a blister pack which would enable the supply of tablets containing codeine to be identified in cases of people who have taken an overdose and where empty packs are available. Since the warning on the pack or on information sheets in packs of codeine states that the medication should not be taken for more than 3-days, it was also proposed that smaller packs at a high retail price be produced which contain only 3-days' supply. Key informants suggested development of a bright logo stamped on boxes of codeine products which indicates to consumers the risk of addiction. In addition tablets containing codeine could be manufactured in a specific colour (black or other unattractive colour).

Product Information and Public Education

The potential deterrent effect of having additional health warnings with greater visibility on the outside of codeine packages was suggested. Suggestions included; '*This medicine contains codeine*' to more specific warnings such as, '*Not to be taken by children, pregnant women or breastfeeding mothers*'. Some remarked that although many countries now have advertising restrictions on codeine containing products, the trade names of some of these products are attractive to customers because they infer a superior product for example, '*Nurofen® Plus*'. To counteract this, it was suggested that the trade name be given less prominence. Several remarked that a major challenge was attracting codeine misusers and individuals dependent on codeine into treatment because they do not identify themselves as addicts. This highlights the importance of public health campaigns which indicate that anyone can (inadvertently) become addicted to codeine.

Responsible Prescribing

It was suggested that emerging evidence states that codeine is of little value for chronic pain and that codeine preparations should become a prescription only medication (POM). However, there was not widespread consensus on this issue. A Cochrane Systematic review to investigate the efficacy of pain medicines available OTC in the UK for acute pain (32) should provide guidance on self-medication for acute pain, as well as responsible prescribing decisions. In 2015, The British Pain Society and Medical Royal Colleges released an opioid prescribing resource (33) and this innovation is aimed at increasing knowledge about all facets of prescribing both weak and strong opioids. Several key informants recommended that a full assessment be undertaken by physicians managing chronic pain and that this should include a focus on the bio-psycho-social issues that might precipitate or support dependence on codeine.

There was widespread agreement on the merits of the need to highlight abuse risk of codeine in prescribing manuals and in prescribing decision computer software. Key informants also noted that prescriptions are often repeated automatically which can perpetuate codeine misuse as prescription renewals often pass unnoticed. One suggestion was that prescribers should be required to hand write repeat prescriptions, rather than simply sign them off. All patients in receipt of prescribed codeine products should be required to register with a community pharmacy and that the prescription is sent to the nominated pharmacy by fax/email. This would enable a second check on repeat prescriptions by the pharmacist. Given the potential risk for codeine dependence within a short time frame, all prescriptions for codeine preparations should ideally be for a maximum of one-week. One participant suggested that prescribers who are addiction specialists should only have prescribing authority to prescribe codeine containing medicines.

It was suggested that doctors and other health professionals rarely consider the possibility of overdose of other drugs within combination codeine preparations. Being alert to this possibility could avoid undetected problems and patient delays in seeking help for potentially serious conditions. The use of opioid agreements establish a written contract between prescriber and patients and highlight to patients the risks involved in taking

codeine. It was also noted that the origins of codeine dependence for a substantial proportion of people is on discharge from pain clinics and hospital. Thus, one suggestion was that patients discharged from pain clinics should be discharged on non-opioid containing pain medications. Furthermore, there is currently no widely accepted 'gold standard' test for assessing opioid dependence and no risk tools for identification of codeine risk and dependence, and therefore, another innovation identified is to develop and test an instrument for screening in practice. Additionally, prescribers and pain and addiction specialists may benefit from further specialised training in assessing and managing coexisting addiction and chronic non-malignant pain.

Monitoring and Surveillance

Electronic patient records which are shared across prescribers and similar systems across community pharmacists, have the potential to provide real time reporting and to deter patterns of misuse through compulsory centralised recording of the name and address of persons that codeine products are issued to. Identity cards can additionally act as deterrence for the purchase of OTC and POM, and could include a chip to produce a personal record of purchases of medicines with the potential for dependence, such as codeine. This could also be built into national health insurance cards where such cards exist. Production of the card at point of purchase of prescription would enable the community pharmacist, the GP or non-medical prescriber to check previous purchases of codeine or other dependence forming medication. An alternative would be for patients/customers to provide their social security/national insurance number.

While development and implementation of a real-time monitoring/reporting scheme using patients' own identity cards (or similar) could raise civil liberties issues and also some technology barriers, several of our key informants thought it would be feasible. The distribution of codeine should be tracked and prescribing practices audited to identify outliers who dispense larger quantities of codeine preparations. Audits could also identify patients whose pain has not been reviewed, those who have been on repeat prescriptions for a long period as well as markers for potential drug misuse, such as frequently losing prescriptions. The

Codeine Care Project launched in South Africa is an ambitious attempt at real-time monitoring of codeine OTC sales in community pharmacies. The initiative uses a barcode printed on the packs of all codeine containing medicines and a very secure central database to monitor the national purchase of these medicines.

Dispensing, Screening and Brief Interventions in Community Pharmacies

Community pharmacies were identified as a good setting for public health posters inviting people to approach the pharmacist if they, or someone they know, might have a problem with painkillers. Pharmacy customers who buy a codeine containing medicine should be required to sign that they have received such a product. Key informants also pointed to the difficulty of identifying people who may be misusing or dependent on codeine. It was further suggested that a self-screening leaflet could be given to all purchasers of codeine related products to identify those with a codeine misuse problem inviting them to speak to the pharmacist.

Key informants suggested that a measure similar to the Alcohol Use Disorders Identification Test (AUDIT) (34) the Drug Abuse Screening Test (DAST) (35) or the Very Brief Advice on Smoking Intervention (36) could be administered to all customers who purchase or are prescribed a codeine combination preparation. If the customer scores above a certain level the pharmacist would give him/her a phone number to ring or, with the customer's agreement, make an appointment for them with a specialist practice nurse or other health professional.

Community pharmacists in some countries currently offer all customers a medication use review (MUR) and in the UK this is a free universal service. It was suggested that codeine use, and painkiller use more generally, should be incorporated into MURs as a matter of routine. Key informants highlighted how the direct referral of patients to general practitioners or secondary services would result in a more integrated service for misusers of OTC codeine containing medicines. A good relationship with the community pharmacist with intervention in the event of suspected problem use is seen as a trigger for help seeking behaviour. Key informants also spoke of the potential for community pharmacists to deliver structured detox treatment programmes for codeine misusers.

Safety in the Workplace and on the Road

A policy of mandatory drug testing to include screening for OTC codeine in the workplace was identified as having the potential to identify potential misusers of codeine. However, we are aware that having a prescription for codeine may legitimate positive urine screening results, but may not necessarily highlight misuse or abuse of the drug. Mandatory drug testing in the workplace may not be acceptable in all settings; but building on the success of employee assistance programmes in the US, these could also be developed to include identification, assessment, support and referral of workers who are misusing OTC and prescribed codeine products. Police may also conduct drug tests on motorists they suspect of driving under the influence of codeine. However, there are technical problems in roadside testing because while the test used for morphine will pick up codeine, codeine can remain in the system for two days.

Internet Supply of Codeine and Online Support

Purchasing trends have diversified to include online pharmacies and this is likely to increase over time, but questions remain about consumer informed decision making of the risks of using online pharmacies. Key informants pointed to the need for doctors to question patients around their use of the Internet for medical information, particularly in the case of pain, and sourcing of medicines. Patient education in partnership with health professionals via medical web-links are a promising development. One innovation that was proposed to curb problems associated with the internet supply of codeine products was for a regulatory or other agency to conduct regular audits of top ranked Google websites to check accuracy of health information on codeine use and misuse. This could confirm that accurate health information about the risks of codeine appear high up on a Google search. It was further proposed that on-line shopping sites be asked to introduce a 'health warning' pop-up and e-health screening in response to searches to purchase codeine containing preparations.

Consumer health technologies which facilitate management of information in computerised systems can also strengthen personal healthcare management. Several informants believed that mobile phone technology has the potential to support patients in treatment through text messaging and help to integrate addiction

treatment into primary care, by enhancing the referral and treatment processes. A series of Cochrane reviews (37-38) highlight the potential of mobile phone messaging as a medium for delivering interventions to facilitate self-management of long term illness and for preventive healthcare. Many respondents believed that M (mobile)-Health had great potential for use in tapering programmes for codeine dependence within integrated primary care and community pharmacy settings. Similarly the Internet offers the potential to engage with and support codeine dependents.

Treatment of Codeine Dependence

There is a need to develop standardised criteria to determine client codeine dependence as well as referral and treatment pathways for OTC codeine dependence. However, the main challenge centres on attracting codeine misusers into treatment, because they do not identify themselves as addicts or believe they have the susceptibility to become an addict. Specific services could be developed for codeine addiction, along with public health campaigns which highlight that anyone can become addicted to codeine. One informant specifically raised the need for specialist residential detoxification facilities for codeine dependence with existing treatment centres. In addition to opiate agonist treatment modalities, key informants commented on the importance of psychosocial adjustment to prevent relapse following successful physical treatments for codeine withdrawal. Amato et al's Cochrane review (39) included five psychosocial treatments (three forms of structured counselling, behaviour therapy and family therapy) which can potentially be used in adjunct therapy for codeine dependence. These were found to have a positive impact compared to pharmacological treatments alone, particularly in increasing abstinence from opiates at follow up. Other more novel psychological therapies have also been proposed as having an important role to play, for example, a Mindfulness Oriented Recovery Programme (40) was able to reduce patients' cravings for opioid drugs and could be considered as part of a holistic treatment for codeine dependence.

Learning Resources and Training for Health Professionals

The importance of trainee community pharmacists and other health professionals having high standards of supervised patient experience and dedicated addiction training as part of their education was highlighted. This could occur through co-location of academic departments in practice settings to minimise the theory-practice gap and maximise opportunities for trainees to apply theory to practice situations and improve their patient interaction skills. Motivational interviewing is now well established as an evidence-based patient-centred, semi-directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence. A Cochrane review of the effectiveness of motivational interviewing for substance abuse also provides some evidence to support this intervention with this distinct group of users (41).

DISCUSSION

To our knowledge, this is a first attempt to go beyond identified best practices in addressing and managing the challenges encountered by codeine use, misuse and dependence, and to identify innovations that can potentially reduce the risk of codeine misuse and dependence. The innovations identified are likely to vary in relation to their potential endorsement by regulatory authorities, pharmaceutical manufacturers, health and community pharmacy practitioners, general public, and the degree to which they might restrict the availability of codeine for therapeutic use. In some instances these best practices are in place for stronger opioids, and warrant consideration for codeine. Given the challenges in ensuring availability of codeine containing medicines for legitimate therapeutic use, whilst minimising misuse, dependence and related health harms these innovations do warrant further consideration and inclusion in current regulatory and policy debate. Limitations in our approach centre on this first attempt in simply identifying routes for innovation. We recommend further research using Delphi strategies to underpin expert opinion globally in terms of impact and challenges to implementation.

To date, attempts to address codeine misuse and dependence have primarily centred on practices that relate to manufacturing, responsible

prescribing, dispensing, monitoring and surveillance, education and psychosocial interventions (3,6,7). While such practices, for example, 'real time monitoring' (The Codeine Care Project) are an important deterrent for misuse and dependence (7, 42-43), they are not solely sufficient. Recent data suggests that individuals who continue to misuse or are dependent on codeine containing medicines intentionally bypass 'real time monitoring' practices and engage communication strategies centred on manipulation and deceitfulness either when negotiating scripts from their doctor or purchasing their medicines. Managing such behaviours require further advanced communications training for medical and pharmacy practitioners, particularly in the area of interpersonal communication strategies with a specific focus on motivational interviewing and brief interventions (44, 45).

Internet supply of medicines, including codeine containing medicines without prescription is a major societal issue (46, 47) with greater access to online information and improved product awareness required. Online interventions targeting alcohol use have shown promising results (48) with Web based social norms interventions also demonstrating effectiveness in reducing alcohol use and promoting smoking cessation (49). Codeine specific services and low threshold substitution treatments and support (51-52) coupled with innovative mechanisms in E & M -Health in treatment and recovery supports for individuals dependent on codeine has potential (53). For instance, the use of mobile phones as a medium for delivery of targeted patient health information and support interventions (38), regular audits of top ranked Google websites to check accuracy of health information on codeine use and misuse and health warnings as a pop-up feature of Internet shopping sites are potential areas for innovation.

There are mixed views with regards the merits or otherwise of retaining codeine in OTC available preparations (6). Jurisdictions with OTC availability of codeine containing products should consider all best practices and innovations prior to up-scheduling. POM availability is not without its problems in terms of both over-prescribing and reducing access to a wide range of people who legitimately use codeine in favour of a minority who are codeine/opioid dependent (5, 54, 55). These issues require responsible and meaningful

consideration by all stakeholders. In terms of the more problematic drug users, pharmaceutical drug formulation technologies are continuously developing in order to create disincentives to reduce the incidence of product tampering and abuse (56-60). For example, physical and chemical barrier approaches for developing abuse-deterrent drugs can reduce risk of tampering with opioids (56). Potential development and manufacturing of abuse-deterrent formulations and novel product designs with regards to codeine containing medicines is recommended, particularly with regards to illicit and prescription opioid dependents abusing codeine containing medicines. Abuse deterrent approaches may deter cold water extraction of codeine from combination products. However, given that the majority of individuals who misuse and are dependent on codeine containing medicines originate from those with legitimate therapeutic need, efforts should focus more on the monitoring of compliance, patient awareness raising, management of iatrogenic dependence and support in the event of problematic use arising. Codeine misusers and those dependent do require intensive psycho-social interventions to support opiate agonist treatment, and do warrant consideration as a distinct patient group [51].

CONCLUSION

Codeine misuse and dependence remains a public health issue and is widely debated at both policy and clinical levels. This paper contributes to such debates around availability, compliance and reduction of harm, and offers policymakers and practitioners' potential innovative ways forward. The challenge of ensuring continued availability of codeine containing medicines for legitimate therapeutic use whilst preventing misuse and related health harms warrants significant consideration. Most promising innovative potential lies across the products' retail lifecycle from manufacture to prescriber and community pharmacy practitioner. While many specific innovations are identified, further expert consensus building approaches, and research on the applied nature of such innovative practices is required.

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REFERENCES

1. International Narcotics Control Board. Narcotic drugs estimated world requirements for 2012. Vienna: INCB, 2012.
2. Foley M, Harris R, Rich E, Rapca A, McGuinness P, Bergin M, Norman I. and Van Hout, M.C. The availability of over the counter codeine medicines across the European Union. *Public Health*. 2015; 129(11):1465-70.
3. Nielsen S, Van Hout MC. Over-the-Counter Codeine—from Therapeutic Use to Dependence, and the Grey Areas in Between. in 'The Misuse of Licit and Illicit Drugs in Psychopharmacology'. Bart Ellenbroek, Mark Geyer and Charles Marsden (Eds) . *Current Topics in Behavioral Neuroscience*. Berlin: Springer Link, 2015.
4. Casati A, Sedefov R, Pfeiffer-Gerschel, T. (2012). Misuse of medicines in the European Union: A systematic review of the literature. *Eur Addict Res*, 2012; 18: 228–245.
5. Van Hout M.C, Bergin M, Foley M, Rich E, Rapca A, Harris R, Norman I. *A Scoping Review of Codeine Use, Misuse and Dependence, Final Report*. CODEMISUSED Project. Brussels: European Commission 7th Framework Programme, EU; 2014. Available at www.codemisused.org Accessed July 19th 2015.
6. Van Hout, M.C, Norman, I. Over the Counter Codeine Misuse: recommendations for detection and reduction of risk in community pharmacies. *Int J Drug Policy*, 2016; 27:17-22.
7. Van Hout, M.C. Doctor Shopping and Pharmacy Hopping: Practice Innovations relating to Codeine. *Drug and Alcohol Today*, 2014, 14 (4): 219-234.
8. Babalonis S, Lofwall MR, Nuzzo PA, Siegel AJ, Walsh SL Abuse liability and reinforcing efficacy of oral tramadol in humans. *Drug Alcohol Depend* 2013; 129(1–2):116–124.
9. Nielsen S, Murnion B, Dunlop A, Degenhardt L, Demirkol A, Muhleisen P, Litzeris N. Comparing treatment-seeking codeine users and strong opioid users: findings from a novel case series. *Drug Alcohol Rev*, 2015; 34(3):304–11.
10. Nielsen S, Cameron J, Pahoki S. *Over the counter codeine dependence*. Melbourne: Turning Point Alcohol and Drug Centre, 2010.
11. Reed K, Bond A, Witton J, Cornish R, Hickman M, Strang J. 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. London: National Addiction Centre, King's College London, and School of Social and Community Medicine, University of Bristol, 2011.
12. Nielsen S, Roxburgh A, Bruno R, Lintzeris N, Jefferson A, Degenhardt L. Changes in non-opioid substitution treatment episodes for pharmaceutical opioids and heroin from 2002 to 2011. *Drug Alcohol Depend*, 2015; 149: 212-9.
 13. Dada, S., Burnhams, N., Van Hout, M.C. Parry, C. Codeine misuse and dependence in South Africa – learning from substance abuse treatment admissions? *South African Med J*. 2015; 105(9): 776-779.
 14. Parry, C., DeLuca, P., Cooper, R. Van Hout, M.C. (2015). Should governments be more worried about the codeine misuse and dependence? *Addiction*. Early Online.
 15. Bergin, M., Norman, I, Foley, M., Harris, R., Rapca, A., Rich, E. Van Hout, M.C. Practice implications and recommendations for managing codeine misuse and dependence. *Acta Pharmacologica*. 2015; 65: 351–364.
 16. National Treatment Agency for the Misuse of Substances. *Addiction to Medicine*. London: National Health Service, 2011.
 17. Van Hout MC. Kitchen chemistry: A scoping review of the diversionary use of pharmaceuticals for non-medicinal use and home production of drug solutions. *Drug Test Anal*. 2014; 6: 778-787.
 18. Cone EJ. Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet. *Drug Alcohol Depend*. 2006; 83; 1(0): S31-S39.
 19. Medicines and Healthcare products Regulatory Agency. MHRA Public Assessment Report. Over-the-counter painkillers containing codeine or dihydrocodeine. 2009. Available at <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON296400>. Accessed July 19th 2015.
 20. Kahan M, Srivastava A, Wilson L, Gourlay D, Midmer D. Misuse of and dependence on opioids Study of chronic pain patients. *Can Fam Physician*. 2006; 52: 1081-7.
 21. Lessenger JE, Feinberg SD. Abuse of prescription and over-the-counter medications. *J Am Board Fam Pract*. 2008; 21(1): 45–54.
 22. Fleming MF, Davis J, Passik SD. Reported lifetime aberrant drug-taking behaviors are predictive of current substance use and mental health problems in primary care patients. *Pain Medicine*. 2008; 9(8):1098–1106.
 23. Savage SR. Long-term opioid therapy: assessment of consequences and risks. *J Pain Symptom Manage*. 1996; 11: 274–86.
 24. UNODC. The non medicinal use of prescription drugs. Vienna, United Nations, 2011. Available at www.unodc.org/.../drug...and.../nonmedical-use-prescription-drugs.pdf. Accessed July 19th 2015.
 25. Le Roux K. Marketing of CPS. *Pharmaceutical Practitioner. SAPJ.*, 2013; 80(5): 43-47.
 26. Shand FL, Campbell G, Hall W, Lintzeris N, Cohen M, Degenhardt L. Real-time monitoring of Schedule 8 medicines in Australia: evaluation is essential. *Med J Aust*. 2013; 198(2): 80-81.
 27. Tobin C, Dobbin M, McAvoy B. Regulatory responses to over-the-counter codeine analgesic misuse in Australia, New Zealand and the United Kingdom. *Aust N Z J Public Health*. 2013; 37(5): 483-488.
 28. Fernandez MMR, Wille SMR, di Fazio VMD. Kummer N, Hill V, Samyn N. Detection of benzodiazepines and z-drugs in hair using an UHPLC-MS/MS validated method: application to workplace drug testing. *Ther Drug Monit*. 2015; 37(5):600-8.
 29. McHugh RK, Hearon BA, Otto MW. Cognitive-behavioural therapy for substance use disorders. *Psychiatr Clin North Am*. 2010; 33 (3): 511-525.
 30. Nielsen S, Bruno R, Carruthers S, Fischer J, Lintzeris N, Stooze M. Investigation of pharmaceutical misuse amongst drug treatment clients. Melbourne, Australia: Turning Point Alcohol and Drug Centre, 2008. Available at https://www.burnet.edu.au/system/publication/file/3364/2008_Investigation_of_pharmaceutical_misuse_amongst_drug_treatment_clients.pdf. Retrieved September 22nd 2013.
 31. Frantsve LM, Kerns RD. Patient-provider interactions in the management of chronic pain: Current findings within the context of shared medical decision making. *Pain Medicine*. 2007; 8(1): 25–35.
 32. Moore RA, Wiffen PJ, Derry S, Roy YM, Tyrrell L, Derry CJ. Non-prescription (OTC) oral analgesics for acute pain- an overview of Cochrane reviews (Protocol). *Cochrane Database of Systematic Reviews*. 2013; 10: CD010794. DOI: 10.1002/14651858.CD010794.
 33. Faculty of Pain Management. *Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain*. London: Royal College of Anaesthetists, 2016. Accessed from <http://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware>
 34. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. *The Alcohol Use Disorders Identification Test, Guidelines for Use in Primary Care*. Second Edition, Department of Mental Health

- and Substance Dependence, World Health Organization, CH-1211 Geneva 27, Switzerland: World Health Organization, 2001. Available at http://apps.who.int/iris/bitstream/10665/67205/1/WHO_MSD_MSB_01.6a.pdf. Retrieved July 10th 2015.
35. Skinner HA. The Drug Abuse Screening Test. *Addict Behav.* 1982; 7:363-71.
 36. Aveyard P, Begh, R, Parsons A, West R. Brief opportunistic smoking cessation interventions: a systematic review and meta-analysis to compare advice to quit and offer of assistance. *Addiction.* 2012; 107(6):1066-73.
 37. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging for facilitating self-management of long-term illnesses. *Cochrane Database of Systematic Reviews.* 2012; 12: CD007459.
 38. Vodopivec-Jamsek V, de Jongh T, Gurol-Urganci I, Atun R, Car J. Mobile phone messaging for preventive health care. *Cochrane Database of Systematic Reviews.* 2012; 12: CD007457.
 39. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database of Systematic Reviews.* 2011; 9: CD005031.
 40. Garland E, Froeliger B, Howard M. Neurophysiological evidence for remediation of reward processing deficits in chronic pain and opioid misuse following treatment with Mindfulness-Oriented Recovery Enhancement: exploratory ERP findings from a pilot RCT. *J Behav Med.* 2015; 38(2): 327-36.
 41. Smedslund G, Berg RC, Hammerstrøm KT, Steiro A, Leiknes KA, Dahl HM, Karlsen K. Motivational interviewing for substance abuse. *Cochrane Database of Systematic Reviews.* 2011; 5: CD008063
 42. Nielsen, S., Cameron, J., Pahoki, S. Opportunities and challenges: Over-the-counter codeine supply from the codeine consumer's perspective. *Int J Pharm Pract.* 2013, 21(3):161-8
 43. Hamer AM, Spark MJ, Wood PJ, Roberts E. The upscheduling of combination analgesics containing codeine: the impact on the practice of pharmacists. *Res Soc Adm Pharm.* 2014 10(4):669–678.
 44. Van Hout, M. C., Horan, A., Santlal, K., Rich, E. and Bergin, M. 'Codeine is my Companion': Misuse and dependence on codeine containing medicines in Ireland. *Irish Journal of Psychological Medicine.* Early Online. 2015 doi:10.1017/ipm.2015.60
 45. Van Hout, M. C., Rich, E., Dada, S. and Bergin, M. Codeine is my Helper: A qualitative study of pharmacy access and codeine misuse in South Africa. *Qualitative Health Research.* Early Online. 2015 doi: 10.1177/1049732315613764
 46. Cooper, R. J. *Respectable Addiction - a Qualitative Study of Over the Counter Medicine Abuse in the UK.* Sheffield, United Kingdom: School of Health and Related Research (SchARR), University of Sheffield, Sheffield, UK 2011.
 47. Forman, R. F., Woody, G.E., McLellan, T., & Lynch, K. G. The availability of web sites offering to sell opioid medications without prescriptions *The American Journal of Psychiatry,* 2006; 163(7), 1233–1238.
 48. Doumas DM, et al. Evaluation of two web-based alcohol interventions for mandated college students. *Journal of Substance Abuse Treatment,* 2008 DOI: 10.1016/j.jsat.2008.05.009
 49. Haug S, Meyer C, Dymalski A, Lippke S & John U. Efficacy of a text messaging (SMS) based smoking cessation intervention for adolescents and young adults: Study protocol of a cluster randomised controlled trial. *BMC Public Health* 2012; 12: 51 doi:10.1186/1471-2458-12-51
 50. Nielsen, S., Cameron, J., & Lee, N. Characteristics of a nontreatment-seeking sample of over-the-counter codeine users: Implications for intervention and prevention. *J Opioid Manag.* 2011;7(5):363-70.
 51. Van Hout MC, Delargy I, Ryan G, Flanagan S, Gallagher H. Dependence on over the counter (OTC) codeine containing analgesics: treatment and recovery with buprenorphine naloxone. *Int J Ment Health Add.* Early Online. doi:10.1007/s11469-015-9618-2
 52. Nielsen S, Bruno R, Murnion B, Dunlop A, Degenhardt L, Demirkol A, Muhleisen P, Lintzeris N. Treating codeine dependence with buprenorphine: Dose requirements and induction outcomes from a retrospective case series in New South Wales, Australia. *Drug Alc Review.* 2015; Early Online. doi:10.1111/dar.12315
 53. Vodopivec-Jamsek, V., de Jongh, T., Gurol-Urganci, I., Atun, R., & Car, J. Mobile phone messaging for preventive health care. *Cochrane Database of Systematic Reviews,* 12. Art. No.: CD007457. 2012; DOI: 10.1002/14651858.CD007457.pub2
 54. Ling, W., Mooney, L., & Hillhouse, M. Prescription opioid abuse, pain and addiction: Clinical issues and implications. *Drug and Alcohol Review,* 30(3), 300-305.55. Maxwell, J. C. (2011). The prescription drug epidemic in the United States: A perfect storm. *Drug and Alcohol Review,* 2011; 30(3), 264-270.
 56. Coleman, J., Schuster, C. R., & DuPont, R. L. Reducing the Abuse Potential of Controlled Substances. *Pharmaceutical Medicine,* 24(1), 21-36.
 57. Coleman, J. J., Bensinger, P. B., Gold, M. S., Smith, D. E., Bianchi, R. P., & Dupont, R. L. (2005). Can drug design inhibit abuse? *Journal of Psychoactive*

- Drugs, 2010; 37(4), 343–362.
58. Cone, E. J. Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet. *Drug and Alcohol Dependence*. 83, Supplement 1(0): S31-S39, 2006.
59. Hamed, E., & Moe, D. Development of tamper deterrent formulations: state of the pharmaceutical industry. *Current Drug Abuse Reviews*, 2010; 3(3), 139–146.
60. Katz, N., Dart, R. C., Bailey, E., Trudeau, J., Osgood, E., & Paillard, F. Tampering with prescription opioids: nature and extent of the problem, health consequences, and solutions. *American Journal of Drug and Alcohol Abuse*, 2011; 37, 205–217.