Submission to the Advisory Committee on Medicines Scheduling on proposed amendments to the Poisons Standard (Medicines) to delete the Schedule 3 entry for codeine, and reschedule the current Schedule 3 codeine entry to Schedule 4 due to potential issues of morbidity, toxicity and dependence.

[redacted]

Declaration of competing interests

I declare that I am not connected, through funding or other mutual interests, with the pharmaceutical industry.

I co-authored a submission to the National Drugs and Poisons Scheduling Committee during its consideration of over-the-counter codeine analgesic scheduling in 2008.

I write in support of the current proposal under consideration by the Committee to reschedule codeine from Schedule 3 to Schedule 4.

In doing so, I draw your attention to a submission to the National Drugs and Poisons Schedule Committee (NDPSC) that I co-authored in 2008, recommending that codeine and ibuprofen combined analgesics should be rescheduled to Schedule 4 in the interests of protecting public health, as 77 cases of serious harm associated with misuse of these medicines had been identified. At this time the NDPSC elected to remove codeine combination analgesics from Schedule 2 and make them available in Schedule 3, reasoning that this provided pharmacists with an opportunity to detect signals of misuse or abuse, while maintaining access for legitimate users without the need for prescription.

I also refer to further evidence since this decision, including new cases of addiction and serious harm, to argue that the current scheduling is not sufficient to minimise misuse and harm, and in support of the proposal to move medicines that combine codeine with non-opioid analgesics to Schedule 4 as well as additional recommendations to minimise harm.

My interest in this area stems from research into the misuse of over-the-counter codeine and policy responses to minimise harm, completed while participating in the Victorian Public Health Training Scheme and during my candidature at Monash University School of Public Health and Preventive Medicine for the Doctor of Public Health research degree (DPH). My views are my own and do not necessarily represent the views of these organisations and institutions.

Submission to the National Drugs and Poisons Scheduling Committee, June 2008: Over-the-counter (OTC) ibuprofen/codeine analgesics: misuse and harm[1]

Our June 2008 submission recommended that codeine and ibuprofen combinations, available at that time in Schedule 2 and Schedule 3, should be rescheduled to Schedule 4 and that pack size should be limited to 18 tablets (or no more than 3 days supply).

The submission identified 77 cases of misuse of OTC codeine-ibuprofen analgesics resulting in dependence and serious harms to physical health across Australia. These cases were rapidly identified as a result of contact by my co-author, Dr Malcolm Dobbin, Senior Medical Advisor (Alcohol and Drugs), Victorian Department of Health and Human Services, with state and territory colleagues, during the short time frame that the NDPSC call for submissions was open in 2008. They therefore most likely under-represented the full scale of the problem at this time.

The key points made in the submission were:

- Codeine had been recognised as a drug of addiction and misuse for many years.
- NSAIDs were among the categories of drugs accounting for serious adverse drug reactions, even when taken at recommended doses.
- NSAID harm is dose-related.

[1] Dobbin M, Tobin C. Over-the-counter (OTC) ibuprofen/codeine analgesics: misuse and harm. Paper prepared for the National Drugs and Poisons Schedule Committee, 2008.

- Escalation of dose is a defining characteristic of addiction. As people develop a tolerance to codeine, they would escalate their dose to achieve the same effect.
- When codeine was combined with ibuprofen, the amount of ibuprofen ingested was also increased and this, given the dose dependant nature of the gastric toxicity of the substance, can produce serious and life-threatening gastric injury.
- High levels of ibuprofen ingestion can also lead to anaemia, renal failure and hypokalemia.
- 77 individual case reports of dependence on OTC codeine and ibuprofen combinations were documented, detailing numerous occurrences of serious and life-threatening injury and one death due to the misuse of this combination. These 77 cases may be indicative of a much larger problem.
- There appeared to be a high prevalence of mental health disorders in substance abuse patients and this may limit their capacity to safely self-medicate with these combination products.
- Many of the practitioners providing case descriptions described the frequently overwhelming morbidity experienced by the patients presenting for care. Some believed that if it were not for the interventions of intensive care units or emergency departments, more of these patients would have died due to their misuse of this combination.
- Many of the practitioners providing case reports expressed concern that codeine and ibuprofen combinations should not continue to be available as an OTC medicine.
- Many codeine dependent people do not fit the stereotypical profile of a drug dependant person, some being employed in well regarded occupations and having no previous history of substance abuse.
- Many of the cases commenced using the OTC codeine-ibuprofen for its registered indication and then escalated their dose to high levels.
- This suggests that this was a hidden population of patients not previously described and that they were not readily identifiable by pharmacists or pharmacy staff. Thus, it would have proven difficult for pharmacists to identify drug dependant or drug-seeking behaviours and limit supply to people addicted to codeine.
- The average number of tablets taken in the 77 case reports was 50 tablets a day, equating to more than two packets of 24 tablets/day and providing a dose of 640 mg codeine phosphate and 10 grams of ibuprofen daily. This use was sustained for an average duration of over a period of months or years. The average duration of use from the cases where data was available was 2.5 years. Six cases were reported to have misused OTC ibuprofen/codeine products for more than 5 years.
- There was a high prevalence of mental health disorder (22 cases).

> Case 17 is a person aged 40-44 years with a history of paranoid schizophrenia and obsessive compulsive disorder (OCD). There was also a history of pharmaceutical drug misuse (Nurofen Plus, nitrazepam) and tobacco use. The patient had attempted detox from opioids on a number of occasions. When seen the patient was taking 50-70 Nurofen Plus tablets a day "taken in two hits" for the previous 18 months. The initial indication for use was headache. The patient presented to a drug and alcohol setting for detox for opioid dependence. Also had a history of gastrointestinal haemorrhage and was anaemic (Hb 10.1) with low iron stores (Iron 4), indicating chronic blood loss. Gastroscopy revealed gastric erosions. Was admitted for 3 days, and treated with buprenorphine maintenance for the treatment of opioid dependence.

- Many cases required treatment for opioid dependence, including pharmacotherapy with methadone, or medicated opioid detoxification.
- There were 39 cases of gastrointestinal haemorrhage or perforation.

> Case 61. A young woman in her early 20s who nearly died. She had a past history of treatment with pharmacotherapy for heroin dependence several years previously. She had been taking 96 Nurofen Plus a day for 4 ½ years, initially for pain. Without any warning symptoms she suddenly perforated a gastric ulcer that penetrated into the pancreas causing pancreatitis and shock. She was critically ill and extremely toxic, required admission to ICU, intubation and life support. She spent many weeks recovering in hospital. She was commenced on methadone to treat her opioid dependence.
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> Case 77. A young female in her early 20s initially presented 18 months ago to a colleague of the reporting gastroenterologist for investigation of iron deficiency anaemia. "Surreptitious" use of Nurofen Plus was suspected but the patient stated that she only took Nurofen Plus occasionally for period pain. Endoscopy and gastroscopy performed by the gastroenterologist identified multiple gastric ulcers. These ulcers did not respond to multiple treatment regimens including gastro-protective treatments and steroids. NSAIDs were suspected as a cause of the ulcerations, but the patient denied any continuing use of these products and so a provisional diagnosis of gastric Crohn's disease was made. On several occasions scarring of the gastric outlet resulting from ulceration caused pyloric stenosis, forcing the patient onto a liquid diet.
>
> Months later, she presented to the Emergency Department very unwell. A giant ulcer, distal to her stomach had bled, resulting in severe anaemia (haemoglobin 3-4 mg/dL), hyperkalaemia and other blood abnormalities. Emergency surgery was performed. The pathologist commented that the gastrectomy specimen taken looked like NSAID-damage rather than Crohn's disease. After surgery the patient required admission to intensive care. When well enough, the gastroenterologist confronted the patient with this information, but she still denied misuse of Nurofen Plus. The patient discharged herself against medical advice. A few days later she was transported by ambulance for another emergency admission. In the process of packing a bag of clothes for her, the patient's mother and sister found multiple empty packets of Nurofen Plus in her cupboard. The patient's gastrectomy wound had broken down and she remained critically ill with sepsis as a hospital inpatient for a number of months.
>
> Since this time she has re-presented on several occasions with problems caused by misuse of Nurofen Plus. Her misuse is now monitored with urine screening.

- There were 7 cases where renal failure was mentioned.

> Case 12 was a woman in her 20s who had previously been an injecting drug user, and had taken 24-48 Nurofen Plus daily for about 5 years, initially prescribed for back pain. She was transferred to a major city hospital fully intubated following a seizure. She was diagnosed with acute renal failure and required dialysis for several days and plasmophoresis. While she was an inpatient she suffered a severe gastrointestinal haemorrhage from a duodenal ulcer, requiring endoscopic management and blood transfusion. She was admitted to ICU twice, and was in hospital for 20 days. She was commenced on a methadone program while in hospital.

- There were 5 cases where hypokalaemia was mentioned.

> Case 37 was a woman in her 30s who was a health professional. She had been treated with Panadeine Forte for back pain for several months, and developed codeine dependence. She was caught stealing this drug from her workplace and subsequently resigned. She started taking her father's supply of Nurofen Plus when she could no longer obtain Panadeine Forte. She started taking 48 Nurofen Plus a day obtained from multiple pharmacies in rural areas and in a state capital city, but one pharmacy provided Nurofen Plus for many months in very large

quantities with little supervision. She developed peptic ulcers, and severe hypokalaemia due to renal failure, and severe weight loss.

- There were 15 cases where anaemia was mentioned.

  Case 47 was a man in his 30s married with small children and in full time employment. He presented for a brief assessment to an alcohol and drug clinic with an 18 month history of Nurofen Plus use - up to 72 per day. Two nurses at first contact were shocked at his pale colour. The attending doctor ordered an urgent full blood examination that revealed an extremely low haemoglobin level (Hb 69 g/L) He was urgently referred to hospital where gastroscopy revealed multiple oozing gastric erosions. His Hb at the hospital was 71 g/L and a decision was made not to transfuse, as he was diagnosed with chronic blood loss and was haemodynamically stable. He was returned to the A&D clinic where he was admitted into the detox unit and commenced on buprenorphine with a very positive result (return to a healthy pink colour) but ultimately required readmission for a further detox some months later - to detox off buprenorphine – no further contact.

Further evidence to support rescheduling

Further evidence in support of rescheduling these medicines is provided against section 52E of the *Therapeutic Goods Act 1989*:

(a) the risks and benefits of the use of a substance

Benefits. Codeine is a weak analgesic, doses of 60 mg having a number needed to treat of 12 before one patient will achieve an analgesic benefit of 50% or more in the 4-6 hours post-operative period[2].

There is little evidence available to support any additional analgesic benefit of combining codeine doses of lower than 30mg with a simple analgesic, which is the dose contained in most OTC combination analagesics containing codeine on the Australian market[3].

Codeine does not have any benefits over morphine, but has a number of adverse effects and risks. The use of codeine as an analgesic is confounded by variable pharmacokinetics that make its efficacy and safety difficult to predict in an individual[4].

The current Australian Medicines Handbook advises that codeine is not recommended, and states that if an opioid is required, it may be more appropriate to use morphine.

Risks. Over-the-counter codeine combination analgesics are likely to be low risk when used according to the recommended dosing schedule, for the short-term treatment of acute pain.

But these medications are unique in that consumers experience one of the most serious adverse drug effects: addiction, leading to escalation of dose. A consequence of the inability to

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[2] Derry S et al. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. *Cochrane Database Syst Rev*; (4): CD008099. 2010

[3] Murnion B. Combination analgesics in adults. Aust Prescr 2010;33:113-5.

[4] Iedema J. Cautions with codeine. Aust Prescr 2011;34:133–5.

separately titrate the doses of the drugs combined in OTC codeine combination analgesics is that an individual escalating their codeine dose above recommended levels risks secondary harms from high doses of the non-opioid analgesic it is combined with.

Cases of misuse and dependence on OTC codeine-ibuprofen resulting in life threatening morbidity including gastric ulceration and haemorrhage, renal tubular acidosis and severe hypokalaemia are now well documented in Australia and New Zealand and are continuing to be identified post moving these medicines to Schedule 3 (Attachment A).

(b) the purposes for which a substance is to be used and the extent of use of a substance;

OTC codeine analgesics have approved indications for the treatment of acute pain. Given these medicines are widely used in the community, with one in three adults reporting their use, even a low rate of misuse may result in a large number of serious adverse events.

This widespread and easy access exposes vulnerable individuals and groups in the community to the risk of addiction. Well recognised risk groups include those with a mental health disorder. This is a highly prevalent group, with the 2007 Mental Health and Wellbeing Survey identifying that one in five Australian adults have experienced a mental health disorder in the previous year[5].

Other vulnerable groups include those with a personal or family history of substance abuse (7% of Australian adults[6]).

Misuse of pharmaceuticals in Australia is becoming more prevalent. In the 2010 National Drug Strategy Household Survey, 4.2% of Australians aged 14 years and older reported non-medical use of pharmaceuticals in the previous twelve months[7]. This is a significant rise, by more than 100,000, from the previous reporting period in 2007 (3.7%). The pharmaceuticals most likely to have been misused in the previous 12 months were painkillers/analgesics (3.0%), and of those who reported recent non-medical use of analgesics, the majority mainly used OTC analgesics (72.7%) over prescription analgesics (27.3%).

C) the toxicity of a substance;

The non-opioid analgesics with which codeine are combined are low risk if used as recommended at OTC doses, but become toxic at the higher doses resulting from escalation of dose due to codeine addiction.

Prolonged exposure to high doses of paracetamol provides a risk of hepatotoxicity.

Prolonged exposure to high doses NSAIDs risks harm to the gastrointestinal tract, kidney, and electrolyte problems, hypoalbuminaemia from protein-losing enteropathy, and anaemia from acute or chronic blood loss from the gastrointestinal tract.

[5] National Survey of Mental Health and Wellbeing, 2007

[6] National Survey of Mental Health and Wellbeing, 2007

[7] Australian Institute of Health and Welfare. 2010 National Drug Strategy Household Survey report. Canberra: AIHW, 2011.

The harms may be life-threatening, and require admission to intensive care units, or surgical and medical intervention.

These harms are described in the cases above and in more than 20 published articles in the medical literature (Attachment A).

(d) the dosage, formulation, labelling, packaging and presentation of a substance;

Dosage and formulation

The central problem with these medicines is the combination of fixed sub-therapeutic doses of an addictive substance, codeine, with non-opioid analgesics that are relatively low risk at OTC doses, but exert highly toxic effects when the daily number of tablets taken escalates as a result of codeine addiction.

Labelling

Regulatory and administrative responses to address the serious adverse outcomes from misuse of OTC codeine analgesics have been examined in other countries and highlight opportunities to utilise additional regulatory levers in Australia[8].

In Australia, current requirements for labelling and packaging do not mandate the prominent warning about the risk of addiction, and the need to limit supply to that necessary for the management of acute pain. This is in contrast to the situation in the United Kingdom, where packs are required to be labelled with a prominent label on the front of the pack: "For three days use only. Can cause addiction" (Attachment B).

Current requirements also do not require provision of a consumer medicines information leaflet in the pack, unlike in the United Kingdom where there is a leaflet in each pack with a prominent and easily understood warning about the risk of addiction and how to recognise it. (Attachment C).

Consumer medicines information leaflets are provided online in Australia, but their use is extremely limited. Online provision provides a barrier to supply of a CMI, requiring a pharmacist to print it out. Pharmacists seldom provide these documents at the time of sale.

(e) the potential for abuse of a substance;

The addictive nature of codeine has been recognised and documented for many decades, and for the first time we have good evidence of the scale of this addiction.

The National Opioid Pharmacotherapy Statistics report that of the 47,576 clients treated for opioid dependence, only 26,229 reported their primary opioid of concern[9]. Of these, one in three reported that pharmaceutical opioids were their primary opioid of concern, and in 1038

[8] Tobin CL et al. Regulatory responses to over-the-counter codeine analgesic misuse in Australia, New Zealand and the United Kingdom. Aust NZ J Public Health. 2013; 37:483-8

[9] Australian Institute of Health and Welfare 2014. National opioid pharmacotherapy statistics 2013. Drug treatment series no. 23. Cat. no. HSE 147. Canberra: AIHW

clients the opioid of concern was codeine. Evidence from Nielsen et al[10] suggests that it is possible 94% of these were dependent on OTC codeine, which is possible given the widespread and easy availability of these opioid combination medicines.

Further evidence from another study by Nielsen et al suggest a steady increase in the number of people presenting to public drug treatment agencies for non-pharmacotherapy treatment of dependence on OTC codeine analgesics[11].

Recommendations

1. Medicines that combine codeine with non-opioid analgesics currently scheduled in Schedule 3 should be rescheduled to Schedule 4, to require supply by prescription only.

Given the availability of alternatives, I concur with others[12][13] who have argued that because of codeine's limited efficacy, pharmacokinetic variability and potential for addiction and other harms, especially when combined with other dose-related toxic medicines, the ACMS and TGA should give consideration to evaluating whether there is a place for codeine in the Australian market at all.

2. Require labelling warning about the risk of addiction on packs of these medicines, which emphasise that they are indicated for three days use only, similar to labelling in the United Kingdom.

3. Require provision of a consumer medicines information leaflet in every pack of these medicines, warning about the risk of addiction and how to recognise it, similar to the United Kingdom version.

[10] Nielsen S et al. Comparing treatment-seeking codeine users and strong opioid users: Findings from a novel case series. Drug Alc Review 2014. Dec 29. doi: 10.1111/dar.12224.

[11] Nielsen S, Roxburgh A, Bruno R et al. Changes in non-opioid substitution treatment episodes for pharmaceutical opioids and heroin from 2002-2011. (Drug Alcohol Depend 2015), http://dx.doi.org/10.1016/j.drugalcdep.2015.02.004

[12] Iedema J. Cautions with codeine. Aust Prescr 2011;34:133–5.

[13] Anderson BJ. Is it farewell to codeine? Arch Dis Child 2013;98:986-8.

ATTACHMENT A. Published cases of harm arising from misuse of OTC codeine-ibuprofen analgesics: Australia and New Zealand, 2008-2014.

Authors (country)	No. cases. No. tablets/day	Description.
Dobbin & Tobin, 2008 [14] (Australia)	77 cases Average 50 tablets per day for an average of 2.5 years	Drug dependence on codeine with serious complications of **upper gastrointestinal toxicity (haemorrhage and perforation of the stomach and duodenum), anaemia, renal tubular acidosis, hypokalaemia and one death**. Many patients needed **life support in intensive care**, as well as emergency surgery. Average age was 33 years, and an equal representation of males and females.
Dutch, 2008 [15] (Australia)	2 cases pack/day, and 16-24/day (Nurofen Plus)	Two cases of **perforated gastric ulcers** attributed to recreational codeine-ibuprofen use. One case required **intensive care unit**, the other 4 units of packed blood cells.
Frei et al, 2010 [16] (Australia)	27 cases mean 34-47/day OTC codeine-ibuprofen	A case series of patients with serious and often multiple NSAID pattern morbidities such as **GI haemorrhage and perforation, pyloric stenosis, renal failure, anaemia and profound hypokalaemia, as well as opioid dependence,** resulting from high dose OTC codeine-ibuprofen misuse obtained from multiple pharmacies over a prolonged period. Some with multiple admissions. Most had no previous history of substance use disorder, with most initiating for self-medication of pain. **Four admitted to ICU**. One required **dialysis**. One **gastrectomy**. Most required pharmacotherapy for opioid dependence.
Ernest D, Chia M, Corallo CE. 2010 [17] (Australia)	2 24/day for 3 days (Nurofen Plus)	**Profound hypokalaemia and rhabdomyolysis** presenting as severe quadriparesis, from overuse of Nurofen Plus with energy drinks**. ICU admission**. Partner also admitted for **detoxification** from Nurofen Plus.
Robinson GM, Robinson S, McCarthy P, Cameron C. 2010 [18] (New Zealand)	7 Nurofen Plus 60-80/day, 48/day, 20/day, up to 72/day, 80/day, up to 120/day, 48/day	Cases of long term high dose Nurofen Plus misuse with severe multiple NSAID pattern morbidities (gastric ulcer and haemorrhage, anaemia, gastrectomy, ileal resection, inflammatory bowel disease with gastric bypass and colectomy), Four cases had co-morbid alcohol use disorders, four cases with mental health disorders.
Evans C, Chalmers-Watson TA, Gearry RB. 2010 [19] (New Zealand)	Describing 1 of 4 cases. > 100 tabs/day	Presented with anaemia, lower leg oedema and epigastric pain. **Gastric ulcer** with **active bleeding** in pyloric channel and **post-bulbar duodenitis with active bleeding.** Balloon dilatation of **pyloric stenosis** later required, and he was treated for **addiction**. He was one of four patients presenting to the service in 2 years with **significant GI pathology** secondary to gross overuse of combination NSAID/codeine products.
Ali A et al. 2010 [20] (Australia)	1 60-80 Nurofen Plus tablets/day for many months	**Renal tubular acidosis** and **hypokalaemic paraparesis**

[14] Dobbin M, Tobin C. Over-the counter (OTC) ibuprofen/codeine analgesics: misuse and harm. Victorian Department of Health, Melbourne. 2008.
[15] Dutch MJ. Nurofen Plus misuse: an emerging cause of perforated gastric ulcer. Med J Aust. 2008;188:56-7.
[16] Frei MY, Nielsen S, Dobbin MDH, Tobin CL. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases. Med J Aust 2010;193:294-6.
[17] Ernest D, Chia M, Corallo CE. Profound hypokalaemia due to Nurofen Plus and Red Bull misuse. Crit Care Resusc 2010;12:109-10.
[18] Robinson GM, Robinson S, McCarthy P, Cameron C. Misuse of over-the-counter codeine-containing analgesics: dependence and other adverse effects. NZ Med J. 2010;123:59-64.
[19] Evans C, Chalmers-Watson TA, Gearry RB. Combination NSAID-codeine preparations and gastrointestinal toxicity. N Z Med J 2010;123:92-3
[20] Ali A, Wong J, Howlin K, Jefferys A et al. Renal tubular acidosis and hypokalemic paraparesis due to neurofen overdose. Nephrology 15: 43, Sept 2010

Miles R et al. 2010 [21] (Australia)	1	**Acute Tubular Necrosis** and **Renal Tubular Acidosis**
Ferguson L, Clarke I, Fisher A, Legg G, Batey R 2010[22] (Australia)	5 60, 50, 60, 40-60,75 tablets/day respectively	Case 1: A young female with past history of sexual abuse, unplanned pregnancy with termination who commenced NSAID's (Nurofen plus) to relieve right sided **abdominal pain** following the termination. Use escalated to over 60 tablets a day. She was seen over an 18 month period by D&A, Mental Health, medical and surgical teams but died of complications of **ulcer disease** with bleeding and **undetected perforation of an ulcer**. Case 2: A young female with past history of physical abuse who was taking 50 plus NSAID's (Nurofen plus) a day for pain. She presented with increasing **muscle weakness** to the point of being unable to walk unaided. On presentation to the ED her **potassium** was 2.4. She had an **associated renal tubular acidosis**. Case 3: A 22 year old female, with a one year history of taking 60 Nurofen Plus per day, was admitted for emergency laparotomy for a **perforated pre pyloric ulcer and peritonitis.** The patient required ICU care and the pathology showed she was **acidotic** and **hypoalbuminemic**. She had initially started Nurofen Plus for post IUD insertion pain, at recommended doses. Discovering euphoric effects from high doses, she escalated the dose after two weeks. The patient has been treated for depression. She had been abstinent from Nurofen Plus for 15 months and had been treated in a residential D&A facility. A relatively brief relapse of 60 Nurofen Plus tablets per day precipitated acute abdominal pain and urgent hospital admissions. **Case 4**: A 32 year old male presented to D&A services with a 2 year history of Nurofen Plus use: 40-60 tablets per day. He commenced use initially for dental pain and found escalating doses decreased anxiety. After point-of-sale changes, he was forced to reduce the dose. He is now stable on buprenorphine 8mg daily. **Case 5**: A 28 year old female with a 2 year history of using 75 Nurofen Plus per day presented to hospital requesting withdrawal. This was driven by inability to purchase high amounts in a rural area, due to point-of-sale changes. Gastroscopy and other pathology was normal. Symptomatic opioid withdrawal was conducted as the patient declined maintenance pharmacotherapy.
Storor D. 2011 [23] (Australia)	56	Opioid dependence on OTC codeine analgesics. **Gastritis, peptic ulcer, scarring and strictures, intestinal obstruction and renal failure**. Some required **blood transfusions**. **Hepatitis** from paracetamol.
Ng JL, Morgan DJR, Loh NKM, Gan SK, Coleman PL, Ong GSY, et al. 2011 [24] (Australia)	2 up to 20 tabs/day, and 24 tabs/day (codeine-ibuprofen)	Four cases of **profound hypokalaemia** associated with excess ibuprofen intake. Two of the cases involved codeine-ibuprofen. One had a history including **iron deficiency anaemia**, **chronic constipation**, migraines, depression and previous intravenous drug use. She was taking up to 20 tabs/day and was admitted with **evolving paralysis** and **profound hypokalaemia**, **renal tubular acidosis**, **oesophageal erosions** and **gastric ulcer**. The other had been taking 24 tabs/day of OTC codeine-ibuprofen for several years and presented with **progressive muscle weakness** and hypokalaemia. Opioid withdrawal symptoms on day 3.

[21] Miles, R., Bofinger, A., Herzig, K. and Searle, J. (2010). Selective Distal Tubular Acute Tubular Necrosis and Renal Tubular Acidosis Due to Abuse of Nurofen Plus (Ibuprofen/codeine Phosphate). In: Nephrology. 2010 (43-43).

[22] Ferguson L, Clarke I, Fisher A, Legg G, Batey R. Over the counter and into the grave: morbidity and mortality related to NSAIDS with codeine dependence. APSAD Conference 2010. Drug and Alc Rev 2010;29 (Suppl. 1):2-82. Unpublished poster of same name at APSAD conference.

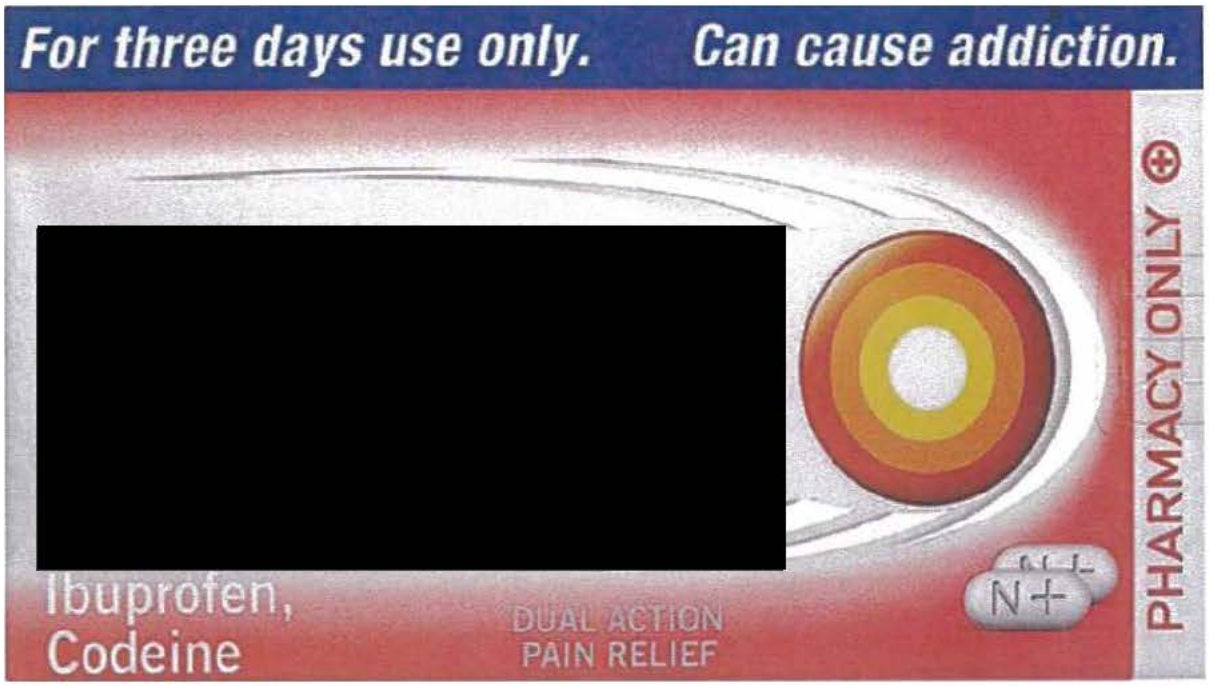
[23] Storor D. National pharmaceutical drug misuse strategy [letter to National Centre for Education and Training on Addiction]. http://nceta.flinders.edu.au/files/7713/1423/8823/Damascus%20Health%20Services%20web%20version.pdf (accessed Jul 2014).

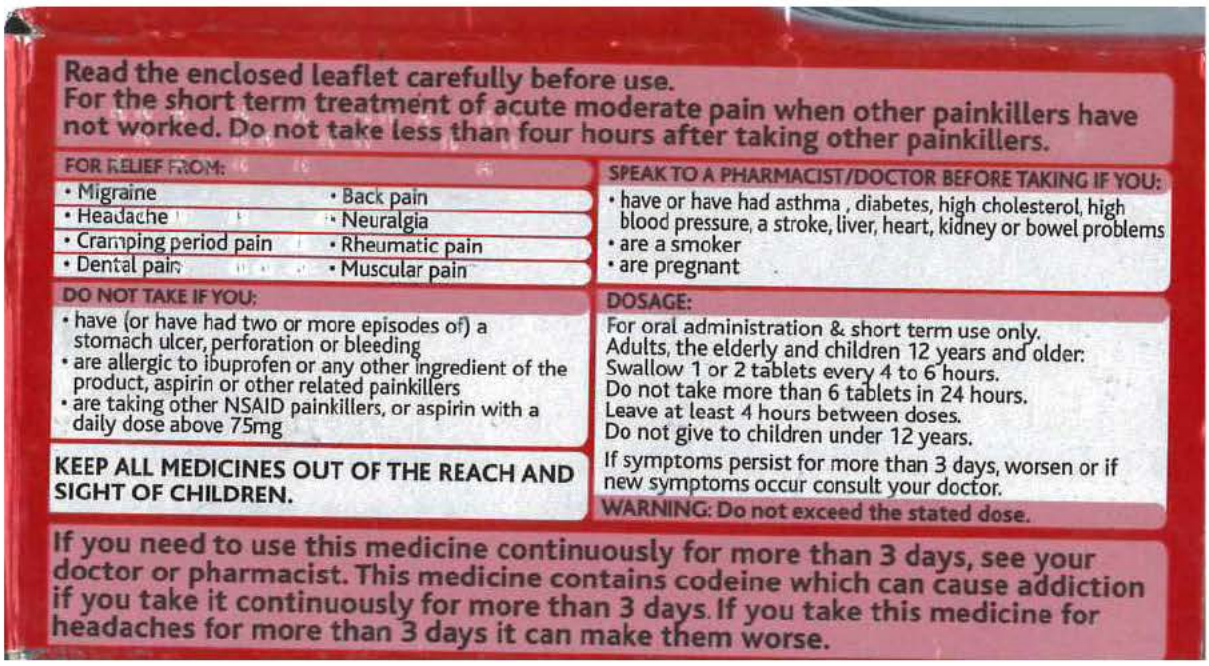
[24] Ng JL, Morgan DJR, Loh NKM, Gan SK, Coleman PL, Ong GSY, et al. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. Medical J Australia. 2011;194:313-16.

Page CB, Wilson PA, Foy A, Downes MA, Whyte IM, Isbister GK. 2011 [25] (Australia)	4 OTC codeine-ibuprofen. Tablets /day 45-90, 25, 40 and unclear but years' duration.	Four cases of **life-threatening hypokalaemia** and ibuprofen-induced **renal tubular acidosis** from long-standing misuse of ibuprofen taken in combination with codeine from over-the-counter (OTC) medications. Two patients **required ICU admission**. Opioid addiction appeared to be the common thread.
McDonough MA 2011 [26] (Australia)	32	Cases referred to one addiction medicine service, all with a history of chronic pain and combination codeine-analgesic use. One 34yo male reported taking more than 70 codeine-ibuprofen tablets daily and sustained **recurrent gastric ulceration** eventually requiring surgery. Despite this he continued to misuse the analgesics and undertook opioid replacement pharmacotherapy. Some cases had severe morbidity including one death from **gastric ulceration**.
Mallett A, Lynch M, John GT, Healy H, Lust K. 2011 [27] (Australia)	1 OTC codeine-ibuprofen. Tablets /day 45-90, 25, 40 and unclear but years' duration.	34-year-old woman in third trimester of pregnancy presented with **renal tubular acidosis** related to ibuprofen codeine abuse. Delivery at 37 weeks was necessary because of concerns about evolving preeclampsia**. Renal tubular acidosis** and **hypokalaemia** were mitigated, but **some renal dysfunction** continued.
Karamatic R, Croese J, Roche E. 2011 [28] (Australia)	3 OTC codeine-ibuprofen. Tablets /day 10, 10-12, and 20 tablets a day, in two cases for 5 years or more.	3 cases of **small bowel NSAID enteropathy**, including **diaphragm disease** and **small bowel ulceration**, all of whom had **iron deficiency anaemia** and **hypoalbuminaemia**.
McAvoy BR et al. 2011 [29] (New Zealand)	15 cases over a 12 week period OTC codeine-ibuprofen average 49 per day for average 27 months	**Gastrointestinal bleeding**, dyspepsia in 53%. **Renal tubular acidosis** in 7%.
Lake H. 2013 [30] (Australia)	1 up to 90/day codeine-ibuprofen	Worsening abdominal pain, **bowel obstruction**. **Small bowel resection. Fibrous stricture.** Delirium and multiple code black interventions - aggressive and violent behaviour.
Pilgrim J, Dobbin M, Drummer OH. 2013 [31] (Australia)	7	Coroners' cases with codeine and ibuprofen detected in post-mortem toxicology, or where codeine–ibuprofen analgesic misuse was described in coroners' findings. 115 cases were identified, and evidence of chronic NSAID toxicity was reported in 7 cases manifesting as **gastric erosions and ulceration** in three individuals, **chronic gastritis** in one, **renal necrosis** and disease in two and **hepatocyte necrosis** in one.
Robertson CG, Kumar B, Bright T, Watson DI. 2014 [32] (Australia)	5	Five young patients with unrecognised NSAID abuse referred with **non-healing gastric ulcers** with or without **perforation** or **gastric outlet obstruction**. Four patients did not volunteer NSAID use until confronted with positive NSAID urine tests. Complex issues during recovery followed surgical intervention.

[25] Page CB, Wilson PA, Foy A, Downes MA, Whyte IM, Isbister GK. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. Med J Aust 2011;194:613-14.
[26] McDonough MA. Misuse of codeine-containing combination analgesics. *Medical Journal of Australia*. 2011;194:486.
[27] Mallett A, Lynch M, John GT, Healy H, Lust K. Ibuprofen-related renal tubular acidosis in pregnancy. Obstetric Medicine 2011;4:122-4.
[28] Karamatic R, Croese J, Roche E. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics. Med J Aust 2011;195(9):516.
[29] McAvoy BR, Dobbin MDH, Tobin CL. Over-the-counter codeine analgesic misuse and harm: characteristics of cases in Australia and New Zealand. N Z Med J. 2011; 124(1346):29-33.
[30] Lake H. Ibuprofen belly: a case of small bowel stricture due to non-steroidal anti-inflammatory drug abuse in the setting of codeine dependence. Aust NZ J Psychiatry 2013;47:1210-11
[31] Pilgrim J, Dobbin M, Drummer OH. Fatal misuse of codieine-ibuprofen in Victoria, Australia. Med J Aust 2013;199(5):329-30.
[32] Robertson CG, Kumar B, Bright T, Watson DI. Beware NSAID abuse: think twice before operating. Aust NZ J Surgery 2014;84:495-6

ATTACHMENT B. [redacted] pack with warning label and information on the front and rear, United Kingdom





ATTACHMENT C [redacted] Consumer Medicines Information included in each pack, United Kingdom

[redacted]

- **This medicine can only be used for the short term treatment of acute, moderate pains which is not relieved by paracetamol, ibuprofen or aspirin alone** (such as rheumatic and muscular pain, backache, migraine, headache, neuralgia, period pain and dental pain)
- **You should only take this product for a maximum of three days at a time. If you need to take it for longer than three days you should see your doctor or pharmacist for advice**
- **This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it**
- **If you take this medicine for headaches for more than three days it can make them worse**

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START TO TAKE YOUR MEDICINE

It contains important information.

Keep this leaflet. You may want to read it again. If you have any further questions after you have read it, ask your doctor or pharmacist.

1. What [redacted] is and what it is used for

The active ingredients (which make Nurofen Plus work) are Ibuprofen and Codeine phosphate.

Ibuprofen belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs provide relief by changing the body's response to pain, swelling, and high temperature. **Codeine** is a painkiller (analgesic) that reduces the communication of pain messages.

- [redacted] **is for the short term treatment of acute, moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone,** such as :
  - migraine, headaches, neuralgia
  - period, dental, back, rheumatic and muscular pains.

2. Before taking this medicine

Do not take :

- **This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it**
- **If you take a painkiller for headaches for more than three days it can make them worse**
- If you have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding
- If you have breathing difficulties
- If you are allergic to ibuprofen, codeine or any of the other ingredients (see section 6) or to aspirin or other painkillers
- If you suffer from severe kidney, heart problems
- If you suffer from chronic constipation
- If you have had gastrointestinal bleeding or perforation when previously taking NSAIDs
- If you have had a worsening of asthma, skin rash, itchy runny nose or facial swelling when previously taking ibuprofen, aspirin or similar medicines
- If you are taking other NSAID painkillers or aspirin with a daily dose above 75mg
- If you are in the last 3 months of pregnancy
- If you are under 12 years old.

Speak to a pharmacist or your doctor before taking this product if you:

- have or have had asthma
- have kidney, heart, liver or bowel problems
- have low or high blood pressure
- have a head injury or raised intracranial pressure
- suffer from a thyroid disorder
- have Systemic Lupus Erythematosus (a condition of the immune system causing joint pain, skin changes and other organ disorders
- have high cholesterol
- have had a heart attack or stroke
- have a history of gastrointestinal disease (such as ulcerative colitis, Crohn's disease)
- are a smoker
- are in the first 6 months of pregnancy.

Can you take [redacted] with other medicines?

Some anticoagulant medicines (i.e. thin blood/prevent clotting e.g. aspirin/acetylsalicylic acid, warfarin, ticlopidine), some medicines that reduce high blood pressure (ACE-inhibitors such as captopril, beta-blockers such as atenolol, or angiotensin-II receptor antagonists such as losartan), and other medicines may affect or be affected by treatment with ibuprofen.

Medicines called Monoamine oxidase inhibitors (MAOIs) for the treatment of depression may affect or be affected by treatment with codeine.

You should therefore always seek the advice of your doctor or pharmacist before you take Nurofen Plus with other medicines.

1859420

Other warnings

- [redacted] belongs to a group of medicines which **may impair fertility in women**. This is reversible on stopping the medicine. It is unlikely that Nurofen Plus, used occasionally will affect your chances of becoming pregnant. However, tell your doctor before taking this medicine if you have problems becoming pregnant.
- Medicines such as Nurofen Plus may be associated with a **small increased risk of heart attack or stroke**. Any risk is more likely with high doses or prolonged treatment. **Do not exceed the recommended dose or take for longer than necessary to control your symptoms (3 days)**
- **If you have heart problems, have had a stroke or think that you might be at risk of these conditions** (for example if you have high blood pressure, diabetes, high cholesterol or are a smoker), you should discuss your treatment with your doctor or pharmacist.

Pregnancy and breastfeeding

Do not take in the last 3 months of pregnancy. Speak to your doctor if you are in the first 6 months of pregnancy or are breastfeeding.

Driving and using machines

This product may cause drowsiness or dizziness. If affected, do not drive or operate machinery.

Driving and using machines

This product may cause drowsiness or dizziness. If affected, do not drive or operate machinery.

3. How to take [redacted]

- **Do not take for more than 3 days. If you need to use this medicine for more than three days you must speak to your doctor or pharmacist**
- **Adults, the elderly and children aged 12 years and older :**
  -Swallow 1 or 2 tablets with water, up to three times a day as required.
  -Leave at least four hours between doses.
  -Do not take more than 6 tablets in any 24 hour period.
  -**Do not give to children under 12 years.**
  -Do not take for longer than 3 days unless your doctor tells you to. If symptoms persist or the pain or fever worsen, or if any new symptoms occur, consult your doctor or pharmacist.
- This product is **for short term use only.** You should take the lowest dose for the shortest time necessary to relieve your symptoms
- **This medicine contains codeine and can cause addiction if you take it continuously for more than three days. When you stop taking it you may get withdrawal symptoms. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms**

4. Possible side effects

Some people may have side-effects when taking this medicine. If you have any unwanted side-effects you should seek advice from your doctor, pharmacist or other healthcare professional.

Also you can help to make sure that medicines remain as safe as possible by reporting any unwanted side-effects via the internet at **www.yellowcard.gov.uk**; alternatively you can call Freephone 0808 100 3352 (available between 10am-2pm Monday - Friday) or fill in a paper form available from your local pharmacy.

STOP TAKING the medicine and **seek immediate medical help** if you develop:

- signs of **intestinal bleeding** such as: bright red faeces (stools/motions), black tarry stools, vomiting blood or dark particles that look like coffee grounds.
- signs of rare but serious **allergic reaction** such as severe skin rashes, peeling, flaking or blistering skin, facial swelling, unexplained wheezing, shortness of breath, easy bruising.

Tell your doctor if you experience:

- indigestion or heartburn
- constipation, stomach pain or other abnormal stomach symptoms
- rashes, itching or worsening of asthma
- sweating, thirst, muscle weakness or tremors, sleeplessness
- chest pain or fast, irregular heart beat
- liver and kidney problems
- headache, nausea, dizziness or drowsiness.

Medicines such as Nurofen Plus may be associated with a small increased risk of heart attack (myocardial infarction) or stroke.

How do I know if I am addicted?

If you take the medicine according to the instructions on the pack it is unlikely that you will become addicted to the medicine. However, if the following apply to you it is important that you **talk to your doctor:**

- *You need to take the medicine for longer periods of time*
- *You need to take more than the recommended dose*
- *When you stop taking the medicine you feel very unwell but you feel better if you start taking the medicine again*

5. How to store [redacted]

Keep out of the sight and reach of children.

Do not use Nurofen Plus after the expiry date stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in a dry place below 25°C. Store in the original pack.

6. Further information

Each tablet contains the active ingredients Ibuprofen 200mg and Codeine phosphate 12.8mg. Also contains microcrystalline cellulose, sodium starch glycollatre, starch pregelatinised, hypromellose, opaspray white M-1-17111 B and talc.

Available in blister packs of 6, 8, 12, 18, 24 or 32 white, torpedo-shaped tablets embossed with the N+symbol.

Licence Holder and Manufacturer:
Crookes Healthcare Limited
Nottingham NG2 3AA
Product Licence No. PL 00327/0082
Date of revision November 2009

NSW poisons Information Centre
the children's hospital at Westmead

[redacted]

7 May 2015
Advisory Committee on Medicines Scheduling
Therapeutic Goods Administration

Consultation: Invitation for public comment - ACMS meeting, July 2015

The NSW Poisons Information Centre (NSWPIC) provides a phone-based advice service on suspected poisonings to the public and health professionals calling from NSW, TAS and ACT on a near full-time basis and a shared after-hours service to the remainder of Australia. This results in approximately half of Australia's poisons-related calls being received by our Centre. The NSWPIC database is available for analysis from 1 January 2004 onwards.

Figure 1. Calls taken by NSWPIC in 2013 by state of origin of caller

State	Number of calls	% of calls
New South Wales	68615	66.2
Queensland	9354	9.0
Victoria	7896	7.6
Unknown	5425	5.2
Tasmania	3285	3.2
Australian Capital Territory	3077	3.0
South Australia	2936	2.8
Western Australia	2733	2.6
Northern Territory	288	0.3
International	96	0.1
TOTAL	103705	

The NSWPIC supports further measures to decrease the potential access to excessive supplies of codeine-based products which are subject to abuse and misuse.

Analysis of calls to NSWPIC relating to people who had misused/abused ibuprofen+codeine products is shown in Figure 2. The re-scheduling of ibuprofen+codeine in 2010 was shown to have a temporary impact on reducing the cases of misuse and abuse reported to NSWPIC but this rebounded in 2013. An average of 13 cases per year have been reported in the past two years. This highlights that the current scheduling and availability is not sufficient in controlling ibuprofen+codeine abuse.

Cases of paracetamol+codeine abuse reported to NSWPIC have also been analysed over the period 1 January 2011 – 20 April 2015 (Figures 3 and 4). There have been an average of 35 cases per year in the past two years. The results show that the majority of cases of misuse and abuse of paracetamol+codeine are from schedule 3 products (49.6 % of cases), followed by schedule 4 products (30.6 % of cases), and lastly schedule 2 (10.7% of cases) [NB: In 9.1% cases the exact formulation was not specified]. This demonstrates that making codeine schedule 4 alone is not sufficient in preventing misuse and abuse.

Possible solutions include:

1. A real-time registry for codeine sales similar to 'Project STOP' used for tracking pseudoephedrine sales may be a system to help combat codeine abuse by reducing access to excessive supplies.
2. Scheduling changes for OTC availability of codeine-based products should be considered in combination with pack sizes and restrictions on multiple pack purchases.

If you required further analysis or information in relation to this data, please contact the NSW Poisons Information Centre on 02 9845 3969 or jared.brown@health.nsw.gov.au

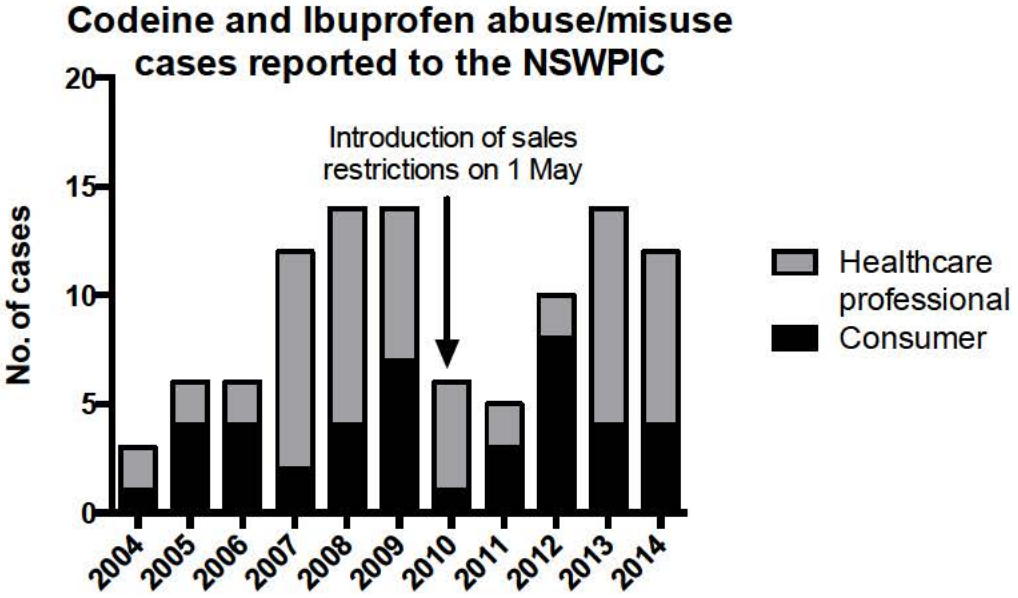
Yours sincerely,

[redacted]

Addendum 12 May 2015

Our clinical director has suggested an addendum to the preamble of our submission, reminding the committee who are not familiar with the Poisons Information Centre that PICs do not receive calls from all hospitals regarding potential poisonings (eg from codeine) - particularly those which have clinical toxicology units, and a lesser amount from tertiary referral hospitals. As these hospitals tend to have access to local expertise. Hence, the data here is a signal of the wider misuse and abuse of codeine and does not represent all cases.

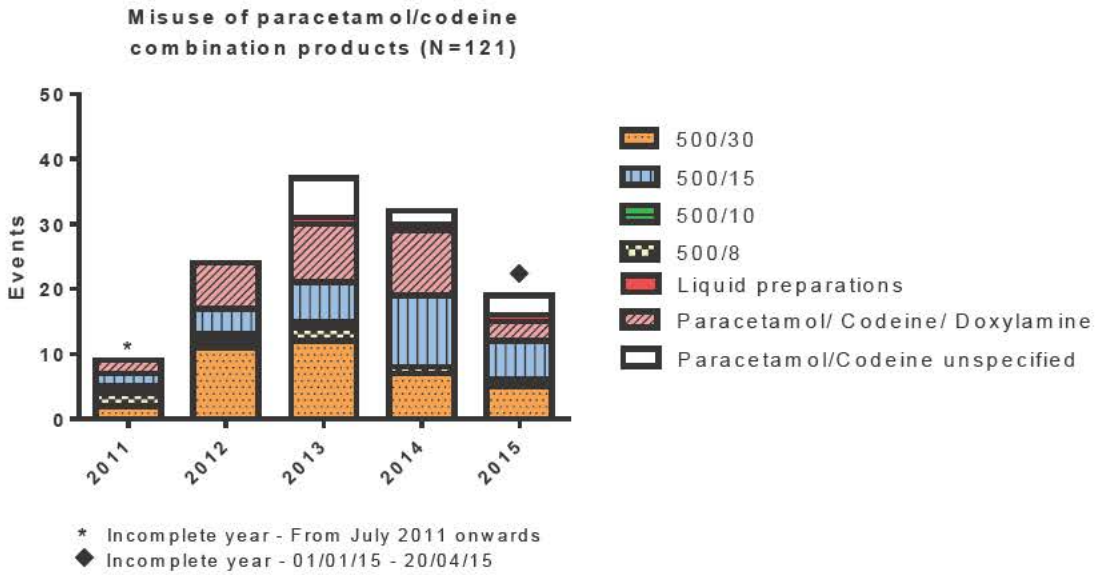
Figure 2. Cases of ibuprofen+codeine misuse/abuse reported to NSWPIC over the period 1 January 2004 – 31 December 2014 by type of caller (N=102)



60 [redacted]
16 [redacted]
1 [redacted]
7 Unknown

33 cases took 5-24 tabs/day
26 cases took 25-72 tabs/day
18 cases took 49-72 tabs/day
4 cases took 73-150 tabs/day

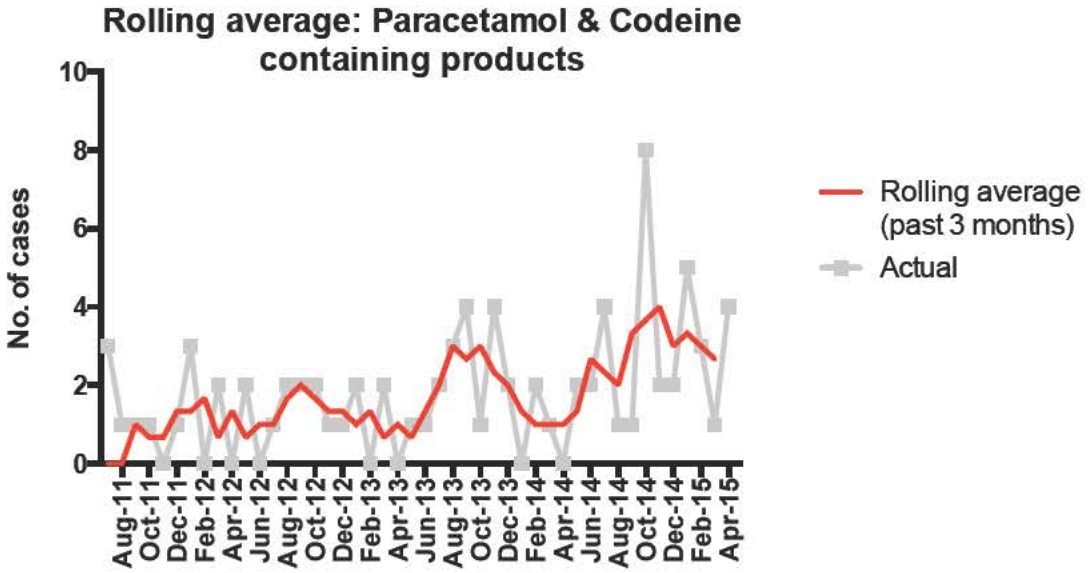
Figure 3. Cases of paracetamol+codeine misuse/abuse reported to NSWPIC over the period 2 July 2011 – 20 April 2015 by type of paracetamol



	500/30	500/8	500/10	500/15	+Codeine+Doxylamine	Liquid preparations	Unspecified
2011	2	2	1	2	2	0	0
2012	11	1	1	4	7	0	0
2013	12	2	1	6	9	1	6
2014	7	1	0	11	10	1	2
2015	5	1	0	6	3	1	3

Of exposures to OTC products:
53 took 1-24 per day
15 took 25-48 tabs per day
7 took unknown dose

Figure 4. Cases of paracetamol+codeine misuse/abuse reported to NSWPIC over the period 2 July 2011 – 20 April 2015 (N=121)



7 May 2015

Medicines Scheduling Secretariat
Medicines Authorisation Branch (MDP 122)
PO Box 100
Woden ACT 2606
Australia

Sent via email to: medicines.scheduling@tga.gov.au

Consumer Healthcare
82 Hughes Avenue
Locked Bag 3
Ermington NSW 2115
Australia

Tel. 61 2 9684 0888
Fax. 61 2 9684 1018

Re: Public Comment on Proposed amendments referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling at the July 2015 Meeting: Codeine

GlaxoSmithKline Consumer Healthcare (GSK) welcomes the opportunity to comment on the above agenda item. The Company markets three codeine-containing analgesic combination products:

- **Panafen Plus** (ibuprofen 200 mg and codeine phosphate 12.8 mg)
  - 15 Tablets (2.5 days supply)
  - 30 Tablets (5 days supply)
- **Panadeine** (paracetamol 500 mg and codeine phosphate 8 mg)
  - 20 Soluble Tablets (2.5 days supply)
  - 24 Tablets (3 days supply)
  - 40 Tablets (5 days supply)
- **Panadeine Extra** (paracetamol 500 mg and codeine phosphate 15 mg)
  - 12 Tablets (1.5 days supply)
  - 24 Tablets (3 days supply)
  - 40 Tablets (5 days supply)

Each of these products is currently indicated for the temporary relief of pain and discomfort associated with headache, migraine headache, tension-type headache, period pain, back pain, muscle pain, arthritis, toothache, neuralgia, cold and flu symptoms dental procedures, sore throat and reduction of fever.

The adverse effects of codeine are reported more frequently following higher or repeated doses and the risk of dependence with continued codeine use may lead to escalation of daily doses thus meaning that people may take more of the product than is recommended on the label.[1]

At present (since 2010) these products are available Pharmacist Only (S3). In fact, a 2009 review of codeine-containing analgesics resulted in a change in schedule of all non-prescription codeine containing analgesics from S2 (Pharmacy Only) to S3 (Pharmacist Only). Since 2010, codeine-containing analgesic combination products have not been advertised to consumers directly and cannot be self-selected by consumers (i.e. they are behind the counter in the pharmacy).

Analysis of GSK pharmacovigilance data (spontaneous and thorough literature review) from Australia was conducted since the change of schedule of codeine to Schedule 3 in 2010 up to and including 31 March 2015. The cases of misuse reported with codeine-containing analgesic combination products marketed by GSK is low. Serious cases have been reported to the TGA as required and therefore will be included in any summary of TGA safety data.

- In the period from 01 Jan 2005 to 31 Mar 2015, approximately 13.5 million packs of Panadeine/Panadeine Extra were sold in Australia. GSK has recorded 83 reports of adverse events with paracetamol-codeine products during this time, none of which were related to drug dependence or abuse.
- In the same time period, approximately 6.7 million packs of Panafen Plus were sold in Australia. GSK has recorded 73 reports of adverse events with ibuprofen-codeine, 35 of which were related to drug dependence or abuse.
- Of these 6 spontaneous adverse event reports listing dependence potentially associated with the use of Panafen Plus have been recorded in the last 5 years. In addition 29 or these reports for ibuprofen-codeine were sourced from three published literature articles (Frie MY et al, 2010[2] = 26 cases; McDonough MA, 2011[3] = 2 cases and Thomson AD, 2010[4] = 1 case).

Even though abuse of codeine-containing analgesic combination products is a documented phenomenon, the available data shows that misuse of these products is infrequent.

The following measures have been taken by GSK for our codeine containing products sold in Australia and we feel that these are good examples of possible public health measures that could be taken for this product:

- **Consumer education**: A NEW voluntary front of pack warning statement "CAN CAUSE ADDICTION. USE FOR 3 DAYS ONLY" has been rolled out for all GSK OTC codeine-containing analgesic combination products (see Attachment 1).
- **Pharmacist education**: A PSA accredited Pharmacist education activity (Up-to-date in the Pharmacy: Codeine; see Attachment 2), which provides information on the efficacy/safety of codeine and strategies for Pharmacists on appropriate supply, was initiated in 2014. As of March 2015, 427 Pharmacists nationwide have completed this activity. Amongst those Pharmacists who have completed this activity 99% either agree or strongly agree that they are now confident in their ability to discuss codeine-containing analgesic combination products with their customers and 91% now have a system in place to discuss codeine with all customers.

The following additional measures could address concerns regarding misuse and abuse of codeine containing products:

- Changes to the Product information for Healthcare Professionals and Consumer Medicine Information to indicate that codeine-containing analgesic combination products are especially suitable for pain that requires stronger analgesia than single ingredient analgesics alone and are for the treatment of acute moderate pain conditions including headache, migraine, muscle ache, dysmenorrhoea, sore throat,

- Front of pack warnings
- Increased information to consumers about the appropriate use of codeine-containing analgesic combination products for acute pain conditions when a single ingredient analgesic is not effective e.g. Consumer Medicine Information (CMI) and improved labelling on pack to ensure that the pain states indicated for product are appropriate and warning statements are clear
- Ensure that packs available without prescription include a maximum of 3 day's product use
- Recommendation for pharmacists to track real time consumer purchases of products and assist in the identification of individuals at risk, including the adoption of a system, such as that employed for pseudoephedrine (Project STOP).

We hope that the information contained in this letter will assist the committee in their review.

Yours sincerely,

GSK Consumer Healthcare

Literature references:

1. Nielsen S, Cameron J, Lee N: **Characteristics of a nontreatment-seeking sample of over-the-counter codeine users: implications for intervention and prevention.** *Journal of Opioid Management* 2011, **7**(5):363-370.
2. Frei MY, Nielsen S, Dobbin MD, Tobin CL: **Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases.** *MJA* 2010, **193**(5):294-296.
3. McDonough MA: **Misuse of codeine-containing combination analgesics.** *MJA* 2011, **194**(9):486.
4. Thomson AD, Weltman MD: **Electronic images of the month. Severe duodenitis after massive chronic Ibuprofen overdose.** *Clin Gast Hepatol* 2010, **8**(11):e114.

Attachment 1

UP-TO-DATE IN THE PHARMACY

QUM and OTC codeine-containing combination analgesics

AUSTRALIAN PHARMACY COUNCIL

2 Group 2 CPD credits

Contents

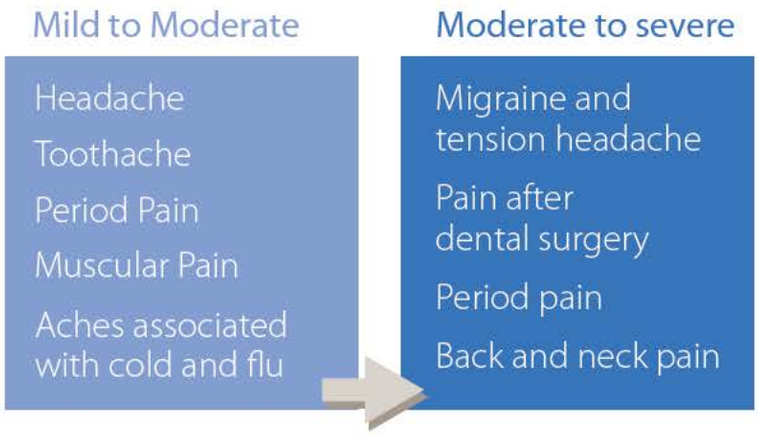
As part of its commitment to Pharmacists' education, GlaxoSmithKline Consumer Healthcare has sponsored the development of this **UP-TO-DATE IN THE PHARMACY** learning module. This Continuing Professional Development initiative is designed to provide Pharmacists with up-to-date evidence on the appropriate use of OTC products to enhance the provision of guidance and advice to consumers.

gsk GlaxoSmithKline

Introduction

Pain is a common condition and analgesics represent one of the leading self-medication categories. The pharmacy is often the first port of call for people with pain, making community pharmacists ideally placed to educate consumers about appropriate choice and appropriate use of over-the-counter (OTC) analgesics.

Moderate to severe pain types are very common; for example up to 54% of people undergoing single- or multiple-visit root canal treatment suffer from postoperative pain[1], and 80% of Australians suffer back and neck pain at some point in their lives.[2]



In Australia, OTC codeine-containing combination analgesic products have been used for some years for the treatment of moderate to severe pain. In May 2010 amendments to the scheduling of codeine came into play, such that all codeine combination products for analgesia were up-scheduled to Schedule 3 and maximum pack sizes were reduced to not more than 5 days' supply.

This education module specifically addresses the quality use of medicines and the supply of Schedule 3 codeine-containing combination analgesics for acute pain management. It provides data on the efficacy and safety of these products while focusing on appropriate strategies to enhance pharmacists in their role in providing advice and guidance to customers.

SCIUS Solutions

Written and produced by the education provider Scius Solutions Pty Ltd,
Level 1, 357 Military Road, Mosman, NSW 2088. Telephone: 02 9904 1077.

Learning Objectives

Summary

After completing this module and the associated assessment, the pharmacist will:

- Be able to describe how codeine works and how it is converted to morphine to provide pain relief
- Have an up-to-date knowledge on the efficacy of OTC codeine combinations
- Understand the suitability and precautions associated with the use of codeine combination products
- Be better equipped to support the quality use of OTC codeine products in the management of acute, self-limiting pain conditions.

Competencies addressed: 1.3, 2.1, 7.1, and 7.3

How To Earn CPD Points

Accreditation number: CX130050

AUSTRALIAN PHARMACY COUNCIL
ACCREDITED CPD

This education activity has been accredited by the Pharmaceutical Society of Australia on behalf of the Australian Pharmacy Council for **1 hour of group 2 CPD points.**
A total of **2 Group 2 CPD credits** will be awarded for successful completion of this program (75% pass mark).

At the end this program there is a short assessment. To obtain CPD credits, carefully read through the program and then complete the assessment sheet. Once completed, please fax the assessment sheet to 02 9904 1322. Assessments will be accepted up to 1 August 2015.

FAX-BACK FORM
02 9904 1322

GlaxoSmithKline

Pre-activity Survey (Page 1 of 1)

UP-TO-DATE IN THE PHARMACY

QUM and OTC codeine-containing combination analgesics

Accreditation Activity Number: CX130050

Instructions

- **Complete this survey BEFORE you start the education program.**
- Please complete your name and address details in the space provided below.
- Please mark your answers to the questions using the grid below.
- Once you have completed the survey, please detach and fax this page only to **02 9904 1322.**

Your Details

First Name | Surname

Address

Suburb | State | Postcode

Email Address

PSA Membership No.

Answer Grid

Please mark your answers by filling in the appropriate circle with black pen below.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I am confident in my ability to discuss codeine combination analgesics with customers in my Pharmacy	○	○	○	○	○
There are data to support the efficacy of OTC codeine-containing combination analgesics	○	○	○	○	○
Potential harms associated with the overuse of OTC codeine-containing analgesics are only related to the codeine content	○	○	○	○	○
Differences in CYP2D6 phenotype may affect both the efficacy and toxicity of codeine	○	○	○	○	○
There is a system or policy in place in my pharmacy to discuss codeine requests with all customers	○	○	○	○	○

Remove this page and follow instructions as provided

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Module overview

This module addresses the pharmacist's role in the supply of OTC codeine-containing combination analgesics. It is divided into the following key sections:

Section	Key Points
Back to basics: Codeine	Codeine is a pro-drug; O-demethylation of codeine into morphine is essential for its analgesic activity.[3] Codeine conversion is dependent on a patient's individual pharmacogenetics.[3-5] Pharmacogenetic differences in drug metabolism can lead to variability in response to codeine, altering its efficacy and/or tolerability.[4] Poor metabolisers receive little or no analgesic benefit whilst ultra-rapid metabolisers receive enhanced efficacy with low doses of codeine and are at risk of experiencing adverse effects.
Efficacy of codeine-containing combination analgesics	Cochrane reviews of paracetamol plus codeine[6] and ibuprofen plus codeine[7] have established that these combinations are effective. Clinical studies demonstrate that codeine-containing combination analgesics at OTC doses are more efficacious than placebo[8, 9] or single ingredient analgesics.[10-12]
Safety considerations for codeine-containing combination analgesics	Patients should be alerted to the potential harms of all the medicines in codeine-containing combination analgesics.[13] Problems and harms associated with the overuse of OTC codeine-containing analgesics can be related to the codeine itself or to other active ingredients in the formulation.[14] Common adverse effects of codeine become more likely with higher or repeated doses.[15] The risk of addiction with continued codeine use leads to escalation of daily doses,[16] potentially leading to exposure to supratherapeutic doses of paracetamol or ibuprofen.[15]
Managing and assessing the need for a codeine-containing combination analgesic	It is important to be vigilant for customers who appear to be using higher than recommended doses of OTC codeine-containing analgesics over a longer period of time than recommended.[16] Setting up a pharmacy policy to assess increased risk when handling customer requests for OTC codeine products provides a professional framework within which all pharmacy staff can address this important issue. When a customer presents asking for a codeine-containing combination analgesic, assess their needs to satisfy yourself that the supply of the medication is appropriate and counsel them on its use. Clinical interventions are not restricted to prescription medicines; recording the interaction with the customer using an appropriate template or system underscores your commitment to improving the quality use of medicines.

Back to Basics

Codeine metabolism

Figure 1 shows the metabolic pathways of codeine biotransformation.[3]

Conversion of codeine into norcodeine by CYP3A4 and into codeine-6-glucuronide by glucuronidation is the major metabolic pathway, accounting for around 80% of codeine clearance.

Codeine is a pro-drug; it exerts its analgesic effect after metabolism to morphine.[3] O-demethylation of codeine into morphine by CYP2D6 is a minor pathway, representing only 10% of codeine metabolism; but it is essential for its analgesic activity.

Morphine is then further metabolised into morphine-6-glucuronide and morphine-3-glucuronide. Morphine and morphine-6-glucuronide have opioid activity.

Codeine is also metabolized to hydrocodone via an unknown mechanism. The clinical effect of this metabolite is unknown.[4]

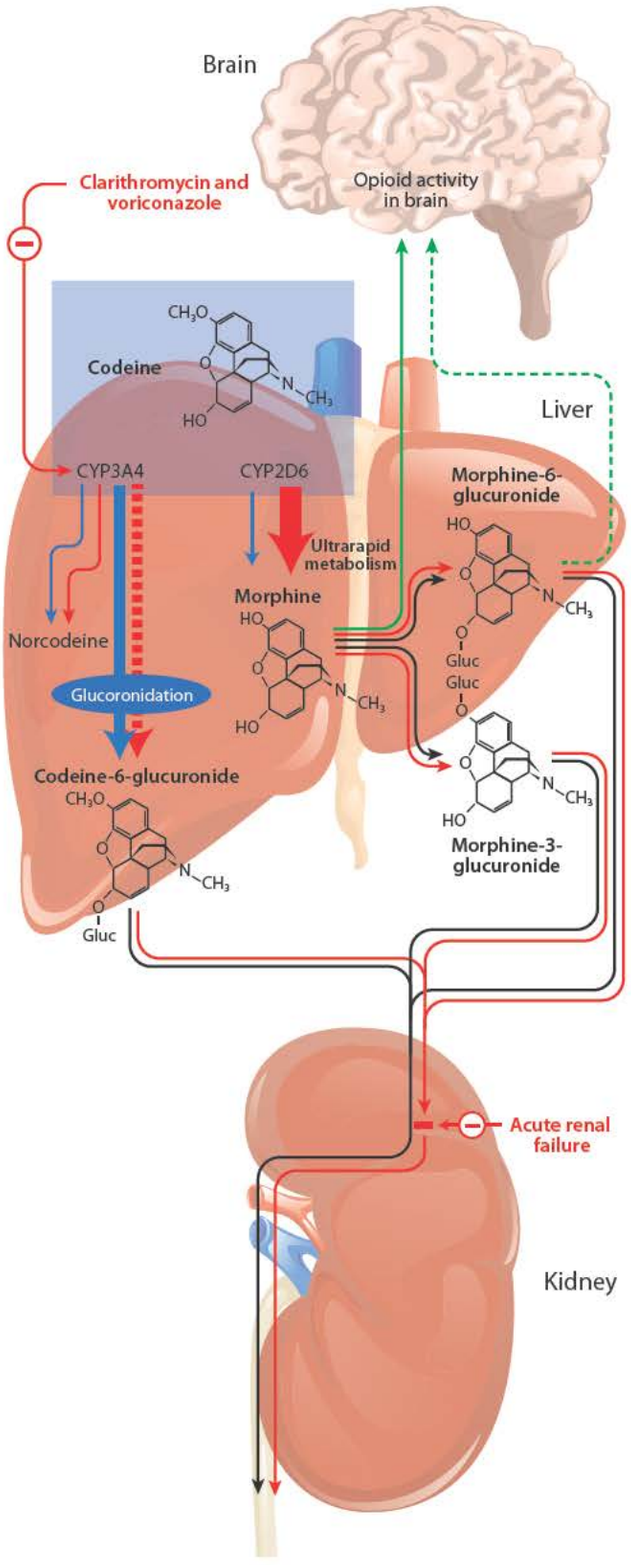

Figure 1: Codeine metabolic pathways. Adapted from 3

Impact of CYP2D6 genetic variants on analgesic effect

Codeine conversion is dependent on a patient's individual pharmacogenetics.[3-5] People with genetic variants that lead to low CYP2D6 activity convert less codeine to morphine, whilst those with duplicated or amplified CYP2D6 can convert more codeine into morphine. Altered metabolism can result in codeine or its active metabolites leaving the body too rapidly, not reaching its therapeutic target, or staying in the body too long and potentially producing side effects.[4]

The association between CYP2D6 metaboliser phenotype and the formation of morphine from codeine is well-defined.[5] In ultra-rapid metabolisers the concentration of codeine metabolites (morphine, morphine-3-glucuronide and morphine-6-glucuronide) can be up to 45 times as high as in those with poor metabolism.[3]

Table 1: Impact of genetic variation in CYP2D6 on the analgesic actions of codeine[4,5]

Population	Variation in CYP2D6 gene	Impact on metabolism	Clinical effect
5-10% Caucasians ≤ 1% Asians 0-34% Africans	2 x non-functional alleles	Poor	⬇ (or no) analgesic benefit
1-7% Caucasians 9-30% Africans	Duplicated or amplified active genes	Ultra-rapid	Enhanced analgesic effect due to ⬆ morphine production and ⬆ risk of side effects and toxicity

Codeine adverse effects may occur irrespective of morphine concentrations and toxicity has been reported in poor and rapid metabolisers.[4] Ultra-rapid metabolisers are at increased risk due to the potential for accumulation of toxic blood levels of morphine.[17]

> Pharmacogenetic differences in drug metabolism can lead to variability in response to codeine, altering its efficacy and/or tolerability.[4]

OTC codeine-containing combination analgesics

The scheduling of codeine-containing combination analgesics is determined by the dose of codeine per tablet, the total number of tablets per pack and other drugs in the combination. The following table provides an overview of currently available OTC codeine-containing analgesic products. Current scheduling allows for a maximum of five days of treatment at the maximum daily dose.

Table 2: OTC codeine-containing analgesics

Combination product	Schedule	Tablets per pack	OTC dosage
Paracetamol (500mg), codeine (8mg)	S3	≤40 tablets	1-2 tabs every 3-4 hours, max 8 tabs in 24 hours
Paracetamol (500mg), codeine (15mg)	S3	≤40 tablets	2 tabs every 4-6 hours, max 8 tabs in 24 hours
Ibuprofen (200mg), codeine (12.8mg)	S3	≤40 tablets	2 tablets every 4-6 hours, max 6 tablets in 24 hours
Paracetamol (500mg), codeine (10mg), doxylamine (5.1mg)	S3	≤20 tablets	1-2 tabs every 4 hours, max 8 tabs in 24 hours

Efficacy of OTC codeine combination analgesics

Codeine is a short-acting weak opioid. Its onset of action is within 15-30 minutes and analgesia is maintained for 4-6 hours.[18] Combining two analgesics with different modes of action affords increased analgesia while reducing the likelihood of side effects.[12] The majority of studies assessing the efficacy of codeine-analgesic combinations have used high (≥60mg) codeine doses.[6,7] The lowest dose of codeine required to produce significant analgesia is not well-defined.[19]

Cochrane reviews

Paracetamol plus codeine: Data from 26 studies comparing paracetamol plus codeine with placebo and 14 studies comparing paracetamol plus codeine with the same dose of paracetamol alone.[6]

Combining paracetamol (300-1000mg) with codeine (30-60mg) provided clinically useful levels of pain relief in about 50% of patients with moderate to severe postoperative pain, compared with under 20% with placebo. The combination has also been shown to extend the duration of analgesia by about one hour compared to treatment with the same dose of paracetamol alone.

Although there were only a small number of studies, more participants experienced adequate pain relief with the usual prescription dose (1000mg paracetamol plus 60mg codeine) than with the same dose of codeine combined with less paracetamol.

Ibuprofen plus codeine: Data from 6 studies comparing ibuprofen plus codeine versus placebo and/or active comparators.[7]

Combining ibuprofen (400mg) with high doses of codeine (25.6-60mg) provided effective pain relief for over 6 in 10 (64%) of patients, compared with just under 2 in 10 (18%) with placebo. The number-needed-to-treat was 2.2 (95% CI 1.8 to 2.6).

In three studies ibuprofen plus codeine (any dose) was better than the same dose of ibuprofen (69% versus 55%) but the result was barely significant with a relative benefit of 1.3 (95% CI 1.01 to 1.6).

In two studies (159 participants) ibuprofen plus codeine appeared to be better than the same dose of codeine alone (69% versus 33%), but no analysis was done. Very limited data suggest that the combination is better than the same dose of either drug alone.

Published studies

When assessing the efficacy of codeine-containing combination analgesics, it is important to look at the dose of each component used. For example, a randomized controlled study comparing paracetamol (1000mg), with paracetamol plus ibuprofen (1000mg/400mg) and paracetamol plus codeine (325mg/30mg) found the paracetamol-ibuprofen combination to be superior.[20] However, the dose of paracetamol used in the codeine combination was much lower than in OTC preparations available in Australia.

Several published studies provide evidence of effective pain relief when standard OTC doses of paracetamol (500mg)[9-12] or ibuprofen (200mg)[8, 9] are combined with doses of codeine (≤15 mg) such as those found in OTC fixed-dose codeine combination analgesics.

Patients express significant preference for paracetamol-codeine over aspirin alone.[10]

In a study comparing paracetamol plus codeine (1000mg/16mg) with aspirin (1000mg), 26 (42%) of the 61 subjects involved preferred the paracetamol-codeine combination whereas only 6 (10%) preferred aspirin.[10] Importantly, there were more occurrences of occult blood in the stools during treatment with aspirin than with the paracetamol-codeine combination — 33 vs 7 (Figure 2).

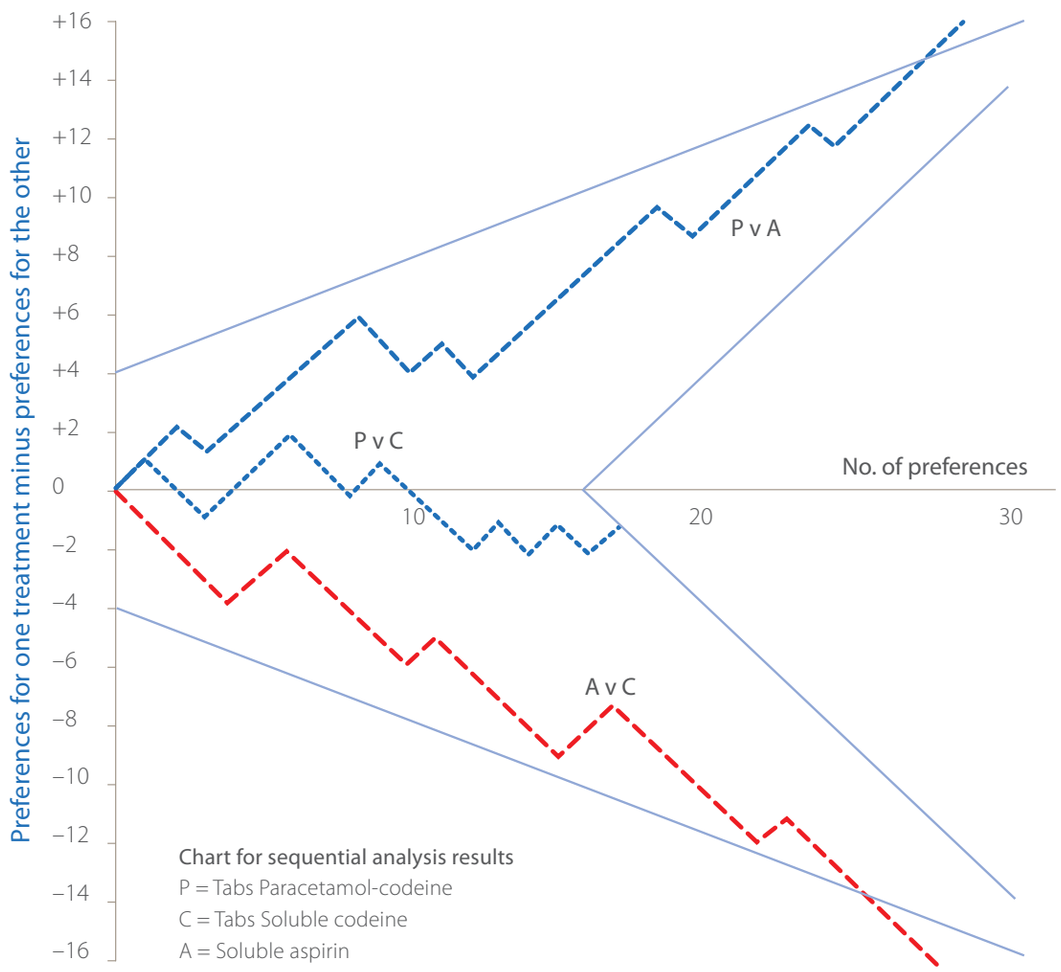

Figure 2: More patients preferred paracetamol-codeine over aspirin alone. Adapted from 10.

OTC ibuprofen-codeine superior to both placebo and aspirin.[8]

A single dose of ibuprofen plus codeine (200mg/15mg) was significantly ($p<0.05$) more effective than either placebo or aspirin 600mg after surgical removal of impacted third molars. Two hours after taking this medication, 62% of patients had achieved adequate pain relief (pain half gone) compared with only 32% of those who had taken aspirin and 14% of those who had taken placebo.

OTC paracetamol-codeine combination shown to be as effective as NSAIDs.[11]

A single dose of paracetamol plus codeine (500mg/8mg), taken every 6-8 hours for 24 hours, was demonstrated to be just as effective as the NSAID etodolac (200mg, taken every 6-8 hours) at relieving pain associated with the surgical removal of impacted third molars.[11] All patients used a 100mm graded horizontal visual analogue scale (VAS) to measure pain intensity. For each study drug, there were significant differences in VAS scores over the five time intervals (Figure 3).

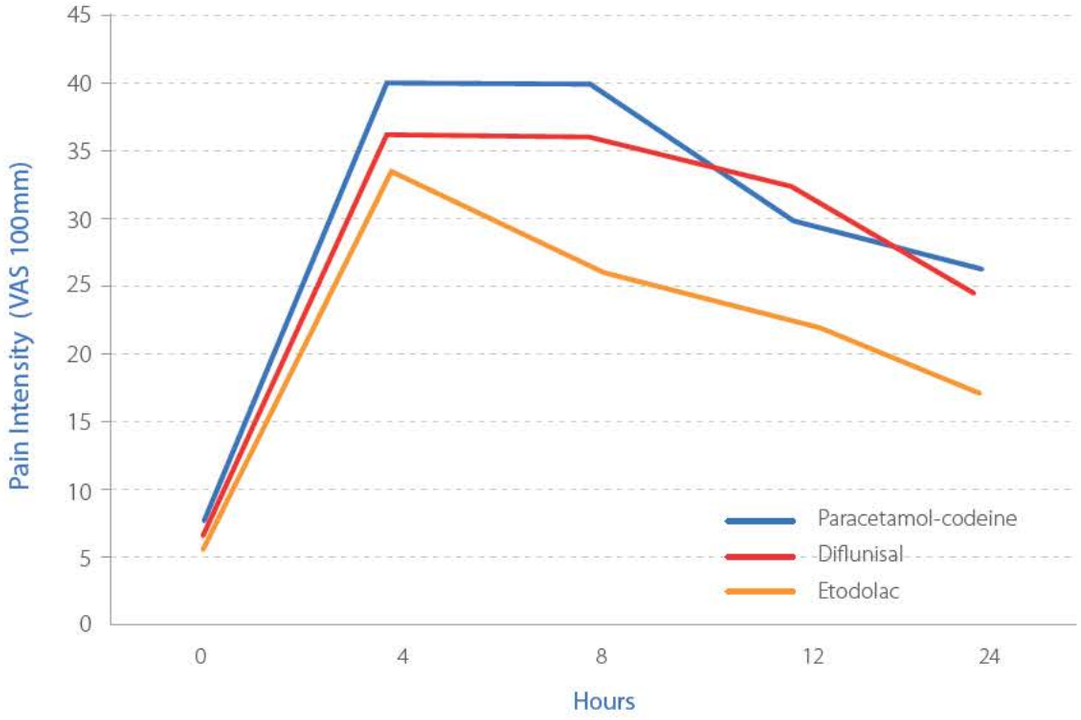

Figure 3: Mean pain scores. Adapted from 11.

OTC paracetamol-codeine more effective than paracetamol alone.[12]

A study found that 2 tablets of paracetamol plus codeine (500mg/15mg) were significantly more effective than paracetamol (2 x 500mg) at relieving pain associated with the surgical removal of impacted third molars.[12] In patients who took three doses of these medications (the first dose 1 hour after their surgery and then two further doses at 4-hourly intervals) and recorded their pain intensity at hourly intervals for 12 hours, the average increase in pain intensity over the 12-hour study period was only 0.45 cm/h in the paracetamol-codeine group compared with 1.81 cm/hr in the paracetamol group.

Patients receiving the paracetamol-codeine combination had significantly better pain control than patients receiving paracetamol alone (p = 0.03). There was no significant difference in the incidence of adverse events between the two treatment groups, and no adverse events were deemed to be directly related to the study medications (Figure 4).

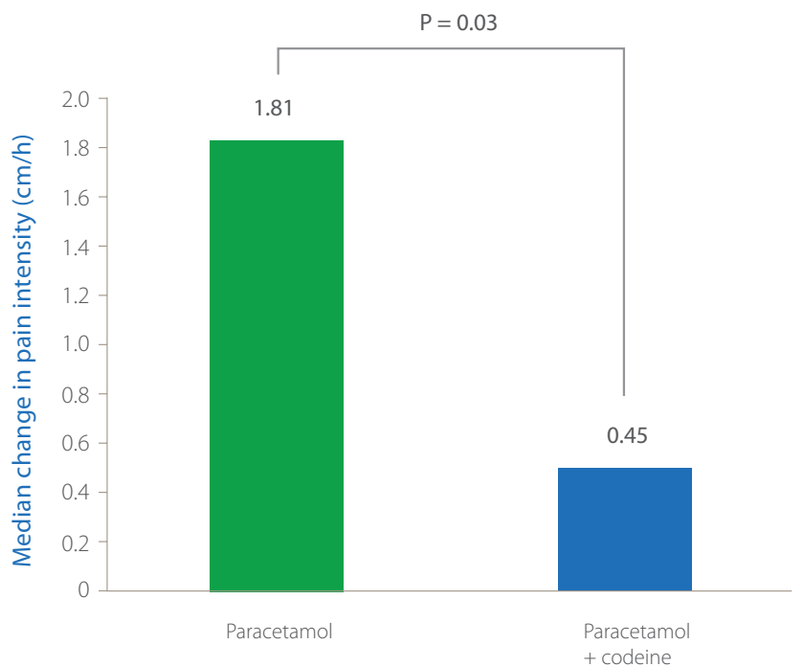

Figure 4: Greater pain relief with paracetamol-codeine versus paracetamol alone. Adapted from 12.

OTC paracetamol-codeine and ibuprofen-codeine more effective than placebo.[9]

In a single-dose comparative efficacy study, 2 tablets of paracetamol plus codeine (500mg/15mg), and 2 tablets of ibuprofen plus codeine (400mg/12.8mg), were both significantly more effective than placebo at relieving pain associated with the surgical removal of impacted third molars.[9] The median time to pain half gone was 45 minutes with either combination product compared to 300 minutes with placebo.

This study found that a combination of paracetamol plus ibuprofen was superior to the codeine-based combination analgesics. This combination might provide a useful alternative for patients not wishing to take codeine. However, appropriate recommendation should be made only after considering the warnings, precautions and contraindications and determining the suitability of both active ingredients.

Safety consideration with OTC codeine combination analgesics

Whilst OTC analgesics are substantially safe for the vast majority of the population when used at recommended doses, it is important to be vigilant with regard to relevant safety considerations.

Problems and harms associated with the overuse of OTC codeine-containing analgesics fall into three broad categories (Figure 5):[14]

- Harms related to the codeine itself
- Harms related to the other active ingredient in a compound formulation
- Problems related to other consequences.

General Safety

Common adverse effects of codeine include nausea, vomiting, constipation, drowsiness and dizziness; they become more likely with higher or repeated doses.[15] The use of repeated doses of codeine should be avoided in breastfeeding women;[21] toxic blood levels of morphine may arise in mothers and neonates that are ultra-rapid metabolisers.[17] It is recommended that codeine should only be used in breastfeeding women on medical advice. This advice should include counselling on how to recognise signs of morphine adverse effects, in particular symptoms suggestive of respiratory depression in neonates.

Chronic use of combination analgesics used to treat headaches may lead to rebound headaches.[14]

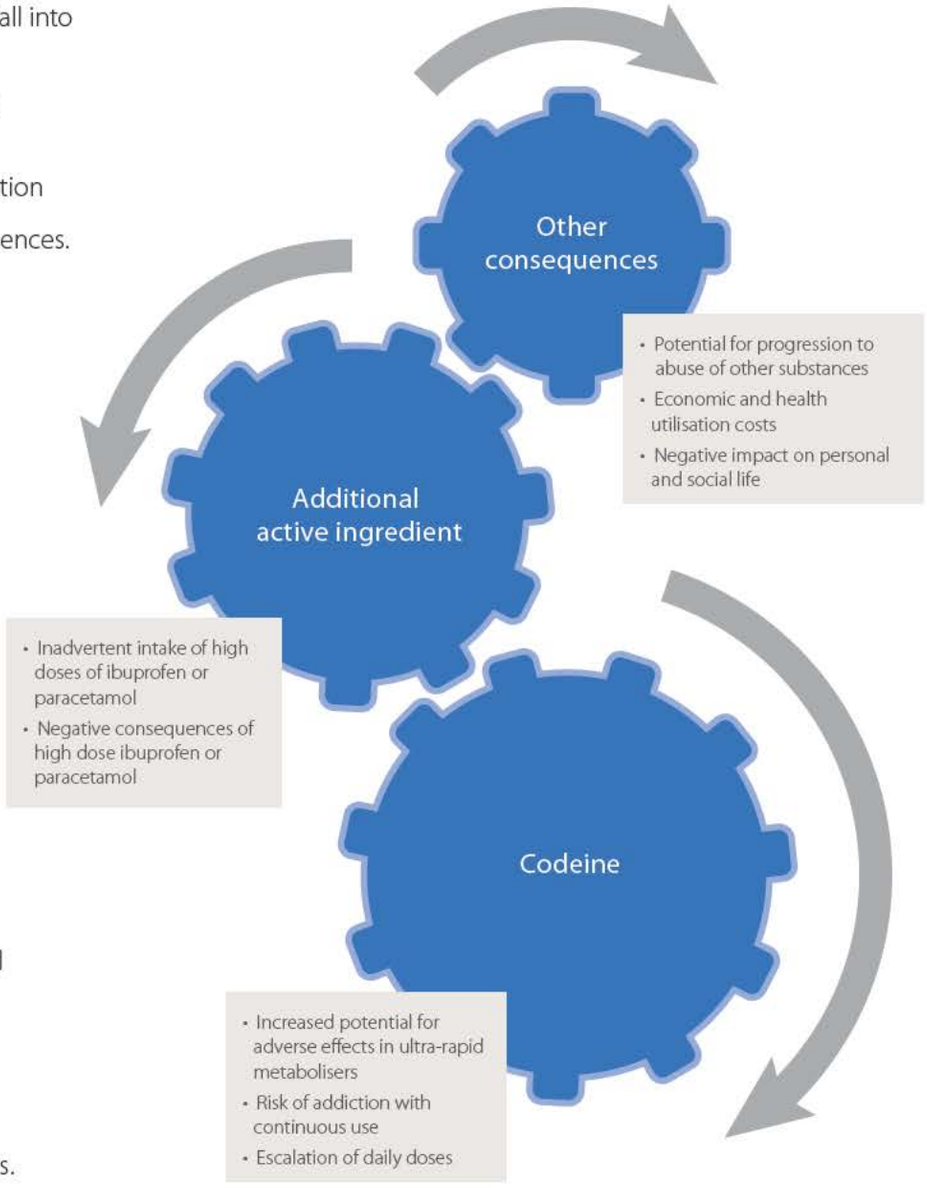

Figure 5: Potential problems and harms associated with the overuse of OTC codeine-containing analgesics. Adapted from 14.

Misuse

The risk of addiction with continued codeine use leads to escalation of daily doses; data suggests that some codeine-dependent patients may be taking at least 10 times the recommended dose of OTC codeine combination analgesics.[16]

Overuse of codeine-containing combination analgesics may result in exposure to supratherapeutic doses of paracetamol or ibuprofen.[15] This, in turn, is associated with substantial negative impact:

- Liver toxicity may result from paracetamol overdose
- Gastrointestinal complications, hypokalaemia, acidosis and anaemia have been reported with high intakes of codeine-ibuprofen combination analgesics.[22]

> **Patients should be alerted to the potential harms of all the medicines in codeine-containing combination analgesics.[13] The paracetamol content of all medications must be considered as should the major adverse effects and suitability of NSAIDs in high-risk patients.[21]**

Opioid dependence and harms from overuse

Although data are limited, compared to the volume of products sold, OTC medications are relatively rare as primary substances of abuse.[14] An internet-based survey conducted to investigate OTC codeine use in Australia identified 800 participants who used these products.[16] The Severity of Dependence Scale was used to classify patients as to their level of codeine dependency – 83% of patients were found to be not codeine-dependent.

Of the 17% that were classified as potentially codeine-dependent, almost two-thirds reported taking more than the recommended dose and most reported using these products on a daily basis over an extended period of time (1-3 years). Compared to non-dependent users, codeine-dependent users were also shown to be younger, had a lower educational level, were less likely to be in full-time employment, and more likely to have previously used illicit drugs or have a family member with a history of drug or alcohol problems.

Table 3: Characteristics of OTC codeine-dependent people reported in Australian and New Zealand literature[16, 23]

Age	Commonly mid-late 30s/40s
Gender	58% female
Common co-morbidities	Chronic pain, mental health, alcoholism
Dose ranges	16->100 tablets/day
Setting identified	Commonly identified through emergency department presentations or hospital referrals to addictions services

Identifying high-risk patients

A significant proportion of patients with serious morbidity associated with misuse of OTC codeine combination analgesics reported initiating use for common painful conditions, such as back ache and headaches.[22] The dose was subsequently escalated by the patient.

It is important to recognize that these patients may have no history of illicit drug use. For example, in a published Australian series, that examined the consequence of prolonged use of supratherapeutic doses of OTC ibuprofen/codeine, most patients reported no history of previous drug or alcohol treatment, and around half had no history of other current or past illicit substance use.[22]

Warning signs for the development of problematic use of OTC codeine-containing analgesics include customers who:[24]

- purchase these products more regularly than would appear necessary for short-term pain relief or over long periods of time
- are buying large quantities or making purchases from multiple pharmacies
- appear intoxicated
- complain of adverse effects, such as gastritis, that are associated with the use of high doses of NSAIDs.

Recent UK-based research has demonstrated that frequency of purchase is a key factor that alerts Pharmacists and Pharmacy Assistants to suspect OTC medicine abuse.[25] Other factors included overfamiliarity with the medicine details and negative reactions to a refused or referred sale.

Characteristics associated with potential dependence on OTC codeine-containing analgesics include using higher than recommended doses over a longer period of time than recommended.[16]

Managing and assessing the need for a codeine-containing analgesic

Assess the patient's needs

When a patient presents asking for a codeine-containing combination analgesic, first assess their needs by considering their symptoms, the duration of the symptoms, lifestyle and medical history, and prior treatment.

- What are the main symptoms or causes of your pain? Codeine-containing combination analgesics are indicated for the temporary relief of moderate to severe pain associated with headaches, dental surgery, toothache, dysmenorrhea, musculoskeletal pain, earache, neuralgia, cold and flu symptoms, sore throat.
- How strong is the pain? Ask the patient to describe the pain and rate the severity on a scale of 0 to 10 (where 0 is no pain and 10 is the worst possible pain).
- How long have you had this pain? OTC analgesics are indicated for short-term use in self-limiting conditions. Patients presenting with chronic pain, recurrent episodes of the same pain, more severe pain or complex pain states such as neuropathic pain should be referred to their GP for further advice.[21]
- Have you used any other pain medicine before trying this one? Establish existing patterns of codeine use; prior treatment with a codeine-based analgesic does not necessarily indicate it is an appropriate treatment choice.[18]

Universal precautions

It is difficult to identify codeine-dependent people on appearance alone. To overcome this, it has been suggested that a preventative approach be taken to codeine sales.[23] This involves ensuring that all patients are:.

- aware that these medications are used for short-term symptomatic pain relief
- informed of the risks associated with codeine use, including the potential for addiction
- informed about the risks associated with taking high doses of ibuprofen and paracetamol
- assessed for indicators of increased risk of developing dependence.

Setting up a pharmacy policy to assess increased risk when handling customer requests for OTC codeine products provides a professional rationale rather than a targeted response based on customer appearance or other external features.[23] Such an approach will also help to establish the assessment as routine and normal, thereby depersonalising the interaction and helping to limit negative issues when considering not supplying a request for OTC codeine.

Developing a pharmacy policy

When developing a policy for the supply of codeine-containing combination analgesics, consider the following key points:

Assess	Commonly mid-late 30s/40s
Counsel	Advise the customer that it is important to follow the dosage instructions on the pack and not to exceed the stated dose. Codeine can cause constipation, nausea, dizziness and drowsiness according to dosage and individual susceptibility. OTC codeine-containing analgesics are for short-term use only, prolonged regular use may lead to physical and psychological dependence. Codeine-containing products should not be taken while breast-feeding unless under the supervision of a doctor. Frequent use of pain-relievers for persistent headaches may make them worse; offer advice, information leaflets and refer to a doctor. Offer alternative products, treatments or advice to people seeking codeine-containing products, where you believe a codeine-containing product to be inappropriate.
If misuse is suspected	Have useful numbers and information leaflets to hand. Politely but firmly inform the patient that you cannot recommend any codeine-containing medicine for them and suggest they talk to their doctor.

Every time a codeine–containing analgesic is supplied the pharmacist must be satisfied that, in his/her professional judgment, the supply of such a medicine is the most appropriate treatment available at the time and that such supply is in the best interest of the patient.

Consider a clinical intervention

A clinical intervention is defined as 'a professional activity by the pharmacist directed towards improving the quality use of medicines'; it need not be restricted to prescription medications. Dealing with customer requests for codeine-containing combination analgesics, particularly where overuse is suspected, provides an opportunity to conduct a clinical intervention. Doing so demonstrates a high level of commitment to the health and well-being of the customer, whilst helping to diffuse a potentially negative or confrontational situation.

A paper-based form for recording clinical interventions can be downloaded from the PSA website (http://www.psa.org.au/download/practice-guidelines/Clinical-Interventions-paper-based-recording.pdf).

If you are developing your own recording system, ensure that you include the following:

- Date of the intervention
- Name or initials of pharmacist who performed the intervention
- Medicines which are relevant to the intervention
- Customer details:
  - > Patient identifier [e.g. name or number]
  - > Age range and gender
  - > Relevant medical history
- Any communication with the customer's doctor or other health professionals.
- Outcome (or expected outcome) of intervention and any follow-up
- Classification of the drug-related problem and recommendation; the most likely problem and recommendation classifications are:
  - > C2 – overuse by consumer
  - > C4 – intentional drug misuse
  - > T1 – Toxicity, allergic reaction or ADR present
  - > R9 – refer to prescriber
  - > R10 – refer to hospital
  - > R13 – Education or counselling session.

Communication and collaboration

The key to effective pain management is communication and collaboration. Once you've established the cause, duration and severity of the patient's pain, discussed prior treatments and satisfied yourself that they do not have any red flags suggestive of abuse or addiction or toxicity, you can make a suitable analgesic recommendation. However, pain management advice doesn't end with the sale of the product. To ensure appropriate use, provide advice on how many to take, when to take it and any special precautions (such as not using two paracetamol-containing products together).

It is particularly important to provide advice on the risks of exceeding the recommended dose or for taking codeine-containing combination analgesics for longer than recommended.

Also, use this as an opportunity to set realistic expectations with the patient (how long it will take for the pain to ease) and counsel them to come back for re-assessment if the symptoms persist for longer than 48 hours despite taking the medication as recommended.

Figure 6 shows an algorithm for the treatment of most patients with acute pain in the Pharmacy, with emphasis on key considerations when responding to requests for codeine-based products.

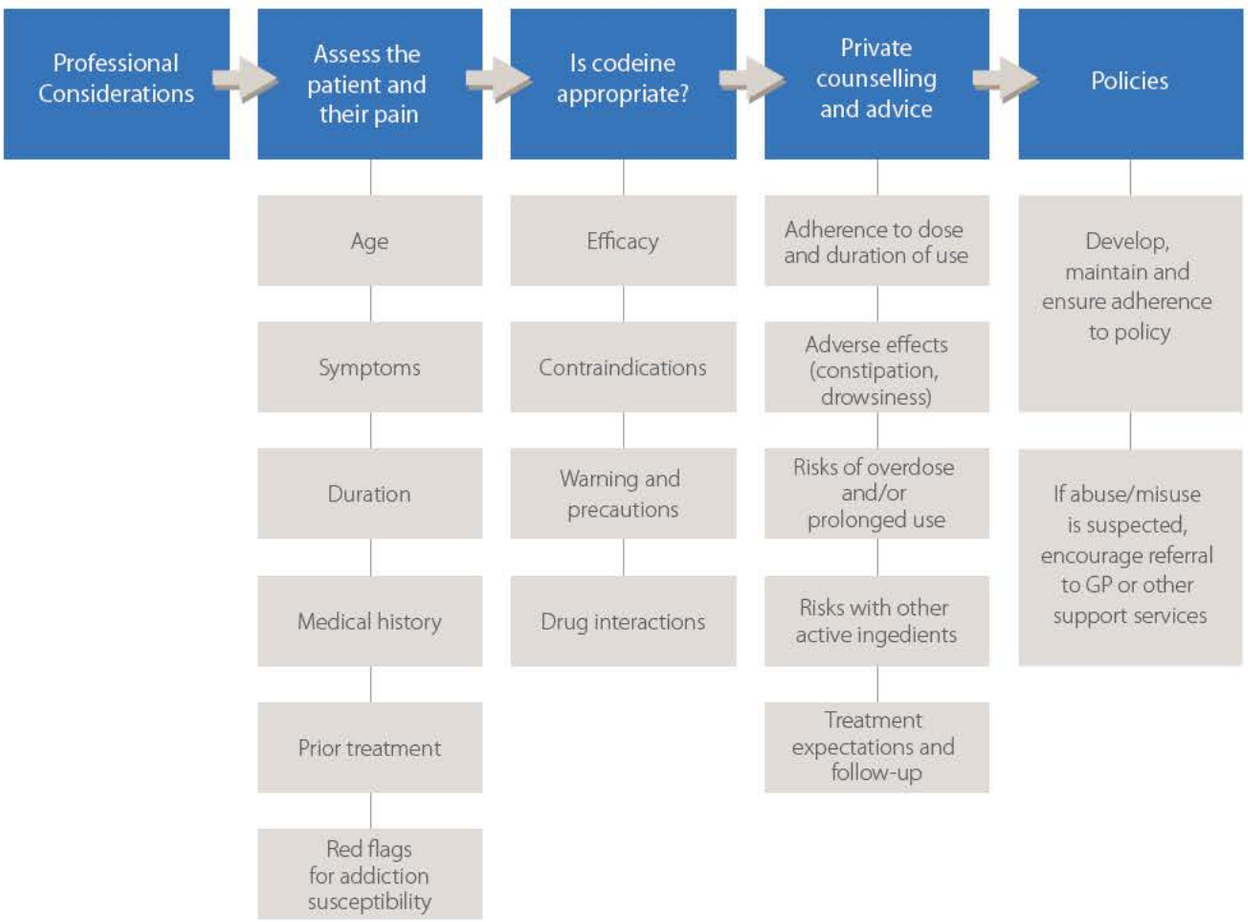

Figure 6: Pharmacy management of acute pain and the use of OTC codeine analgesics

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Notes

Notes

Assessment Questions

Accreditation Activity Number: CX130050

Each question has only ONE correct answer.

Q1. What proportion of codeine is metabolized via CYP2D6?

A. 5%
B. 10%
C. 15%
D. 20%
E. 30%

Q2. Which patients obtain an enhanced analgesic effect when taking codeine?

A. Poor metabolisers
B. Ultra-rapid metabolisers
C. Those with normal morphine formation
D. All patients obtain the same level of analgesia
E. Only patients with non-functional CYP2D6 alleles

Q3. The scheduling of codeine-containing combination analgesics is determined by:

A. Codeine dose
B. Number of tablets per pack
C. Other drugs in the combination
D. A, B and C
E. None of the above

Q4. Which of the following statements is NOT true:

A. A Cochrane review supports the efficacy of paracetamol-codeine combination analgesics
B. A Cochrane review lends support to the efficacy of ibuprofen-codeine combination analgesics
C. There are no studies of evaluating the efficacy of codeine-containing analgesics containing <15mg codeine
D. Available data support the efficacy of paracetamol-codeine at OTC doses
E. Available data support the efficacy of ibuprofen-codeine at OTC doses

Q5. In a study looking at OTC paracetamol-codeine and ibuprofen-codeine, how long did it take for patients' pain to be relieved by half (time to pain half gone)?

A. 15 minutes
B. 30 minutes
C. 45 minutes
D. 60 minutes
E. 300 minutes

Q6. Potential harms associated with the overuse of OTC codeine-containing analgesics are only related to…

A. Pharmacological or psychological effects of the codeine
B. Adverse effects of another active ingredient in the compound formulation
C. Other consequences such as economic and social costs
D. A, B and C
E. None of the above

Q7. In a survey of OTC codeine users, what proportion of the respondents were found to be codeine-dependent?

A. 17%
B. 27%
C. 35%
D. 58%
E. 83%

Q8. Which of the following are warning signs for the development of problematic use of OTC codeine-containing analgesics?

A. Frequency of purchase or purchase over long periods of time.
B. Purchase of large quantities or making purchases from multiple pharmacies
C. Appear intoxicated
D. Complaining of adverse effects such as gastritis.
E. All of the above

Q9. True or false? It is particularly important to provide advice on the risks of exceeding the recommended dose, or for taking codeine-containing combination analgesics for longer than recommended.

A. True
B. False

Q10. What is the rationale for setting up a pharmacy policy to handle all customer requests for OTC codeine-containing analgesics?

A. It negates the need to makes decisions based on the customers appearance alone
B. It provides a professional framework within which you can address all such requests
C. It may help to depersonalise negative interactions
D. It helps to establish the assessment as routine and normal
E. All of the above

Q11. True or false? Clinical interventions only apply to prescription medications

A. True
B. False

Q12. When supplying a codeine-containing combination analgesic, which of the following actions is appropriate?

A. Satisfy yourself that the supply of this medicine is in the best interest of the patient.
B. Provide advice on the recommended dose
C. Provide specific advice on the risks of exceeding the recommended dose and duration
D. Set realistic expectations regarding how long it will take for the pain to ease and when to come back for re-assessment
E. All of the above

Notes

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Assessment Form (Page 1 of 2)

UP-TO-DATE IN THE PHARMACY

QUM and OTC codeine-containing combination analgesics (Accreditation No. CX130050)

Education Provider: Scius Solutions Pty Ltd Sponsor: GlaxoSmithKline Consumer Healthcare Australia

Instructions

- Please complete your name and address details in the space provided below.
- Please mark your answer to the assessment questions using the grid below. **Each question has only ONE correct answer.**
- Once you have completed the survey, please detach and fax **BOTH** Assessment Form pages to **02 9904 1322.**
- The closing date for submission of assessment forms is 1 August 2015.

Your Details

First Name	Surname		
Address			
Suburb		State	Postcode
Email Address			
PSA Membership No.			

Section 1

Please mark your answers by filling in your preferred response with black pen below. Please provide comments if appropriate.

To what extent have the learning objectives for this activity been met?	Not Met	Partially Met	Entirely Met
To describe how codeine works and how it is converted to morphine to provide pain relief	○	○	○
To have an up-to-date knowledge on the efficacy of OTC codeine combinations	○	○	○
To understand the suitability and precautions associated with the use of codeine combination products	○	○	○
To be better equipped to support the quality use of OTC codeine products in the management of acute, self-limiting pain conditions.	○	○	○
Rate to what degree your overall learning objectives where met?	○	○	○

How relevant was the content of this program to your practice?	Not Relevant	Partially Relevant	Entirely Relevant
Comments	○	○	○

Please rate your overall satisfaction with this activity	Not Satisfied	Partially Satisfied	Entirely Satisfied
Comments	○	○	○

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Assessment Form (Page 2 of 2)

Section 1 *(cont'd)*

Please mark your answers by filling in your preferred response with black pen below. Please provide comments if appropriate.

Please rate the suitability of the delivery of this activity	Not Suitable	Partially Suitable	Entirely Suitable
Comments	○	○	○

Section 2

Use the following grid to answer the Assessment Questions provided on pages 33-34 of this booklet.
Please mark your answers by filling in the appropriate circle with black pen below.

Q1.	A	B	C	D	E	Q7.	A	B	C	D	E
Q2.	A	B	C	D	E	Q8.	A	B	C	D	E
Q3.	A	B	C	D	E	Q9.	A	B	C	D	E
Q4.	A	B	C	D	E	Q10.	A	B	C	D	E
Q5.	A	B	C	D	E	Q11.	A	B	C	D	E
Q6.	A	B	C	D	E	Q12.	A	B	C	D	E

Section 3

Having completed this activity, please mark your answers by filling in the appropriate circle with black pen below.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I am confident in my ability to discuss codeine combination analgesics with customers in my Pharmacy	○	○	○	○	○
There are data to support the efficacy of OTC codeine containing combination analgesics	○	○	○	○	○
Potential harms associated with the overuse of OTC codeine-containing analgesics are only related to the codeine content.	○	○	○	○	○
Differences in CYP2D6 phenotype may affect both the efficacy and toxicity of codeine	○	○	○	○	○
There is a system or policy in place in my pharmacy to discuss codeine requests with all customers	○	○	○	○	○

Declaration

I have completed the QUM and OTC codeine-containing combination analgesics module and my assessment responses are provided above.

First Name

Surname

Signature

Date

Remove this page and follow instructions as provided

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Notes

As part of its commitment to Pharmacists' education, GlaxoSmithKline Consumer Healthcare has sponsored the development of **UP-TO-DATE IN THE PHARMACY.**

Written and produced by the education provider Scius Solutions Pty Ltd, Level 1, 357 Military Road, Mosman, NSW 2088. Telephone: 02 9904 1077.

TGA,

136 Narrabundah Lane,

Symonston ACT 2609,

Australia

medicines.scheduling@tga.gov.au

7th May 2015

Dear Sir or Madam

I write to **support** the re-scheduling of codeine to Schedule 4.

I am a general practitioner who has worked in a rural practice in central Victoria for over a decade. In addition to this clinical role, I have also worked for many years as a medical educator, with a special interest in addiction medicine, teaching at the medical student, vocational registrar and continuing professional development levels. I have been a member of the RACGP's Victorian Drug and Alcohol committee (current Chair) and am also a member of the RACGP National Faculty of Specific Interest's Addiction Medicine network.

I am a co-signatory of a separate joint submission which outlines my many of my concerns with the current scheduling of combination-codeine products as Schedule 3.

I regularly teach GP registrars and international-graduate community GPs about prescribing and the rules behind them. Whenever I explain Schedules 2, 3 4, and 8, I am asked why codeine is Schedule 8 except when in a compounded format. The audience asks (appropriately) why are many dual, or triple, therapy compounded-codeine formulations available without prescription, when in effect, the risk of dependence is the same and the risk of paracetamol or ibuprofen toxicity is possibly higher (due to the risk of codeine dependence leading to too high doses). This is a question I share. It does not make clinical sense.

I believe that it may be useful for the TGA to understand the impact the current combination-codeine's S3 scheduling has on patients and their communities, through three different stories (all de-identified).

> *Laura is a patient in her late 20s, who had struggled through years of anorexia, schizophrenia and a troublesome childhood. Forever struggling with her chronic mental health conditions and their clinical fluctuations, Laura started taking Neurofen Plus® to help initially with her period pains and pain after purging (as part of her eating disorder). Over time, Laura described*

increasing her dose to the point where she was taking two packets a day (48 tablets). She had a significant health team involved in the care of the above, but Katy had decided not to disclose her compounded codeine intake to anyone, other than her pharmacist who had repeatedly suggested she was taking too much. Eventually, Laura presented to an emergency department with 'bad period pains', seeking further analgesia. An astute doctor interpreted her signs and symptoms as that of opioid withdrawal and arranged further workup, which revealed a dangerously low serum potassium level and a peptic ulcer. Her admission was complicated with gastric bleeding, an intensive-care stay after she had life-threatening arrhythmias. She tells me that she 'died twice' during her stay and that she was informed that her excessive ibuprofen intake was the cause of her acute complications. Two weeks later she was discharged to me with an appointment pre-arranged and directions to see me straight after leaving the hospital. She presented shaking, handing over a packet of Neurofen Plus® across my desk, stating "please take these away, I don't want them." According to Laura, despite "not wanting to" she could not resist a compulsion to access and ingest compounded codeine within an hour of discharge. Through a lot of work, she remains in remission from her addiction, through a medicated opioid substitution program.

Liz was booked in to see me, quite embarrassed. She had lost her license following 'yet another speeding fine', and was quite distressed with an obvious tremor, sweating, pacing the room. After some supportive questions, she opened up to describe a twelve month history of codeine 'pharmacy shopping' to support her self-treatment for chronic headaches. Her local pharmacy has refused to dispense any more codeine-containing products after 2-3 months of weekly attendances. This pattern had repeated until Liz found herself driving increasingly greater distances to pharmacies that were not familiar with her. Her loss of license had created a crisis where she couldn't drive to access her over-the-counter codeine and the local pharmacy continued to refuse to dispense the same. She also could no longer visit her elderly father (who lived in a different town) and had to rely upon a neighbour to pick up her children from their (driving distance) secondary school. After accessing medical services, she was able to withdraw from her opioid and was eventually diagnosed with medication-overuse headache. Her father had to move into residential care after a period of deterioration without Liz' assistance.

I was recently called out to our local residential aged care facility. One of the residents, Mrs K age 72, was causing difficulties for the facility's staff. She was repeatedly absconding throughout the week, returning with mildly slurred speech and an unsteady gait. She had refused assessment to this point, but the staff had requested that I review her. Mrs K presented in a mildly drowsy state, with the above features, but was otherwise clinically stable. The staff's history of her 'walks' triggered a thought to check with the town's local (sole) pharmacy – yes, Mrs K frequently purchased over-the-counter combination paracetamol-codeine tablet products. The pharmacist thought that Mrs K was purchasing increased amounts for her less ambulant co-residents, so didn't think to question Mrs K about her use. After some time to develop rapport with Mrs K, and confirmatory urine drug testing, Mrs K admitted to a long standing dependence and eventually stabilised on buprenorphine/naloxone opioid substitution therapy, ceasing her drug-seeking behaviours.

Many other patients have informed me how easy it is to access S3 codeine through pharmacies. They describe the 'routine': "I'm asked the following questions and I know how to answer the questions. The pharmacist never seems to wish to go any further with their assessment than the minimum they have to do.

- "Is this medication for yourself?'
- "Have you had this medication before?"
- "Are you on any other medication?"
- "Do you suffer from asthma?'
- "Make sure you don't take it on an empty stomach"
- "Make sure you don't mix it with any other codeine or paracetamol based products"

Keeping codeine-related products as Schedule 3 will do nothing to assist patients such as those described in this submission. Covert (undisclosed) use, dependence (eg continued use despite life-threatening consequences) , lack of medical review, effects on family and close community members, stigma, barriers for thorough pharmacy assessment, etc are all issues that will continue to place an extra health burdon in our community, which can be significantly addressed by re-scheduling all codeine-combination products to Schedule 3.

Sincerely,

Considerations for the proposed rescheduling of Codeine to Schedule 4

We are writing this submission to state that we believe a decision to reschedule codeine should be delayed for the following reasons:

1) There is a large international body work in development that will greatly inform more effective community pharmacy supply of over-the-counter codeine
2) There is evidence that further restrictions on codeine supply will have a disproportionate effect on Australians in regional/rural areas, who may have lesser access to alternative analgesic medications
3) We do not currently know if prescribed or OTC codeine is causing the majority of harms. In the absence of routine data collection in hospitals and drug treatment identifying the source of codeine, there is the risk that unintended harms may result from shifting codeine users to higher strength products.

While awaiting the outcomes of ongoing work examining codeine use in Australia and internationally, we suggest that a decision to reschedule codeine be delayed.

[redacted]

In 2010 codeine was up-scheduled to schedule 3, in response to evidence of considerable harm from overuse and non-medical use. This measure was not accompanied by formal evaluation or systematic measurement of outcomes following the rescheduling. As a result we have little further information to determine the effect of this policy change, or to determine the need for further regulatory changes in response to codeine related harms.

There are challenges with making changes to availability of medications that have both harms and benefits for the community. Firstly, often there is little concrete evidence of the impact of rescheduling, both in terms of benefits and unintended harms. In the case of codeine the evidence of efficacy of low dose codeine (i.e. the doses typically available in OTC products) is limited, though there is more evidence for the higher strength OTC products (See Box 1). For many complaints simple analgesics appear as effective as codeine combination products. It should be noted that the research conducted on these products is not exhaustive. Research is limited to specific conditions and limited populations. The role of OTC codeine products in pain management may have been overstated, but there is evidence supporting some higher dose codeine products with respect to efficacy.

Box 1. Evidence for effectiveness **(Extract from Book under review: Nielsen, S., Van Hout, MC (2015). 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 . SpringerLink)**

Continued debate around availability of non-prescription codeine focus on abuse potential, adverse health effects associated with presence of simple analgesics (paracetamol, ibuprofen) in combination with codeine, and the lack of pharmacological evidence to support effectiveness of low dose codeine in combination analgesics [1-3]. Standards advise that products containing codeine should only be supplied when single ingredient medicinal products are ineffective, as '*second line*' products for the treatment of pain and only used in accordance with marketing authorisations for short term use (no longer than three days). The World Health Organisation has placed codeine as a '*step 2*' on its pain ladder. Recent debates center on the suggestion to skip '*step 2*' due to problems with codeine (and tramadol), due to limited evidence of effectiveness, variations in patient metabolism and availability of more predictable opioids [4]. Cochrane reviews have underscored the lack of data to support low dose codeine (<10mg) and limited data to support medium dose (10-20mg) codeine for analgesic efficiency, with combined ibuprofen (400mg) and codeine (25.6 to 60mg) incurring good analgesic efficiency [6]. There is also limited evidence for single dose oral ibuprofen plus codeine being more effective for post-operative pain than either drug in isolation[8]. A meta-analysis of opioids for osteoarthritis of the knee or hip reported that modest benefits of codeine were outweighed by adverse consequences [10]. Given the low dose of codeine in non-prescription medicines (equivalent often to approximately 2 mg of morphine), non-opioid analgesics may often perform just as well [3]. The evidence for efficacy must therefore be considered when trying to create the right balance between availability and harms.

There are reasons to believe that at least some of the populations are likely to receive benefit from OTC codeine in terms of effective analgesia. Further, in rural and regional areas where OTC codeine use is highest (Degenhardt et al 2015, manuscript in preparation), disadvantages in access to effective analgesia may result from up-scheduling that would disproportionately affect these those living in regional areas, with potentially greater reliance on OTC medication due to access to prescribers.

Although there are unquestionable data illustrating harms from codeine, very few of our data bases are able to differentiate between over-the-counter versus prescribed codeine. For example, in a series of cases of mortality from codeine (confidential communication: Roxburgh et al 2015– under review – Medical Journal of Australia), the majority of codeine related fatalities (60%) did not have the source of codeine clearly identified, and where the source is identified, the majority are prescribed codeine. It is possible through data-linkage to determine if decedents have been prescribed codeine to more concretely determine which codeine products are responsible for the majority of deaths, however this is not routinely done. Further, routine recording of OTC codeine supply in pharmacy would provide additional evidence as to the source of codeine, however this has not yet been implemented.

In the case of treatment seeking, from smaller case series conducted in NSW it appears that the majority of drug and alcohol treatment cases are from OTC codeine [5]. However, the more comprehensive data

that covers national treatment admissions do not currently differentiate the source of codeine, though it does clearly identify that codeine related treatment presentations are increasing [7]. This recently published data [7] reports an analysis of treatment presentations until 2011, which is too soon to determine the effect of codeine rescheduling in 2010.

Currently hospital and ambulance data sets do not differentiate between prescribed and OTC codeine, meaning that while there is evidence of significant harm associated with pharmaceutical opioids more generally, very few of the data sets we have can inform whether OTC or prescribed codeine are responsible for the majority of the harms.

Given the lack of data on source (prescribed or OTC) that is currently collected we do not know if how much harm is attributed specifically to OTC codeine, and also cannot determine the outcomes of previous rescheduling on harms. We do not know if rescheduling is an effective way of addressing codeine use. Research conducted in Sweden identified that the removal over the counter codeine in Sweden resulted in only a transient decrease in codeine use, rather than a long term change in consumption [9].

The National Drug and Alcohol Research center is conducting a number of ongoing studies that may further inform the need for, and the impact of codeine rescheduling:

1) Time series analysis of codeine sales in Australia (currently in progress, data access negotiated, data received, and planned analysis to be completed in 2015). This will give a more detailed picture of areas of high codeine use and correlated of high codeine use.
2) Time series analysis of codeine related treatment presentations 2002-2014 (currently in progress, data access negotiated, and analysis planned for 2015).
3) The most recent data collection round for the national drug strategy household survey collects the most detailed data yet about non-medical use of OTC codeine. This nationally representative data may inform systematic responses to at-risk populations of codeine users. Ethical approval is granted for these analysis and data have been provided. These analyses are also planned for 2015.

Finally, a body of work has been developed to help pharmacists respond more systematically to identify those at risk of codeine dependence. Collaborative work with the National Drug and Alcohol Research Centre and the University of Tasmania has led to the development of a validated screening tool for codeine dependence in community pharmacy (Masters Thesis J McCoy, available on request), and the extension of this work as part of Ms Mcoy's doctoral work will oversee the testing and implementation of this screening tool in Australian pharmacies. We believe this is an optimal response for this problem as this will provide a way for pharmacists to engage with all people requesting codeine in a prevention framework, and for the first time address many of the challenges in a community pharmacy setting of training and privacy through the use of available technologies. Through this project we will also have planned representative data collection on problematic codeine use that would give a much more detailed picture of the scale of the problem.

Globally there is a large body of work underway to inform how to respond to concerns around problematic use of OTC codeine. I serve as the nominated scientific expect for the mid-term review of this large project (http://www.codemisused.org/). I am currently writing the mid-term review for the project and believe there is considering learning about responses to codeine dependence that will

result, including innovations for sales monitoring and brief intervention. This 48 month project was selected for funding under the FP7 Marie Curie Industry-Academia Partnerships & Pathways strand and is supported by an Expert Advisory Panel with representatives of the EMA, EMCDDA, South African Central Drug Authority and Royal Pharmaceutical Society UK. The project will be completed in 2016. Included in the deliverables for this project are continuing education for pharmacists and development of further innovations to be used at a pharmacy setting to help pharmacists effectively engage with pain medication requests approximately. This work represents an enormous advance in the current knowledge about codeine problems and responses, and Australia is in a position to capitalize from the knowledge gained due to existing collaborations with this international research group.

Prior to implementing greater regulatory responses that may limit the medications available for use in Australia, better evidence in needed in the areas of:

1) the harms specifically attributable to OTC codeine
2) the potential to implement more systematic approaches to prevent harm through pharmacists involvement in supply of OTC codeine

We are on the cusp of an enormous body of additional work that would greatly inform prevention responses and the scale of codeine related harms. Discussions with organizations such as the Pharmaceutical Society of Australia reveal a commitment to developing stronger partnership approaches to research in this area. We strongly support policy responses in the area of problematic OTC codeine use, and advocate of evidence-based decisions in this area. It appears to be too soon to make a determination in favour of rescheduling with the current evidence available, and there exists the risk that up-scheduling is not the optimal response for reducing harm.

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Appendices

Appendix A: This work presents findings from a case series of treatment entrants in New South Wales, of which 53 reported codeine use (prescribed or OTC)

Drug and Alcohol REVIEW

APSAD

Drug and Alcohol Review (2014)
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Comparing treatment-seeking codeine users and strong opioid users: Findings from a novel case series

SUZANNE NIELSEN[1,2,3], BRIDIN MURNION[2], ADRIAN DUNLOP[4,5], LOUISA DEGENHARDT[1,6,7,8], APO DEMIRKOL[3,9], PETER MUHLEISEN[4] & NICHOLAS LINTZERIS[2,3]

[1]*National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia,* [2]*Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia,* [3]*Drug and Alcohol Services, South Eastern Sydney Local Health District, Sydney, Australia,* [4]*Drug and Alcohol Services, Hunter New England Local Health District, Newcastle, Australia,* [5]*School of Medicine and Public Health, Faculty of Health, University of Newcastle, Newcastle, Australia,* [6]*School of Population and Global Health, University of Melbourne, Melbourne, Australia,* [7]*Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia,* [8]*Department of Global Health, School of Public Health, University of Washington, Seattle, USA, and* [9]*School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia*

Abstract

Introduction and Aims. *Few studies have described those seeking treatment for codeine dependence. This study aimed to compare patients presenting for treatment where either codeine or a strong pharmaceutical opioid (oxycodone or morphine) was the principal drug of concern to understand if codeine users may have unique treatment needs.* ***Design and Methods.*** *Retrospective case review of 135 patients from three geographical areas in New South Wales, Australia. Cases where the principal drug of concern was codeine (*n = 53*) or a strong pharmaceutical opioid (oxycodone or morphine,* n = 82*) were compared. Differences in demographic characteristics, pain history, mental health, substance use history and, subsequently, the treatment that was received were examined.* ***Results.*** *People whose principal drug of concern was codeine were more likely to be female (66% vs. 37%,* $P < 0.001$*), employed (43% vs. 22%,* $P < 0.01$*) and use only one pharmaceutical opioid (91% vs. 49%,* $P < 0.001$*). There was no difference in age between the codeine group (mean 38.6 years) and the strong opioid group (39.3 years). Opioid substitution therapy was the most common treatment received by both groups although codeine patients were more likely to be treated with buprenorphine than methadone (odds ratio = 7.7, 95% confidence interval 2.2–27.2,* $P < 0.001$*) and more likely to attempt withdrawal (odds ratio = 2.6, 95% confidence interval 1.2–5.3,* $P = 0.010$*).* ***Discussion and Conclusions.*** *There are important differences between codeine-dependent patients and strong prescription opioid-dependent patients. Further work should explore the outcomes of withdrawal versus maintenance treatment for codeine users.* [Nielsen S, Murnion B, Dunlop A, Degenhardt L, Demirkol A, Muhleisen P, Lintzeris N. Comparing treatment-seeking codeine users and strong opioid users: Findings from a novel case series. *Drug Alcohol Rev* 2014]

Key words: codeine, oxycodone, morphine, dependence, treatment.

Introduction

The use of pharmaceutical opioids has increased dramatically in many parts of the world [1–3], with non-medical pharmaceutical opioid analgesic (POA) use described as an 'epidemic' in the USA [4]. The incidence of POA-related problems appears to be markedly increasing in Australia, as evidenced by increases in hospital poisoning presentations for pharmaceutical opioids, which now exceed those related to heroin [5]. There is a growing body of research suggesting that POA treatment entrants differ from heroin users. People entering treatment with POA dependence in North America are more likely to have employment, to

Suzanne Nielsen BPharm, PhD, Research Fellow, Bridin Murnion B.Sc., MB ChB, FRACP, FFPMANZCA, FAChAM, Staff Specialist, Adrian Dunlop, PhD, MBBS, FAChAM, D&A Clinical Services, HNELHD, Louisa Degenhardt PhD, Professor, Apo Demirkol MD, MSc, PhD, FAFPHM, FAChAm, Staff Specialist, Peter Muhleisen BPharm, Pharmacist, Nicholas Lintzeris MBBS, PhD, FAChAM, Director, D&A Services, SESLHD. Correspondence to Dr Suzanne Nielsen, National Drug and Alcohol Research Centre, University of New South Wales, 22-32 King Street, Randwick, NSW 2031, Australia. Tel: + 61 2 8936 1017; Fax: + 61 2 9385 0222; E-mail: suzanne.nielsen@unsw.edu.au

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report oral rather than injecting use, and have more severe pain and mental health problems [6–9] and a longer time to onset of problematic use [10] compared with heroin users.

Few studies have examined if there are differences in individuals using different types of POA. One study found POA users were a heterogeneous group, depending in part on their heroin use history [11]. Differences have also been identified in the USA between those with non-medical use of oxycodone compared with other prescription opioids [12,13]. However, there has been little research examining treatment presentations where a weaker opioid such as codeine is the principal drug of concern. This is despite the growing concerns about codeine use, dependence, and related harms [14–16] and regulatory changes in Australia restricting sales and requiring greater pharmacist involvement in over-the-counter (OTC) supply [17].

There are unique concerns with harms from OTC codeine products that warrant a particular focus on codeine dependence. In most countries, OTC codeine is sold in combination preparations with paracetamol or non-steroidal anti-inflammatory drugs such as ibuprofen. In addition to the well-known harms associated with opioid dependence, there is a range of serious harms associated with chronic and high dose use of simple analgesics that are chronically ingested in high doses with OTC codeine dependence. Harms with consuming high doses of anti-inflammatory drugs such as ibuprofen include gastric bleeds, hypokalaemia and organ failure [14,15,18,19], and high doses of paracetamol can cause liver toxicity [20,21]. Given these serious harms, it is critical to gain a better understanding of the characteristics and treatment needs of codeine-dependent people and particularly to understand if their needs differ from other opioid-dependent people who have been already the subject of a greater amount of research interest.

There are few studies that have described codeine-dependent people. One study of OTC codeine-dependent people in Australia found that they had high levels of education, employment and were predominantly female [22], in contrast to heroin users [23]. A review of administrative data from treatment presentations in South Africa similarly found codeine users to be predominantly female [24]. To our knowledge, no studies have directly compared codeine-dependent people with those dependent on other POA.

The primary aim of this study was to examine whether there were differences between pharmaceutical opioid users presenting to drug treatment according to the main pharmaceutical opioid used—specifically comparing those where the principal drug of concern is codeine and those presentations where either oxycodone or morphine (defined as 'strong opioids' in World Health Organization guidelines) was the principal drug of concern [25]. A further aim was to examine if those using weaker opioids receive different treatment compared with those use using stronger opioids. Based on previous research with other samples of codeine users [15,22], we hypothesised that these codeine users would have different demographic characteristics, such as higher levels of employment, and may be more likely to receive short-term detoxification treatment approaches.

Methods

Participants

Data were collected as part of a retrospective case file review. Cases were drawn from patients who had presented to drug treatment services in three Local Health Districts in New South Wales (NSW): South Eastern Sydney Local Health District (The Langton Centre), Sydney Local Health District (Royal Prince Alfred Hospital, Concord General Repatriation Hospital) and Hunter New England Local Health District (John Hunter Hospital, Newcastle Pharmacotherapy Service and the Calvary Mater Hospital) with codeine, morphine or oxycodone recorded in the as the 'principal drug of concern'. Principal drug of concern, a mandatory data item of the National Minimum Data Set for Australian drug treatment episodes that is collected by all government-funded treatment agencies [26], was used to identify cases. The accuracy of the principal drug of concern was confirmed at the point of data extraction to ensure that the principal drug of concern listed on the administrative data was consistent with the substance use pattern reported at treatment entry.

Procedures

Study sites were chosen to give a representation of both metropolitan and regional/rural cases, representing two of the eight sites metropolitan health districts and the most populous of the seven regional/rural local health districts in NSW. The Local Health Districts covered by this study represent approximately 30% of the New South Wales population. A lead drug treatment clinician in each of the three sites was asked to identify 30–40 consecutive cases over a 12- to 24-month period where a pharmaceutical opioid was recorded as the principal drug of concern. The principal drug of concern was defined as the main drug, as stated by the client, that has led a person to seek treatment from the service, as represented by a code [26]. Consecutive cases were collected to remove the possibility of recall bias for memorable cases. The study included cases across the three sites from March 2010 to November

2013. The cases were not intended to represent the total number of cases seen over the 3.5-year period and were collected over a staggered time period of 3 years due to logistical reasons.

Data were collected from medical records by two researchers (SN, PM) using a specifically designed data extraction form. Data collected included demographic information (age, gender, employment, marital status), details of the presentation including opioid use, other substance use, previous drug treatment history, drug treatment received, pain diagnosis (if any) and treatment, and comorbidities reported. Where dose of pharmaceutical opioids at time of admission was documented ($n = 125$), oral morphine equivalent doses were calculated using available references [27].

All study procedures were approved by the Sydney Local Health District Ethics Review Committee (Royal Prince Alfred Hospital Zone), with site-specific approvals received for all clinical sites involved in the study.

Analyses

Participants were grouped by principal drug of concern as either the codeine group or the 'strong opioid' (morphine/oxycodone) group. These two groups were chosen as they represent the overwhelming majority of pharmaceutical opioid users presenting for treatment in the treatment services examined. There were a small number of cases ($n = 11$) where other opioids were listed as the principal drug of concern [e.g. dihydrocodeine ($n = 1$), tramadol ($n = 2$), hydromorphone ($n = 1$), methadone ($n = 5$) or buprenorphine($n = 2$)]. These cases were excluded, as their inclusion was felt to reduce the focus of the comparison. Descriptive statistics were used to compare the two groups (χ^2-tests for dichotomous variables and *t*-tests for continuous variables). Where odds ratios (ORs) were generated, the strong opioid group was the reference group. Where non-normal distribution was detected, medians are reported and non-parametric tests were used to compare medians (Mann–Whitney *U* Test). Where one or more cells had a value of less than 5, the results of the Fisher's exact test was used. Logistic regression analysis was used to explore if any characteristics, including opioid type, were independently associated with entering maintenance treatment.

Results

Participants

One hundred thirty-five cases were reviewed; 82 (61%) were strong opioid users [oxycodone ($n = 62$, 44%) or morphine ($n = 20$, 15%)] and 53 were codeine users (39%). OTC codeine (i.e. non-prescription products purchased in pharmacies) was reported by 47 of the 53 cases (89%) where codeine was recorded as the principal drug of concern. Three cases indicated prescription codeine use, and three cases did not identify the specific codeine product used. Forty-four of the 53 cases (83%) indicated that OTC codeine was the only opioid used.

Demographics

The codeine group was comparable in age with the strong opioid group, with a mean age of 39 years in both groups (Table 1). The codeine group was more likely to be female [OR = 3.37, 95% confidence interval (CI) 1.63–6.96] and more likely to be employed (OR = 2.68, 95% CI 1.26–5.71) than the strong opioid group. No differences were detected in relationship status.

Reasons for opioid initiation

The most common reason for POA initiation among both groups was a pain-related condition, with smaller numbers reporting previously established histories of opioid dependence (including heroin dependence) as the reason they started using pharmaceutical opioids (Table 1). Starting opioids for acute types of pain such as dental pain, headaches and period pain was only reported in the codeine group (data not shown).

Mental health

Most people also had mental health problems documented (Table 1). The codeine group had higher odds of having psychiatric commodities documented (OR 2.99, 95% CI 1.35–6.61). More specifically, the codeine group was more likely to report depression (OR 2.32, 95% CI 1.15–4.69) and bipolar disorder 12.17 (1.45–102.08), though only small numbers reported bipolar.

Substance use

Current stimulant and cannabis use were more frequent in the strong opioid group. The codeine group was less likely to report a history of heroin use (OR 0.16, 95% CI 0.07–0.40). Similarly, around half (52%) of the oxycodone/morphine group reported injecting opioids, which was not reported by anyone in the codeine group.

Those in the codeine group reported using their current opioid for a median of 4.75 years compared with a median of 2 years in the strong opioid group (Table 1). There was also a difference in the number using only the principal opioid of concern at the time of admission: In the strong opioid group, 49% reported

Table 1. *Sample characteristics*

	Strong opioids (oxycodone/morphine) ($n = 82$)	Codeine ($n = 53$)	OR (95% CI)	*P*
Demographics				
Age in years, mean (SD)	39.3 (10.0)	38.6 (8.3)	0.99 (0.96–1.03)	0.669
Females	30 (37%)	35 (66%)	3.37 (1.63–6.96)	0.001
Married or de facto	25 (31%)	15 (28%)	0.90 (0.42–1.93)	0.786
Employed	18 (22%)	23 (43%)	2.68 (1.26–5.71)	0.009
Reason for opioid initiation				
Pain (not including cancer pain)	48 (59%)	35 (66%)	Ref	0.134
Opioid dependence	17 (21%)	4 (8%)	0.32 (0.10–1.04)	0.059
Other (anxiety/cancer/not stated)	17 (21%)	14 (26%)	1.13 (0.49–2.59)	0.774
Pain condition reported	56 (69%)	33 (62%)	0.74 (0.36–1.53)	0.410
Opioid use characteristics				
Time using current opioids in years, median (IQR)	2 (4)	4.75 (6)	NA	0.001
Used only principal opioid	39 (49%)	48 (91%)	10.09 (3.64–27.99)	<0.001
Median oral morphine equivalents dose (mg) at treatment entry ($n = 125$)	390 (23–4225)	59 (6–282)	NA	<0.001
Mental health				
Psychiatric comorbidity	46 (56%)	42 (79%)	2.99 (1.35–6.61)	0.006
Anxiety disorder	15 (19%)	14 (26%)	1.58 (0.69–3.62)	0.278
Depression	31 (38%)	31 (59%)	2.32 (1.15–4.69)	0.019
Schizophrenia	4 (5%)	3 (6%)	1.16 (0.25–5.28)	1.00
Bipolar disorder	1 (1%)	7 (13%)	12.17 (1.45–102.08)	<0.05
Post-traumatic stress disorder	3 (4%)	5 (9%)	2.74 (0.63–12.00)	0.262
Eating disorder	1 (1%)	2 (4%)	3.18 (0.28–35.93)	0.561
Substance use				
Current nicotine use	46 (56%)	24 (45%)	0.65 (0.32–1.30)	0.219
Current cannabis use	23 (28%)	5 (9.4%)	0.27 (0.09–0.76)	0.009
Current stimulant use	17 (21%)	3 (6%)	0.23 (0.06–0.83)	0.016
Current problematic alcohol use	14 (17%)	14 (26%)	1.74 (0.75–4.03)	0.191
Current benzodiazepine use	37 (45%)	17 (32%)	0.57 (0.28–1.18)	0.131
History of heroin use	40 (49%)	7 (13%)	0.16 (0.07–0.40)	0.001
Current injecting drug use	43 (52%)	0 (0%)	NA	0.001

CI, confidence interval; IQR, interquartile range; OR, odds ratio; SD, standard deviation.

using only the principal opioid of concern. Of the remainder, 39% reported using one opioid in addition to their principal drug of concern, and 13% reported using two opioids in addition to their principal opioid of concern. In the codeine group, most (91%) reported using only codeine, with five people (9%) reporting also one additional opioid at the time of presentation.

There were significant differences in the oral morphine equivalent dose of opioids reported by the strong opioid group (median of 390 mg oral morphine equivalents, range 23–4225 mg) and the codeine group (median of 59 mg, range 6–282 mg) (see Table 1).

Drug treatment

Similar proportions of each group reported previous drug treatment, with a prior treatment history documented in 55% of the total sample (Table 2). There were differences in the nature of treatments received, with three people (6%) of the codeine group receiving methadone treatment compared with 24 people (30%) of the strong opioid group. Buprenorphine maintenance treatment was the most common treatment received by both groups.

The codeine group was more likely to receive buprenorphine maintenance (OR = 6.4, 95% CI 1.72–23.83) or buprenorphine reduction (OR = 9.88, 95% CI 2.54–38.50) compared with the strong opioid (oxycodone/morphine) group. The codeine group was more likely to attempt a form of withdrawal treatment, which included buprenorphine withdrawal, withdrawal off their currently opioid or treatment with non-opioid medications (OR = 2.6, 95% CI 1.2–5.3), rather than enter any form of maintenance treatment.

Among those that received any form of methadone or buprenorphine treatment ($n = 119$), we conducted further analysis to see if there was a difference in the choice of pharmacotherapy treatment. We found that

Table 2. *Drug treatment characteristics*

	Oxycodone/morphine $n = 82$ (%)	Codeine $n = 53$ (%)	OR (95% CI)/*t*	*P*
Previous alcohol or drug treatment	47 (57)	27 (51)	0.77 (0.39–1.55)	0.467
Current treatment received				
Methadone maintenance	24 (30)	3 (6)	Reference category	0.009
Buprenorphine maintenance (±naloxone)	30 (37)	24 (45.3)	6.4 (1.72–23.83)	0.006
Buprenorphine reduction (±naloxone)	17 (21)	21 (40)	9.88 (2.54–38.50)	0.001
Other	10 (12)	5 (9)	4.00 (0.80–20.02)	0.092
Received methadone or buprenorphine (any form)	71 (87)	48 (91)	1.49 (0.49–4.55)	0.485
Received any form of maintenance treatment	59 (73)	27 (51)	0.39 (0.19–0.80)	0.010
Received any form of withdrawal treatment	22 (27)	26 (49)	2.6 (1.25–5.35)	0.010

CI, confidence interval; OR, odds ratio.

Table 3. *Predictors of entering maintenance treatment*

	Received maintenance treatment $n = 86$ (%)	Received withdrawal treatment $n = 47$ (%)	OR (95% CI)	Adjusted OR (95% CI)
Female	42 (49)	23 (48)	1.04 (0.51–2.10)	1.92 (0.84–4.41)
Codeine principal drug of concern	27 (31)	26 (54)	0.39 (0.19–0.80)*	0.64 (0.42–0.97)*
Employed	24 (28)	17 (36)	0.82 (0.32–1.46)	0.91 (0.40–2.05)
Pain diagnoses noted	57 (66)	32 (67)	0.98 (0.47–2.08)	0.99 (0.45–2.18)
Heroin use history	36 (42)	11 (23)	2.42 (1.09–5.38)*	2.44 (0.97–6.14)

*$P < 0.05$.
CI, confidence interval; OR, odds ratio.

the codeine group was more likely than the strong opioid users to receive buprenorphine in any form (OR = 7.7, 95% CI 2.2–27.2, $P < 0.001$).

Logistic regression analysis was used to explore factors potentially associated with receiving a maintenance treatment, including gender, employment, having a pain diagnoses and principal drug of concern (codeine or oxycodone/morphine). After controlling for other variables, codeine users had lower odds of entering maintenance treatment (adjusted OR = 0.64, 95% CI 0.42–0.96) (Table 3).

Discussion

We report on a series of 135 cases presenting for drug treatment where a pharmaceutical opioid was the principal drug of concern. One of the striking findings of this study is the number of treatment presentations where OTC codeine was the principal drug of concern and the only opioid used. Although there has been growing concern around non-medical use of strong opioids such as oxycodone, a broadly similar number of treatment presentations in this sample were identified where codeine was the principal drug of concern, indicating it is also an important drug of dependence among drug treatment presentations. Although the harms associated with OTC codeine products have been reported in the literature [15,28], less attention has been given to the potential demand for treatment among this group of opioid users. We also found a higher proportion of female among codeine users, consistent with a previous study examining administrative data for treatment presentations in South Africa, where OTC codeine dependence has also been reported [24].

Consistent with our hypothesis, the principal opioid used (codeine or morphine/oxycodone) was associated with the type of treatment received, with codeine users being less likely to enter a form of maintenance treatment. This may be partially due to the lower oral morphine equivalent doses reported by codeine users, which may give clinicians the impression that a milder opioid dependence exists, and shorter treatment duration is required. There is a good reason to challenge this thinking. The largest randomised controlled trial of buprenorphine treatment for POA users demonstrated that despite the more favourable prognostic characteristics and less severe dependence seen with POA users compared with heroin users [29], most POA users

(94%) had unsuccessful outcomes from brief withdrawal treatment [30]. It should be noted that the design of this study did not enable examination of longer-term outcomes following withdrawal episodes and specifically if treatment outcomes for codeine users differ from strong opioid users. To date, most treatment studies have recruited only prescription opioid users (as opposed to those people using OTC opioids) [30,31]. To address this gap, studies to understand long-term outcomes for OTC codeine users are of particular importance given the long use histories and potential serious risks associated with relapse to OTC codeine use.

A further interesting finding was that buprenorphine treatment was more common than methadone treatment in this sample of pharmaceutical opioid users. This is in contrast to the broader population of predominantly heroin-dependent opioid substitution treatment patients in NSW, where almost 75% receive methadone pharmacotherapy [32]. Although methadone has historically been the most commonly used pharmacotherapy for heroin dependence, there are a number of possible reasons for the greater proportion of pharmaceutical opioid-dependent patients who received buprenorphine. These include the possibility of providing buprenorphine treatment with fewer requirements for daily attendance for supervised dosing, which is favourable in a population with higher employment and appropriate for a population where a history of injected drug use is less common. There may also be a preference for using a partial opioid agonist for the treatment of lower potency opioids such as codeine and less stigma compared with methadone [33–35]. The use of buprenorphine for the treatment of POA dependence in Australia may be mirroring the large expansion of buprenorphine treatment for POA dependence that has been reported in the USA, where it has been reported that the expansion was for many of the reasons listed above [36,37]. Further work is required to better understand reasons for treatment selection among pharmaceutical opioid users and if different pharmacotherapies have benefits for subpopulations of patients such as those with pain conditions.

The findings raise a number of clinical implications. Two-thirds of the sample reported initiating opioids for pain, and pain-related conditions were highly prevalent in this group, highlighting the importance of systematically assessing pain among pharmaceutical opioid users entering drug treatment. It also emphasises the importance of strategies aimed at prevention or early identification of dependence in patients using opioid analgesics. Examples include universal screening of patients to identify risk for developing opioid dependence and monitoring patients in long-term opioid treatment for aberrant medication behaviours and opioid-related problems [38,39]. Of equal relevance, approximately two-thirds had a psychiatric diagnosis recorded. In effect, many of this sample had a 'triple diagnosis' of combined chronic pain, psychiatric comorbidity and substance use disorder, highlighting the complexity of this patient group.

The predominance of people using only OTC codeine highlights the potential importance of pharmacist and pharmacy customer interventions. Many patients who had entered treatment with codeine dependence reported initiating codeine use for transient pain conditions such as headaches and dental pain, and this group may have limited contact with health professionals other than pharmacists. In balancing the benefits and risks associated with these products, further consideration should also be paid to the limited evidence base supporting the efficacy of codeine in the doses available in OTC products, in addition to the limited evidence supporting safety and efficacy of long-term opioids for chronic non-cancer pain [40,41].

Limitations

There are inherent limitations with retrospective data collection from clinical files. Patient files are maintained primarily for the purpose of patient care rather than research. Some of the domains examined were not consistently recorded between sites and between patients. There may be cases where co-morbidities or characteristics were not documented, either because they were not disclosed to the clinician, or were not assessed or recorded by the treating clinician. There were two domains of note that were affected: First, smoking status was not documented in 25% of cases, and cannabis use was not documented in 20% of cases compared with other substance use where 85% or more cases had documented status of stimulant, alcohol use and benzodiazepine use. This may have led to underestimates of use of these substances as substance use was only reported where it was either documented or reported in toxicology results. Secondly, participants were often prescribed psychiatric medications in the absence of a recorded mental health indication or diagnosis (particularly benzodiazepines, antidepressants and antipsychotic medication). Due to the common off-label use of these medications, particularly for pain conditions, psychiatric comorbidities were only reported where a specific diagnosis was noted in the file, rather than being assumed from medications. This may have led to lower estimates of psychiatric co-morbidity that existed within the sample. Nevertheless, the majority of patients had a psychiatric co-morbidity identified in the medical records. Finally, for future prospective studies, there are a number of

variables that would be valuable to collect to better be able to understand if codeine users are receiving different treatment based on their use of codeine or if greater update of withdrawal treatment is related to other characteristics such as severity of dependence. Further work to better understand the perspective of prescribers and patients would be particularly informative in this regard.

Conclusions

There are important differences between those dependent on codeine and those dependent on strong opioids, in addition to the differences identified in treatments received. Many of these patients had combined pain and psychiatric and substance use disorders, reflecting the complex treatment needs of this patient group. Our findings, considered together with the findings by Weiss et al. [30] regarding poorer outcomes with short-term treatment, support the need for further research to understand how treatment type may impact on the long-term outcomes of OTC codeine-dependent people.

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Conflict of interest

None of the authors have any connections with the tobacco, alcohol or gaming industry. Authors S. N., A. D., L. D. and N. L. have been investigators on untied educational grants from Reckitt Benckiser, and A. D., P. M. and N. L. have received honoraria from Reckitt-Benckiser to present at professional development courses. Authors N. L. and L. D. are investigators on an untied educational grant from Mundipharma. All other authors have nothing to declare.

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Appendix B - This work represents and analysis of national treatment data for codeine (and other drug) dependence

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Changes in non-opioid substitution treatment episodes for pharmaceutical opioids and heroin from 2002 to 2011

S. Nielsen[a,b,*], A. Roxburgh[a], R. Bruno[a,c], N. Lintzeris[b,d], A. Jefferson[e], L. Degenhardt[a]

[a] National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales 2052, Australia
[b] Drug and Alcohol Services, South Eastern Sydney Local Health District, 591 South Dowling St, Surry Hills 2010, Australia
[c] School of Medicine, University of Tasmania, Level 1, Medical Science 1, 17 Liverpool Street, Hobart 7000, Australia
[d] University of Sydney, Department of Addiction Medicine, Missenden Road, Camperdown 2006, Australia
[e] Tobacco, Alcohol and Other Drugs Unit, Australian Institute of Health and Welfare, 1 Thynne Street, Fern Hill Park, Bruce 2617, Australia

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ABSTRACT

Background: There has been a well-documented increase in the non-medical use of pharmaceutical opioids (PO) worldwide. However, there has been little detailed examination of treatment demand, or the characteristics of those presenting for treatment, particularly for treatments other than opioid substitution.

Methods: Data from closed drug and alcohol treatment episodes from the Alcohol and Other Drug Treatment Services National Minimum Data Set (AODTS-NMDS, representing non-opioid substitution treatment) in Australia for 2002–2003 to 2010–2011 were examined. In the four jurisdictions where detailed data were available, episodes where heroin was the principal drug of concern were compared to episodes for the four most frequently reported pharmaceutical opioids (morphine, codeine, fentanyl and oxycodone).

Results: In 2002–2003, most (93%) opioid treatment was related to heroin with seven percent of all opioid treatment episodes reporting a PO as the principal drug of concern. In 2010–2011, 20% of all opioid treatment episodes were attributed to POs. Distinct changes over time were observed for different opioids. There was an increase in the average age at the start of treatment for heroin and oxycodone episodes, and a reduction in the proportion of females for codeine episodes, with 67% in 2002–2003 compared with 44% in 2010–2011. Codeine and oxycodone episodes had the lowest current or past injection rates.

Conclusions: Clear differences were observed over time and between different opioids. Monitoring these emerging patterns will be important to inform treatment needs, particularly in light of different patterns of poly drug use, different routes of administration and changing demographic characteristics.

1. Introduction

Pharmaceutical opioid (PO) use and associated harms are an important international issue (Fischer et al., 2013c; Maxwell, 2011). Increases in mortality have been described as an 'epidemic' (Calcaterra et al., 2013; ONCDP, 2011). Over the past 10–15 years, substantial increases in prescribing and non-medical use of a range of opioids have been reported globally (Atluri et al., 2014; Degenhardt et al., 2007; Leong et al., 2009). In Australia, clear patterns of increased opioid prescribing (Leong et al., 2009) and increased non-medical use of analgesics and 'other opiates' (including morphine and oxycodone) have been seen in the general population (Australian Institute of Health and Welfare, 2014a). Likewise, increases in morphine and oxycodone use amongst sentinel samples of people who inject drugs have been reported (Stafford and Burns, 2012).

One important indicator of harm associated with PO use is seeking treatment for drug dependence. In the US, the proportion of all treatment admissions related to prescription opioid abuse increased from 2.2% to 9.8% between 1998 and 2008, with 26.5% of admissions for medication-assisted treatment being for the treatment of prescription opioid dependence (Substance Abuse and Mental Health Services Administration, 2010). Increased treatment admissions for codeine have been reported in South Africa (Myers et al., 2003). Australia has recorded an increase in hospital presentations for PO poisoning (Roxburgh and Burns, 2013), and increases

* Corresponding author at: National Drug and Alcohol Research Centre, University of New South Wales, 22-32 King St, Randwick 2031, Australia. Tel.: +61 2 8936 1017; fax: +61 2 9385 0222.
E-mail address: suzanne.nielsen@unsw.edu.au (S. Nielsen).

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in oxycodone- and fentanyl-related deaths have also been documented (Rintoul et al., 2010; Roxburgh et al., 2011, 2013).

Studies of PO users indicate that some non-treatment seeking populations of pharmaceutical opioid dependent people, such as codeine users, may differ from heroin users in important ways such as employment and education (Nielsen et al., 2011). Further, a recent case series of drug treatment entrants identified differences between codeine and strong opioid users in terms of presenting characteristics and types of treatment received (Nielsen et al., 2014). To date, limited information is available to give a broader picture of PO treatment at a jurisdictional or national level, or to examine the patterns of drug and alcohol service utilization over the time period during which increased pharmaceutical opioid use has been observed. Recent indicators from opioid substitution pharmacotherapy treatment (OST) suggest a significant minority (around one in three) of people on OST report pharmaceutical opioids as the principal drug of concern at treatment entry (Australian Institute of Health and Welfare, 2014c).

Oxycodone has been the subject of much research interest, with new formulations of oxycodone being developed to counter concerns with misuse (Coplan et al., 2013; Sees et al., 2005). Less is known about opioids such as fentanyl and codeine. Fentanyl is a potent opioid with higher efficacy at the mu opioid receptor. Increased fentanyl prescribing has been reported in Australia and the US, with associated increases in mortality, and intentional misuse and injection described in the majority of deaths (Kuhlman et al., 2003; Roxburgh et al., 2013). Recent US studies have identified that between 9 and 20% of patients prescribed fentanyl display signs of non-adherent medication use (Layton et al., 2014; Passik et al., 2014). Reports are emerging of misuse and harms associated with codeine (Dutch, 2008; Frei et al., 2010; McDonough, 2011; Myers et al., 2003; Pilgrim et al., 2013; Sproule et al., 1999), particularly in those countries where access to codeine is less restricted. Estimates on rates of misuse and harms are less readily available.

The aim of this study was to use national drug treatment statistics to examine patterns of pharmaceutical opioid related presentations to services other than opioid substitution therapy (OST), including withdrawal, counselling, case management and support, information and education, and residential rehabilitation services. The two key areas we sought to examine were: (1) numbers of drug treatment episodes where a pharmaceutical opioid was reported as the principal drug of concern compared with episodes where heroin was reported as the principal drug of concern; and (2) to examine if there were differences in demographic and substance use characteristics reported with treatment episodes for 'weaker', less restricted opioids such as codeine and strong opioids such as morphine, oxycodone and fentanyl.

2. Methods

2.1. Design and participants

All closed treatment episodes from the Alcohol and Other Drug Treatment Services National Minimum Data Set (AODTS-NMDS) were examined for the financial years 2002–2003 to 2010–2011. Data for the AODTS-NMDS are collected to provide national information about drug treatment, to inform policy and strategy decisions, as well as to provide individual service providers information about drug problems and treatment responses in their area. A closed treatment episode refers to a period of contact between a treatment agency and a client, which has a start and an end date. As closed treatment episodes were used, data does not include episodes where the patient did not finish treatment within that financial year. As such, 'an episode' reflects the number of defined treatment periods, rather than the number of clients. It is possible that one client may have multiple treatment episodes. Only episodes where people were seeking help for their own drug use were included (these comprise the vast majority, around 95%, of AODTS-NMDS episodes). The AODTS-NMDS represents government funded drug and alcohol service episodes. The AODTS-NMDS includes the majority of all non-OST treatment provided but does not include most opioid substitution pharmacotherapy services (e.g., most methadone and buprenorphine provided through clinics), services provided by many private treatment providers (e.g., private medical practices), services that may provide drug treatment as a small part of a broader service (e.g., halfway houses, sobering-up shelters, correctional institutions), health promotion services (e.g., needle syringe programmes) or many acute hospital settings where drug treatment was not the primary reason for presentation. 'Principal drug of concern' refers to the main substance that the client stated led them to seek treatment from the alcohol and other drug treatment agency. The AODTS-NMDS also collects information on (up to 5) other or additional drugs of concern.

For these analyses, pharmaceutical opioid treatment episodes are defined as treatment episodes where a pharmaceutical opioid other than methadone or buprenorphine was listed as the principal drug of concern. Cases where methadone or buprenorphine were listed as the principal drug of concern were excluded due to the inability to differentiate cases where people were seeking help with methadone or buprenorphine provided for the assistance in the treatment of heroin dependence (e.g., reducing off methadone that was initially prescribed for heroin dependence may be recorded with methadone as the principal drug of concern), or for a pain indication (e.g., oral methadone tablets transdermal buprenorphine patch), or cases where illicit methadone or buprenorphine may be the principal drug of concern. These represent 11% (n = 23,630) of opioid-related treatment episodes across all jurisdictions from 2002/3 to 2010/11. Pharmaceutical opioids individually examined included morphine, oxycodone, fentanyl and codeine. Heroin-related treatment episodes were also analyzed for comparison.

To examine correlates of pharmaceutical opioid treatment episodes, opioids were classified into three groups (heroin, codeine, and strong opioids [oxycodone, morphine, and fentanyl]). In this way it was possible to compare codeine, an opioid of weaker potency (defined as a 'weak' opioid by the World Health Organization (WHO; Zech et al., 1995) with the three most common 'strong' opioids as defined by the WHO (morphine, oxycodone and fentanyl). As not all jurisdictions reported details of specific pharmaceutical opioids, data for these analyses were from the jurisdictions that consistently coded the specific pharmaceutical opioid of concern: New South Wales, Queensland, South Australia and Tasmania over the time period examined. Data from other jurisdictions were excluded from theses analyses. Treatment episode characteristics examined included: age, sex, location of treatment service, method of use, injection history and treatment type. Age is defined as age at the commencement of the treatment episode. Cell sizes of less than 5 were not reported, in order to protect confidentiality of clients. As a result, episodes where fentanyl was the principal drug of concern were not presented in some analyses. Treatment episodes in the four jurisdictions examined represent 40% of all opioid-related treatment episodes over the time period examined. The four jurisdictions represent 62% of the whole population of Australia.

2.2. Statistical analyses

Trends in numbers of closed treatment episodes relating to heroin and pharmaceutical opioids (excluding methadone or buprenorphine) were examined using regression analyses. Linear and higher-order models were considered but higher order models did not offer improved fit, hence linear models are uniformly reported. Similarly, models were tested for outliers and no standardized residuals were identified >2.1, hence all data points were universally retained. Univariate multinomial logistic regression models were applied to compare the groups in relation to categorical variables; with nonparametric tests used for continuous variables. Cases relating to heroin were used as a reference category for all analyses given their predominance in the treatment system. Data were examined for quality, with the only variables amended relating to 229 (<0.3%) cases where the age of treatment commencement was greater than age 70.

Rates of treatment episodes per 1,000,000 people were calculated using ABS population estimates of the resident population of Remoteness Areas of Australia for June 30 of each year from 2003 to 2011, according to the 2006 edition of the Australian Standard Geographical Classification (ASGC). Remoteness information included in the AODTS-NMDS is based on the location of the service delivery outlet (or location where the service is delivered) rather than on the residence of the client.

3. Results

3.1. Changes in opioid-related presentations over time

In 2002–2003, there were 123,032 closed treatment episodes for all drugs, with heroin (as the principal drug of concern) accounting for 18.4% (n = 22,642) and PO as the principal drug of concern accounting for 1.5% (n = 1799) of all treatment episodes. PO presentations represented 7% of all opioid-related presentations in 2002–2003. In 2010–2011, there were 144,022 closed treatment episodes for all drugs, with heroin accounting for 9.3% (n = 13,354) and PO accounting for 2.4% (n = 3386). PO presentations represented 20% of all opioid-related episodes in 2010–2011 (Fig. 1a). There were significant linear declines in the numbers of treatment episodes where heroin was listed as one of the drugs of

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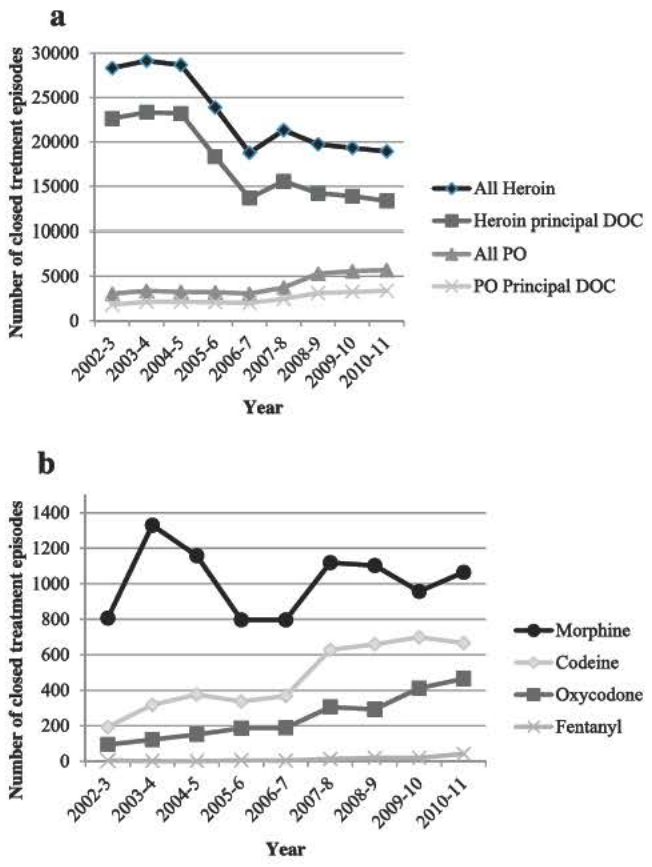

Fig. 1. (a) Number of closed treatment episodes related to pharmaceutical opioids (PO) and heroin were the reported as any drug of concern or the principal drug of concern (DOC) over time. (b) Number of closed treatment episodes where morphine, codeine, oxycodone or fentanyl were reported as the principal drug of concern over time in Queensland, New South Wales, Tasmania and South Australia.

concern ($\beta = -1457$, SE = 280; $t_{(14)} = 5.21$, $p = 0.001$, $_{adj}R^2 = 0.77$) or as the principal drug of concern ($\beta = -1437$, SE = 263; $t_{(14)} = 5.46$, $p = 0.001$, $_{adj}R^2 = 0.78$), though heroin remains the most frequently identified principal opioid of concern despite this decline. In contrast, there were significant linear increases in the numbers of treatment episodes where PO was mentioned as a drug of concern ($\beta = 367$, SE = 78; $t_{(14)} = 4.70$, $p = 0.002$, $_{adj}R^2 = 0.73$) or was the principal drug of concern ($\beta = 200$, SE = 35; $t_{(14)} = 5.75$, $p = 0.001$, $_{adj}R^2 = 0.80$). In the four jurisdictions where the POs of interest were consistently reported, significant linear increases in closed treatment episodes were apparent where codeine ($\beta = 65$, SE = 9.24; $t_{(14)} = 7.03$, $p < 0.001$, $_{adj}R^2 = 0.86$), oxycodone ($\beta = 46$, SE = 5; $t_{(14)} = 9.93$, $p < 0.001$, $_{adj}R^2 = 0.93$), and fentanyl ($\beta = 4$, SE = 1; $t(14) = 4.33$, $p = 0.003$, $_{adj}R^2 = 0.69$) were reported as the principal drug of concern. Presentations related to morphine fluctuated over time with no clear trend apparent ($\beta = 2$, SE = 26; $t_{(14)} = 0.08$, $p = 0.94$, $_{adj}R^2 = 0.01$), but peaking in 2003 (Fig. 1b).

3.2. Changes in demographics over time

In the four jurisdictions where PO were reported, gender of presenting clients remained relatively stable between 2002–2003 and 2010–2011 for heroin ($p = 0.33$) and morphine ($p = 0.37$). However, there was a significant linear increase in the proportion of male patients over time apparent for codeine ($\beta = 2.8$, SE = 0.4; $t_{(14)} = 7.73$, $p < 0.001$, $_{adj}R^2 = 0.88$) and oxycodone ($\beta = 0.9$, SE = 0.4; $t_{(14)} = 2.34$, $p = 0.052$, $_{adj}R^2 = 0.36$). The rate of change was significantly faster for codeine than for oxycodone ($t_{(14)} = 3.69$, $p = 0.002$) (Fig. 2a).

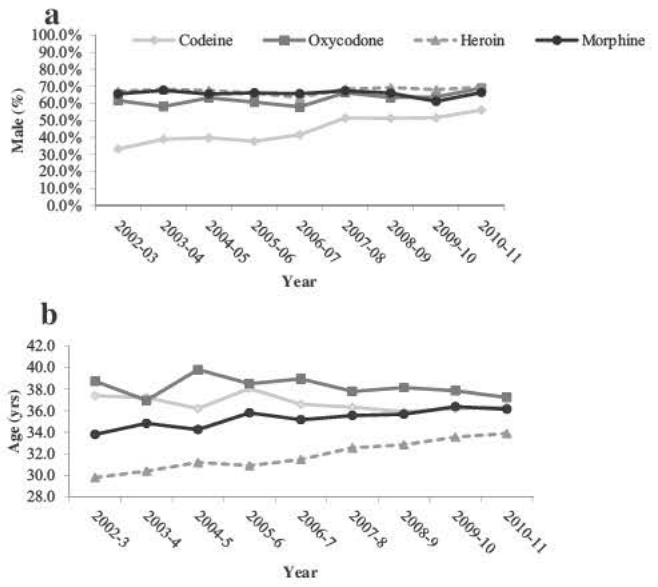

Fig. 2. (a) Gender distribution (%male) over time by principal drug of concern, (b) changes in age at start of treatment over time by principal drug of concern (NSW, SA, TAS and QLD).

There were no significant linear trends apparent in age (at commencement of treatment episode) for oxycodone ($p = 0.32$) or fentanyl ($p = 0.18$). Increases in age at commencement of treatment were apparent for heroin-related treatment ($\beta = 0.51$, SE = 0.04; $t_{(14)} = 14.2$, $p < 0.001$, $_{adj}R^2 = 0.96$), and for morphine ($\beta = 0.28$, SE = 0.06; $t_{(14)} = 4.92$, $p = 0.002$, $_{adj}R^2 = 0.74$), with the rate of change significantly faster for heroin than for morphine ($t_{(14)} = 2.34$, $p = 0.052$). There was a trend to a declining age at commencement of treatment for codeine ($\beta = -0.16$, SE = 0.08; $t_{(14)} = 2.05$, $p = 0.080$, $_{adj}R^2 = 0.29$).

3.3. Correlates of treatment episodes by opioid type

In the four jurisdictions where PO types were specified, the nine years of data were collapsed and correlates of treatment presentations for heroin, strong opioids (morphine, oxycodone, fentanyl), and weak opioids (codeine) examined (Table 1). The average age for treatment episodes where codeine was the principal drug of concern was significantly older than for strong opioids or heroin; age for treatment episodes where a strong opioid was the principal drug of concern was older than for episodes with heroin. Similarly, gender differences were observed with a lower proportion of males for treatment episodes relating to codeine (47%) in comparison to the other opioids.

Injection of the principal drug of concern and injection history was significantly less likely among episodes where codeine was the principal drug of concern compared with heroin or strong opioids. Injecting rates were lower among treatment episodes relating to strong opioids in comparison to those presenting for heroin. The vast majority of codeine episodes had oral administration reported as the method of use, with swallowing being more commonly reported in codeine episodes compared to episodes where heroin or strong opioids were the principal drug of concern. Episodes for strong opioids were more likely to include swallowing as the main method of use compared to episodes for heroin (Table 1).

Differences were also detected for other drugs of concern that were reported in conjunction with the principal drugs of concern. Most (58.5%) episodes reported at least one additional drug of concern. Episodes where codeine or a strong opioid was the principal drug of concern were more likely to include benzodiazepines as

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Table 1
Characteristics of heroin, codeine, morphine, oxycodone and fentanyl episodes[b] 2002–2003 to 2010–2011 for NSW, QLD, TAS, SA.

	A. Heroin (n = 68,517)	B. Strong opioids combined (n = 11,458)	Strong opioids			C. Codeine (n = 4424)	A (REF) vs B OR (95%CI)	A (REF) vs C OR (95%CI)	B (REF) vs C OR (95%CI)
			Oxycodone (n = 2216)	Fentanyl (n = 109)	Morphine (n = 9133)				
Median age (IQR)[a]	30.0 (12.0)	35 (15.0)	37.0 (14.8)	35.5 (17.0)	24.0 (14.0)	36.0 (14.0)	z = −43.58***	z = −33.79***	z = −4.04***
Gender (%male)	67.6	65.5	64.0	58.7	65.9	47.4	0.91 (0.87–0.95)***	0.43 (0.41–0.46)***	0.48 (0.44–0.51)***
Regional or remote location	16.1	49.5	41.6	49.5	51.5	34.2	5.12 (4.91–5.34)***	2.71 (2.54–2.90)***	0.53 (0.49–0.57)***
Method of use of principal DOC									
Injects	89.9	55.7	27.7	22.9	62.9	13.1	0.14 (0.14–0.15)***	0.02 (0.02–0.02)***	0.12 (0.11–.13)***
Swallow	1.1	35.7	61.1	21.1	29.7	82.6	51.21 (47.17–55.59)***	436.68 (392.42–486.27)***	8.53 (7.81–9.31)***
Reports 'never injected'	4.4	16.6	33.2	37.6	12.4	52.5	4.31 (4.05–4.58)***	23.87 (22.25–25.61)***	5.54 (5.13–5.99)***
Other drugs of concern									
Benzodiazepine	12.0	16.2	17.1	13.8	16.0	14.5	1.42 (1.35–1.50)***	1.25 (1.14–1.36)***	0.88 (0.79–0.97)**
Alcohol	10.3	10.8	9.1	5.5	11.3	14.6	1.06 (0.99–1.13)	1.49 (1.37–1.63)***	1.41 (1.27 1.56)***
Cannabis and related drugs	24.4	19.8	12.5	11.0	21.6	10.9	0.76 (0.73–0.80)***	0.38 (0.34–0.42)***	0.50 (0.45–0.55)***
Meth/amphetamines	16.8	13.3	7.9	4.6	14.7	6.0	0.76 (0.72–0.80)***	0.32 (0.28–0.36)***	0.42 (0.37–0.48)***

[a] Inter quartile range, IQR.
[b] *Note:* Data represent treatment episodes rather than individuals.
** $p < 0.01$.
*** $p < 0.001$.

an additional drug of concern compared with heroin treatment episodes. Episodes where codeine was the principal drug of concern reported higher rates of benzodiazepine problems than strong opioid episodes (Table 1). Episodes where codeine was the principal drug of concern were more likely to include alcohol as an additional drug of concern compared with heroin or strong opioid treatment episodes. Episodes where heroin was the principal drug of concern had higher rates of illicit drugs (cannabis or stimulants) as additional drugs of concern compared to both codeine and strong opioid treatment episodes; rates of secondary illicit drug use problems were higher among strong opioid episodes in comparison to those episodes where codeine was the principal drug of concern.

3.4. Treatment characteristics

Differences between the opioid types were identified between main treatment type and treatment setting (Table 2). Codeine episodes were more likely to involve withdrawal management (detoxification) compared to both heroin and strong opioids. Strong opioids were more likely to involve information, assessment or education only, and were also less likely to involve withdrawal/detoxification or counselling, support or case-management compared to heroin episodes. Heroin episodes were most likely to involve rehabilitation.

3.5. Rates of episodes by location of treatment service

Heroin was the only opioid where numbers of episodes were clearly reducing in major cities over time (adjusted for the population living in major cities) (Fig. 3). Rates of episodes for codeine and oxycodone appear to be increasing in both major cities and regional/remote locations (adjusted for changes in population), with higher rates of episodes per million people observed in regional/remote locations being consistently reported for morphine over time, and for oxycodone in the final two years of observation.

4. Discussion

This study represents the first detailed analysis of Australian treatment episodes for heroin and pharmaceutical opioids. This study has confirmed that there are increasing numbers of non-OST treatment episodes where pharmaceutical opioids are the principal drug of concern, in contrast to fewer heroin treatment episodes over time, though heroin remains the most common opioid reported. Important differences were identified between different pharmaceutical opioids, and between pharmaceutical opioids and heroin. Overall, consistent with previous research (Brands et al., 2004; Moore et al., 2007), there appeared to be clear differences between heroin and PO users. In this analysis, what appears to distinguish pharmaceutical opioid treatment episodes from heroin episodes were that clients were older, less likely to inject, more likely to be presenting in regional and remote services, and more likely to report concurrent benzodiazepine problems. Codeine treatment episodes were least likely to report injecting as a route of administration, and were more prevalent among females compared to strong opioid and heroin presentations, although this was changing over time.

Interesting trends over time were also observed for location of treatment service with regional and remote locations showing the greatest increase among PO treatment episodes. In contrast, there has been a significant decline over time for heroin episodes in metropolitan areas.

There are a number of implications of these findings. Firstly, the increasing rate of codeine presentations over time has not

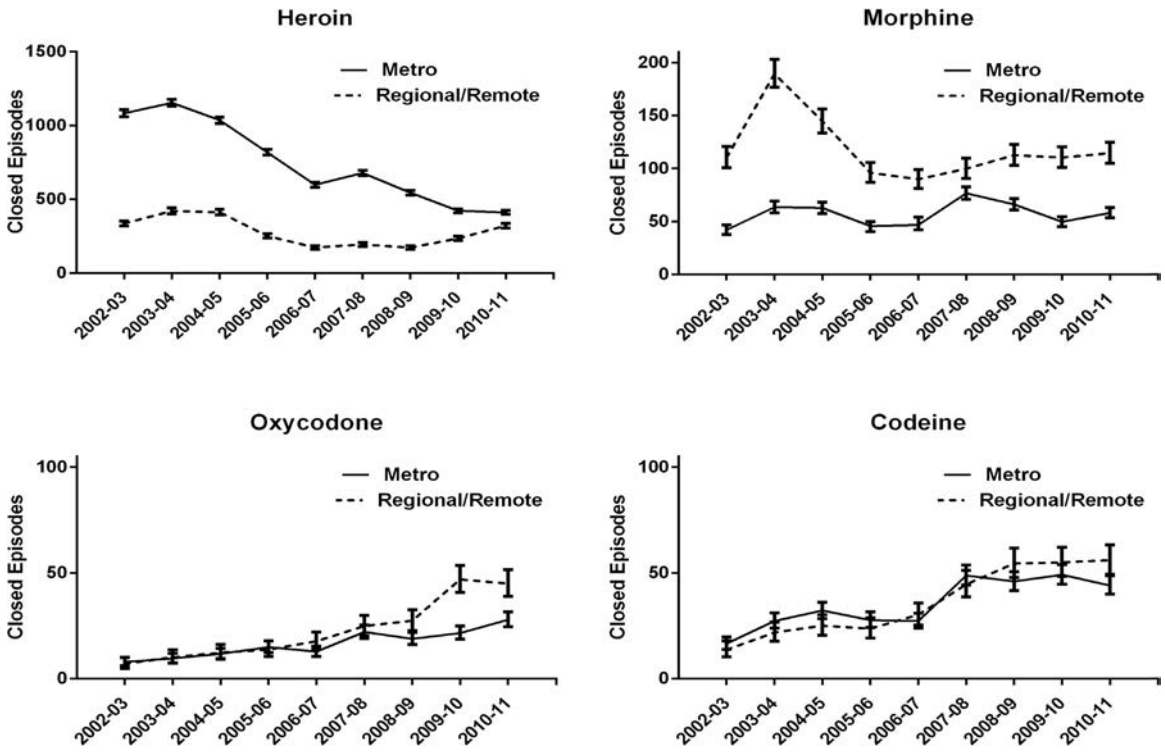

Fig. 3. Treatment episodes per million people over time for heroin, morphine, oxycodone and codeine for regional/remote and metropolitan locations (Major Cities) (QLD, NSW, SA, TAS).

previously been documented. This is one of the first population level databases that has been able to highlight this issue in Australia, though several case series have acted as early warnings of this emerging problem, notably with non-prescription codeine products which represent the overwhelming majority of codeine-related treatment presentations identified (Frei et al., 2010; Nielsen et al., 2014). As codeine falls outside most prescription drug monitoring programmes, and is widely available without a script in a number of countries, identifying those affected by codeine dependence may prove difficult. Novel approaches, such as screening and brief intervention at a retail pharmacy level are needed to target this growing problem. While much attention has been paid to stronger opioids such as oxycodone and fentanyl (e.g., Fischer et al., 2013b; Rintoul et al., 2010; Roxburgh et al., 2013) the rate of treatment episodes for codeine dependence suggests attention should be paid to this 'weaker' opioid.

Secondly, pharmaceutical opioid treatment presentations appear to have differing treatment needs, with higher rates of co-morbid drug dependence (particularly for benzodiazepines), lower rates of injection, and higher proportions of females. Increasing rates of detection of neonatal abstinence highlights one potential complication of increasing pharmaceutical opioid use amongst women (Patrick et al., 2012). The presence of benzodiazepine problems among PO presentations raises the issue of prescribing multiple drugs, as the concurrent use of both these substances clearly increases the risk of overdose (Dietze et al., 2005; Jann et al., 2014). The older age of PO clients may also present unique clinical challenges, particularly with increasing physical co-morbidities with age. The higher levels of concurrent benzodiazepine use, along with the older age of this group presents multiple risk factors for overdose, and further work exploring these risk factors is warranted.

Thirdly, the increasing demands being placed on rural and regional treatment services points to the need for greater resources in these settings as well as clinical training on how best to respond to rising regional and rural PO presentations. PO presentations are complex, and are often accompanied by multiple mental and physical health problems including chronic pain (Lusted et al., 2013). Non-medical PO use is disproportionally observed in rural areas (Day et al., 2006; Fischer et al., 2013a). Integrated models of care that address co-morbid pain and dependence are recommended to respond effectively to PO presentations, yet are least likely to be available in geographically remote areas. Innovative treatment approaches such as telemedicine may be needed to meet these complex treatment needs. Further, the impact of treatment being located far from where patients reside should be considered (Oser and Harp, 2015). Additionally, pharmaceutical drug use may place an increased burden on regional and remote health services more generally, given the nature of pharmaceutical opioid acquisition (e.g., through health professionals such as primary care prescribers and emergency rooms) and the known harms including overdose and injection related harms specific to pharmaceuticals. Given the dynamic changes that appear to be occurring, ongoing monitoring is important, and targeted regional/rural responses are required.

Also, the types of treatment received varied markedly between opioids. For example, consistent with previous research (Nielsen et al., 2014) codeine episodes report the highest rates of detoxification. Further, a large proportion (for example one third of oxycodone treatment episodes) consisted of information and education or assessment only, suggesting minimal or brief interventions were provided. While it is beyond the scope of this data to explore treatment outcomes, further work is warranted to understand the capacity or readiness of drug treatment services to respond to PO users, and to examine the outcomes and effectiveness of different interventions for PO users. Finally, with the introduction of abuse-deterrent oxycodone, monitoring of treatment patterns may inform if there are resulting changes to other pharmaceutical opioids or increasing heroin use, as has been observed in other jurisdictions (Cicero et al., 2012; Coplan et al., 2013).

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Table 2
Treatment characteristics of heroin, codeine, morphine, oxycodone and fentanyl episodes[b] 2002–2003 to 2010–2011 for NSW, QLD, TAS, SA.

	A. Heroin (n = 68,517)	B. Strong Opioids combined (n = 11,458)	Strong opioids			C. Codeine (n = 4424)	A (REF) vs B OR (95%CI)	A (REF) vs C OR (95%CI)	B (REF) vs C OR (95%CI)
			Morphine (n = 9133)	Oxycodone (n = 2216)	Fentanyl (n = 109)				
Main treatment type (%)									
Withdrawal/ detoxification	25.4	22.7	22.6	23.0	24.8	31.9	0.86 (0.82–0.90)***	1.38 (1.29–1.47)***	1.60 (1.48–1.73)***
Counselling, support or case management	33.7	26.6	27.4	23.7	21.1	29.7	0.71 (0.68–0.75)***	0.83 (0.76–0.89)***	1.16 (1.07–1.26)***
Rehabilitation	9.5	4.6	5.2	2.2	1.8	3.0	0.46 (0.42–0.50)***	0.29 (0.25–0.35)***	0.64 (0.53–0.78)***
Pharmacotherapy	2.3	3.2	3.5	1.9	4.6	2.2	1.53 (1.27–1.60)***	0.95 (0.77–1.18)	0.67 (0.53–0.84)**
Information, assessment or education only	19.4	30.3	29.6	33.1	31.2	24.0	1.80 (1.72–1.88)***	1.31 (1.22–1.41)***	0.73 (0.67–0.79)***
Other[a]	9.6	12.5	11.6	16.1	16.5	9.2	1.35 (1.27–1.43)***	0.95 (0.86–1.06)	0.71 (0.63–0.80)***

[a] Includes treatment types such as outdoor therapy.
[b] *Note:* Data represent treatment episodes rather than individuals.
** $p < 0.01$.
*** $p < 0.001$.

4.1. Limitations

There are some important caveats to understand about the data available through AODTS-NMDS. While administrative data sets are valuable sources of healthcare information, this data may be subject to biases and potential inconsistencies between services and jurisdiction. For example, only four out of the eight jurisdictions were consistently coding the specific principal pharmaceutical opioid of interest over the time period examined. It is also important to understand the subset of treatment that this data represent, as almost all pharmacotherapy treatments are provided by private prescribers, or clinics that are not reflected in the AODTS-NMDS data. As the data from OST providers does not currently enable a detailed examination of pharmaceutical opioid cases, it is not possible to determine if there may be a selection bias in the data presented here (for example, if codeine cases are more likely to present to, or be referred for, detoxification, due to their perception as 'weaker opioids'). This has been suggested in preliminary studies of codeine users (Nielsen et al., 2014) and is an important trend to monitor, both because of the lesser evidence for short-term opioid treatments, and in terms of understanding the prevalence of codeine dependence and the associated treatment burden.

It should also be noted that data reported are at the treatment episode level rather than representing discrete individuals. It is not possible to estimate the numbers of clients, or what proportion of all opioid treatment is represented by this data set. OST is the most commonly accessed opioid treatment (increasing from approximately 34,000 people in 2002, to 46,446 people in 2011). Notwithstanding this, the AODTS-NMDS represents the majority of non-OST treatment, and further, many people in OST may be receiving additional services such as counselling that are represented in this data set. Planned changes will enable analysis of these data at a client level in future years, which will support trend analysis, and allow better comparisons with other client/person-based data collections (Australian Institute of Health and Welfare, 2014b). Finally, due to the inability to classify methadone and buprenorphine treatment episodes they were not included in this analysis. There is evidence that methadone and buprenorphine are drugs of concern in their own right (Cicero et al., 2014; Jenkinson et al., 2005; Ritter and Di Natale, 2005) meaning that the treatment demand related to pharmaceutical opioids is likely to be greater than that estimated by the data here.

Despite these limitations, this provides a detailed first look at changes in non-OST treatment episodes relating to pharmaceutical opioids and heroin over time. The changing patterns observed, and their potential implications on treatment delivery support the importance of monitoring specific opioids in other regions with emerging patterns of PO use, such as Europe and Asia (Casati et al., 2012; Larance et al., 2011). Examining treatment demands and patterns relating to codeine, oxycodone and fentanyl, in addition to other indicators of harm will be of particular importance in the future as national and international data suggests the non-medical use of these opioids continues to increase (Atluri et al., 2014; Australian Institute of Health and Welfare, 2014a; Fischer and Argento, 2012). While considerable international research has focused on oxycodone, codeine appears to be an important pharmaceutical for which numbers of treatment presentations are increasing, and a changing demographic appear to be encountering problems with their codeine use over time.

4.2. Conclusion

There have been striking changes in the number and profile of treatment episodes related to heroin and prescription opioids over the past decade. For treatment services, monitoring the changes in treatment data may help to inform the unique service needs of this

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newer population of opioid dependent people and tailor service provision to these changing patterns of opioid use.

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Contributors

The study was conceptualized by S.N. and L.D. All authors had input proposed analysis, S.N. and R.B. completed the analysis. All authors were involved in the interpretation of the results and writing of the manuscript.

Conflict of interest

None of the authors have any connections with the tobacco, alcohol, or gaming industry. Authors SN, NL and LD have been investigators on untied educational grants from Reckitt-Benckiser, and NL has received honoraria from Reckitt-Benckiser to present at professional development courses. LD, RB and NL have received an untied educational grant from Mundipharma for post-marketing surveillance studies of Reformulated OxyContin® (the National Opioid Medication Abuse Deterrence, or NOMAD, study). All other authors have nothing to declare.

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None.

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painaustralia
working to prevent and manage pain

Submission
Proposed Amendments to Poison Standards (Medicines)

Who we are:

Painaustralia is a national not-for-profit body formed in 2011 to work with governments health care professionals, consumers, funders and other stakeholders to implement the recommendations of the National Pain Strategy. [1]

We write with regard to the proposal for the Advisory Committee on Medicines Scheduling to consider deletion of the Schedule 3 entry for codeine and reschedule the current Schedule 3 codeine entry to Schedule 4 due to potential issues of morbidity, toxicity and dependence.

Recommendation:

Painaustralia supports measures to ensure the safety and quality of medicines available to the public, however we are concerned that this focus on the rescheduling of codeine, ignores the much bigger community health issue of managing chronic pain which affects one in five Australians including adolescents and children and one in three people over the age of 65.

The issues around misuse of codeine and simultaneous efforts by government to cut unnecessary costs from the health system highlight the urgent need for government to address the massive health and economic burden of chronic pain, by implementing the National Pain Strategy (NPS).

The NPS offers a comprehensive nationwide plan to improve the management of chronic pain through use of non-pharmacological strategies. This is by far the most effective way of dealing with inappropriate reliance on analgesics like codeine and other opioids which pose an even greater safety risk, and reducing hospitalization and demand for other health services.

Evidence for this:

In NSW, which is implementing a State-wide Pain Management Plan in line with the NPS, and in some other health districts we are already seeing improved

[1] National Pain Strategy
http://www.painaustralia.org.au/images/pain_australia/National%20Pain%20Strategy%202011%20Exec%20Summary.pdf

health outcomes with reduced demand for pain services in public hospitals and reduced reliance on pain relief medications and other health services, including surgery.

Benefits are being achieved through:

- Education and training of health care professionals to equip them to better treat people with chronic pain using a holistic approach involving special exercise and psychological strategies which are more effective than medication alone. GPs have great difficulty in managing people with chronic pain which is a complex condition, influenced by multiple factors including physical, genetic, psychological and family and workplace environments. Effective treatment requires the involvement of trained allied health professionals working as part of a GP led team.

- Education of consumers – people living with pain, their families and carers to assist them develop active self-management strategies which help control their pain, minimize reliance on medication and reduce use of hospital- based services including surgery. [2]

- **Economic Benefits to Government and Employers:**

In addition to positive patient outcomes the National Pain Strategy offers economic benefits to government and the business community. Chronic pain- primarily back problems and arthritis- is the most common reason for people to drop out of the workforce accounting for 40% of forced retirements – around 280,000 people in 2012. This has a significant economic impact with productivity costs associated with arthritis and musculoskeletal conditions estimated to cost over $7.4 Billion dollars in 2012.

A study conducted by a team at Concord Hospital in NSW has demonstrated that early intervention after injury can prevent development of chronic pain and long term disability, with associated savings of 25% for employers and insurers. A more comprehensive study spanning 18 public hospitals in NSW is currently being run funded by NSW Health and SiCorp (NSW Treasury) with Workcover insurer EML. [3]

[2] Agency for Clinical Innovation – Pain Management Model of Care: Formative Evaluation 2014

[3] Pre Budget Submission 2015-16
http://www.painaustralia.org.au/images/pain_australia/HomePageNews/PA9847_2015_16_Pre_Budget_Submission_FA_LR.pdf

painaustralia
working to prevent and manage pain

A Duty to Care for People in Pain:

People living with chronic pain are desperate to get relief and half of these people suffer an associated mental disorder such as depression or anxiety. If effective solutions are not available – they will resort to potentially unsafe options including misuse of codeine and even stronger opioids, illegal drugs, alcohol and in desperate circumstances, suicide.

The Government has a duty of care to these people, many of whom will live for years with poorly treated pain, frequently stigmatized by family, work mates and even health professionals and becoming frustrated, angry and in many cases, progressively disabled. And as our population ages, becoming an even greater burden on the health system and the economy.

Community-wide Education is Urgently Needed:

There is an urgent need for community wide education about quality use of medicines in pain management and best practice non-pharmacological strategies for chronic pain. We urge the government to fast-track the proposed community education program currently being planned by NPSMedicinewise. We believe GP clinics and community pharmacies both play a critical role in facilitating this education.

We also support proposals for mandatory monitoring of selected medications listed under Schedule 3, 4 and 8. (including OTC codeine) to minimise potential for misuse.

We request your serious consideration of this submission and hope that recommendations will take into account the urgent need to address the massive health and economic burden of chronic pain.

We believe there is a significant opportunity the Federal Government to show leadership by making this a priority focus for the new Primary Health networks, building on work that was commenced by Medicare Locals.

[redacted]

Waitemata
District Health Board
Best Care for Everyone

CADS
COMMUNITY
ALCOHOL & DRUG
SERVICES
Te Wai Awhina
Rongoatia O Tamaki

Community Alcohol and Drug Services
50 Carrington Rd
Pt Chevalier, Auckland 1025
New Zealand

7 May 2015

The Secretary,
Advisory Committee on Medicines Scheduling
Therapeutic Goods Administration
136 Narrabundah Lane
Symonston ACT 2606
Australia

Dear Sir or Madam

RE: Proposed amendments for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling (Codeine)

We write to you to in support of the proposal to amend the scheduling of codeine from pharmacist only (schedule 3) to prescription only (schedule 4) in Australia, with the rationale that such a change in Australia is likely to result in similar consideration of codeine scheduling in New Zealand (NZ), and lead to a subsequent reduction in the incidence of opioid related harm and dependence in the NZ community.

Community Alcohol and Drug Services (CADS) is a regional service in Auckland, comprised of both detoxification and opioid substitution services as well as a number of other specialist services. CADS is the largest alcohol and drug service in Australasia, and our opioid substitution service manages 1200 patients, around one quarter of the total number of opioid dependent patients currently in treatment in NZ. We imagine that the committee will have received a number of substantive submissions from similar services in Australia, and with that in mind we will provide a brief account of our reasons for supporting this proposal.

Over the counter (OTC) codeine containing preparations have been the primary drug of dependence for an increasing number of patients presenting to our services in recent years. A study conducted in 2010 found that 8% of all new attendances of patients to CADS detoxification services over a 12 week period were dependent upon OTC codeine containing products[1]. Around two thirds of these patients had recently been hospitalised as a result of their OTC codeine use. An audit of new admissions to our opioid substitution treatment service in 2012-2013 found that around 14% of 197 admissions in that timeframe had been using OTC codeine containing products in the 4 weeks prior to treatment entry[2].

Escalation of dose is a core feature of opioid dependence and as dependence develops recommended doses of OTC codeine products are routinely exceeded, exposing the user to well documented medical sequellae[3]. Additionally, once opioid dependence is established, there is a risk of transference to other sources of opioid, either prescribed or illicit, with accompanying increases in mortality risk. This has been demonstrated with findings of temporal relationships between changes in prescription opioid and heroin overdoses in the United States [4].

It is our view that the public health benefits of rescheduling over the counter codeine preparations to prescription only outweigh any risk of reducing access to pain relief in the community. The efficacy of codeine as an analgesic in the doses currently regulated in OTC preparations is low, and is not superior to paracetamol or ibuprofen alone [5]. We note that according to one author, the efficacy of the combination of codeine and ibuprofen or paracetamol has never been determined [6].

We hope that this information is of assistance to you in assessing the likely impact of the proposed scheduling changes. Thank you for the opportunity to submit feedback to this proposal. We are happy to provide clarification or further information should that be required.

Yours faithfully

[redacted]

[redacted]

[redacted]

1 McAvoy B, Dobbin MDH, Tobin C. (2011) Over-the-counter codeine analgesic misuse and harm: characteristics of cases in Australia and New Zealand. NZMJ 124;(1346) 29-33.

2 Walters C, Gray A. (2014) Unpublished data. Audit of opioid use at admission to Auckland opioid treatment services 2012-2013.

3. Frei MY, Nielsen S, Dobbin MDH, Tobin CL. (2010) Serious morbidity associated with misuse of over-the-counter codeine and buprofen analgesics: a series of 27 cases. MJA 193, 294-296.

4 Kolodny A, Courtwright DT et al (2015). The prescription opioid and heroin crisis: A public health approach to an epidemic of addiction. Annu. Rev. Public Health 36:559–74

5 Derry S, Moor RA, McQuay HJ (2010) Single dose oral codeine, as a single agent, for acute postoperative pain in adults. Cochrane Database Syst Rev 4;CD008099.

6 Anderson BJ (2013). Is it farewell to codeine? Arch Dis Child 98(12): 986-988

ATTACHMENT TO TGA SUBMISSIONS COVER SHEET;

[redacted]

[redacted]

To whom it may concern,

I think the suggestion to further restrict the availability of codeine containing medication unreasonable, and maybe even a little alarming. Well meaning as I'm sure the proposed changes are, and as well qualified the decision makers may be, a balanced panel must include equal people who themselves have experienced chronic pain. Secondly, a decision to further restrict codeine availability must accompany an actually real world alternative.

I have been using codeine [redacted]) regularly for the past two years. Through a work place injury to my lower back two years ago (see foot note if needed), and apparently an unhealed foot fracture that I dismissed as a bad bruise, I have now gotten myself into a place of debilitating pain that persists for 24 hours of every day. I cannot sit or stand in the same place for more than 20 mins. Simple tasks requiring even a slight but sustained bend, like shaving, cleaning my teeth, washing dishes are literally agony. Despite some very enthusiastic and determined attempts, I have been unable to work again since. This is by the way the first time ever in the past 34 years I have not worked. More importantly though for the perspective of this submission, my hopefully temporary disability has actually forced me into the enviable position of trying doing things I really want to do. I say "more importantly" because now there can be no doubt that I am purely trying to relieve pain, rather than relieve pain *and* make tasks like work, that I've mostly hated to this point, a little easier. In other words, I believe I am not using any psychological excuse for using codeine.

I include in "things I really want to do", retraining via online university studies. I initially attempted a pre-apprenticeship in metal fabrication, but this soon proved impossible. Apart from studies, I'm an obsessively keen food plant gardener, which includes bush walking to collect specimens; amateur master chef; trying to get an old Lada car roadworthy again (I had to sell my newer car); and "Tracking" with my fantastic little dog. Even these pursuits are extremely limited, if not close to impossible though at the moment. Pain quickly becomes so distracting that I can't enjoy these things and just have to stop.

I very regularly consult my GP about this. I have no money left to use the private medical system, so I have to add to the already absurdly over burdened public one. My GP sent Rheumatology referrals to two major hospitals. The first to reply gave me an appointment that was 17 months away. I have also been advised that the waiting list for treatment at a public chronic pain management clinic is at least two years long. I have pleaded with my GP as to what I am supposed to do in the mean time. Her reply was (very apologetically) there's nothing else she could do for me. Try another doctor? Firstly, many clinics in my area are unable to take new patients, and second, I already had. After our family GP of 30 years retired, it took me about 3 years to find the one I see now, who is otherwise fantastic. I am well aware of the dangers of "doctor shopping", or presenting to ED for "one-off" prescriptions and do not want to, and should not have to, do this.

Unfortunately, the medication that she is willing to prescribe is simply not adequate for me to have any sort of “life”. This is not withstanding just having to endure pain all day every day. This includes her sanctioning of any form of opiate medication. It seems that the current medical thinking places the spectre of addiction above all else. Of course this is a consideration, and one that I have experienced. In the past, for around three years, the issues with my teeth (see footnote), again caused unbearable pain. Had I not refused to wear dentures, I may have avoided this, so one could argue that this pain was of my own doing. The point is though, I did find myself with codeine dependency, I was aware of this, and I forced myself to stop once dental treatment had progressed to the point of relieving the more acute pain. There was at least a four gap, until two years ago, without any codeine use whatsoever.

Yes, codeine can be addictive, in the full sense of the WHO definition. From what I have read though, these more severe consequences are limited to very few. Many many more of us have to be concerned merely with tolerance and withdrawal aspects. With a little discipline and research and maybe support, these aspects are successfully dealt with and are far far outweighed by the pain relief obtained. Why always does it seem that decisions like this have to be biased for the very few, at the expense of the majority. And, before we label a medication as addictive, hence a user addicted, I think it is absolutely crucial too to fully distinguish wether the user has become “Addicted”, or is just understandably desperate to obtain the pain relief provided.

In terms of toxicity, from what I have surmised, the dangers here result from excessive paracetamol and/or ibuprofen consumption, rather than from the codeine itself. If this is the case, it seems illogical to me to consider further restricting codeine just because it is currently packaged with unnecessary amounts of paracetamol or ibuprofen. I actually worked for several years at a pharmaceutical company- compounding Panadeine and Cold and Flu tablets. Not only would it be simple to replace some of the paracetamol with some more corn flour, the makers would save money.

Finally, I have also read that the proposal to further restrict codeine availability is made more straightforward because it is an inadequate pain killer anyway. This really baffles me. I would love to not have to go through the stigma, glares and interrogations from pharmacists, and in front of all the other customers!, if the codeine containing medication I use was not effective. The trip to the chemist is something I really dread.

So I have to ask- are any of the decision makers sufferers of chronic pain, of the crippling sort, that’s with them 24 hours of every day, who while condition is diagnosed, cannot obtain relief from what doctors are currently willing (ethically?) to prescribe, pain that quickly takes the pleasure from hobbies, artistic pursuits, recreation, even quietly reading, ruins sleep, let alone those things that one doesn’t want to do.

And if it is decided to restrict codeine availability further, can you please provide a viable alternative that actually will work in the real world, taking into account treatment waiting lists and the needs of the majority of pain sufferers who just desperately want some form of life.

Thank you for taking my submission into consideration.

Sincerely, [redacted]

FOOTNOTE:

Just over two years ago I hurt my lower back at work, for which of course, I do need to take some responsibility. The situation was a team of three, processing (blending, crushing, cleaning up) four and thousand tonnes of copper ore that had been shipped from Peru. The mining company we worked for was extremely keen to prove the viability of their novel extraction technique- we were very much “under the pump”. The work was exceedingly strenuous, and my colleagues were much younger, bigger and stronger and younger than me (I am nearly 50). Though in past work situations, I have excelled in daily forklift driving despite (secretly) having an eye condition that, while I can easily pass any standard workplace/driving eye test, makes my vision unreliable. My co-worker was exceptionally gifted and it quickly became clear that he was going to do most of the forklift driving and me, more of the (heavier) manual tasks. Importantly too, while the mining company obsessively promoted their culture of safety above all else and once all the boxes had been ticked were beyond reproach. Underneath this facade, by ourselves in our temporary converted warehouse, under unrelenting pressure from management; apart from some level of common sense, anything goes, as long as we get the ore back to them in time.

I have to take some responsibility of course, I could have said NO. However, the pay was generous for those 14 months. My earning capacity in the past had been severely restricted in the past my eye condition, exasperated by having to pay for 3 corneal grafts and 4 attempts at laser surgery to try to fix it.

Additionally, as I refuse to wear dentures, my teeth have cost me over 17 thousand dollars over the past 8 years, with two implants still required. This has included in hospital surgical attempt to try to remove an abscess; seemingly endless periodontist visits to try to control gum infection; 3 incisor root fillings; 5yrs 5mths orthodontics , followed by orthognathic surgery to correct the my original bite problem; and now 2 front implants - I felt desperate for that money and I kept going.

Consumers
Health Forum
of Australia

Submission on Proposed Amendments to the Poisons Standard (Medicines)

May 2015

Introduction

The Consumers Health Forum of Australia (CHF) is the national peak body representing the interests of Australian healthcare consumers. CHF works to achieve safe, quality, timely healthcare for all Australians, supported by accessible health information and systems.

The TGA is seeking comments on some proposed amendments for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling (ACMS). We welcome the opportunity to provide comments on the proposals as we want to ensure that Australian health consumers have access to affordable and appropriate medicines to ensure we have the best health outcomes.

Our submission reflects the consultations we have undertaken across our membership to ensure we cover the issues around the place of codeine in a broader pain management regime. In particular it includes input from Chronic Pain Australia.

The Proposal

This submission addresses the proposals around the scheduling of codeine. The proposed amendments are:

- delete the Schedule 3(S3) entry for codeine and reschedule the current Schedule 3 codeine entry to Schedule 4(S4);
- consideration may be given as to whether all current Schedule 3 preparations should be rescheduled to Schedule 4, or whether any rescheduling to Schedule 4 should only apply to combination analgesic products containing codeine; and
- consideration may be given as to whether the Schedule 2 entry for codeine should also be amended.

The rationale for the proposed amendment is that there are potential issues of morbidity, toxicity and dependence around the use of codeine that make it preferable to move it to away from an over the counter medicine to one requiring a prescription.

Issues

Painaustralia estimates that one in five Australians live with chronic pain and this rises to one in three for people over 65 years[1]. In addition there are people who have episodes of pain at some time during their lives. All of these people are looking for safe and appropriate access to effective medicines to deal with the pain. Consumers want medicines to be affordable and they want to be able to get them when they need them and use them to manage their own lives.

CHF acknowledges that there is quite a significant body of evidence that shows the problems that can arise from the use of OTC codeine analgesics. There is also evidence that the number of people overusing codeine and the numbers presenting with symptoms of toxicity and dependence is growing. We share the Faculty of Pain Medicine's and other clinicians concerns about this growing problem. However we believe they still only account for a minority of people who use codeine. We believe the majority of users, particularly those using it for ongoing or chronic pain, are using

[1] http://www.painaustralia.org.au/the-national-pain-strategy/why-we-need-the-nps html

responsibly and many would be doing so as part of a pain management plan that they have developed with their doctor.

Codeine is used for both short term pain relief and assisting with chronic or ongoing pain. It is important to look at both situations when assessing the proposal to reschedule.

Codeine is often used as a first aid only medication to deal with a sudden onset of pain, often on a one use only basis and or as a stop gap until the person is able to see a GP or other health professional such as a dentist if that is what they need. The codeine product is only supplied after discussion with a pharmacist who is well qualified to assess the request and make other recommendations if they think codeine is not the appropriate pain relief. Requiring people to get a prescription for such use means they cannot access the pain relief they need until they are able to access a GP which can take some time and may cost them more money if they do not access a bulk billing GP. As well as the negative impact on the consumer it puts extra pressure of GP services and increases Government expenditures.

For codeine taken more regularly to address chronic or ongoing pain the situation is more complex. For many types of codeine taken in combination with other analgesics is an integral part of their pain relief regime. They value their access to it as and when required and the fact they can self- manage control their use of it.

There are a number of disadvantages of the proposed rescheduling. The first is that it could mean increased costs to consumers as they will have to pay for a GP appointment unless they are able to see a GP who bulk bills. There are other costs involved in getting to a GP which will also have to be borne by the consumer. Requiring people to attend a GP will put increased pressure on GPs and increased cost to government for the GP visits.

Many consumers are concerned with the reduced access to necessary pain relief particularly in areas where it is hard to get a GP appointment, or out of hours etc.

There is also the possibility that if people have to go to a doctor for a codeine script then they may end up being prescribed inappropriate antibiotics or stronger S8 medications which are more expensive.

People can and do misuse prescription products so rescheduling will not address the issue of codeine misuse. There are two alternative measures that could help to minimise misuse and not have the negative consequences for responsible users. These were both raised by all the organisations with whom we consulted. Whilst these are not within the control of the TGA or the ACMS we include them to demonstrate that there are other ways to address the concerns of the clinicians.

The first is the implementation of real time monitoring. There is no nationally coordinated mechanism for collection, analysis or reporting of data on dispensing and usage of codeine. As a first step pharmacists should record all sales of OTC analgesics containing codeine in their dispensing systems. This would allow them to monitor usage by individuals and should assist with identifying people who are in danger of over using.

To address the issue of consumers going to multiple pharmacists and /or multiple doctors to disguise their usage there needs to be a national register with real time recording and monitoring. The Pharmaceutical Society of Australia has identified the benefits of the Electronic Recording and Reporting of Controlled Drugs (ECRRCD) initiative which was funded under the Fifth Community

Pharmacy Agreement and has suggested there should be a national rollout.[2]ECRRD would allow prescribers and pharmacists to access real-time date relating to patient or consumer, drug dispensed and any previous dispensing history.

The second is the need for increased pain management resources and a public awareness campaign on the quality use of pain medicines. The proposed changes do not address the fundamental issue of a lack of good pain management programs to help people living with unrelieved pain. It also does not address the need for consumers to be more aware of the potential health issues related to the use of certain OTC medications and what alternatives may be available to them.

It is argued by some clinicians that codeine is an ineffective pain relief for many people and that better pain relief can be achieved by using a combination of ibuprofen and paracetamol. Clearly there needs to be an education campaign for both consumers and pharmacists explaining this and encouraging them to switch.

Another part of the awareness campaign would be to have mandatory front of pack warnings about codeine's potential for addiction and to ensure pharmacists warn people of this when dispensing codeine products.

Conclusion

Codeine when used properly has a legitimate place in assisting with the management of pain, both short term and chronic. Whilst acknowledging that there are issues of dependence and toxicity when codeine is misused and that there is some evidence that the rate of misuse is increasing the majority of use is safe and appropriate. Any rescheduling would reduce access, make the medication less affordable and mean that many people suffer from not being able to appropriately manage their pain. Rescheduling penalises people who are using codeine appropriately and would not, on its own, address the misuse issue.

CHF does not support the proposed rescheduling of codeine to Schedule. We would support reviewing the position again if the Government had implemented some of the other measures and the evidence showed that there is still a significant problem of misuse.

[2] PSA 2015 Minimising harm from the inappropriate use of over the counter analgesics: Position statement

Consumers Health Forum of Australia

The Consumers Health Forum of Australia (CHF) is the national peak body representing the interests of Australian healthcare consumers. CHF works to achieve safe, quality, timely healthcare for all Australians, supported by accessible health information and systems.

CHF does this by:

1. advocating for appropriate and equitable healthcare
2. undertaking consumer-based research and developing a strong consumer knowledge base
3. identifying key issues in safety and quality of health services for consumers
4. raising the health literacy of consumers, health professionals and stakeholders
5. providing a strong national voice for health consumers and supporting consumer participation in health policy and program decision making

CHF values:

- our members' knowledge, experience and involvement
- development of an integrated healthcare system that values the consumer experience
- prevention and early intervention
- collaborative integrated healthcare
- working in partnership

CHF member organisations reach Australian health consumers across a wide range of health interests and health system experiences. CHF policy is developed through consultation with members, ensuring that CHF maintains a broad, representative, health consumer perspective.

CHF is committed to being an active advocate in the ongoing development of Australian health policy and practice.

MISUSE AND HARM FROM MISUSE OF SCHEDULE 3 CODEINE COMBINATION ANALGESICS IN AUSTRALIA.

CONTENTS.

Addressing matters mentioned in section 52E of the Therapeutic Goods Act 1989.

Submissions must address a matter mentioned in Section 52E of the 52E of the Therapeutic Goods Act 1989 Section 52E is noted in Box 1.

Box 1.

Section 52E

Secretary to take certain matters into account in exercising powers

(1) In exercising a power under subsection 52D(2), the Secretary must take the following matters into account (where relevant):

(a) the risks and benefits of the use of a substance;
(b) the purposes for which a substance is to be used and the extent of use of a substance;
(c) the toxicity of a substance;
(d) the dosage, formulation, labelling, packaging and presentation of a substance;
(e) the potential for abuse of a substance;
(f) any other matters that the Secretary considers necessary to protect public health.

(2) In exercising a power under subsection 52D(2), the Secretary must comply with any guidelines of:

(a) the Australian Health Ministers' Advisory Council; and
(b) the subcommittee of the Council known as the National Coordinating Committee on Therapeutic Goods (or any replacement subcommittee);

notified to the Secretary for the purposes of this section.

(3) In exercising a power under subsection 52D(2), the Secretary must have regard to any recommendations or advice of the Advisory Committee on Medicines Scheduling or the Advisory Committee on Chemicals Scheduling.

(4) In exercising a power under subsection 52D(2), the Secretary may seek advice from either or both of the following:

(a) any committee that the Secretary considers appropriate (whether or not the committee is established under this Act or the regulations);
(b) any person.

(5) Subsections (2) to (4) do not limit the information the Secretary may consider in exercising a power under subsection 52D(2).

Accessed from: **http://www.austlii.edu.au/au/legis/cth/consol_act/tga1989191/s52e html**

In addressing the proposal:

> "To delete the Schedule 3 entry for codeine, and reschedule the current Schedule 3 codeine entry to Schedule 4 due to potential issues of morbidity, toxicity and dependence.
>
> Consideration may be given as to whether all current Schedule 3 preparations should be rescheduled to Schedule 4, or whether any rescheduling to Schedule 4 should only apply to combination analgesic products containing codeine.
>
> Consideration may be given as to whether the Schedule 2 entry for codeine should also be amended.

The current Schedule 3 entry for codeine is described in Box 2:

Box 2.

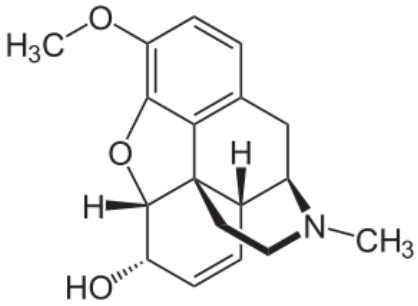
CODEINE when:
(a) not combined with any other opiate substance;
(b) compounded with one or more other therapeutically active substances, of which not more than one is an analgesic substance:
(i) in divided preparations containing 12 mg or less of codeine per dosage unit; or
(ii) in undivided preparations containing 0.25 per cent or less of codeine;
(c) labelled with a recommended daily dose not exceeding 100 mg of codeine; and
(d) in packs containing not more than 5 days' of supply at the maximum dose recommended on the label,
except when included in Schedule 2.

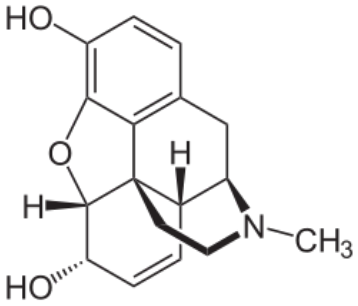
Addressing matters mentioned in Section of the 52E of the Therapeutic Goods Act 1989

(a) the risks and benefits of the use of a substance;

RISKS. Codeine is an opioid present in opium in small quantities, but pharmaceutical codeine is manufactured from morphine by methylation to produce 3-methylmorphine, also known as codeine.

Codeine itself has little analgesic action and requires demethylation back to morphine, to exert its analgesic activity. It is a prodrug for morphine, a powerful and addictive opioid.





CODEINE (METHYLMORPHINE) demethylation → MORPHINE

Unpredictable codeine metabolism. This conversion to the active morphine differs between different individuals because of pharmacogenomic variability. This means that both the analgesic benefit and the risk of morphine toxicity are unpredictable: patients getting either no analgesic benefit because they are non-metabolisers, or potentially toxic morphine levels because they are ultra-metabolisers, resulting in morphine levels that in some cases have led to death.

This unpredictable effect and the incidence of deaths because of this have led to some authors to reassess the place of codeine in the current Western pharmacopoeia[1] [2].

Addiction. Codeine is an opioid, and as such is subject to addiction. This addiction risk is well recognised. In effect, as a prodrug of morphine, it is an addictive opioid.

Addiction is one of the most serious adverse drug effects of opioid drugs.

While codeine is present in low dose in Schedule 3 preparations, because of its easy accessibility it is used by about 1 in 3 Australian adults, exposing vulnerable individuals to the risk of addiction. An estimate 16 million packs are sold each year.

Certain categories of risk have been described, and are incorporated into screening instruments such as the Opioid Risk Tool (ORT) that medical practitioners are encouraged to use in assessing patients prior to prescribing prescription opioids. Categories in the ORT include: a personal history of psychological disease – ADD, OCD, schizophrenia, depression; a family or personal history of

[1] Anderson BJ. Is it farewell to codeine? Arch Dis Child 2013;98:986-8.
[2] Iedema J. Cautions with codeine. Aust Prescr 2011;34:133–5.

substance abuse, and a personal history of preadolescent sexual abuse. Many of these conditions are prevalent in Australian society, and involve asking intimate questions more suited to take place in the privacy of a consulting room rather than in the public space of a community pharmacy, possibly in the hearing of other customers.

The addictive nature of codeine in OTC codeine analgesics is demonstrated in descriptions of the results of addiction described in the medical and published literature recounted in Attachments A and B of the attached document.

Secondary harm from non-opioids combined with codeine. Combination analgesics provide a unique and dangerous risk: one of the defining characteristics of addiction is the escalation of dose, and it is this escalation of dose of not only codeine, but the fixed dose of the accompanying non-opioid analgesic that leads to prolonged exposure to high and potentially toxic doses of these other analgesics, that cause hepatotoxicity from paracetamol, or serious NSAID adverse drug effects due to high dose ibuprofen described in Attachment A.

Overdose. One of the most serious adverse drug effects of opioids is opioid-induced ventilator impairment (OIVI), sometimes mistakenly described as respiratory depression. This description is incorrect and incomplete, because it does not describe the upper airway collapse that often results from opioid overdose. There have been a number of poisoning deaths involving OTC codeine analgesics, usually in combination with other CNS depressants, but often involving codeine blood levels well above therapeutic levels, with the presence of the non-opioid analgesic with which codeine is combined in OTC preparations also present in blood.

It is regrettable that these non-opioid analgesics, which are relatively low risk in over-the-counter formulation doses, when combined with codeine, lead to serious harm.

BENEFITS. Codeine is a weak opioid, described as a 'mild opioid' in the World Health Organisation pain ladder for adults[3]. A recent Cochrane review describes that the number of people necessary to treat with codeine post-operatively for one of them to achieve 50% or more pain relief in the 4-6 hours after surgery is 12 (NNT = 12)[4].

The addition of non-opioid analgesics provides little additional analgesic benefit.

Codeine and Ibuprofen. Derry et al (2015) compared the combination of ibuprofen 400mg/codeine 25.6-60 mg (high dose codeine) with ibuprofen 400 mg alone[5]. When the combination was compared to the same dose of ibuprofen alone, the relative benefit was 1.4 (95% CI 1.01-1.6). With the confidence interval almost overlapping 1, the authors commented that the difference only just reached statistical significance. The NNT for the ibuprofen-codeine combination compared with ibuprofen alone was 7.1 (3.7-12.6). The combinations assessed included those with 60 mg codeine.

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[3] World Health Organisation. WHO's pain ladder for adults. http://www.who.int/cancer/palliative/painladder/en/

[4] Derry S et al. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. *Cochrane Database Syst Rev.* ; (4): CD008099. 2010

[5] Derry S, Karlin SM, Moore RA. Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No.: CD010107. DOI: 10:1002/14651858. CD010107.pub3. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010107.pub3/pdf/standard

Codeine and paracetamol. Tomes et al compared paracetamol 1000mg with codeine 60 mg with the same dose of paracetamol alone, in a systematic review of the literature[6]. The NNT for at least 50% pain relief over four to six hours was 6.1 (3.6 to 19). For every six participants treated with 800 mg to 1000 mg paracetamol plus 60 mg codeine, one would experience at least 50% pain relief who would not have done so with the same dose of paracetamol alone. The dose of codeine in OTC combination anlagesics in Australia ranges well below this, I many case only 8 mg codeine phosphate.

Thus it can be seen that codeine adds little additional benefit in combination with non-opioid analgesics, but increases the risk of the most serious of adverse effects of opioids: addiction. In the case of combinations, this addiction leads to escalation of dose and serious secondary toxicity.

(b) the purposes for which a substance is to be used and the extent of use of a substance;

PURPOSE OF USE. The medicines under consideration are purportedly used for the treatment of mild or moderate acute pain, and intended for short-term use, reflected in the pack size being limited to 5 days' supply.

EXTENT OF USE. Use of over-the-counter (OTC) codeine analgesics is widespread, with 33.3% (6.34 million) Australian adults aged 14 or more years using them each year[7]. The peak age group for use was 20-29 years (44.1%).

Annual sales of OTC codeine analgesics amount to 16 million packs worth AU$145 million[8].
It is this widespread use, and easy availability without a full assessment of therapeutic need and risk of misuse, addiction and serious harm, or drug-seeking, that makes Schedule 3 availability instrumental in leading to the extent of serious harm currently being experienced. Even the best-intentioned pharmacist is handicapped in the kind of intimate inquiry required to make this asseswsment by the public circumstances of supply in a community pharmacy.

(c) the toxicity of a substance;

TOXICITY. There have now been 250 Australian and New Zealand published cases in the medical literature of patients experiencing secondary harm resulting from opioid addiction to Schedule 3 codeine combination analgesics. These are described in Attachment A in the attached document.

There are also a number of cases of death involving misuse of these analgesics identified by Coroners.

Toxic effects of prolonged exposure to supratherapeutic doses of the NSAID ibuprofen results in serious NSAID pattern toxicity, with many individuals experiencing multiple NSAID comorbidities

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[6] Toms L et al. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Cochrane Database Syst Rev 2009 Jan 21;):CD001547

[7] Australian Institute of Health and Welfare 2014. National Drug Strategy Household Survey detailed report 2013. Drug statistics series no. 28. Cat. no. PHE 183. Canberra: AIHW.

[8] Browne R. Doctors and pharmacists call for tighter controls on codeine due to rise in addiction. Sydney Morning Herald 14 September 2014. *http://www.smh.com.au/nsw/doctors-and-pharmacists-call-for-tighter-controls-on-codeine-due-to-rise-in-addiction-20140913-10g0um.html* Accessed 7 April 2015).

including upper gastrointestinal tract ulceration with perforation and bleeding, together with other manifestations such as chronic blood loss anaemia or renal tubular acidosis, electrolyte imbalance such as potentially dangerous hypokalaemia. Many cases require surgery, transfusion, or intensive care.

There are also a number of cases of paracetamol hepatotoxicity secondary to codeine addiction[9]

(d) the dosage, formulation, labelling, packaging and presentation of a substance;

LABELLING. At present, labelling of Australian packs of these medications is seriously deficient in warning about the risks of addiction. Or that the consumer should not use the product for prolonged period. This is in stark contrast to the information provided to United Kingdom purchasers of these products, where the label: "Can cause addiction. For three days use only" is prominently displayed in large type on the front of the pack. There is also further warning and detail on the back of the pack.

Australian packs do have a warning on the pack, but in type so small that it is difficult to read, and lost among a long list of information on the rear of the pack.

There have been efforts by the Pharmaceutical Society of Australia, and industry represented by the Australian Self Medication Industry, to encourage the Therapeutic Goods Administration to mandate this necessary warning, without success. Nevertheless some of the major companies marketing these products have voluntarily undertaken to label their packs prominently with a similar warning, in recognition of the addictive nature of these products.

PACKAGING: CONSUMER MEDICINES INFORMATION. There is no consumer medicines information (CMI) readily available to the consumer. There is an approved CMI available online, but the provision of this by pharmacists, or access by the consumer, is seriously deficient. For instance CMIs for Nurofen Plus, Panadeine, and Mersydol readily available and prominently presented when searched for, are seldom accessed.

From 01/01/2015 - 31/03/2015, Better Health Channel was accessed as follows during this period:

- Nurofen Plus (rccnurop.pdf) - 17 pageviews
- Nurofen cold and flu (rccnurcf.pdf) - 8 pageviews
- Panadeine (gccpanad.pdf) - 26 pageviews
- Panadeine Forte (swcpanaf.pdf) - 50 pageviews
- Panadeine Extra (gccpanex.pdf) - 12 pageviews
- Panafen Plus (gccpanaf.pdf) - 2 pageviews
- Mersynd0l (swcmersy.pdf) - 7 pageviews

This is despite sales of OTC codeine analgesics amounting to 16 million packs a year.

Inquiries should be made of other online sources of CMI to examine access.

[9] Corduroy A. Paracetamol poisoning: how addiction to over-the-counter medication took Imogen Cunningham's life. Sydney Morning Herald 3 May 2015. http://www.theage.com.au/nsw/paracetamol-poisoning-how-addiction-to-overthecounter-medication-took-imogen-cunninghams-life-20150502-1mye1g.html

There is no evidence of the scale of supply of this CMI by pharmacists, but it appears to be very infrequent. Online provision provides a barrier to provision by pharmacists. The recent investigation of use of CMIs by pharmacists described below reported that pharmacists are reluctant to print out CMIs because of the time and cost involved.

The current CMI provides little effective and accessible information about the risk of addiction, merely referring to the term 'habit forming', which lacks impact, and is buried in the depths of the CMI. This is in contrast to the sample CMI drafted for Mersyndol by a team funded under the pharmacy agreement to investigate CMIs[10].

The information provided in the CMI is a stark contrast to that provided in those included in the United Kingdom packs of these products, which provides in readily understood language the risk of addiction and how to recognise addiction in the customer.

PACK SIZE. Scheduling allows for supply for treatment for five days. In the case of products containing tablets with 15 mg codeine phosphate dosed at 8 tablets a day, this amounts to 40 tablets, altogether providing 600 mg codeine phosphate. This is the same amount of codeine provided by a Schedule 4 prescription for 20 tablets of paracetamol 500 mg/ codeine phosphate 30 mg. It is also the same amount provided by a Schedule 8 prescription for 20 tablets of codeine phosphate 30 mg This is an anomalous situation that provides a substantial amount of codeine without the benefit of a medical consultation in the privacy of a consulting room, access to a medical history in a medical history, and an examination.

It may also be that many pharmacists prefer to stock and sell large pack sizes rather than keep a range of pack sizes, thus facilitating high dose supply to codeine addicts by decreasing the number of pharmacy visits a codeine addicted drug-seeking patient has to visit to sustain a daily intake of 40-8o tablets or more a day.

(e) the potential for abuse of a substance;

ABUSE. Codeine (methylmorphine) is manufactured from morphine, and is a prodrug of morphine, converted in the body to morphine, a powerful and addictive opioid.

It is evident from the accompanying document and attachments that easy and widespread access without the benefit of a medical assessment, consultation of medical history notes, and examination in the privacy of a consulting room, provides for provision of these codeine products for abuse.

DSM IV criteria describing abuse:
☐Tolerance: Does the patient tend to need more of the drug over time to get the same effect?
☐Withdrawal symptoms: Does the patient experience withdrawal symptoms when he or she does not use the drug?
☐ Continued use of drug despite harm: Is the patient experiencing physical or psychological harm from the drug?
☐ Loss of control: Does the patient take the drug in larger amounts, or for longer than planned?
☐ Attempts to cut down: Has the patient made a conscious, but unsuccessful, effort to reduce his or her drug use?

[10] Aslani P et al. Investigating Consumer Medicine Information (I-CMI) Project. THE RESEARCH AND DEVELOPMENT PROGRAM IS FUNDED BY THE AUSTRALIAN GOVERNMENT DEPARTMENT OF HEALTH AND AGEING AS PART OF THE FOURTH COMMUNITY PHARMACY AGREEMENT (2011?)

☐ Salience: Does the patient spend significant time obtaining or thinking about the drug, or recovering from its effects?
☐ Reduced involvement: Has the patient given up or reduced his or her involvement in social, occupational or recreational activities due to the drug?

Descriptions of cases in the medical literature provide good evidence that many of those described meet many of these criteria, including:

- tolerance and the need to escalate the dose reflected in the large number of tablets taken each day (see attachment A
- withdrawal symptoms: many patients have sought help after attempting withdrawal, experience withdrawal symptoms, and come to treatment when they relapse.
- Continued use despite harm: many present multiple times for treatment of the various NSAID comorbidities, and will describe family disruption, and difficulty stopping use.
- Loss of control: patients continue high dose misuse for months or years.
- Other criteria are also described.

MISUSE, ADDICTION AND HARM FROM MISUSE OF OTC CODEINE ANALGESICS IN AUSTRALIA

Summary

- Codeine (methylmorphine) is a weak analgesic, metabolised to morphine in the body.
- Combining codeine with non-opioid analgesics provides limited additional analgesic benefit: seven patients need to be treated with ibuprofen 400 mg/codeine 25.6-60 mg for one to obtain at least a 50% reduction in postoperative pain when compared to treatment with ibuprofen 400 mg alone (NNT=7.1)
- Codeine is an opioid, subject to misuse and addiction.
- OTC codeine analgesics in combination with ibuprofen, paracetamol or aspirin are widely and easily available, with 1 in 3 Australian adults using them each year.
- There have been numerous published reports about misuse and addiction, and secondary harm due to high dose exposure to the non-opioid analgesic with which it is combined.
- Apart from the 250 Australian and New Zealand cases of addiction and serious[11] NSAID toxicity resulting from high dose exposure to ibuprofen described in published reports (Attachment A), it has been difficult until recently to describe the magnitude of the problem
- Several recent data sources suggest that hundreds of Australians are now seeking treatment for addiction to OTC codeine analgesics each year.
- Pharmacists face a number of challenges in preventing supply of OTC codeine analgesics to drug-seeking users addicted to codeine.
- Codeine dependent individuals are able to sustain high levels of use (up to 80 tablets a day) for prolonged periods, usually obtained from multiple pharmacies.
- Despite rescheduling OTC codeine analgesics to require involvement of a pharmacist in supply, the number of people seeking treatment for codeine dependence is increasing.
- Concern about regulatory change to make OTC codeine analgesics more difficult to obtain is mitigated by recent evidence that a combination of ibuprofen and paracetamol provides better analgesia than OTC codeine analgesics, without the risk of codeine addiction.
- There are now two products available on the Australian market (Maxigesic®, and Nuromol®) providing a combination of ibuprofen and paracetamol.

Codeine (methylmorphine) is a weak opioid analgesic with a 200-fold weaker affinity for the mu-opioid receptor than morphine[12]. A single 60 mg dose provides good analgesia to few adults: 12 patients need to be treated for one to achieve a 50% reduction in post-operative pain (NNT 12)[13].

Pharmaceutical codeine (methylmorphine) is manufactured from morphine, and is a prodrug metabolised in the body to morphine, a strong opioid agonist. Conversion of codeine to morphine varies between individuals and is dependent upon genotype: Poor metabolisers receive no analgesic benefit, and ultra-rapid metabolisers may experience toxic concentrations of morphine.

Codeine (methylmorphine) analgesics are marketed as:

- prescription tablets of 30 mg codeine phosphate with or without paracetamol 500 mg, and
- over-the-counter (OTC) (non-prescription) tablets containing low doses of 8-15 mg codeine phosphate combined with a non-opioid analgesic (paracetamol, ibuprofen or aspirin).

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[11] Serious adverse drug events. US FDA describes adverse events as any undesirable experience associated with the use of a medical product in a patient, which are serious if they involve: death, life-threatening, hospitalisation, disability or permanent damage, required intervention to prevent permanent impairment, or important medical events including drug dependence or drug abuse. U.S. Food and Drug Administration. What is a serious Adverse Event? http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm

[12] Crews KR, Gaedigk A, Dunnenberger HM et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. Clin Pharmacol Therapeutics 2014;95:376-82.

[13] Derry S, Moore RA, McQuay HJ. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. Cochrane Database Syst Rev 2010;4:CD008099

Use of over-the-counter (OTC) codeine analgesics is widespread, with 33.3% (6.34 million) Australian adults aged 14 or more years using them each year[14]. The peak age group for use was 20-29 years (44.1%).

Annual sales of OTC codeine analgesics amount to 16 million packs worth AU$145 million[15].

Misuse and addiction to *prescription* opioids in the treatment of chronic non-malignant pain is not uncommon: in a 2015 systematic review and data synthesis of 38 published studies Vowles et al described rates of misuse averaging between 21% and 29%, and of addiction averaging between 8% and 12%[16].

Rates of misuse and addiction might be expected to be lower in the treatment of acute pain with a weak opioid such as codeine (methylmorphine) in low dose OTC codeine analgesics, but even with low risk, the widespread and easy availability exposes a large number of vulnerable individuals to this opioid, and may result in a substantial number of people misusing and becoming addicted.

In 2008 misuse and harm arising from misuse of the OTC codeine-ibuprofen products was referred to the National Drugs and Poisons Schedule Committee. On 1 May 2010 OTC codeine analgesics were removed from Schedule 2 and confined to Schedule 3, requiring supply by a pharmacist.

Since then concerns about this problem have continued, but until recently it has been difficult to describe the magnitude of the problem, and there have been concerns about restricting access to OTC codeine analgesics that might limit the ability of Australians to self-medicate acute pain.

Recent developments.

1. New information about the scale of misuse and harm from misuse (Attachments A and B).

- **Published case studies of serious harm.** More than 20 studies published prior to 2015, including 18 from Australia and New Zealand, have described cases of serious harm from misuse of OTC codeine-ibuprofen analgesics, including life-threatening harm. Together, published A&NZ reports have described 250 cases (224 Australian and 26 NZ). Published cases represent only some of those from the serious-harm end of a broad spectrum of cases.

  Multiple cases suggest that harm is more common. Seven published case series describe multiple cases of serious NSAID pathology at single institutions and another 4 describe multiple cases from a single addiction treatment agency/agent, suggesting these adverse outcomes are more common than if only a single case was identified at each.
- **Neilsen et al (2014)** investigated the characteristics of 145 clients presenting for treatment of opioid dependence on pharmaceutical opioids in 3 NSW local health districts[17]. They identified 145 patients, of whom 53 (36%) nominated codeine as their principle opioid of concern. Of these, 47 (94%) reported OTC codeine as their source, and 3 (6%) reported prescription codeine as the source. The source was not reported in 3 cases.
- **Nielsen et al (2015)** described changes in treatment for opioid dependence that did not involve opioid substitution treatment (OST) in government funded drug and alcohol services

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[14] Australian Institute of Health and Welfare 2014. National Drug Strategy Household Survey detailed report 2013. Drug statistics series no. 28. Cat. no. PHE 183. Canberra: AIHW.

[15] Browne R. Doctors and pharmacists call for tighter controls on codeine due to rise in addiction. Sydney Morning Herald 14 September 2014. *http://www.smh.com.au/nsw/doctors-and-pharmacists-call-for-tighter-controls-on-codeine-due-to-rise-in-addiction-20140913-10g0um.html* Accessed 7 April 2015).

[16] Vowles KE, McEntee ML, Julnes PS et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain 2015;156:569-76.

[17] Nielsen S et al. Comparing treatment-seeking codeine users and strong opioid users: Findings from a novel case series. Drug Alc Review 2014. Dec 29. doi: 10.1111/dar.12224.

in four states: treatments included withdrawal, counselling, case management and support, and residential rehabilitation services[18]. They describe an increase in treatment from 193 treatment episodes in 2002-03 to 666 in 2010-11 where codeine was the principle drug of concern. Data did not include treatments in other States/Territories or treatment by private practitioners or clinics.

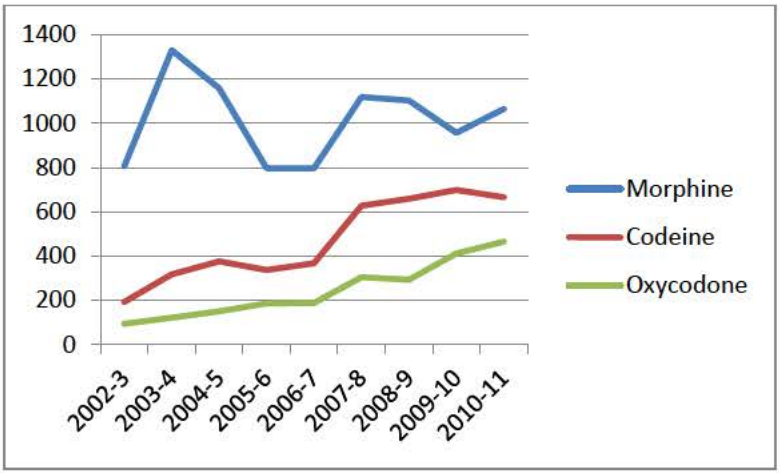

Figure: Number of closed non-OST treatment episodes where morphine, codeine, oxycodone were reported as the principal drug of concern in public AOD clinics in Queensland, New South Wales, Tasmania and South Australia.

- **National Opioid Pharmacotherapy Statistics (NOPS).** In 2014 the National Opioid Pharmacotherapy Statistics (NOPS) reported the primary opioid of concern for people treated with opioid substitution treatment (OST) for opioid dependence[19]. On a snapshot day in 2013 there were 47,576 clients treated for opioid dependence, with the primary opioid of concern reported for 26,229 (55%). Of these about one-third (33%) reported pharmaceutical opioids as the principle drug of concern, including codeine for 1038 clients (4%). There was no information whether the source was prescription or non-prescription (OTC) codeine.
- **Estimate from NOPS data and Nielsen et al's fraction (94%) of OST.** If Nielsen et al's (2014) fraction of codeine dependent patients presenting for treatment in NSW (94%) was applied to the national figures of 1038 clients dependent on codeine in 2013, it suggests an estimate of 975 Australian clients being treated with OST for dependence on OTC codeine in 2013. This is likely to be a substantial underestimate because principle drug of concern was not reported for 45% of patients on pharmacotherapy for opioid dependence.
- **Trends in number of treatment episodes at Warinilla Drug and Alcohol Treatment Centre (Adelaide).** There has been a steady increase in the number of treatment episodes for clients for whom the principle drug of concern was codeine, except for a decrease in fiscal year 2010-2011.

  The source in all cases was non-prescription (OTC) codeine.

  The number of treatment episodes increased from 31 in 2002-2003 to 174 in 2013-2014. This was an increase from 2.6% to 15.9% of treatment episodes for all opioids (including heroin), and from 7.8% to 26.6% of all pharmaceutical opioids over this period.

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[18] Nielsen S, Roxburgh A, Bruno R et al. Changes in non-opioid substitution treatment episodes for pharmaceutical opioids and heroin from 2002-2011. (Drug Alcohol Depend 2015), http://dx.doi.org/10.1016/j.drugalcdep.2015.02.004

[19] Australian Institute of Health and Welfare 2014. National opioid pharmacotherapy statistics 2013. Drug treatment series no. 23. Cat. no. HSE 147. Canberra: AIHW. Table A9.

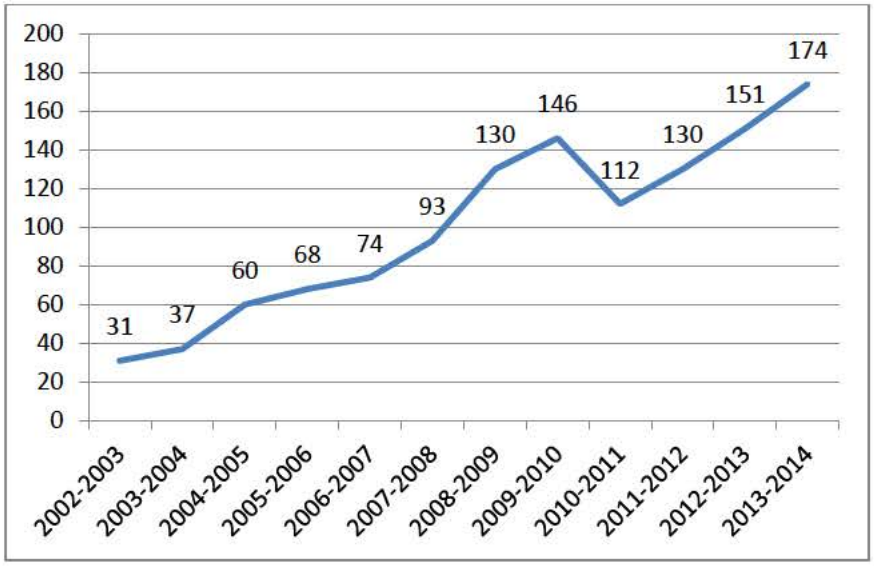


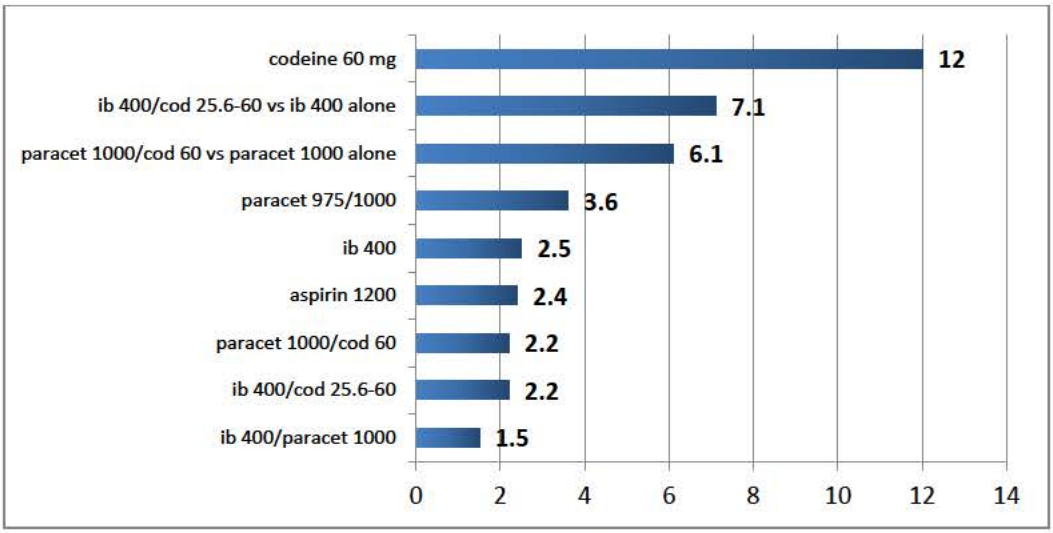
Figure: Closed opioid episodes for codeine: Warinilla, by FY 2002-14

- **Western Australia** began identifying treatment episodes for OTC codeine preparations in all State Government funded AOD services in WA including Next Step in December 2013. In 2013/14 there were 121 episodes, and in the 6 months July – December 2014 there were 176 treatment episodes.

2. Cochrane evaluation of analgesic efficacy of oral analgesics (Attachment C).

A number of Cochrane Database Systematic Reviews have examined the analgesic efficacy of oral medications. They found that the addition of codeine to ibuprofen added limited analgesic benefit to that of the same dose of ibuprofen alone (NNT 7.1)

The figure below summarises the Cochrane systematic review findings.



Note: ib = ibuprofen, cod = codeine, paracet = paracetamol, unit for numbers is mg.
Note: 2nd and 3rd top bars refer NNT for additional benefit of adding codeine to a similar dose of non-opioid analgesic alone.

Fig: Number needed to treat (NNT) for at least 50% maximum pain relief over 4-6 hours for acute postoperative pain, compared to placebo, or the codeine combination compared to the same dose of the non-opioid analgesic ibuprofen or paracetamol alone (2nd and 3rd top bars).

3. **Recent studies of the analgesic efficacy of a combination of ibuprofen and paracetamol.**

Self-medication of minor conditions is desirable for a number of reasons, and acute pain is a prevalent condition suited to self-medication if this is safe. Arguments to support continued availability of OTC codeine combination analgesics have included the need for consumers to effectively manage acute pain.

A number of studies have now identified that combinations of ibuprofen plus paracetamol provide superior analgesic efficacy to OTC codeine combination analgesics. One study reported that 1 or 2 tablets of a single-tablet combination of ibuprofen 200 mg/paracetamol 500 mg were statistically significantly more efficacious than 2 tablets of paracetamol 500 mg/codeine 15 mg. Two tablets offered significantly superior pain relief to ibuprofen 200 mg/codeine 12.8 mg (P = 0.0001), and 1 tablet was found noninferior to this combination [20].

There are now two brands of combination ibuprofen 200 mg/paracetamol 500 mg on the Australian market: Maxigesic®, and Nuromol®, introduced by Reckitt Benckiser in 2015.

4. Is pharmacy the appropriate setting to provide OTC codeine analgesics subject to misuse?

Pharmacists are aware that people seek OTC medicines for purposes other than therapeutic use. A UK pharmacist provided the first published report in 1998 in a letter to the Pharmaceutical Journal, warning about the ease of separating ibuprofen from codeine in Nurofen Plus as it was then constituted[21]. Pates et al (2002) summarised a number of surveys of pharmacists' experiences from Northern Ireland, Scotland, the United Kingdom and South Wales, reporting that they identified a number of OTC drugs as medicines sought for non-medical use[22] . Opioid-containing preparations were among the leading medicines sought.

Australian pharmacists are concerned about the potential for adverse consequences from misuse of OTC codeine analgesics[23].

Surveys of pharmacists and codeine dependent people seeking OTC codeine describe a number of themes about the difficulty of managing the safe supply of OTC codeine analgesics [24] [25] [26]:

- Many pharmacists rely on the appearance of customers, some thinking that codeine dependence was based on deviance and a deteriorating general appearance
- Codeine dependent users recognise the need to manage their attire, presentation and appearance. Good appearance was linked to their ability to ensure codeine supply
- Codeine dependent users report that access to OTC codeine was 'easy', and they mostly purchased it themselves
- Codeine dependent subjects report rarely being refused supply, with limited pharmacist intervention (study prior to removal of OTC codeine from Schedule 2)

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[20] Daniels SE, Goulder MA, Aspley S, Reader S. A randomised, five-parallel-group, placebo-controlled trial comparing the efficacy and tolerability of analgesic combinations including a novel single-tablet combination of ibuprofen/paracetamol for postoperative dental pain. Pain 2011; 152;632–642

[21] BBC News. Pharmacist's painkiller warning. http://news.bbc.co.uk/2/hi/health/214759.stm (accessed 7 April 2015).

[22] Pates R et al. Misuse of over-the-counter medicines: a survey of community pharmacies in a South Wales health authority. Pharm J 2002;268:179-182.

[23] Haggan M. Pharmacists worried by OTC codeine. Aust J Pharmacy 16 March 2015. http://ajp.com.au/news/pharmacists-worried-by-otc-codeine/

[24] Nielsen S, Cameron J, Pahoki S. Over the counter codeine dependence final report 2010. Victoria: Turning Point, 2010. http://atdc.org.au/wp-content/uploads/2011/02/OTC_CODEINE_REPORT.pdf

[25] Hamer AM, Spark MJ, Wood PJ et al. The upscheduling of combination analgesics containing codeine: the impact on the practice of pharmacists. Research Soc Admin Pharmacy 2013;

[26] Cooper R. Surveillance and uncertainty: community pharmacy responses to over the counter medicine abuse. Health Soc Care Community 2013;21:254-62.

- Codeine users report that little information or advice about the risk of dependence was provided, none described a pharmacist directly raising concerns about abuse or dependence, refer them for help or suggest they seek assistance
- Refusals tended to result in users purchasing the product at another pharmacy
- Some pharmacists keep records within the pharmacy of all sales, others of only some sales when they identify a concern. These records are not easily shared between pharmacies.
- Supervision by a busy community pharmacist may be perfunctory[27],
- There is a potential conflict of interest in the business environment of community pharmacy[28]
- Pharmacists describe a number of challenges in managing drug-seeking for OTC codeine:
    - The difficulty of establishing therapeutic need.
    - Lack of confidence in discussing misuse.
    - Resentment from customers when pharmacists were involved in sales.
    - Discussing addiction risk or refusing supply was challenging, particularly over-the-counter around other people.
    - Involvement in sales was time-consuming and there was a lack of time to have a detailed conversation.
    - Concern about sales at other pharmacies providing easy access.
    - Some customers resent the subject of misuse or dependence being discussed.
    - Some customers become angry when refused supply, described by a pharmacist as "codeine tantrums"[29].
    - Recognition that some OTC codeine dependent people were driving long distances to different pharmacies, described as "codeine road trips"[30].

Codeine users sustain high dose use for prolonged periods. Cases of patients experiencing serious NSAID adverse effects such as perforated gastric ulcers, renal tubular acidosis and hypokalaemia described in the medical literature report that they have been able to sustain using a large number of tablets each day for prolonged periods. Dobbin and Tobin (2008) described 77 Australian cases of misuse of OTC codeine-ibuprofen analgesics who sustained high daily intake for a prolonged period. In these cases the average use was 50 tablets per day for an average duration of 2.5 years[31].

Conclusion.

- Adding low dose codeine to non-opioid analgesics provides little additional analgesic benefit
- Pharmacists face challenges in addressing drug-seeking by codeine dependent users.
- An increasing number of Australians are seeking treatment for dependence on OTC codeine analgesics, many experiencing serious, sometimes life-threatening NSAID adverse effects.
- Good evidence now demonstrates that under current arrangements (Schedule 3 Pharmacist Medicine) there is a substantial level of harm from the easy and widespread availability of these opioid medicines.
- Consumers can now successfully self-medicate acute pain using newly available OTC analgesic products that provide better analgesia without the risk of codeine addiction and its consequences.

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[27] Ferner R, Beard K. Over the counter medicines: proceed with caution, BMJ 2008;336:694-696.

[28] Blenkinsopp A, Over the Counter Drugs: Patients, society, and the increase in self-medication, BMJ 1996;312:629-632.

[29] Dow A. Codeine addicts abuse pharmacists. Sydney Morning Herald 24 Aug 2014. http://www.theage.com.au/victoria/codeine-addicts-abuse-pharmacists-20140424-zqyjx.html

[30] Duffy C. Codeine abuse leads to calls for painkiller rethink. ABC 7.30. 6 Nov 2012. http://www.abc.net.au/news/2012-11-06/codeine-abuse-leads-to-calls-for-painkiller-rethink/4356816

[31] Dobbin M, Tobin C. Over-the counter (OTC) ibuprofen/codeine analgesics: misuse and harm. Paper prepared for the National Drugs and Poisons Schedule Committee. 22 May 2008.

ATTACHMENT A. Published cases (250 cases) of NSAID harm arising from misuse of OTC codeine-ibuprofen analgesics: Australia and New Zealand, 2008-2014.

Authors (country)	No. cases. No. tablets/day	Description.
Dobbin & Tobin, 2008 [32] (Australia)	77 cases Average 50 tablets per day for an average of 2.5 years	Drug dependence on codeine with serious complications of **upper gastrointestinal toxicity (haemorrhage and perforation of the stomach and duodenum), anaemia, renal tubular acidosis, hypokalaemia and one death**. Many patients needed **life support in intensive care**, as well as emergency surgery. Average age was 33 years, and an equal representation of males and females.
Dutch, 2008 [33] (Australia)	2 cases pack/day, and 16-24/day (Nurofen Plus)	Two cases of **perforated gastric ulcers** attributed to recreational codeine-ibuprofen use. One case required **intensive care unit**, the other 4 units of packed blood cells.
Frei et al, 2010 [34] (Australia)	27 cases mean 34-47/day OTC codeine-ibuprofen	A case series of patients with serious and often multiple NSAID pattern morbidities such as **GI haemorrhage and perforation, pyloric stenosis, renal failure, anaemia and profound hypokalaemia, as well as opioid dependence,** resulting from high dose OTC codeine-ibuprofen misuse obtained from multiple pharmacies over a prolonged period. Some with multiple admissions. Most had no previous history of substance use disorder, with most initiating for self-medication of pain. **Four admitted to ICU**. One required **dialysis**. One **gastrectomy**. Most required pharmacotherapy for opioid dependence.
Ernest D, Chia M, Corallo CE. 2010 [35] (Australia)	2 24/day for 3 days (Nurofen Plus)	**Profound hypokalaemia and rhabdomyolysis** presenting as severe quadriparesis, from overuse of Nurofen Plus with energy drinks**. ICU admission**. Partner also admitted for **detoxification** from Nurofen Plus.
Robinson GM, Robinson S, McCarthy P, Cameron C. 2010 [36] **(New Zealand)**	**7** **Nurofen Plus 60-80/day, 48/day, 20/day, up to 72/day, 80/day, up to 120/day, 48/day**	**Cases of long term high dose Nurofen Plus misuse with severe multiple NSAID pattern morbidities (gastric ulcer and haemorrhage, anaemia, gastrectomy, ileal resection, inflammatory bowel disease with gastric bypass and colectomy), Four cases had co-morbid alcohol use disorders, four cases with mental health disorders.**
Evans C, Chalmers-Watson TA, Gearry RB. 2010 [37] (New Zealand)	Describing 1 of 4 cases. > 100 tabs/day	Presented with anaemia, lower leg oedema and epigastric pain. **Gastric ulcer** with **active bleeding** in pyloric channel and **post-bulbar duodenitis with active bleeding.** Balloon dilatation of **pyloric stenosis** later required, and he was treated for **addiction**. He was one of four patients presenting to the service in 2 years with **significant GI pathology** secondary to gross overuse of combination NSAID/codeine products.
Ali A et al. 2010 [38] (Australia)	1 60-80 Nurofen Plus tablets/day for many months	**Renal tubular acidosis** and **hypokalaemic paraparesis**

[32] Dobbin M, Tobin C. Over-the counter (OTC) ibuprofen/codeine analgesics: misuse and harm. Victorian Department of Health, Melbourne. 2008.
[33] Dutch MJ. Nurofen Plus misuse: an emerging cause of perforated gastric ulcer. Med J Aust. 2008;188:56-7.
[34] Frei MY, Nielsen S, Dobbin MDH, Tobin CL. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases. Med J Aust 2010;193:294-6.
[35] Ernest D, Chia M, Corallo CE. Profound hypokalaemia due to Nurofen Plus and Red Bull misuse. Crit Care Resusc 2010;12:109-10.
[36] Robinson GM, Robinson S, McCarthy P, Cameron C. Misuse of over-the-counter codeine-containing analgesics: dependence and other adverse effects. NZ Med J. 2010;123:59-64.
[37] Evans C, Chalmers-Watson TA, Gearry RB. Combination NSAID-codeine preparations and gastrointestinal toxicity. N Z Med J 2010;123:92-3
[38] Ali A, Wong J, Howlin K, Jefferys A et al. Renal tubular acidosis and hypokalemic paraparesis due to neurofen overdose. Nephrology 15: 43, Sept 2010

Miles R et al. 2010 [39] (Australia)	1	**Acute Tubular Necrosis** and **Renal Tubular Acidosis**
Ferguson L, Clarke I, Fisher A, Legg G, Batey R 2010 [40] (Australia)	5 60, 50, 60, 40-60,75 tablets/day respectively	Case 1: A young female with past history of sexual abuse, unplanned pregnancy with termination who commenced NSAID's (Nurofen plus) to relieve right sided **abdominal pain** following the termination. Use escalated to over 60 tablets a day. She was seen over an 18 month period by D&A, Mental Health, medical and surgical teams but died of complications of **ulcer disease** with bleeding and **undetected perforation of an ulcer**. Case 2: A young female with past history of physical abuse who was taking 50 plus NSAID's (Nurofen plus) a day for pain. She presented with increasing **muscle weakness** to the point of being unable to walk unaided. On presentation to the ED her **potassium** was 2.4. She had an **associated renal tubular acidosis**. Case 3: A 22 year old female, with a one year history of taking 60 Nurofen Plus per day, was admitted for emergency laparotomy for a **perforated pre pyloric ulcer and peritonitis.** The patient required ICU care and the pathology showed she was **acidotic** and **hypoalbuminemic**. She had initially started Nurofen Plus for post IUD insertion pain, at recommended doses. Discovering euphoric effects from high doses, she escalated the dose after two weeks. The patient has been treated for depression. She had been abstinent from Nurofen Plus for 15 months and had been treated in a residential D&A facility. A relatively brief relapse of 60 Nurofen Plus tablets per day precipitated acute abdominal pain and urgent hospital admissions. **Case 4**: A 32 year old male presented to D&A services with a 2 year history of Nurofen Plus use: 40-60 tablets per day. He commenced use initially for dental pain and found escalating doses decreased anxiety. After point-of-sale changes, he was forced to reduce the dose. He is now stable on buprenorphine 8mg daily. **Case 5**: A 28 year old female with a 2 year history of using 75 Nurofen Plus per day presented to hospital requesting withdrawal. This was driven by inability to purchase high amounts in a rural area, due to point-of-sale changes. Gastroscopy and other pathology was normal. Symptomatic opioid withdrawal was conducted as the patient declined maintenance pharmacotherapy.
Storor D. 2011 [41] (Australia)	56	Opioid dependence on OTC codeine analgesics. **Gastritis, peptic ulcer, scarring and strictures, intestinal obstruction and renal failure**. Some required **blood transfusions**. **Hepatitis** from paracetamol.
Ng JL, Morgan DJR, Loh NKM, Gan SK, Coleman PL, Ong GSY, et al. 2011 [42] (Australia)	2 up to 20 tabs/day, and 24 tabs/day (codeine-ibuprofen)	Four cases of **profound hypokalaemia** associated with excess ibuprofen intake. Two of the cases involved codeine-ibuprofen. One had a history including **iron deficiency anaemia**, **chronic constipation**, migraines, depression and previous intravenous drug use. She was taking up to 20 tabs/day and was admitted with **evolving paralysis** and **profound hypokalaemia**, **renal tubular acidosis**, **oesophageal erosions** and **gastric ulcer**. The other had been taking 24 tabs/day of OTC codeine-ibuprofen for several years and presented with **progressive muscle weakness** and hypokalaemia. Opioid withdrawal symptoms on day 3.

[39] Miles, R., Bofinger, A., Herzig, K. and Searle, J. (2010). Selective Distal Tubular Acute Tubular Necrosis and Renal Tubular Acidosis Due to Abuse of Nurofen Plus (Ibuprofen/codeine Phosphate). In: Nephrology. 2010 (43-43).

[40] Ferguson L, Clarke I, Fisher A, Legg G, Batey R. Over the counter and into the grave: morbidity and mortality related to NSAIDS with codeine dependence. APSAD Conference 2010. Drug and Alc Rev 2010;29 (Suppl. 1):2-82. Unpublished poster of same name at APSAD conference.

[41] Storor D. National pharmaceutical drug misuse strategy [letter to National Centre for Education and Training on Addiction]. http://nceta.flinders.edu.au/files/7713/1423/8823/Damascus%20Health%20Services%20web%20version.pdf (accessed Jul 2014).

[42] Ng JL, Morgan DJR, Loh NKM, Gan SK, Coleman PL, Ong GSY, et al. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. Medical J Australia. 2011;194:313-16.

Page CB, Wilson PA, Foy A, Downes MA, Whyte IM, Isbister GK. 2011 [43] (Australia)	4 OTC codeine-ibuprofen. Tablets /day 45-90, 25, 40 and unclear but years' duration.	Four cases of **life-threatening hypokalaemia** and ibuprofen-induced **renal tubular acidosis** from long-standing misuse of ibuprofen taken in combination with codeine from over-the-counter (OTC) medications. Two patients **required ICU admission**. Opioid addiction appeared to be the common thread.
McDonough MA 2011 [44] (Australia)	32	Cases referred to one addiction medicine service, all with a history of chronic pain and combination codeine-analgesic use. One 34yo male reported taking more than 70 codeine-ibuprofen tablets daily and sustained **recurrent gastric ulceration** eventually requiring surgery. Despite this he continued to misuse the analgesics and undertook opioid replacement pharmacotherapy. Some cases had severe morbidity including one death from **gastric ulceration**.
Mallett A, Lynch M, John GT, Healy H, Lust K. 2011 [45] (Australia)	1 OTC codeine-ibuprofen. Tablets /day 45-90, 25, 40 and unclear but years' duration.	34-year-old woman in third trimester of pregnancy presented with **renal tubular acidosis** related to ibuprofen codeine abuse. Delivery at 37 weeks was necessary because of concerns about evolving preeclampsia**. Renal tubular acidosis** and **hypokalaemia** were mitigated, but **some renal dysfunction** continued.
Karamatic R, Croese J, Roche E. 2011 [46] (Australia)	3 OTC codeine-ibuprofen. Tablets /day 10, 10-12, and 20 tablets a day, in two cases for 5 years or more.	3 cases of **small bowel NSAID enteropathy**, including **diaphragm disease** and **small bowel ulceration**, all of whom had **iron deficiency anaemia** and **hypoalbuminaemia**.
McAvoy BR et al. 2011 [47] (New Zealand)	15 cases over a 12 week period OTC codeine-ibuprofen average 49 per day for average 27 months	**Gastrointestinal bleeding**, dyspepsia in 53%. **Renal tubular acidosis** in 7%.
Lake H. 2013 [48] (Australia)	1 up to 90/day codeine-ibuprofen	Worsening abdominal pain, **bowel obstruction**. **Small bowel resection. Fibrous stricture.** Delirium and multiple code black interventions - aggressive and violent behaviour.
Pilgrim J, Dobbin M, Drummer OH. 2013 [49] (Australia)	7	Coroners' cases with codeine and ibuprofen detected in post-mortem toxicology, or where codeine–ibuprofen analgesic misuse was described in coroners' findings. 115 cases were identified, and evidence of chronic NSAID toxicity was reported in 7 cases manifesting as **gastric erosions and ulceration** in three individuals, **chronic gastritis** in one, **renal necrosis** and disease in two and **hepatocyte necrosis** in one.
Robertson CG, Kumar B, Bright T, Watson DI. 2014 [50] (Australia)	5	Five young patients with unrecognised NSAID abuse referred with **non-healing gastric ulcers** with or without **perforation** or **gastric outlet obstruction**. Four patients did not volunteer NSAID use until confronted with positive NSAID urine tests. Complex issues during recovery followed surgical intervention.

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[43] Page CB, Wilson PA, Foy A, Downes MA, Whyte IM, Isbister GK. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. Med J Aust 2011;194:613-14.
[44] McDonough MA. Misuse of codeine-containing combination analgesics. *Medical Journal of Australia*. 2011;194:486.
[45] Mallett A, Lynch M, John GT, Healy H, Lust K. Ibuprofen-related renal tubular acidosis in pregnancy. Obstetric Medicine 2011;4:122-4.
[46] Karamatic R, Croese J, Roche E. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics. Med J Aust 2011;195(9):516.
[47] McAvoy BR, Dobbin MDH, Tobin CL. Over-the-counter codeine analgesic misuse and harm: characteristics of cases in Australia and New Zealand. N Z Med J. 2011; 124(1346):29-33.
[48] Lake H. Ibuprofen belly: a case of small bowel stricture due to non-steroidal anti-inflammatory drug abuse in the setting of codeine dependence. Aust NZ J Psychiatry 2013;47:1210-11
[49] Pilgrim J, Dobbin M, Drummer OH. Fatal misuse of codieine-ibuprofen in Victoria, Australia. Med J Aust 2013;199(5):329-30.
[50] Robertson CG, Kumar B, Bright T, Watson DI. Beware NSAID abuse: think twice before operating. Aust NZ J Surgery 2014;84:495-6

ATTACHMENT B: Indicators of number of Australians experiencing harm from misuse of OTC codeine analgesics.

Until recently estimates of the magnitude of this problem in Australia have been limited to a number of published articles in the medical literature describing individual cases or case series. More recent information from late-2014 provides a more concrete description of the magnitude of this problem. Current information is outlined in Table 1 and described in the text that follows.

Source	Numbers/estimates
Case studies Australia New Zealand	250 224 26
Nielsen et al's novel case series	47
National Opioid Pharmacotherapy Statistics snapshot: estimate using Nielsen et al's 'novel case series' proportion 2013	975
Nielsen et al's non-opioid substitution treatment episodes FY 2010-11	650 +
Warinilla treatment episodes 2013	147
Western Australia OTC codeine treatment episodes July-Dec 2014	176

Table 1: Summary of number of cases or estimated cases or episodes of treatment for codeine dependence involving OTC codeine analgesics.

Case series and case descriptions prior to 2015. A total of 250 cases of serious adverse drug events from NSAID toxicity resulting from opioid addiction and high dose misuse of OTC codeine-ibuprofen analgesics in Australia (224 cases) and New Zealand (26 cases) published from 2008-2014 are described in Table 2.

Publication of Frei et al's paper describing 27 cases of serious harm from misuse of OTC codeine-ibuprofen[51] prompted further articles describing multiple cases in the same hospital of serious NSAID morbidity from high dose misuse of OTC codeine-ibuprofen analgesics:

- 3 cases of life-threatening hypokalaemia from renal tubular acidosis admitted to the same Western Australian tertiary care hospital within 3 months and another admitted to a peripheral hospital the previous year[52]. Two of these cases involved OTC codeine-ibuprofen misuse.
- 4 cases of life-threatening hypokalaemia from renal tubular acidosis at Calvary Mater Newcastle, New South Wales [53]
- 3 cases of small bowel NSAID enteropathy identified at Townsville Hospital in Queensland [54]

[51] Frei MY, Nielsen S, Dobbin MDH, Tobin CL. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases. Med J Aust 2010;193:294-6.
[52] Ng JL, Morgan DJR, Loh NKM, Gan SK, Coleman PL, Ong GSY, et al. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. Med J Aust. 2011;194:313-16.
[53] Page CB, Wilson PA, Foy A, Downes MA, Whyte IM, Isbister GK. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. Med J Aust 2011;194:613-14.

Other papers also described multiple cases of NSAID morbidity from misuse of OTC codeine-ibuprofen at a single health institution:

- 2 cases with perforated gastric ulcer presenting at a peripheral Melbourne hospital over 6 months[55].
- 2 cases, one of profound hypokalaemia and rhabdomyolysis, and one presenting for opioid detoxification for codeine dependence[56]
- 4 cases treated for serious NSAID gastrointestinal morbidity at Christchurch Hospital, New Zealand[57].
- 5 young patients referred to surgeons at Flinders Medical Centre, Adelaide with non-healing gastric ulcers unresponsive to treatment, with or without perforation or gastric outlet obstruction [58].

Additionally 3 published cases series and one narrative account describe multiple cases of individuals seeking treatment for addiction to OTC codeine-ibuprofen analgesics, many of whom have experienced serious NSAID morbidity

- 15 clients presenting to a regional detoxification clinic in Auckland over 3 months [59].
- 7 cases with NSAID morbidity referred to a hospital detoxification unit in New Zealand[60].
- 56 cases treated by an Addiction Medicine Physician at a private hospital in Brisbane[61].
- 32 cases described by an Addiction Medicine Physician treated by Drug and Alcohol Services at Western Hospital, Victoria[62].

Multiple cases at single institutions suggest that these adverse outcomes are more common than if only a single case was identified at each institution.

Cases described in the medical literature represent those from the severe end of the spectrum of people likely to be suffering the effects of misuse of high daily doses of OTC codeine-ibuprofen, and may represent only some of those coming to treatment in the community. It suggests that there is a large pool of people misusing and/or addicted who have not presented for treatment.

National Opioid Pharmacotherapy Statistics (NOPS). In 2014 the National Opioid Pharmacotherapy Statistics (NOPS) reported the primary opioid of concern for people treated with opioid substitution

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[54] Karamatic R, Croese J, Roche E. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics. Med J Aust 2011;195(9):516

[55] Dutch MJ. Nurofen Plus misuse: an emerging cause of perforated gastric ulcer. *Medical Journal of Australia*. 2008;188:56-7.

[56] Ernest D, Chia M, Corallo CE. Profound hypokalaemia due to Nurofen Plus and Red Bull misuse. Crit Care Resusc 2010;12:109-10.

[57] Evans C, Chalmers-Watson TA, Gearry RB. Combination NSAID-codeine preparations and gastrointestinal toxicity. N Z Med J 2010;123:92-3

[58] Robertson CG, Kumar B, Bright T, Watson DI. Beware NSAID abuse: think twice before operating. Aust NZ J Surgery 2014;84:495-6

[59] McAvoy BR, Dobbin MDH, Tobin CL. Over-the-counter codeine analgesic misuse and harm: characteristics of cases in Australia and New Zealand. N Z Med J. 2011; 124(1346):29-33.

[60] Robinson GM, Robinson S, McCarthy P, Cameron C. Misuse of over-the-counter codeine-containing analgesics: dependence and other adverse effects. NZ Med J. 2010;123:59-64.

[61] Storor D. National pharmaceutical drug misuse strategy [letter to National Centre for Education and Training on Addiction]. http://nceta.flinders.edu.au/files/7713/1423/8823/Damascus%20Health%20Services%20web%20version.pdf (accessed Jul 2014).

[62] McDonough MA. Misuse of codeine-containing combination analgesics. *Medical Journal of Australia*. 2011;194:486.

treatment (OST) for opioid dependence[63]. On a snapshot day in 2013 there were 47,576 clients treated for opioid dependence, with the primary opioid of concern reported for 26,229. Of these about one-third (33%) reported pharmaceutical opioids as the principle drug of concern, including codeine for 1038 clients (4%). There was no information whether the source was prescription or non-prescription (OTC) codeine.

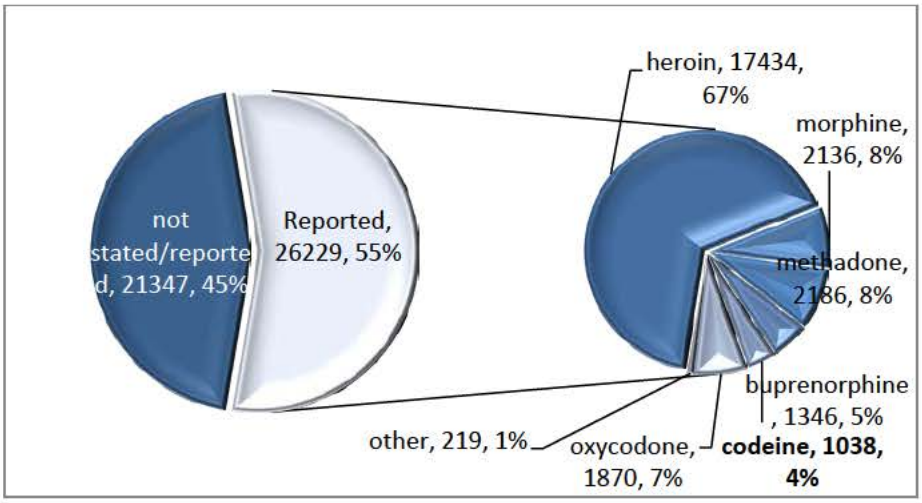

Figure: National Opioid Pharmacotherapy Statistics: principle opioid drug of concern where stated/reported: Australia, 2013.

Neilsen et al 2014. This study examined the characteristics of 145 clients presenting for treatment of opioid dependence on pharmaceutical opioids in 3 NSW local health districts[64].

They identified 145 patients, of whom 53 (36%) nominated codeine as their principle opioid of concern. Of these, 47 (94%) reported OTC codeine as their source, and 3 (6%) reported prescription codeine as the source.

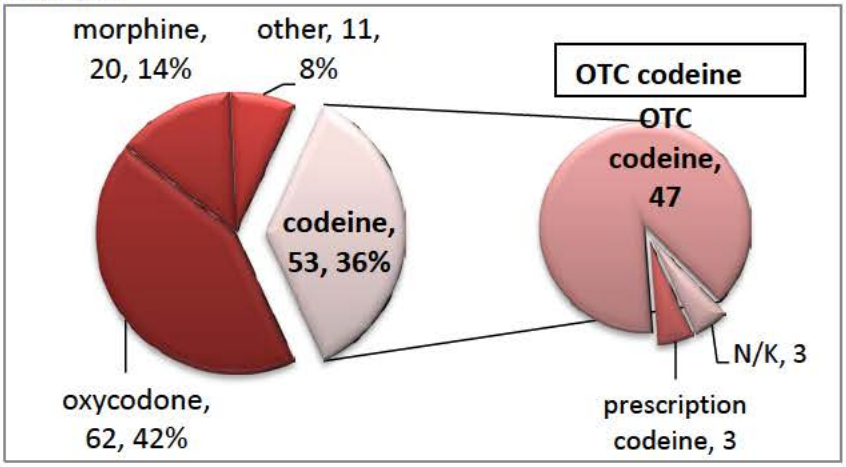

Figure: Principle opioid drug of concern for clients attending for treatment of opioid dependence: three local health districts in NSW.

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[63] Australian Institute of Health and Welfare 2014. National opioid pharmacotherapy statistics 2013. Drug treatment series no. 23. Cat. no. HSE 147. Canberra: AIHW.

[64] Nielsen S et al. Comparing treatment-seeking codeine users and strong opioid users: Findings from a novel case series. Drug Alc Review 2014. Dec 29. doi: 10.1111/dar.12224.

Estimate from NOPS data and Nielsen et al's fraction (94%) of OST. Nielsen et al's fraction of codeine dependent patients presenting for treatment in NSW (94%) was applied to the national figures of 1038 clients dependent on codeine in 2013.

This resulted in an estimate of 975 Australian clients being treated with OST for dependence on OTC codeine in 2013. The number is likely to be much larger because no primary opioid of concern was reported for 45% of pharmacotherapy clients.

Nielsen et al (2015). This study described changes in treatment in government funded drug and alcohol services in four states for opioid dependence that did not involve opioid substitution treatment: treatments included withdrawal, counselling, case management and support, and residential rehabilitation services[65]. This information does not include data from other States and Territories, or patients treated privately by GPs , Addiction Medicine Physicians or other health professionals.

They describe an increase from about 200 treatment episodes in 2002-03 to more than 650 in 2010-11. It does not include people treated privately by GPs or Addiction Medicine Physicians.

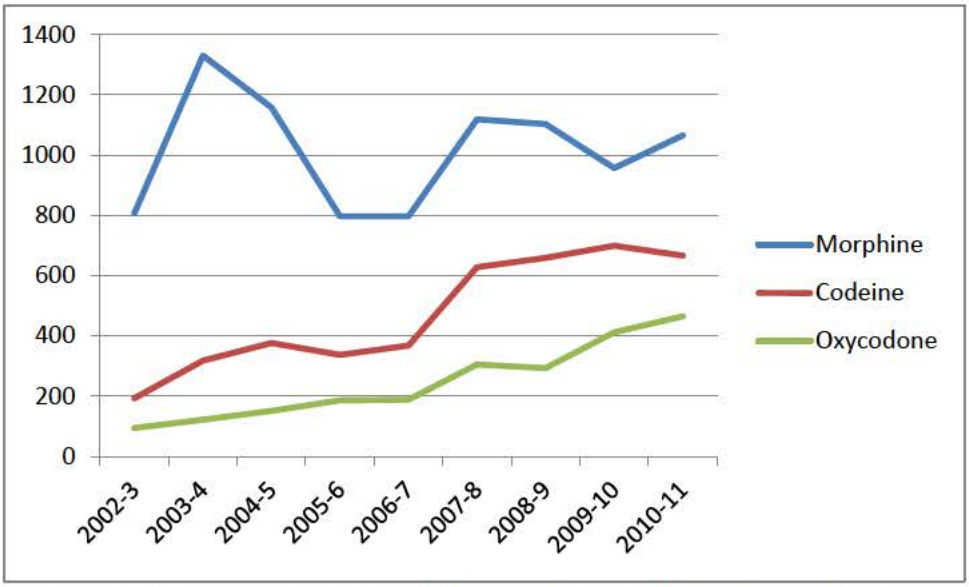

Figure: non-opioid substitution treatment episodes for morphine, codeine and oxycodone: Queensland, NSW, South Australia, Tasmania, 2002-03 to 2010-11.

Trends in number of treatment episodes for patients attending Warinilla Drug and Alcohol Treatment Centre in Adelaide. Data from Warinilla describes that there has been a steady increase in the number of treatment episodes for clients for whom the principle drug of concern was codeine, except for a decrease in numbers in fiscal year 2010-2011.

The source in all cases was non-prescription (OTC) codeine.

The number of treatment episodes increased from 31 in 2002-2003 to 174 in 2013-2014. This was an increase from 2.6% to 15.9% of treatment episodes for all opioids (including heroin), and from 7.8%

[65] Nielsen S, Roxburgh A, Bruno R et al. Changes in non-opioid substitution treatment episodes for pharmaceutical opioids and heroin from 2002-2011. (Drug Alcohol Depend 2015), http://dx.doi.org/10.1016/j.drugalcdep.2015.02.004

to 26.6% of all pharmaceutical opioids over this period. It does not include patients treated privately by GPs or Addiction Medicine Physicians or other health professionals.

The decrease in numbers in fiscal year 2010-2011 was co-incident with the removal of OTC codeine from Schedule 2, supporting that dependence on OTC codeine may be responsible for this trend.

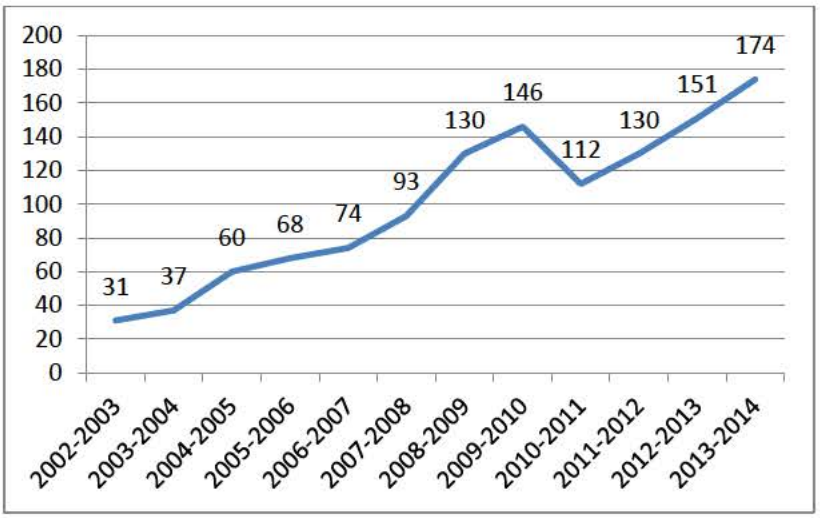

Figure: Closed opioid episodes for codeine: Warinilla, South Australia: Fiscal year 2002-2014.

Queensland Opioid Treatment Program. Of the 836 first time clients attending the Queensland opioid treatment program in 2013, 43% reported morphine, oxycodone or codeine as their drug of dependence[66]. More than 10% of all first time clients and approximately 5% of about 5,500 other clients reported codeine as their principle drug of concern.

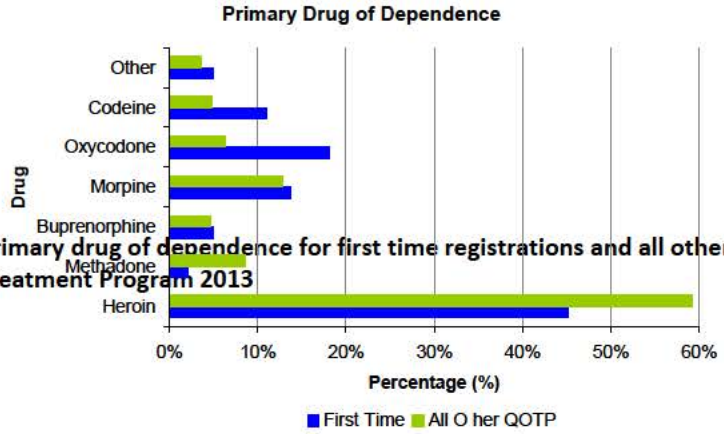

Figure: Primary drug of dependence for first time registrations and all other registrations: Queensland Opioid Treatment Program 2013

Western Australia began identifying treatment episodes for OTC codeine preparations in all State Government funded AOD services in WA including Next Step in 2013. In 2013/14 there were 121 episodes (although these may not have been for a complete year) and in the 6 months July – December 2014 there were 176 treatment episodes.

[66] Medicines Regulation and Quality, Queensland Department of Health. Queensland Opioid treatment Program. Year: 2013.

ATTACHMENT C: Analgesic efficacy of oral analgesics.

A summary of 35 Cochrane reviews of randomised trials evaluating the efficacy of different oral analgesics in different dose/drug combination for the treatment of acute postoperative pain listed the number of individuals needed to treat (NNT) for one patient to obtain at least 50% pain relief over 4-6 hours postoperatively compared to placebo[67].

Codeine is a weak analgesic, with a NNT of 12 to obtain at least 50% pain relief postoperatively[68].

Drug/dose combinations with low NNTs included ibuprofen 400 mg (2.5; 95% confidence interval (CI) 2.4-2.6), and codeine 60 mg/paracetamol 800-1000 mg (2.7; 95% CI 1.8-2.9). Less favourable NNTs were reported for paracetamol 975/1000 mg (3.6; 95% CI 3.2-4.1), and codeine 60 mg (12; 95% CI8.4-18).

Analgesic efficacy of ibuprofen/codeine compared to ibuprofen alone.

McQuay et al (1989) compared ibuprofen 400 mg/codeine 20mg with ibuprofen 400 mg alone in the management of pain following third molar extraction[69]. The combination provided at least 50% pain relief for 16/24 subjects, and 11/23 of subjects treated with ibuprofen alone.

Po and Zhang (1998) conducted a systematic overview of published randomised, controlled trials comparing the analgesic efficacy of ibuprofen alone or in combination with codeine or caffeine in post-surgical pain[70]. In their introduction they describe that some reports suggest that codeine adds to the analgesic effects of ibuprofen, but others had failed to show any superiority of the combination. The meta-analysis described that codeine 60 mg enhanced the analgesic effect of ibuprofen 400 mg by about 8% in the total pain-relief scale, but also increased its adverse effects.

Derry et al (2015) conducted a Cochrane review of trials examining single dose oral ibuprofen plus codeine for acute postoperative pain in adults. Their analysis included the McQuay et al (1989) study described above, and two subsequent studies comparing a combination of ibuprofen 400mg/codeine 60 mg (high dose codeine) with ibuprofen 400 mg alone[71] [72]. They analysed the three studies together and reported a NNT for ibuprofen 400 mg/codeine 25.6-60 mg (high dose) compared to placebo: (2.2; 95% CI 1.8-2.6)[73]. When the combination was compared to the same dose of ibuprofen alone, the relative benefit was 1.4 (95% CI 1.01-1.6). With the confidence interval almost overlapping 1, the authors commented that the difference only just reached statistical

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[67] Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2011; (9): CD008659. http://www.ncbi.nlm.nih.gov/pubmed/21901726

[68] Derry S et al. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. *Cochrane Database Syst Rev*. ; (4): CD008099. 2010

[69] McQuay HJ, Carroll D, Watts PG et al. Codeine 20 mg increases pain relief from ibuprofen 400 mg after third molar surgery. A repeat-dosing comparison of ibuprofen and an ibuprofen-codeine combination. Pain 1989;37:7-13.

[70] Po AL, ZAhang WY. Analgesic efficacy of ibuprofen alone and in combination with codeine or caffeine in post-surgical pain: a meta-analysis. Eur J Clin Pharmacol 1998;53:303-11.

[71] Sunshine A, Roure C, Olson N et al. Analgesic efficacy of two ibuprofen-codeine combinations for the treatment of postepisiotomy and postoperative pain. Clin Pharmacol Therapeutics 1987;42(4):374–80.

[72] Cooper SA, Engel J, Ladov M et al. Analgesic efficacy of an ibuprofen-codeine combination. Pharmacotherapy 1982;2(3):162–7.

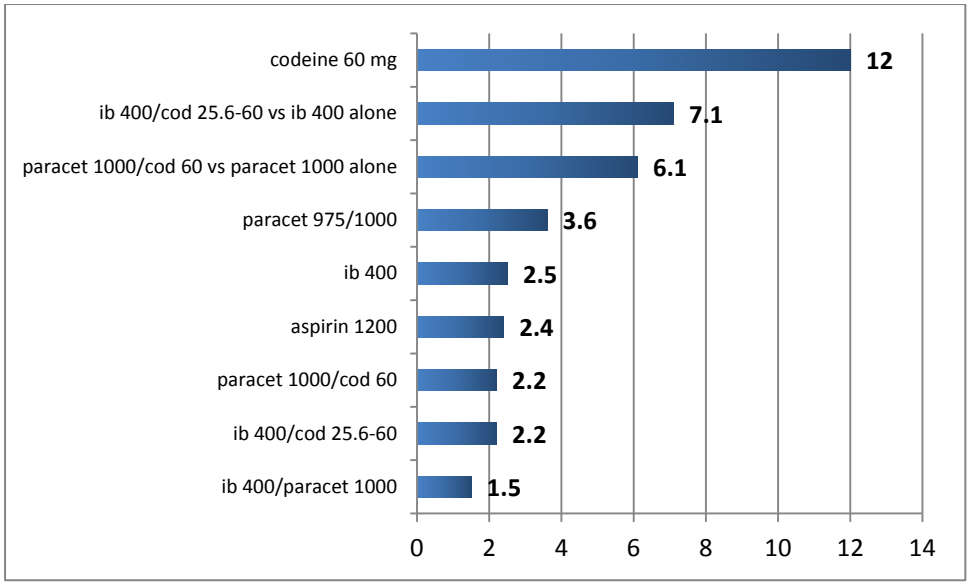
[73] Derry S, Karlin SM, Moore RA. Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No.: CD010107. DOI: 10:1002/14651858. CD010107.pub3. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010107.pub3/pdf/standard

significance. The NNT for the ibuprofen-codeine combination compared with ibuprofen alone was 7.1 (3.7-12.6). The combinations assessed included those with 60 mg codeine.

Similarly, when OTC codeine 60mg/paracetamol 1000 mg is compared to paracetamol 1000 mg alone, the NNT was 6.1.

This evidence supports that codeine is a weak analgesic, and it appears that it adds little to the analgesic efficacy of ibuprofen or paracetamol combination analgesics, while at the same time creating a risk of adverse effects, including the serious adverse drug effect of addiction and its unique, potentially serious and life-threatening consequences with these combinations.

Analgesic efficacy of a combination of ibuprofen with paracetamol.
A further Cochrane review reported on the analgesic efficacy of a combination of ibuprofen with paracetamol[74]. Ibuprofen 200 mg/paracetamol 500 mg and ibuprofen 400 mg/paracetamol 1000 mg had a NNT of 1.6 (95% (CI 1.5 to 1.8) and 1.5 (95% CI 1.4 to 1.7) for the lower and higher doses respectively compared with placebo.



Note: ib = ibuprofen, cod = codeine, paracet = paracetamol, unit for numbers is mg.
Note: 2nd and 3rd top bars refer NNT for additional benefit of adding codeine to a similar dose of non-opioid analgesic alone.

Fig: Number needed to treat (NNT) for at least 50% maximum pain relief over 4-6 hours for acute postoperative pain, compared to placebo, or the codeine combination compared to the same dose of the non-opioid analgesic ibuprofen or paracetamol alone (2nd and 3rd top bars).

The alternative combination of non-opioid analgesics ibuprofen/paracetamol provides better analgesic efficacy, with an NNT well below 2, and without the adverse drug effects of codeine that , including constipation, and addiction, with its unique harms resulting from escalation of dose and high dose toxicity of paracetamol including hepatotoxicity, and NSAID injury due to ibuprofen secondary to codeine addiction.

There are now two products with this combination available on the Australian market: Maxigesic®, and Nuromol®.

[74] Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. Cochrane Database Syst Rev 2013 Jun 24;6:CD010210. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010210.pub2/pdf