The rescheduling of codeine: a Tasmanian perspective

Background Paper for the Codeine Rescheduling Implementation Group

Department of Health and Human Services

Tasmanian Government

1. Background

The Therapeutic Goods Administration (TGA) announced on 20 December 2016 that from 1 February 2018 combination analgesics containing codeine (CACC) currently available over the counter (OTC) in community pharmacies will be rescheduled from Schedule 2 (Pharmacy Medicine) and Schedule 3 (Pharmacist Only Medicine) to Schedule 4 (Prescription Only Medicine) (1).

This decision will mean that low-dose codeine will only be available by prescription from February 2018.

Such medications include analgesics (eg Panadeine paracetamol-codeine, Nurofen Plus ibuprofen-codeine) used for temporary relief of pain, and cold and flu medications used for treatment of coughs and colds.

These medications contain a low-dose of codeine (up to 15g per tablet) and are presently restricted to five-day pack sizes. High-dose codeine (over 15mg per tablet) is currently only available by prescription (Schedule 4).

In making this decision the TGA considered the evidence of harms related to overuse and abuse of these medications such as codeine dependency, liver damage, gastrointestinal perforations, renal damage, respiratory depression and death; the limited evidence of additional efficacy of including low-dose codeine in a combination product; the availability of safer and effective management for temporary relief of pain; the extent of use of these medications to self-treat chronic pain; and the modelling of social and economic benefit to society from rescheduling resulting in reduced deaths from accidental or deliberate codeine overdose, improved quality of life, reduced codeine dependence and risk of dependency, and reduced healthcare costs. (2)

Requiring a prescription for all codeine medicines will bring Australia into alignment with international regulators such as the US, most of Europe, Hong Kong, Japan, the United Arab Emirates and several other countries.

International evidence supports regulation of codeine availability to reduce abuse and misuse of low-dose OTC codeine. (3-5)

Despite the previous decision by the TGA to reschedule some OTC CACCs from Schedule 2 to Schedule 3 in 2010, there is evidence of increasing misuse in Australia (6).

The decision by the TGA will have implications in Tasmania for consumers, pharmacists, GPs, other medical specialists, hospital EDs, specialist alcohol and drug services, and persistent pain services.

2. Codeine

Codeine is an opioid drug closely related to morphine and is derived from opium poppies. It is a prodrug, which is metabolised by the liver into morphine. This is must have a therapeutic effect. There is significant genetic variation across the community in terms of an individual's ability to metabolise of codeine.

Up to 10 per cent of the population are poor metabolisers who experience very little therapeutic benefit from codeine. Around 10% of the population have ultrarapid metabolism and a higher risk of toxicity at recommended doses. (2, 3)

Codeine is available in low dose (up to 15mg per tablet) OTC CACCs used for temporary relief of pain and for treatment of coughs and colds; and in high dose (over 15mg per tablet) prescription only medications, either alone (Schedule 8) or in combination with paracetamol (Schedule 4).

High dose codeine containing analgesics are prescribed for the treatment of pain including cancer related pain, post-operative pain and other acute pain conditions.

While opioids are effective in the temporary treatment of strong pain and treatment of cancer pain, evidence to support ongoing use in chronic non-cancer pain is lacking (7-10).

There is also a lack of evidence to support the effectiveness of low-dose codeine in a combination with other analgesics for the relief of pain while there is evidence of significant harms (11).

The Australian Therapeutic Guidelines for acute pain do not include the use of codeine for mild acute pain and when it is introduced in the treatment of moderate pain it is at a dosage of "30 to 60mg orally, six-hourly as necessary".

The guidelines also note "there is evidence that a lower dose of codeine, less than 30 mg six-hourly, is no more effective than simple analgesia". (7)

Opioid analgesics are not considered suitable first-line therapy to treat chronic non-cancer pain, nor are they appropriate for long-term use.

Clinical therapeutic guidelines for analgesia state that the management of chronic non-cancer pain is better achieved via medical practitioner evaluation and advice with regards to both appropriate non-opioid pharmacological and non-pharmacological treatments. (7-9)

The Australian Therapeutic Guidelines for chronic non-cancer pain states "opioids work well in acute pain, but their role in chronic non-malignant pain management is limited … evidence for long-term benefit is lacking." These guidelines include all opioids of which the majority are more potent than low dose codeine. (7)

The Faculty of Pain Medicine (Australian and New Zealand College of Anaesthetists) and the US Centers for Disease Control and Prevention recognise the lack of definitive evidence to support the long-term effectiveness of opioid analgesics in people experiencing chronic non-cancer pain and the substantial evidence of harm (8, 9).

3. Rationale for TGA decision

The TGA decision was based on an extensive review of evidence and consultation. The rationale for rescheduling included:

- There is a lack of evidence that codeine in low doses provides any more pain relief than medicines that do not contain codeine.
- There is extensive evidence of harm caused by the overuse and abuse of over the counter codeine-containing medicines.
- Codeine demonstrates marked variability in its metabolism to morphine in different individuals, with the potential for severe toxicity in ultra-rapid metabolisers at recommended doses. This applies to medicines intended for treating coughs and colds, and those intended for the treatment of pain.
- Low-dose codeine is capable of producing dependence at recommended doses and, in overdose, respiratory depression and reduced level of consciousness and death.
- The medicines combined with codeine in OTC combination medicines, such as paracetamol and ibuprofen, can cause significant harms when overused. Over use of paracetamol is associated with liver damage and overuse of ibuprofen is associated with gastrointestinal perforation and kidney damage.

- Low dose codeine is intended for the short term relief of acute pain only; however their availability over the counter has seen a significant increase in their long term use for the self-treatment of chronic pain despite these medicines being intended for the short term relief of pain only. This can lead to patients inadvertently becoming addicted to codeine.
- The risks associated with unregulated codeine use, such as dependence, toxicity and death, are too high.
- The use of and harms from opioid analgesics in Australia increased considerably from 2001with the over the counter availability and affordability being suggested as one of the main driving factors for this.
- The availability of safer and effective analgesics for temporary relief of pain (such as combination paracetamol-ibuprofen).
- Substantial health economic benefits will result from the rescheduling, $5.3 billion nationally over 10 years. (2)

Further information regarding the TGA decision is available at www.tga.gov.au/scheduling-decision-final/scheduling-delegates-final-decision-codeine-december-2016.

Further information regarding the health economic benefits is available at www.tga.gov.au/publication/economic-modelling-and-financial-quantification-regulatory-impact-proposed-changes-codeine-scheduling.

4. Chronic pain and the use of OTC CACCs

Chronic pain is an important public issue. One in five Australians will suffer chronic pain in their lifetime, with up to 80 per cent missing out on treatment that could improve their quality of life (12).

Access Economics estimated that chronic pain costs the Australian economy $34 billion a year in 2007 and was the nation's third most costly health problem (13).

The National Pain Strategy recognises the importance of a whole-of-system response to pain to improve quality of life for people with pain and their families, and to minimise the burden of pain on individuals and the community (12).

Individuals take OTC CACCs for many reasons. These include for the relief of acute pain, chronic non-cancer pain, or cancer-related pain; and for reasons other than relieving pain, such as for intended intoxication.

Most people taking OTC CACCs will be at low risk of harm, with infrequent use within the recommended dosage range for the relief of short term pain.

Despite this some individuals may develop a pattern of use over time that increases the risk of harms.

These harms include codeine dependency which can occur within the recommended dosage range of CACCs. Frequent use of OTC CACCs within the recommended dosage frequency can lead to dependency over time regardless of the reasons for use. (14)

Some individuals taking CACCs will have a pattern of use associated with a higher risk of harm. Misuse can be defined as consumption outside of acceptable medical guidelines, medical direction or indication; when self-medicating at higher doses and for longer than recommended; or for intoxicating purposes. (14)

Studies of codeine dependent individuals identify three patterns of use of OTC CACCs:

1. Regular use within recommended therapeutic doses, despite limited effectiveness to treat underlying medical condition.
2. Recreational codeine use without a medical reason, including time-consuming extraction of codeine from CACCs.
3. Daily use exceeding recommended therapeutic doses, often very high doses and at risk of severe harms. (15,16)

There are many published case reports and series including individuals who have experienced serious harm(s) who are taking large amounts of OTC codeine-ibuprofen analgesics of up to 90 tablets a day (15,17-22).

A web-based study of 800 people in Australia who self-reported OTC CACC use found a higher proportion of women and higher proportion of unemployed compared to the general population.

Seventeen per cent of individuals taking OTC CACCs were assessed as dependent on codeine. Individuals taking OTC CACCs who were assessed as dependent on codeine were more likely to be younger, have lower levels of employment and education, report chronic pain, have poorer overall health and mental health compared to individuals not dependent on codeine.

Additionally, those individuals dependant on codeine were more likely to have sought help for a previous alcohol and other drug problem than those not dependent on codeine. There was no difference between the codeine dependent and non-dependant individuals in the proportion that had ever used illicit drugs. (18)

5. Extent of OTC codeine containing medicine sale and related harms in Tasmania

There are an estimated 380 000 to 460 000 packets of OTC CACCs and 120 000 to 145 000 packets of OTC codeine containing cough and cold medicines sold each year in Tasmania. This is on average more than one packet per year per person in Tasmania.

Between 12-17 per cent of people buying OTC CACCs are likely to be dependent on codeine and at risk of serious harms (2,18).

The National Drug Strategy Household Survey 2013 reported "pain-killers/analgesics" were the most commonly misused pharmaceutical drug for non-medical purposes, misused by 3.3 per cent of Australians aged 14 years or older, with one third of misuse involving OTC CACCs (23).

Modelling based on these findings and reported national data, estimates that over 5 000 Tasmanians are taking OTC codeine medicines for non-medical purposes and these people are likely to be dependent on codeine and at risk of serious harms.

This averages out to about 30 customers per pharmacy and eight patients per GP in Tasmania. These numbers may be higher, as codeine use is higher in regional and rural areas, and in populations of lower socio-economic status (24).

There is evidence that opioid dependence arising from the use of OTC CACCs is an increasing problem (25). A study of clients admitted to a New Zealand and an Australian detoxification unit in 2010 found that 8% of new attendees received care for a dependence on OTC CACCs (22). Anecdotal evidence from the Tasmanian Alcohol and Drug Service is that around 10 per cent of their clients present as a consequence of a dependence on OTC codeine containing analgesics.

Serious complications are common in people who are dependent on OTC CACCs. A study of the patients attending the Drug and Alcohol Services of South Australia over a five year period with primary codeine dependence who abused OTC CACCs found that 87 per cent of those abusing ibuprofen-codeine containing analgesics experienced serious complications; including gastrointestinal blood loss or perforation, anaemia and kidney damage.

Of the 60 patients abusing ibuprofen-codeine containing analgesics identified, two deaths occurred. (17)

A recent study conducted at the Royal Adelaide Hospital (590 beds) identified 99 admissions involving 30 patients over five years with harms associated with OTC CACCs.

Surgery was required for 13 per cent of admissions and intensive care was required for 10 per cent of admissions. The mean length of stay per admission of was six days. The average cost per admission was $10 183. (21)

Coding of the reason for emergency department presentation or hospital admission in Tasmania does not allow specifying harms related to OTC CACCs. As a result it is difficult to reliably determine clearly the burden on our hospitals related to OTC CACCs.

Despite this, Tasmanian gastroenterologists report they are seeing ongoing cases of significant gastrointestinal morbidity related to the overuse of OCT codeine-ibuprofen combination analgesics.

6. Extent of prescribed opioids and related harms in Tasmania

It is important to consider the issues associated with OTC CACCs within the broader context of opioid related harms. The use of OTC CACCs is a common pathway to opioid dependency.

As a result of their ease of access they are misused by people who are opioid dependent, often taking amounts far in excess of the recommend maximum dosage. (17)

Tasmania has the highest rate of opioid prescribing of any state or territory in Australia. According to the Australian Atlas on Healthcare Variation, 73 641 opioid prescriptions were dispensed per 100 000 people for Tasmania compared to the Australian rate of 55 126 in 2013-14 (aged-standardised rates).

The local areas of Central Highlands, South East Coast, Brighton, and Hobart - North West were among the 10 local areas with the highest rates of opioid prescribing nationally.

Key factors associated with higher rates of opioid prescribing in local areas across Australia include lower socioeconomic status and regional areas (compared with major cities or remote areas). (26)

Pharmacists and medical practitioners in Tasmania are recognising an increasing number of people who are misusing opioids, especially codeine.

The total number of circulars issued by the Tasmanian Department of Health and Human Services Pharmaceutical Services Branch (PSB) regarding people identified by pharmacists or medical practitioners seeking drugs which are subject to misuse more than doubled between 2013 and 2016.

The overall proportion of circulars relating to CACCs also doubled between 2013 and 2016. In 2016 more 200 circulars where issued regarding people seeking drugs which are subject to misuse with around half of these involving codeine.

While the rate of opioid prescribing is high for Tasmania, there has been a recent reduction in the average Oral Morphine Equivalent Daily Dose (OMEDD) of 60 per cent between 2004 and 2015 with respect to the prescribing of opioids for chronic pain patients.

National Schedule 8 reporting data obtained from the Commonwealth supports this data and indicates for the past five years Tasmania has fallen from well above to below the national average OMEDD in grams per 1 000 people for the six most commonly used Schedule 8 opioid analgesics. (27)

There is a significant burden on Tasmania hospitals associated with harms related to prescribed opioids. The number of hospitalisations a year to Tasmanian hospitals with an opioid related diagnosis has steadily increased from 29 admissions in 2011 to 61 admissions in 2015.

This is likely to be very conservative given the limitations of case finding, clinical recognitions and coding related issues. During this period 66 per cent of admissions related to codeine, morphine or oxycodone. (28)

National Coronial Information System data shows that national codeine-related deaths more than doubled between 2000 and 2009, during which the consumption of codeine increased significantly.

For every two opioid related deaths due to strong opioids (Schedule 8), there was one codeine related death. While most codeine related deaths involved multiple drug toxicity, OTC sources of codeine is recognised as a contributing factor to many deaths. (29)

Prescribed opioids contribute to many preventable deaths per year in Tasmania. Between 2005 and 2009, before the implementation of the Drugs and Poisons Information System Online Remote Access (DORA) real time reporting system, an average of 25 deaths per year in Tasmania were related to prescribed opioids.

After the implementation of real time reporting, the number of deaths in Tasmania related to prescribed opioids reduced by a third to an average of 17 deaths a year between 2010 and 2014 (27).

The technology used in Tasmania to monitor Schedule 8 dispensing events has been supported by a collaborative clinical-regulatory approach between PSB, addiction specialists, general practitioners and pain medicine specialists.

The National Drug and Alcohol Research Centre (NDRAC) Review of Opioid Prescribing in Tasmania Report (2012) recognises many of the key system-level drivers of opioid prescribing and related harms in Tasmania.

This report provided 61 recommendations to address this issue. Since the report was released, many of these recommendations have been implemented across the health system in Tasmania. (30)

7. Overview of opioid regulation in Tasmania

The Tasmanian *Poisons Act 1971* (Act) provides a legal basis for protecting clinical and public safety in relation to the handling of drugs and poisons.

The value of this legislation in supporting good clinical practice is often under-estimated, and sometimes criticised as unnecessary red tape.

The Commonwealth's *Poisons Standard* consists of decisions regarding the classification of medicines and poisons into Schedules for inclusion in the relevant legislation of the States and Territories.

It provides the framework for uniform scheduling of substances and uniform labelling and packaging requirements throughout Australia. The *Poisons Standard* is the legal title of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

The SUSMP is adopted by reference in Tasmania. Further information can be found at www.tga.gov.au/scheduling-basics. Of particular interest to healthcare are Schedules 2 (Pharmacy Only), Schedule 3 (Pharmacist Only Medicine), Schedule 4 (Prescription Only Medicine) and Schedule 8 (Controlled Drug).

Schedule 8 substances are of particular public health interest. These substances have tight controls within clearly defined clinical boundaries as they are substances of such danger to health as to warrant strong regulation of sale, supply and use.

Examples of these substances include oxycodone, morphine, fentanyl, buprenorphine. Codeine is a Schedule 8 substance when not in combination with other Scheduled substances.

Long term prescribing (more than two months) of Schedule 8 drugs such as strong opioid analgesics requires an authority in Tasmania, issued in accordance with specific provisions within the Act. There are some substances and instances where authority is required before prescribing.

A small team of DHHS pharmacists are appointed as delegates for the purposes of administering the Act and issuing authorities to prescribe. In order for an authority to be issued, a doctor must provide sufficient information demonstrating the proposed Schedule 8 prescription regimen meets quality and safety standards.

While the focus quite understandably is on the safety of the regimen, in Tasmania processes for the regulation of medicines which are subject to misuse has evolved into a broader set of metrics and joined up clinical-regulatory processes that are focussed on best (evidence based) clinical practice, particularly in the clinical management of persistent non-malignant pain and concurrent opioid dependence.

Following receipt of an application, if the delegate identifies a particular patient is at higher than standard risk, they will seek the advice of a consultant medical officer.

Those patients demonstrating particularly complex pain conditions and high risk behaviours concerning their prescribed and/or non-prescribed drug use or management are referred to an expert advisory panel consisting of a pain medicine specialist, addiction medicine specialist, general practitioner and one or more of the delegates.

This panel scrutinises available, relevant clinical information and provide advice to the delegate.

The pain specialist(s) focus on whether the current or proposed medication regimen is likely to be effective in treating this patient's pain in the context of current best practice and where feasible, considering what might be appropriate in the context of a broader multimodal, multidisciplinary treatment framework.

The addiction medicine specialist focuses on whether this regimen is likely to be safe and appropriate in the context of any evidence of concurrent drug dependence and associated clinical and/or public health risk.

The GP focuses on practical matters eg will the applying GP be able to be safely manage the proposed regimen in the primary health care setting.

A recommendation may be made for further specialist assessment in order to map out a best practice treatment approach.

This real time information is made possible by Tasmania's leading edge work in developing DAPIS (its Drugs and Poisons Information System), available to all medical practitioners and pharmacists in Tasmania through a light version known as 'DORA'.

DAPIS and DORA formed the basis for the development of a National Electronic Recording and Reporting Controlled Drugs (ERRCD) System which the Commonwealth Government has made available to all states and territories with a view to establishing a nationwide real-time reporting of controlled drugs system.

8. Implications for Tasmania

The rescheduling of codeine will result in significant public health benefits in Tasmania.

Key tasks for the CRIG will be to identify the implications (challenges and benefits) of codeine rescheduling for individuals and the healthcare system, and to develop actions to maximise the short, medium and long term public health benefits.

The following questions will help members with these tasks:

1. What are the challenges resulting from the rescheduling of codeine for individuals using OTC CACCs?
2. What are the benefits resulting from the rescheduling of codeine for individuals using OTC CACCs?
3. What are the challenges resulting from the rescheduling of codeine for pharmacists and GPs to provide safe and effective care for individuals who use OTC CACCs?
4. What do pharmacists and GPs need to provide safe and effective care for individuals who use OTC CACCs?
5. Do other health professionals such as medical specialists, allied health professionals and dentists need support to provide safe and effective care for individuals who use OTC CACCs?
6. How we will know if we have been successful?

9. References

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