HOW TO MANAGE

Codeine Reclassification

LINDA BRYANT AND JOHN DUNLOP

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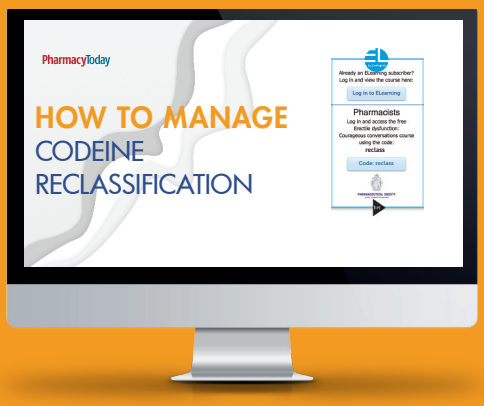

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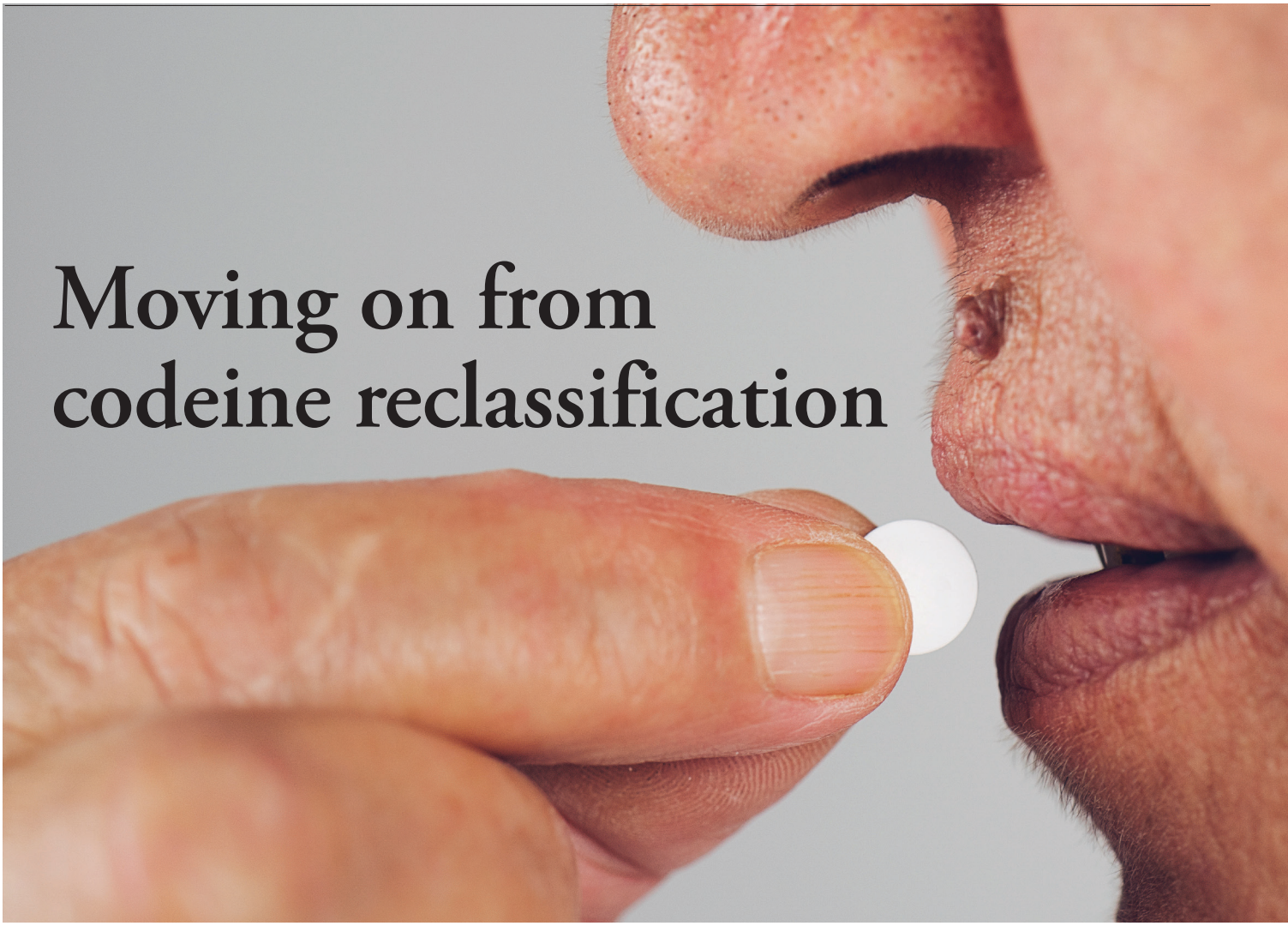


Moving on from codeine reclassification

Concern about the increasing frequency of codeine misuse and abuse resulted in the Medicines Classification Committee recommending that all medicines containing codeine be reclassified as prescription medicines. This came into force on 5 November. Clinical advisory pharmacists **Linda Bryant** and **John Dunlop**, discuss reasons for this decision and provide tips for pharmacists to help patients with the transition

LEARNING OBJECTIVES

1. Describe the reason for, and evidence supporting, the reclassification of codeine in combination medicines to prescription-only
2. Identify the risks associated with codeine use, including those associated with metabolism
3. Describe ways in which pharmacists can help patients who can no longer access codeine-containing products

On 7 November 2017, the Medicines Classification Committee recommended that, from 31 January 2020:[1]

- "All codeine in combination medicines, both analgesics and those used for cough and colds, should be reclassified as prescription medicines."
- "Medicines containing codeine as the only active ingredient should be reclassified from prescription to restricted medicine; for oral use in adults and children over 12 years of age in medicines containing not more than 15mg per solid dosage unit with a maximum daily dose not exceeding 90mg of codeine for use as an analgesic and when sold in a pack of not more [than] three days' supply."

However, the minister's delegate requested further information from Medsafe on this recommendation before making a decision, and the reclassification was pushed back over subsequent MCC meetings. At the 63rd meeting of the MCC on 10 October 2019, the committee recommended that:[2]

- "All medicines containing codeine should be classified as prescription medicines."

Medsafe worked with industry stakeholders to revise the time frame, and the reclassification of codeine came into effect on 5 November. Codeine-containing products on pharmacy shelves must have been removed from self-selection or pharmacist recommendation on or before that date, and stock will only be able to be supplied on a prescription, regardless of how it is labelled.[3]

A number of combination products are affected (see table over the page).

Why has codeine been reclassified?

There is rising national and international concern about the increasing frequency of codeine misuse and abuse, and resultant mortality.

According to the National Coronial Information System, from January ➳

TABLE PRODUCTS AFFECTED BY THE CODEINE RECLASSIFICATION

ANALGESICS	BRANDS
Paracetamol 500mg *plus* codeine 8mg	Panadeine, Codcomol
Paracetamol 500mg *plus* codeine 15mg	Panadeine Extra
Paracetamol 450mg *plus* codeine 9.75mg *plus* doxylamine 5mg	Mersyndol
Ibuprofen 200mg *plus* codeine 12.8mg	Nurofen Plus, Panafen Plus, Ibucode
COUGH AND COLD MEDICINES	**BRANDS**
Contain codeine 9.5mg	Codral Cold and Flu, Codral Day and Night, Codral Multi Action*

** Products containing codeine are no longer supplied to New Zealand but may still be in pharmacies*

2008 to December 2014, there were 53 deaths in New Zealand due to codeine, 26 per cent of which were considered unintentional. Codeine was ranked as the fourth primary contributor to death due to a pharmaceutical agent. The mean age of patients who died was 48.[4]

There are limited data in the New Zealand setting, but an Auckland open-access addictive disease clinic analysed 15 people who were addicted to OTC codeine and attended their clinic over a three-month period in 2010. They compared them with 77 similar clients who attended Australian clinics and seven who attended an in-patient detoxification clinic in New Zealand.

The New Zealand subjects behaved similarly to their Australian counterparts, consuming an excessive number of tablets over a long duration of time, with many having a history of previous drug and alcohol misuse.[5]

Research from Australia found an increase in the proportion of people seeking opiate substitute therapy for codeine dependency: from 2.7 per cent in 2014 to 4.6 per cent in 2016.

Codeine was the sole substance being used by 39 per cent of opioid dependents, with 83 per cent of those using only OTC codeine.[6]

Similarly, a household survey found that over three years between 2013 and 2016, of people who had misused pharmaceuticals, the proportion misusing OTC codeine-containing analgesics rose from 33 per cent to 75 per cent; that is, three out of four recent painkiller misusers had misused OTC codeine in the last 12 months.[6]

The Australian not-for-profit, evidence-based organisation NPS MedicineWise reported the occurrence of 99 hospitalisations in a 593-bed hospital over five years due to misuse of OTC codeine. Most of these were women aged between 21 and 54. The reason for using OTC codeine-containing products was musculoskeletal pain (27 per cent) and headaches/migraine (13 per cent), with most using excessive daily doses over prolonged periods.[7]

Furthermore, a smaller Australian study reviewed 27 people admitted to a hospital-based addiction clinic for codeine–ibuprofen misuse. It found the reason for admission was primarily for dependence and gastrointestinal haemorrhage, with 15 people misusing OTC codeine products, and most having no history of substance use disorder.[8]

26%
of NZ codeine-related deaths considered unintentional

In Australia, the number of codeine-related deaths almost doubled between 2000 and 2009 to nine per million, with close to 50 per cent of these being accidental, and 40 per cent from OTC codeine-containing products.[9]

Surveys of customers buying OTC codeine products in France found 19 per cent of purchasers used codeine-containing products daily for six or more months: 7 per cent were misusing codeine and 18 per cent had possible dependence.[10]

And in the UK, South Africa and Ireland, 6–16 per cent of people were found to be purchasing codeine-based products weekly. Although there was some awareness and knowledge of the risks, this did not seem to impact on their purchasing behaviour.[11]

Pharmacists have also expressed concerns about OTC codeine use. From a cross-sectional survey of pharmacists in the UK, Ireland and South Africa, 58 per cent (UK) to 65 per cent (Ireland) of pharmacists considered OTC codeine to be a significant health problem.[12]

What are the benefits?

Although codeine or low-potency opiates are considered step two on the WHO analgesic ladder – the framework that offers guidance for the pharmacological treatment of pain – the vast majority of studies for the effectiveness of codeine relate to post-operative use for acute pain, as opposed to more persistent pain. Also, the concept of a stepwise progression of pain is probably more complex than that of a simple ladder as it does depend on the type and duration of pain.

A meta-analysis of codeine 60–90mg as a single post-operative dose found an analgesic effect in a few individuals, but it did not compare favourably with common alternatives such as NSAIDs and paracetamol.[13]

A single dose of codeine 60mg plus paracetamol 800–1000mg provides effective (≥50 per cent) pain relief in more than 50 per cent of people experiencing moderate to severe post-operative pain. However, the addition of codeine 60mg to a dose of paracetamol increases the number of individuals achieving effective pain relief by only 10 to 15 per cent compared with paracetamol alone (a number needed to treat [NNT] of 6.1–8.2).[14]

Similarly, a single post-operative dose of codeine 25.6–60mg plus ibuprofen 400mg provides effective pain relief in 64 per cent of people, although placebo achieves this in 18 per cent of people. The benefit of the codeine combination compared with ibuprofen alone is barely significantly different, with just 15 per cent more people obtaining at least a 50 per cent reduction in pain.[15]

There is a paucity of evidence for codeine use in osteoarthritis, although a meta-analysis of opioids for osteoarthritis found that any modest benefits were outweighed by the number of adverse events. The mean improvement in pain was only 0.7cm on a 10cm visual analogue

Panel 1 | Medsafe recommended contraindications for codeine[4]

It is recommended that codeine-containing medicines be contraindicated in:

- children under age 12
- adolescents under age 18 for post-tonsil and adenoidectomy
- adolescents under age 18 with compromised respiratory function
- adolescents under age 18 for cough
- breastfeeding mothers.

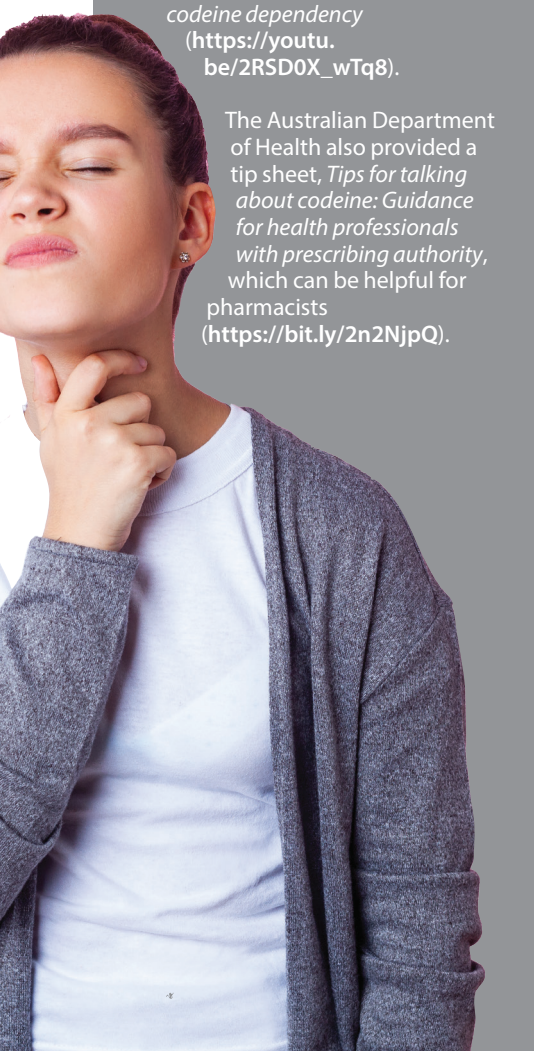
Panel 2 | Pharmacist resources

- New Zealand Formulary – Patient Information Leaflets (**nzf.org.nz/nzf_70421**)
- Health Navigator (**healthnavigator.org.nz**)

Australia made the transition from OTC codeine to prescription-only codeine in February 2018. There were some excellent resources made available for this switch by NPS MedicineWise, some of which are available on YouTube:

- NPS MedicineWise – search for "codeine" (**nps.org.au**)
- *Codeine: Advice For Prescribers* (**https://youtu.be/TRn8vFOimXc**)
- *Medicines with Codeine: Advice for Pharmacists* (**https://youtu.be/BXulMAOKa5Y**)
- *Malcolm Dobbin, understanding codeine dependency* (**https://youtu.be/2RSD0X_wTq8**).

The Australian Department of Health also provided a tip sheet, *Tips for talking about codeine: Guidance for health professionals with prescribing authority*, which can be helpful for pharmacists (**https://bit.ly/2n2NjpQ**).



scale, or a 12 per cent improvement between opioids and placebo, with an NNT of 10 to get one additional treatment response.[16]

In heterogenous, short-duration studies involving different types of pain and populations, the overall benefit of codeine as an analgesic has been shown to be disappointing and small when compared with placebo. There is little evidence of benefit in musculoskeletal pain, especially at low dosage and, similarly, a paucity of evidence for use for headaches. There is, however, a risk of chronic daily headaches from chronic overuse.

> On the potential harm side of the equation, there is the risk of misuse and dependence, along with dizziness, constipation, cognitive impairment, nausea, sedation and falls, particularly in older people

Risks are present

On the potential harm side of the equation, as indicated above, there is the risk of misuse and dependence, along with dizziness, constipation, cognitive impairment, nausea, sedation[17] and falls, particularly in older people.

These risks are present and need to be balanced against the minimal benefit of the low doses of codeine found in OTC products. Two tablets of codeine 8mg, in combination with paracetamol, is equivalent to approximately morphine 1.6mg, which is subtherapeutic.

Similarly, for persistent or chronic pain, defined as pain for more than six months, the role of any opiate is dubious. So again, the risks are present without an expected sustained benefit.

A problem with OTC codeine combination products is that people who are misusing codeine take excessive amounts. Hence, they are also getting excessive doses of paracetamol or ibuprofen. Chronic high doses of paracetamol in combination with codeine can lead to hepatoxicity.

In New Zealand, seven people admitted to a detoxification unit over two years due to OTC codeine dependency were misusing excessive amounts of codeine 12.8mg *plus* ibuprofen 200mg. This resulted in gastric ulceration (four people) and gastric bleeding (three people).

Pharmacokinetics

Adding to the benefit–harm balance, codeine is dependent on being metabolised to its active moiety, morphine, via the cytochrome P450 2D6 pathway. In a "normal" person, 30mg of codeine is metabolised to 1.5–4.5mg of morphine.

In a slow metaboliser (8–10 per cent of the European population and about 1 per cent of people of Asian descent), codeine will not be metabolised. In these people, there will be little, if any, benefit, although the chance of adverse effects is still present.

Conversely, some people are ultra-fast CYP2D6 metabolisers and at increased risk of morphine toxicity and fatal respiratory depression. In an increasingly diverse population, this is important because up to 20 per cent of people of Middle Eastern descent, particularly those from the Horn of Africa, Somalia and Ethiopia, are ultra-fast CYP2D6 metabolisers.

Reports of fatalities have led to repeated warnings from Medsafe and their recommended list of contraindications (Panel 1).

Metabolism of codeine by the CYP2D6 enzyme system also means it is vulnerable to CYP2D6 inhibitors, particularly paroxetine, fluoxetine, bupropion and, to a lesser extent, sertraline and terbinafine. The inhibition results in reduced efficacy of codeine.

Harmonisation

Other countries have brought in restrictions for codeine access. In particular, from 1 February 2018, Australia rescheduled all codeine products to prescription-only. This was after switching codeine to a restricted medicine in 2010.

Based on calls to Australia's largest poisons centre, the initial switch in 2010 did not reduce the number of calls. From 2005 to 2015, there was a 19.5 per cent average annual increase in paracetamol/codeine-related calls and a 17.9 per cent increase for ibuprofen/codeine.[18]

However, after rescheduling codeine to prescription-only, there was an abrupt and significant drop in monthly opioid-related calls (-37.2 per cent) and monthly codeine-related poisonings (-50.8 per cent).[19]

For New Zealand, harmonisation with Australia will help prevent pressure on our community pharmacies to sell codeine-containing products to international visitors.

What can pharmacists do to help this transition?

Pharmacists may find they are challenged by people who have previously purchased OTC codeine products. Panel 2 provides some resources to help pharmacists talk about codeine.

One of the notable comments from the Australian experience is that people who are dependent on codeine may not:[6]

- recognise their dependence
- appear to fit the normal profile of a drug seeker – the Australians found that a "typical" codeine misuser was well educated and employed.

Dependence doesn't mean excessive daily dosing, as such, but consistent use means that withdrawal symptoms emerge when the medicine is stopped or even tapered. The symptoms, particularly pain, recur and so reinforce that the medicine is necessary; although, looking at the pathology and mechanisms for persistent pain, it is unlikely that the analgesic is actually treating the pain. This is a complex situation as the dependence may be unrecognised, well-hidden and/or embarrassing for the person to recognise or admit.

≥50%
pain relief considered effective

Discussion about pain syndromes

People may be concerned because "nothing else works", so it is important to be reassuring and acknowledge their pain. The dose of codeine in combination products is unlikely to be more beneficial than the partnered product alone. The paracetamol/ibuprofen combination may be preferable if a single agent alone is inadequate. If these are ineffective, then a medical review is recommended.

The request for codeine or a codeine-based product from a long-term user is a good opportunity to discuss the difference between acute pain and chronic or persistent pain.

Pharmacological intervention for persistent pain is of limited benefit, and referral to a chronic pain programme involving physiotherapy and psychological support and techniques is preferable. It is very important to manage expectations for chronic pain using the bio-psycho-social approach as the harms of long-term opioids generally outweigh the benefits. Evaluation and treatment require medical input.

The dose of codeine in combination products is unlikely to be more beneficial than the partnered product alone

For acute pain, such as headaches, period pain and muscle pain, codeine has not been shown to be particularly effective and there are preferable alternatives.

A good pain assessment using open-ended questions is important. Acute pain usually improves considerably within two weeks and resolves within three months.

For headaches, paracetamol is the first step. As an alternative, some people respond to an NSAID. Remember the non-pharmacological approaches as well – good hydration, stress reduction, massage, physiotherapy and lifestyle changes.

Musculoskeletal pain can be due to inflammation, so a topical or oral NSAID can be helpful if paracetamol is inadequate, or other topical agents, such as capsaicin, can be tried.

People should be informed that, in studies, good analgesia is considered to be at least a 50 per cent reduction in pain. A primary reason for analgesia is to maintain function, even if there is still some pain.

If the person is expecting complete resolution of pain so they can immediately function as before, explain that it is important to maintain some activity (usually), but complete pain resolution is unlikely, especially within the first week or so after an injury. Pain of longer duration requires referral.

Discussion about cough and cold medicines

There is a wide range of medicines available as alternatives to medicines containing codeine. The availability of cough and cold medicines containing codeine has already reduced in New Zealand, with products being withdrawn from the market.

Conclusion

Now is the time to encourage users to seek help for pain and/or dependence. Education about the addictive potential of codeine and harms from inappropriate use is important.

Remember, tolerance, dependence and addiction to opiates, including codeine, develops quickly and may be subtle. PT

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NOTES

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For more information please refer to the data sheet available at www.medsafe.govt.nz. AFT Pharmaceuticals, Auckland. TAPS PP6587. NZ Patent No. 552181.